THE ACTION OF DIGITALIS IN PNEUMONIA.

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PLATE 12.

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Digitalis has been used for many years in the treatment of pneumonia but there is still discussion as to whether its use is advantageous. A decision has been difficult because the difference between action as such and beneficial action has not been sharply drawn. We show in this paper that action on the heart by digitalis takes place in pneumonia, and also that its action under certain circumstances is beneficial.

HISTORICAL.

Schmiedeberg (1) has given the early history of the use of digitalis in pneumonia. It was recommended by Ferrier (1799) for the purpose of slowing the heart rate instead of resorting to phlebotomy. Currie (1804) preferred it to cold water treatment in cerebral, cardiac, and pulmonary inflammations. Cuming (1804) gave it after phlebotomy. Then, says Schmiedeberg, its use was almost forgotten. Traube (1850), who learned the value of digitalis in Schoenlein's clinic, reintroduced it. Because it slowed the pulse Traube believed that it was an antipyretic but, as von Leyden showed, he failed to recognize the fact that if the pulse rate was slowed to the point of lowering temperature, this result was due to collapse. At this point Schmiedeberg leaves the history. He believed that giving digitalis in pneumonia was a matter still open to investigation.

More recently clinicians have been divided in opinion on its usefulness in this disease. Gibson (2) is doubtful; and Mackenzie (3) says: "I have never seen much good follow the administration of digitalis in acute febrile states. The factors exciting the heart, such as high temperature, toxins, or the invasion of the heart by specific organisms, exert an influence over the heart which the digitalis can not overcome." Lauder Brunton (4), in discussing the effect of temperature (not fever) on the action of drugs goes so far as to say: "Perhaps one of the most marked examples of this is digitalis, which at a high temperature completely loses its power of slowing the heart through the vagus." In the United States, certain authors, as Hare (5), share Brunton's view. Others, like

Elsner (6), enumerate specific indications for giving digitalis. In Germany, on the other hand, digitalis is more commonly administered now. Romberg (7) gives it to all pneumonia patients suffering from heart disease as soon as the diagnosis is made. Meyer (8) reports that it is constantly used in Krehl's clinic with gratifying results. Fraenkel (9) gives large doses (3 to 4 gm. a day for the first 3 days) in accordance with the Traube tradition.

An effort has been made to ascertain by experiment whether in the presence of fever any agents are at work which interfere with the action of digitalis. All these experiments have been employed for the purpose of determining whether heat interferes with the action of the drug. Trendelenburg (10), Weizsäcker (11), Gunn (12), and von Issekutz (13) have all performed such experiments either on rabbit or frog hearts, with digitalis or amorphous or crystalline strophanthine preparations. The result of all these efforts has been to show that by elevating the temperature of the perfusion fluid containing the digitalis body, the end-point of the reaction appears earlier than in the controls; that, in other words, elevation of temperature facilitates the action of digitalis bodies.

In the experiments performed by Jamieson (14) on dogs and cats, on the other hand, the problem investigated was whether pneumonic infection had an influence on the action of digitalis other than that exerted by temperature alone. He could find no difference in the minimal lethal dose of crystalline *g*-strophanthine in normal animals and in infected animals when the infection was at its height. He concluded, therefore, that there was nothing in the nature of the infection to interfere with the action of the drug. This conclusion does not, however, mean that the heart in pneumonia is an altogether unchanged and intact organ. Newburgh and Porter (15), for instance, have shown that it must be altered, for the hearts of animals infected with the Friedländer bacillus continue to beat when nourished with pneumonic blood, whereas such blood quickly poisons control hearts from non-infected animals. It is clear, however, from the results of Jamieson's work that, whatever the poison to which pneumonic hearts have accommodated themselves, its nature is not such as to interfere with digitalis activity.

Method.

Our observations have been carried out on 105 cases of pneumonia treated in the Hospital of The Rockefeller Institute. Digitalis was given to 49 patients; the other 56 received no digitalis and served as controls. The drug was usually given by mouth in the form of tablets of digipuratum, each tablet containing the equivalent of 0.1 gm. of the powdered leaves. The daily dose was usually 0.4 gm. Electrocardiograms were made of all the patients. In the patients to whom digitalis was administered the curves were made frequently, usually once, or oftener, each day. At the beginning of the study,

TABLE I.

	Control. No digitalis.			With digitalis.				Total available.	Total.
	Repeated records.	Single records.	Total.	Repeated records. Available.	Repeated records. Not available.	Single records. Not available.	Totals.		
Recovered	41	8	49	28	3	—	31	77	80
Died	4	3	7 (12.5%)	11 (28.2%)	3	4	18 (36.7%)	18 (18.9%)	25
Total	45	11	56	39	6	4	49	95	105

Detail of Cases.

	Fever.		No fever.	Fever.		No fever.	Per cent.		Fever.		No fever.	Fever.		No fever.	Fever.		No fever.	Total. Per cent.		Available. Per cent.		
	Recovered.	Died.	Recovered.	Recovered.	Died.	Recovered.	Fever and no fever.	Fever.	Recovered.	Died.	Recovered.	Recovered.	Died.	Recovered.	Recovered.	Died.	Recovered.	Fever and no fever.	Fever.	Fever and no fever.	Fever.	
Changes P-R and T.	2						3.5	4.0	21	7	2							61.2	60.8	76.9	77.77	97.2
" T alone.	3	1	4			1	16.0	8.0	3	3		1	2			2		22.4	23.9	15.3	16.66	
" P-R "									1		1							4.08	2.1	5.1	2.77	
" neither.	32	3		6	3	1	80.3	88.0		1		2	1			2		12.2	13.04	2.5	2.77	
Totals	37	4	4	6	3	2	56	50	25	11	3	3	3			4		49	46	39	36	
	45			11					39			6			4							

however, daily electrocardiograms were not made because the importance of frequent observations for the purpose of this investigation was not appreciated.

We have utilized as criteria for judging the action of digitalis the effect upon the length of the auriculoventricular interval (the P–R time) and the effect on the T wave of the electrocardiogram. The length of the auriculoventricular interval was calculated from electrocardiograms. The changes in the T wave for which we looked were the ones described in an earlier paper (16). In certain cases the effect of digitalis on the rate of the ventricles when the auricles were fibrillating has been an important additional criterion.

RESULTS.

In general the criteria we employed permitted us to judge satisfactorily whether digitalis was acting. We found that the signs appeared after the same amount had been given and following the same length of time in which these signs appeared in the non-febrile cases originally studied. When no digitalis was given the signs did not appear.

In 45 of the 56 control cases (Table I) we were able to make two or more observations (repeated records), while in 11 others only single electrocardiograms (single records) were obtained.

Of the 49 patients to whom digitalis was given, 39 are represented by two or more electrocardiograms (repeated records). They are grouped as available because they received amounts of digitalis sufficient to influence the curve. 6 patients are classified as unavailable because they took total amounts of digitalis (from 0.3 to 0.6 gm.) which as a matter of experience are regarded as too small to influence the curve. The remaining 4, on whom only single observations were made, are rejected for the same reason. The doses given to them were 0.7, 0.1, 0.4, and 0.2 gm.[1] The amount regarded as sufficient to produce the changes we looked for was fixed at 0.8 gm. No one showed changes after taking an amount less than this, except a single patient to whom the drug may have been given before admission to the hospital.

[1] In the last three cases the amounts given are approximate.

We distinguish further, both in the control and in the digitalis groups, between those patients who showed alterations in the curves during fever and those in whom defervescence had already taken place when the alterations were found. This distinction is necessary because what we wish to ascertain is the action of digitalis during the continuance of fever. The cases have been further subdivided into (1) those which showed changes both in P–R time (auriculoventricular interval) and in the T wave; (2) those which showed changes in the T wave alone; (3) those which showed changes in the P–R time alone; and (4) those which showed changes neither in the P–R time nor in the T wave. We base our percentage figures, therefore, on 50 cases of pneumonia who received no digitalis during the febrile period of the disease; and on 36 to whom digitalis was administered, and who took a sufficient amount of the drug.

Of the 50 control patients, 88 per cent (44 cases) showed no change in either P–R time or in the T wave; 8 per cent (4 cases) showed changes in the T wave alone; 4 per cent (2 cases) showed changes in both the P–R time and in the T wave. Of the 36 patients to whom digitalis was given, on the other hand, 77.7 per cent (28 cases) showed changes both in the P–R time and in the T waves; 16.6 per cent (6 cases) showed changes in the T wave alone; 2.7 per cent (1 case) showed changes in the P–R time alone; and 2.7 per cent (1 case) showed changes in neither the P–R time nor in the T wave. The results show briefly, therefore, that during the febrile period 88 per cent of the control cases showed no change in the electrocardiogram; while 97.2 per cent of the cases to whom digitalis was given, did show changes.

Besides the effect on conduction and on the form of the electrocardiogram (T wave), we were able to study the action of digitalis on the rate of the ventricles when the auricles were fibrillating. In five separate instances when this rhythm set in, digitalis reduced the resulting high ventricular rate while fever was present. These cases will be described in detail in a separate communication.

The facts given permit us to conclude that digitalis acts in pneumonia.

Exceptions.—The cases here described are those which were not included in the two percentage figures (88 and 97.2 per cent) just given. These include

6 control cases during fever, 5 others after defervescence, and 4 (1 febrile and 3 non-febrile) available and 10 non-available cases to which digitalis was given. We shall take up first the 6 control cases during fever. 2 showed changes both in the P–R time and in the T wave. It cannot be definitely stated that these changes occurred spontaneously, because it is not known whether digitalis was given outside the hospital. 4 other control patients showed changes in the T wave alone. 2 of these (a mother and her son) entered the hospital rather late in the course of the disease (the son on the 5th day). The 3rd showed the change only in the first curve; the 4th in a curve a week before death, on the 4th day in the hospital. In addition to these, 5 other control patients showed changes in the T wave in the period after defervescence. We can offer no explanation for their occurrence. The point of immediate interest lies in the fact that when no digitalis was given, the occurrence of electrocardiographic changes during fever was infrequent (6 in 49 cases).

We take next the single patient to whom a sufficient amount of digitalis was given and in whose curves during the febrile period the expected alterations did not take place. This patient died. Three curves were made in the 3 days he was in the hospital, and all showed that the T wave in Lead I was inverted. Whether this was normal for him, or whether it represented a change is unknown. No further change in his curves was observed, and we classify him accordingly as having shown none. In the other three available cases it is necessary only to notice that the changes occurred after the fever ceased.

We consider finally the 10 unavailable cases to which digitalis was given during fever. 5 showed changes in the T wave alone; 5 showed changes in neither. In the latter 5 no change is expected (they had taken insufficient amounts); they require no further discussion. The other 5 took digitalis, but in insufficient amounts. Of these, 1 recovered and 4 died. The one who recovered took 0.5 gm. before the electrocardiogram changed. After convalescence his T wave again became upright. The 4 who died took, respectively, 0.6 gm., 0.5 gm., 0.2 gm., and the last probably less than 0.5 gm. (The time when the electrocardiogram was taken is not recorded.) Whether doses so small caused the change must remain undecided. We doubt that the drug can have been the cause. In these 5 cases to which digitalis was given and in the 6 (febrile) control cases, then, changes took place when no digitalis had been administered, at least in the hospital, or when it was given in amounts insufficient to satisfy one that digitalis was responsible for the change.

Although our report deals with the changes which occur primarily during fever, we have included in separate columns in the table those cases in which changes took place in the postfebrile period, and we have given the percentages of each variety of change in the total of febrile and non-febrile cases. In the cases to which digitalis was given the total available and the total non-available cases are given separately. The general interpretation we draw from our observations is not altered by this division. The conclusion that digitalis acts on the febrile heart in pneumonia is, of course, better seen when only the available cases in each group are considered.

DISCUSSION.

Auriculoventricular Conduction (P–R) Time.—The effect of pneumonia or the intoxication of pneumonia on heart muscle has generally been supposed to bring about an increase in the difficulty of auriculoventricular conduction. A number of cases have indeed been reported in which delay in, or block to the passage of impulses has occurred. But in the 50 control cases on which we report, it is striking that a significant increase in conduction did not occur. On the contrary, we observed an opposite tendency with equal frequency. A decrease in the conduction time was observed in 11 cases (Table II). The decrease was, however, slight; it was usually 0.02 to 0.03 second, twice 0.04 second, once 0.05 second, and once 0.06 second. When

TABLE II.

Hospital No.	P-R time.
2,315	Fell from 0.16—0.14 = 0.02 sec.
2,309	" " 0.16—0.13 = 0.03 "
2,270	" " 0.17—0.14 = 0.03 "
2,276	" " 0.20—0.17 = 0.03 "
2,325	" " 0.17—0.14 = 0.03 "
588	" " 0.18—0.15 = 0.03 "
2,187	" " 0.16—0.13 = 0.03 "
2,286	" " 0.17—0.13 = 0.04 "
2,202	" " 0.18—0.14 = 0.04 "
2,195	" " 0.18—0.13 = 0.05 "
2,269	" " 0.21—0.15 = 0.06 "

lengthening took place, as it did in 6 patients, the change occurred within limits as narrow (Table III) and did not extend beyond 0.3 second.

TABLE III.

Hospital No.	P-R time.
2,335	Rose from 0.15—0.17 = 0.02 sec. during fever.
2,296	" " 0.14—0.16 = 0.02 " " "
2,344	" " 0.14—0.17 = 0.03 " " "
2,184	" " 0.17—0.20 = 0.03 " " "
2,216	" " 0.13—0.16 = 0.03 " after "
2,168	" " 0.15—0.18 = 0.03 " " "

The absence of lengthening in conduction leading to heart block in this series[2] is the more striking on account of the fact that we are taught to look for its occurrence in the course of infectious fevers. In our control cases, as we have shown, it did not take place.[3] In the cases to which digitalis was given, on the other hand, there was with only three exceptions an increase of 0.04 second or more. In seven instances the rise led to block.

It is conceivable that delayed conduction in patients with pneumonia may occur simply as the result of the increased rate of the pacemaker; and second, that it may be a direct effect of the intoxication due to pneumonia itself. As far as the effect of increased rate is concerned, Lewis and Cotton (17) have shown satisfactorily that when normal individuals exercise, no lesion of the junctional tissues being present, the hearts respond by an increase in rate and a decrease in the auriculoventricular interval of 0.01 to 0.03 second. In our patients the conduction interval tended, indeed, during the height of the fever, to be lessened. This may have been due to the elevation in rate. When lengthening occurred it was distinctly within the range found in normal hearts. The influence which the intoxication of pneumonia exerts on this function will be discussed later.

A reasonable explanation for the failure of a marked change in conduction to occur spontaneously may be found in a consideration of the histological pathology of pneumonia. The infections which have an influence on auriculoventricular conduction are acute rheumatism, diphtheria, typhoid fever, syphilis, and occasionally influenza. The mechanism which brings this effect about in these diseases probably does not exist in pneumonia. In the other infections mentioned, definite anatomical changes may take place, as, for instance, focal necroses in typhoid fever; infiltrating and destructive

[2] In another series of patients, now being studied, an irregularity occurred in the postfebrile period in one case caused by premature auricular beats, which were blocked. These occurred during the systole of the preceding ventricle. The ventricle may have been in its refractory period. The conduction time was uniformly 0.14 second. Incomplete block in the ordinary sense was therefore absent.

[3] The conduction changes reported by others did not, except rarely, occur until a sufficient dose of digitalis had been administered. This subject will be discussed in a later paper.

inflammatory invasions in rheumatism and syphilis; fatty, granular, and waxy degeneration of the muscle and interstitial round cell infiltration in diphtheria. Any one of these alterations may involve the conduction pathway and may terminate in functional disturbance. Of the pathological histology of the heart in pneumonia there is still insufficient knowledge, but it does not appear that extensive alterations occur.

Hearts from pneumonia patients have been described by Romberg, Meyer, Aschoff and Tawara, Eyselein, Zadek, Thorel, Fraenkel, and Liebmann. In a recent review of the literature, Thorel[4] (18) says: that from the point of view of pathological anatomy the changes in the heart in pneumonia are insignificant. Serious myodegenerations do not occur. Fatty degeneration is occasionally seen in older individuals. Romberg and his associates (19), in experiments on animals, were struck by the absence even of a slight effect on the behavior of the heart in pneumococcal infections. They saw only small and unimportant changes in the heart muscle.[5] Zadek (20) found no lesion in one case and myodegeneration in another case (the second had slight albuminuria) dying late in convalescence. Aschoff and Tawara (21) examined five cases and could find no myocardial process or extensive specific parenchymatous change. Liebmann (22) in a more than ordinarily careful examination of eleven hearts, found lesions in only three, but in these three he found inflammatory infiltration. Such lesions in suitable locations might cause disturbances in rhythm. Eyselein (23) examined twenty-three cases; nineteen hearts showed no particular changes, four showed some fatty change, and three of these an advanced degree of this alteration (Table IV).

TABLE IV.

Author.	Total.	Lesions.
Zadek	2 cases.	1 case.
Aschoff and Tawara	5 "	0 cases.
Liebmann	11 "	3 "
Eyselein	23 "	4 "
	41 "	8 "

Anatomical lesions are, according to these investigations, infrequent and on the whole insignificant. This conclusion strengthens the belief, formed by clinical observation, that where moderately

[4] Thorel (18), p. 432.

[5] Romberg, Pässler, Bruhns, and Müller (19), p. 713.

lengthened conduction occurs, it is not due to an anatomical cause. Whatever the nature of the agent, it is clear that its action is not uniform, for within the narrow limits in which changes in our series took place, they were, as we have shown, in the direction both of lengthening and shortening.

T Wave.—In our earlier paper (16) we suggested that the occurrence of the T wave phenomenon was probably explained by the fact that since "cardiac action currents depend on electrical changes as an expression of muscular activity, then the changes in the T wave must be attributed to an alteration in muscular state under the influence of the drug" (digitalis). We pointed out at the same time that the change in the T wave we were describing was not specific for digitalis, but that it occurred under the influence of muscarin, under the alteration of physical states (as the application to the heart of heat and cold), and as the result of stimulating the vagus nerve by interrupted electrical currents. There is a temptation to add the intoxicating substance in pneumonia to the agents able to cause it, in view of the fact that a number of untreated cases showed a change in the T wave. But we do not include it because the change occurs so infrequently and because of the possibility that patients may have been given digitalis before being brought to the hospital. Furthermore, the T wave in nine control cases suffered no decrease in amplitude, but actually increased distinctly (Fig. 1). When to these considerations is added the fact that the change occurred in five patients after defervescence or after the crisis, then it becomes improbable that the intoxicating agent in pneumonia possesses this influence. What circumstance is responsible for the unexpected changes which we found we are not able to decide.

We shall report next on the dose required, and the order in which the effects on the T wave and on conduction take place. It is impossible to decide on the smallest efficient dose. That was possible in the non-febrile cases described in our earlier report, where there was no complicating intoxication, and where one could be sure that no digitalis had been given before treatment. The dose we regarded as effective was about 1 gm. To the pneumonia cases we have given almost uniformly 0.4 gm. in 24 hours. The largest total doses we gave were 4.45 gm. (1 patient), 3.8 gm. (1 patient), 3.3. gm. (1 pa-

tient), 3 gm. (1 patient), and 2.9 gm. (1 patient). The other 44 patients took 2.5 gm. or less.

We found in the group of available cases that alterations in the T wave alone were observed in 16.6 per cent, and changes in the P–R time alone in only 2.7 per cent. Where only one of the changes takes place, that change accordingly is more likely to affect the T wave. But where both alterations were observed (28 cases, 77.7 per cent) we found that they occurred simultaneously in 15 patients, that the T wave was altered with smaller doses in 8 patients, and that the P–R interval lengthened earlier in 5 (Table V).

TABLE V.

Hospital No.	Change in P-R time.	Change in T wave.
	gm.	*gm.*
2,338	After 0.9	After 0 (−T before digitalis.)
2,381	" 1.8	" 0.8
2,208	" 1.2	" 0.9
2,277	" 3.4	" 1.1
1,991	" 1.7	" 1.3
2,247	" 3.0	" 1.5
1,858	" 2.4	" 1.6
2,287	" 2.6	" 2.3
2,413*	After 0.4	After 0.8
2,284	" 0.8	" 1.2 (No fever.)
2,222	" 1.1	" 1.5
2,175	" 1.3	" 1.5
2,399	" 1.3	" 1.7

* This patient probably was given digitalis before admission to the hospital.

We conclude, therefore, that digitalis alters the T wave oftener and sooner than it does the P–R time. This result is in agreement with that found formerly by us when the results of giving digitalis to patients suffering from heart disease were reported. There, in all but five instances the changes in the T wave occurred before the change in conduction. In the present series, in all but five cases, the change in the T wave occurred at the same time with, or before the change in P–R time. As a guide, therefore, to giving digitalis to patients suffering from pneumonia, we ascribe a distinct value to the use of the T wave as a sign.

Method of Selection.—The frequency with which changes in P–R time and in the T wave occurred in the digitalis group might lead to the belief that, since in this group the mortality was high, the changes were due to approaching death. In other words, the great number of electrocardiographic changes in the cases to which digitalis was given may have been due either to the method of selection or to the influence on the heart exercised by the mechanism of approaching death.

The most satisfactory method of selection consists, obviously, in studying alternately control and treated cases. We did not adopt this method because we were unwilling to withhold digitalis from patients who were seriously ill. In the early cases, indeed, it was only the severe ones that were treated. They show, consequently, a larger number of deaths than would ordinarily be expected. The mortality of the control cases was low (Table I), 12.5 per cent (7 in 56 cases), but of the available treated cases it was more than twice as great, 28.2 per cent (11 in 39 cases). Of the untreated and available treated cases it was 18.9 per cent (18 in 95 cases). The average percentage of mortality in the hospital covering the period in which these cases were studied was 27.8 per cent (Table VI). That the

TABLE VI.

Year.	No. of cases examined.	Received digitalis.	Died.		Hospital mortality.
			No.	Per cent.	
		per cent			*per cent*
1911–12	6	50	4	66.6	47.6
1912–13	16	50	6	37.5	17.3
1913–14	19	68.4	8	42.1	20.2
1914–15	82	56.9	21	25.6	26.1
	123	56.3	39	42.9	27.8

mortality of the treated cases is high on account of the method of selection is suggested by the fact that in the year 1914–15, when we studied all the cases (with seven exceptions), we had the lowest mortality (25.6 per cent), whereas in the year 1911–12, when we studied only severe cases, the mortality was 66.6 per cent. The mortality of all the patients treated in the hospital during the same

TABLE VII.

Relation of Time of Death to Time of Making Electrocardiogram.

Case No.	Hospital No.	P-R + T.	T alone.	P-R alone.	No change.	Digitalis. Total.	Digitalis. Effective.	Time before death of: Change in electrocardiogram.	Time before death of: Last electrocardiogram.	Time in hospital.
						Without digitalis.				
						gm.	gm.			
1	2,305		+				0	7-0-0*	7- 0- 0	
2	1,918				0	0.4	0		1-12-39	
3	2,314				0	0.4	0		1- 1-20	1 curve
4	1,776				0		0		1- 0- 0	
5	2,157				0	0.4	0		0- 7-45	1 "
6	535				0		0		0- 5-10	Lead II only.
7	438				0		0		0-12-?0	" II " 1 curve. 2-5-25
						With digitalis.				
8	2,322†				0		0.7		0- 7-17	About 0-24-0 2 curves.
9	1,919‡				0		0.7		0- 7-50	" 2-0-0 1 curve.
10	2,308				0		1.3		0- 1- 0	3 curves.
11	2,205‡				0	0.3	0		0- 1- 0	About 0-24-0 1 curve.
12	1,899‡		+				About 0.4		0-12- 0	1-23-2 1 curve.
13	2,231‡		+			0.5	0.2		0- 8-50	About 1-4-55 1 curve.
14	2,339†		+			0.7	0.6	0-3-43	0- 3-43	1-4-13 2 curves.
15	2,355†		+			1.0	0.6	1-6-30		
16	2,268		+			0.9	0.8	0-4-50	0-4-50	About 2-2-20 3 curves.
17	1,963	+					1.2	0-8-0	0-8- 0	2 curves.
18	2,287	+				2.7	2.3	1-11-10		
19	2,295		+			1.6	0.9	1-21-8		
20	2,201		+			1.9	1.5	2-9-50		
21	2,230		+			2.2		3-0-0		
22	2,277	+	+				0	9-0-0		
				+		3.8	2.0	5-0-0		
23	2,208	+				1.3	1.1	6-0-0		
24	1,858	+	+				2.4	6-0-0		
				+		4.45	1.6	7-0-0		
25	2,247	+				3.3	1.1-1.5	12-0-0		

* The numbers 7-0-0, etc. refer to days, hours, and minutes, respectively.

† Repeated records not available.

‡ Single records not available.

year was 47.6 per cent. The number is small to serve as a basis for generalization, but it is clear that the administration of digitalis had nothing to do with the high mortality rate, for in each year approximately one-half the patients observed took the drug.

If the number of electrocardiographic changes was due to the high rate of mortality among the treated cases, the ground for this must be sought in alterations in the heart occurring during the agonal period or in the period 1 or 2 days before death. If the changes occur in the heart at that time, a high rate of mortality would naturally increase their number. It is necessary, therefore, to decide whether these changes occur at or about the time of death. We have accordingly analyzed the curves of all the patients (25) that died.

10 cases (Nos. 2 to 11) showed no changes (Table VII). 7 (Nos. 2 to 7, and 11) of these had taken no digitalis, while of the 3 (Nos. 8, 9, and 10) who had, 2 (Nos. 8 and 9) took insufficient amounts; that is, 9 (Nos. 2 to 9, and 11) behaved in the expected way. Of the 15 (Nos. 1, and 12 to 25) that showed changes, 1 (No. 1) had taken no digitalis, and 4 (Nos. 12 to 15) had taken insufficient amounts. The remaining 10 cases require no separate consideration; they had all taken enough digitalis to account for the result. The results, in summary, show that 19 of the 25 (76 per cent) patients either showed no changes when digitalis was not given, or given in insufficient amounts, or showed changes when sufficient amounts had been taken. The last curves examined in cases in which there were no changes in the curves were all taken from 1 to 36 hours before death; all but four were taken within 8 hours, and two within 1 hour. The fact that so many died without changes must be taken to mean that the proximity of death was not associated with the electrocardiographic changes on which we rely, even in those who had taken small amounts of the drug.

From a consideration of all the evidence we have been able to gather, we believe that the intoxication due to pneumonia exerts no influence against the action of digitalis. Digitalis produces the same effects in pneumonia, judged by the criteria we use, that it does in the absence of fever. We believe ourselves justified in assuming, therefore, that whatever actions the drug possesses, are exercised also during pneumonia. If the action is beneficial, advantage

may be expected from its use. That other observers have seen no results from giving it during severe pneumonia may depend on the fact that unjust criteria were employed for estimating its action.

SUMMARY.

We have shown in a series of 105 cases of pneumonia, 95 of which we have selected as available for statistical study, that digitalis given by mouth has an action on the heart. We have judged this action to be present because changes occurred in the auriculoventricular conduction time and in the form of the T wave of the electrocardiogram, just as they do in the non-febrile heart. This conclusion is strengthened by finding that the pulse rate in fibrillating and fluttering cases fell in the presence of fever, exactly as it does in non-febrile cases. The dose and the time required to produce these effects are given and are the same as in the non-febrile cases. When there was a difference in the amount necessary to produce one or the other of the changes, it was found that the T wave is more often and more readily affected than the conduction interval. We have shown that the intoxication due to pneumonia is probably not responsible for the changes found, both from a study of the statistics and because in the control cases reverse tendencies were often found (that is, decrease in conduction time and increase in the size of the T wave). We have shown that the method of selection in consequence of which we treated a large number of severe cases did not prejudice our results, because it could be demonstrated that the proximity of death, whether in control or treated cases, was not necessarily associated with the changes we are describing. We have also, by referring to the literature of the subject, brought evidence to show that heart muscle does not undergo those changes in pneumonia, as it does in other infectious diseases, which would lead one to expect changes in conduction found in other diseases. The changes in conduction which have been reported by others were almost entirely associated with the giving of digitalis.

CONCLUSIONS.

1. Digitalis acts during the febrile period of pneumonia.

2. It produces a beneficial, possibly a life-saving effect in cases of auricular irregularity (fibrillation and flutter).

3. Whatever beneficial action it has on the function of the normally beating non-febrile heart may be expected from its use in the febrile heart in pneumonia.

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EXPLANATION OF PLATE 12.

Fig. 1. Divisions of the ordinates equal 0.1 millivolt. Divisions of the abscissæ equal 0.04 second. In each set of these electrocardiograms, Leads I, II, and III are arranged from above downward.

A. These electrocardiograms were taken on January 24, 1915, the 3rd day after the onset of pneumonia. The temperature on this day ranged between 103° and 104.6°F. The P–R time was 0.15 second.

B. These curves were taken on January 26. The temperature ranged between 102.2° and 103.6° F. T_1, T_2, and T_3 are taller than in A. The P–R time was 0.16 second.

C. These curves were taken on February 3 during convalescence. T_1 and T_2 are taller than in either A or B; T_3 is less tall. The R–T_3 period is lengthened. The P–R time is 0.16 second. Apparently the T_1 and T_2 waves increased in size throughout the period of observation. The P–R time lengthened, and on February 28 was 0.21 second.

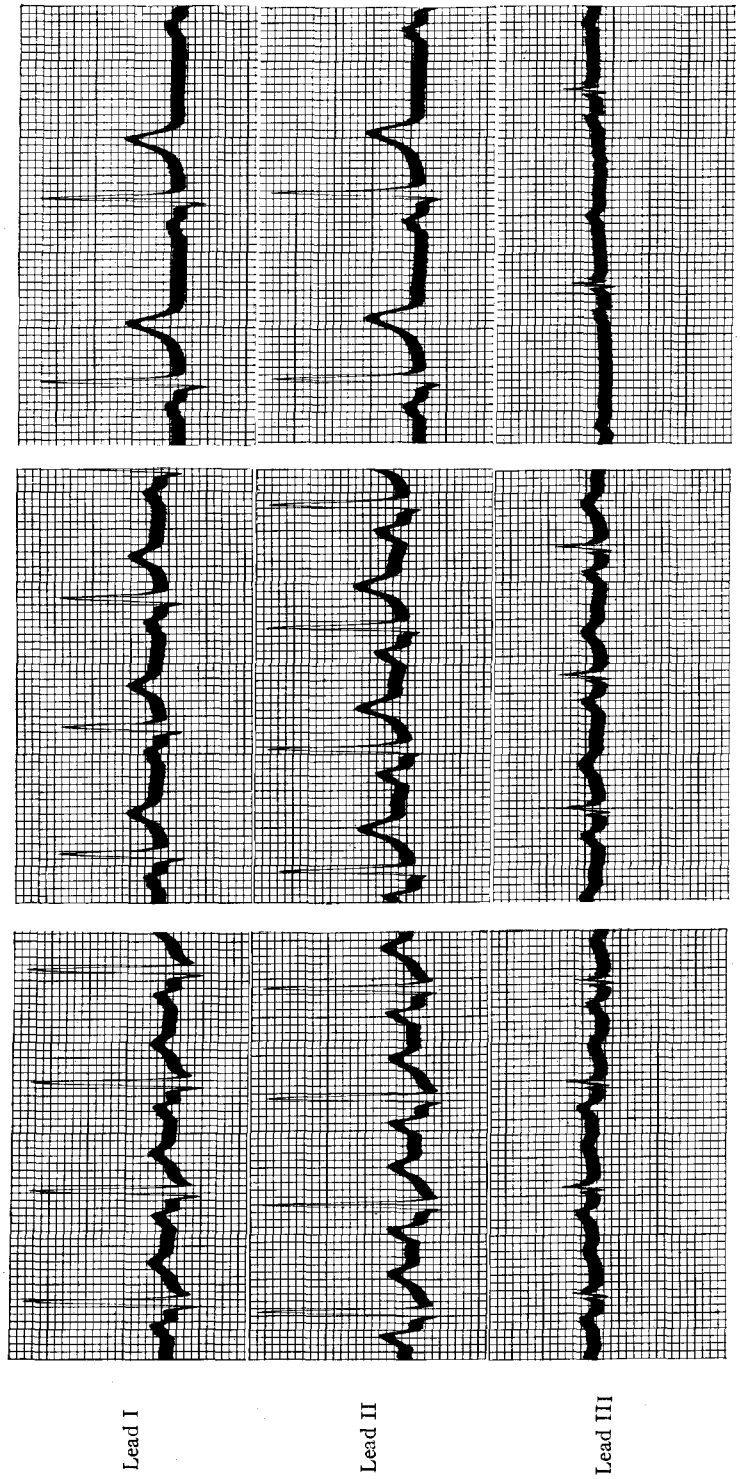

FIG. 1.

(Cohn and Jamieson: Action of Digitalis in Pneumonia.)