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Research Article

THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART IN NORMAL MAN

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INTRODUCTION

There is a general agreement of opinion that digitalis increases the output of the heart per unit of time. This opinion is based in large part upon pharmacological experiments upon animals. Although in some of these experiments, as Cohn (1915) has pointed out, the dose was greater than that administered to patients there is little doubt that in animals which have been subjected to operative procedures the output of the heart is increased by digitalis. The careful studies of Wiggers (1927), to which further reference will be made, have recently added support to this generally held opinion.

It is also generally considered that the familiar manifestations of heart failure are brought about by a reduction in the output of the heart per minute. Because of this conception of heart failure and because of the favorable results following the administration of digitalis to patients with heart failure, it has been assumed by many observers that digitalis increases the output of the heart in patients. Nevertheless Harrison and Leonard (1926) observed a diminution in the output of the intact dog's heart after the administration of digitalis in doses calculated to be of the same order as those given to patients. This diminution occurred in all the dogs studied, both narcotized and non-narcotized. This reversal of previous findings has such significance, not only as regards the conception of digitalis action but also as applied to existing theories of cardiac failure, that a study of the effect of digitalis upon the output of the human heart seemed worth while.

Direct measurements of the output of the human heart before and after the administration of digitalis have been made only by Eppinger, von Papp and Schwartz (1924). Their single subject, who was suffering

from heart failure, showed a fall in cardiac output during a period of clinical improvement which followed the administration of digitalis. For reasons which will presently be discussed, however, it is believed that measurements of the cardiac output by existing methods in persons with congestive heart failure are to be looked upon with scepti-

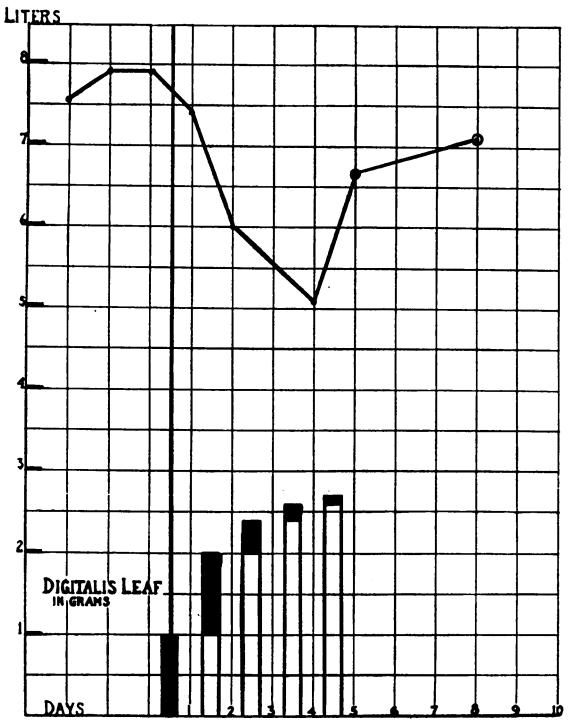

FIG. 1. CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 1

In this and in subsequent figures the points surrounded by circles indicate determinations made during periods of nausea.

cism. Cohn and Stewart (1924) studied the effect of digitalis in patients by means of a moving x-ray film. They observed an increase in the amplitude of the left ventricular excursion after digitalis in 4 subjects suffering from heart disease. No other observations seem to bear directly on the problem of the effect of the drug on the cardiac out-put of man.

METHODS

The output of the heart was observed before and after the administration of digitalis leaf of known potency in a series of normal men. During the studies, observations were also made of changes in "basal" pulse rate and other changes were recorded. The output of the heart was measured by the method of Field, Bock, Gildea and Lathrop (1924), a method which requires no punctures of blood vessels and therefore lends itself to repeated application to the same subject. It involves the determination by respiratory methods of the carbon dioxide tension in the blood entering and leaving the lungs, and the measurement of the total gas exchange by the gasometer method. During the necessary procedures, 8 to 12 half-minute counts of the pulse rate were made, the average of these counts is designated the "basal pulse rate."

TABLE 1

The effect of digitalis upon the output of the heart of subject 1

Date	Conditions	A-V difference	CO_2 per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.	Remarks
			cc.	*cc.*					
October 15	Normal	2.29	173	7,550	64	118	0.78	−7	
October 26	Normal	2.42	191	7,900	69	115	0.81	−5	
October 27	Normal	2.24	177	7,900	67	118	0.80	−10	
October 29	Digitalis 1.0 gram	2.20	163	7,400	62	119	0.78	−16	
October 30	Digitalis 2.0 grams	2.90	174	6,000	59	102	0.79	−11	
November 1	Digitalis 2.6 grams	3.37	171	5,080	57	88	0.75	−9	
November 2	Digitalis 2.7 grams	2.82	189	6,700	61	110	0.75	±0	Toxic
November 5		2.42	172	7,100	60	119	0.75	−8	Toxic
November 8		2.55	182	7,140	60	119	0.81	−10	Toxic

Care was exercised to maintain the conditions of the experiment as uniform as possible from day to day. All observations were made in the morning with the subject in the post-absorptive condition. The subject rested in a reclining position in a wheel chair for 30 to 45 minutes before the experiment; his position in the chair was not changed during an experiment or from day to day. Fluctuations of room temperature were kept at a minimum.

The usual procedure was to train the subject in the necessary respiratory measures on one or two occasions before his cardiac output was actually determined. The control observations were made on successive days until an apparently normal level was established. If, as was sometimes the case, the first one or two experiments gave higher values than subsequent ones, these high figures were discarded.

Digitalis leaves were given by mouth. The initial dose was usually one gram, and this was followed by smaller daily doses (0.2 to 0.8 gram) until a stage of undoubted digitalis effect was reached, as judged by changes in the pulse rate and the electrocardiogram, and by the occurrence of nausea. Observations of cardiac output and of basal pulse rate were made daily during the periods of administration and of maximum effect and at slightly longer intervals during the recovery period.

Five such experiments were carried out upon four individuals. In the case of the individual who was studied twice a period of two months elapsed between the last dose of digitalis in the first study and the beginning of the second.

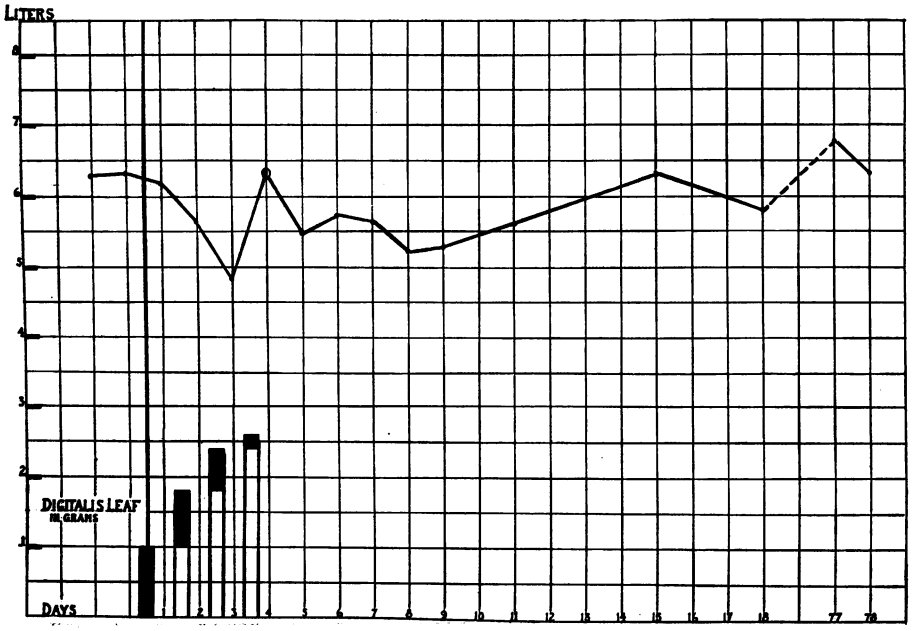

FIG. 2. CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 2

RESULTS

The observations on the output of the heart are summarized in Tables 1 to 5, and represented graphically in figures 1 to 5.

The tables also record the observations upon the difference in the carbon dioxide contents of venous and arterial blood (A-V difference); the excretion of carbon dioxide per minute (CO_2 per minute); the output of the heart per minute; the pulse rate; the output of the heart per beat; the external respiratory quotient (R.Q.); and the basal metabolic rate (B.M.R.).

The output of the heart

Analysis of the tables and figures indicates that the care given to maintaining nearly identical conditions in successive experiments succeeded in its object, as the subjects had relatively stable outputs during the control observations. Following the administration of the first gram of digitalis leaf there was usually no definite change. The ingestion of the second gram was in each case followed by a slight diminution in the output of the heart and succeeding doses were followed by a further reduction.

TABLE 2

The effect of digitalis upon the output of the heart of subject 2

Date	Conditions	A-V difference	CO_2 per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.	Remarks
			cc.	*cc.*					
November 15	Normal	3.07	193	6,280	59	106	0.79	−11	
November 16	Normal	3.13	196	6,300	58	109	0.78	−9	
November 17	Digitalis 1.0 gram	3.19	197	6,180	57	108	0.80	−7	
November 18	Digitalis 1.8 grams	3.32	187	5,640	53	107	0.73	−8	
November 19	Digitalis 2.4 grams	3.86	186	4,820	50	96	0.79	−14	Toxic
November 20	Digitalis 2.6 grams	3.07	194	6,320	53	119	0.79	−10	Toxic
November 21		3.44	188	5,460	53	103	0.75	−9	Toxic
November 22		3.23	185	5,720	51	112	0.82	−16	Toxic
November 23		3.44	194	5,640	53	107	0.84	−15	Toxic
November 24		3.70	198	5,220	52	100	0.87	−16	
November 26		3.61	190	5,260	53	100	0.82	−15	
November 28		3.36	188	5,600	56	100	0.84	−17	
December 1		3.02	190	6,300	57	110	0.80	−13	
December 4		3.15	183	5,800	55	105	0.79	−15	

With the occurrence of nausea, however, in each case the output of the heart increased toward the pre-digitalis level, and in one instance (fig. 3) actually exceeded that level. With the onset of nausea the administration of the drug was discontinued. The first subject (table 1, fig. 1) was studied only up to this point, i.e., the occurrence of nausea and the return of the cardiac output toward the pre-digitalis level. The other subjects were observed throughout the period of

nausea and the later period of diminishing digitalis effect. These subjects during the period of nausea continued to have a cardiac output little if any below their usual levels. With the subsidence of the nausea, however, there occurred in 3 instances out of 4 a second period of diminished cardiac output, in which the reduction was comparable to that observed during the initial digitalis effect. The other subject (fig. 5) received a smaller dose than the others and had slight nausea

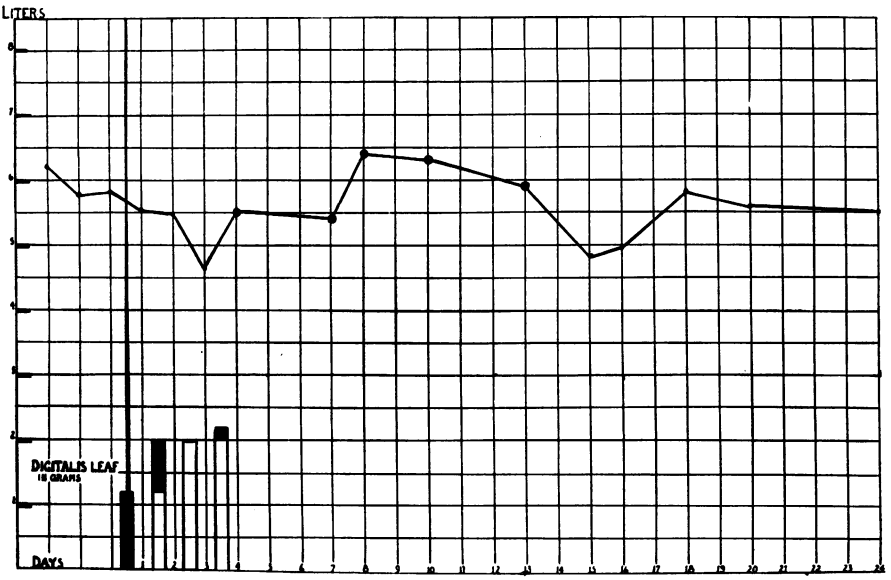

FIG. 3. CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 3

for only a few hours. In his curve the rise usually associated with nausea is not present.

Following this secondary drop the curve in each case returned to the pre-digitalis level or slightly below it. The return to the zone of cardiac output usual for the individual occurred in from 11 to 14 days after the cessation of digitalis administration.

Table 6 and figure 6 represent the results of an arbitrary division of our experiments into 5 periods or phases, as follows:

1. Before digitalis
2. Between the first dose and the onset of nausea

3. The duration of nausea
4. Between the termination of nausea and complete recovery
5. Recovery

The division was suggested by the occurrence of phases in the curves corresponding to these periods. This grouping of results serves to emphasize the change already noted and to permit the calculation of the average change in cardiac output produced by digitalis. Figure 6 shows the average results: the average fall during the period of admin-

TABLE 3

The effect of digitalis upon the output of the heart of subject 3

Date	Conditions	A-V difference	CO_2 per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.	Remarks
			cc.	*cc.*					
December 14		3.13	194	6,200	60	103	0.79	−14	
December 15		3.36	193	5,740	58	100	0.79	−14	
January 11		3.12	181	5,800	55	105	0.76	−17	
January 12	Digitalis 1.2 grams	3.31	183	5,530	54	102	0.79	−19	
January 13	Digitalis 2.0 grams	3.36	184	5,490	50	110	0.78	−18	
January 14	Digitalis 2.0 grams	3.86	179	4,630	51	91	0.78	−20	
January 15	Digitalis 2.2 grams	3.36	186	5,500	49	112	0.80	−18	Toxic
January 18		3.44	185	5,400	51	106	0.73	−14	Toxic
January 19		2.90	186	6,400	50	128	0.72	−11	Toxic
January 21		3.04	191	6,300	49	128	0.80	−17	Toxic
January 24		3.04	179	5,900	49	120	0.79	−20	Toxic
January 26		3.77	182	4,830	47	103	0.77	−18	
January 27		3.77	187	4,950	52	95	0.74	−13	
January 29		3.22	186	5,790	50	116	0.77	−16	
January 31		3.40	189	5,560	46	121	0.83	−20	
February 4		3.27	180	5,500	55	100	0.75	−17	

istration was to 84 per cent of the normal level. During the period of nausea the cardiac output was 94 per cent of the volume before digitalis, but with the subsidence of nausea it fell to 82 per cent, to return ultimately to 96 per cent of the previous level. That the output of the heart remained, even after the lapse of weeks, somewhat below the pre-digitalis level, may be ascribed to greater coöperation and less effort on the part of the subject.

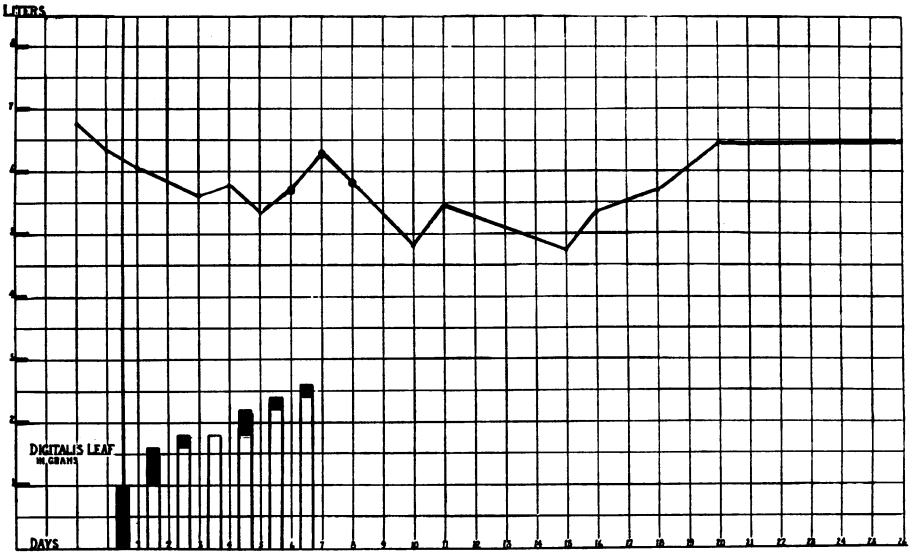

FIG. 4. CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 2 (TWO MONTHS AFTER HE RECEIVED DIGITALIS PREVIOUSLY)

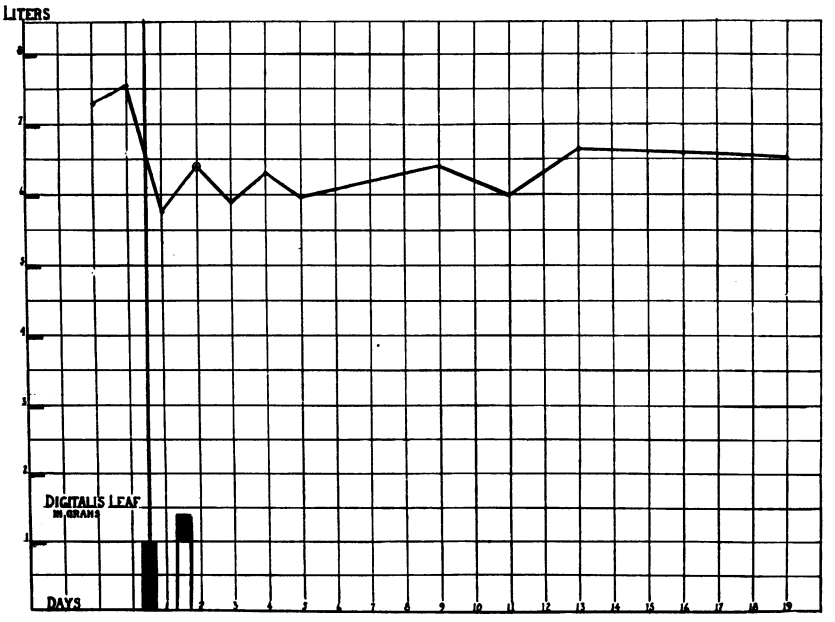

FIG. 5. CURVE SHOWING THE EFFECT OF DIGITALIS UPON THE OUTPUT OF THE HEART OF SUBJECT 4

TABLE 4

The effect of digitalis upon the output of the heart of subject 4 (two months after he received digitalis previously)

Date	Conditions	A-V difference	CO_2 per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.	Remarks
			cc.	*cc.*					
February 19	Normal	2.90	196	6,760	61	110	0.82	−12	
February 20	Normal	3.15	199	6,320	61	104	0.81	−11	
February 21	Digitalis 1.0 gram	3.28	190	5,800	55	105	0.80	−12	
February 23	Digitalis 1.8 grams	3.36	188	5,600	54	104	0.80	−14	
February 24	Digitalis 1.8 grams	3.32	192	5,790	55	105	0.79	−11	
February 25	Digitalis 2.2 grams	3.70	197	5,320	54	99	0.83	−13	
February 26	Digitalis 2.4 grams	3.44	197	5,700	54	105	0.81	−11	Toxic
February 27	Digitalis 2.6 grams	3.15	198	6,290	54	117	0.81	−11	Toxic
February 28		3.36	196	5,820	54	108	0.81	−11	Toxic
March 2		3.82	183	4,800	52	92	0.77	−14	
March 3		3.40	185	5,440	54	100	0.79	−14	
March 7		3.82	181	4,740	54	88	0.75	−13	
March 8		3.65	196	5,360	53	102	0.79	−10	
March 10		3.32	189	5,700	53	108	0.79	−13	
March 12		3.02	195	6,460	56	115	0.77	−8	
March 18		2.90	188	6,480	58	112	0.77	−11	

TABLE 5

The effect of digitalis upon the output of the heart of subject 4

Date	Condition	A-V difference	CO_2 per minute	Cardiac output	Pulse rate	Output per beat	R.Q.	B.M.R.
			cc.	*cc.*				
March 15	Normal	2.86	208	7,290	68	107	0.80	+5
March 16	Normal	2.65	201	7,560	73	103	0.78	+3
March 25	Digitalis 1.0 gram	3.50	201	5,740	58	99	0.86	−5
March 26	Digitalis 1.4 grams	3.02	193	6,400	62	103	0.84	−6
March 27		3.44	203	5,900	59	100	0.86	−3
March 28		3.19	201	6,300	55	115	0.86	−4
March 29		3.32	198	5,960	57	105	0.86	−6
April 2		3.06	196	6,400	58	110	0.81	−1
April 4		3.36	201	6,000	64	94	0.81	±0
April 6		2.98	198	6,650	60	111	0.83	−3
April 9		3.11	205	6,600	62	106	0.81	+2
April 12		3.07	200	6,520	63	103	0.84	−3
April 15		3.36	207	6,200	68	91	0.82	+2
April 19		2.98	192	6,450	67	96	0.78	−1
April 23		2.94	192	6,630	63	104	0.80	−2

The pulse rate

In each of the five experiments there occurred a definite drop in the basal pulse rate. The difference between the average pulse rate during the control experiments and those during the initial digitalis

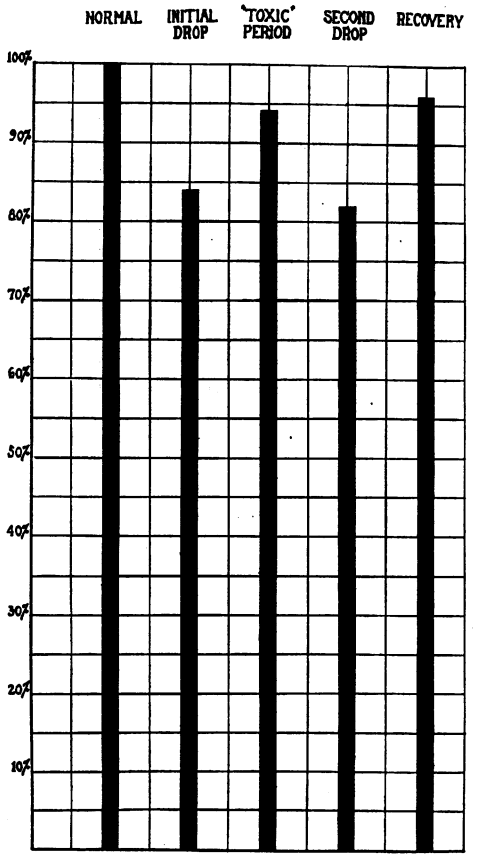

FIG. 6. THE PERCENTAGE CHANGE IN CARDIAC OUTPUT DURING SUCCESSIVE PHASES OF DIGITALIS EFFECT

effect varied from 5 to 12 and averaged 7 beats per minute. The onset of nausea was associated with an acceleration of only 1 or 2 beats per minute, and its subsidence with a fall to the lowest level observed in each case. Figure 7 is a graphic portrayal of the average pulse rates

TABLE 6

The average output of the heart, output per beat, and basal pulse rate before digitalis and during successive phases of digitalis effect

	Cardiac output						Output per beat						Pulse					
Subject	1	2	3	4	5	Average	1	2	3	4	5	Average	1	2	3	4	5	Average
Normal	7,780	6,250	5,770	6,540	7,420	6,490	117	108	103	107	105	108	67	58	57	61	70	61.5
Initial drop	6,160	5,230	5,130	5,630	5,740	5,430	103	101	101	103	99	101	59	51	52	54.5	58	54
"Toxic" period	6,980	5,780	5,900	5,940	6,400	6,000	116	110	119	110	103	110	60	53	50	54	62	55
Second drop		5,360	4,890	5,210	5,930	5,350		100	99	98	102	100		54	49	53	58	53.5
Recovery		6,150	5,620	6,460	6,540	6,190		107	112	113	107	110		56	50	57	62	56
Maximum drop below average normal	35%	23%	20%	23%	23%	25%												

before digitalis and during successive weeks after its administration. It will be seen that there is in each case a fall and then a gradual return to the normal level, which is usually reached in the fourth week. The effect on the pulse rate thus outlasts the effect on the cardiac output.

The output of the heart per beat

The diminution in the output of the heart per minute is relatively greater than the fall in pulse rate. Hence there must be a diminution in the systolic output, that is to say, the output per beat, as may be seen in tables 1 to 6. The period of nausea with increase in output

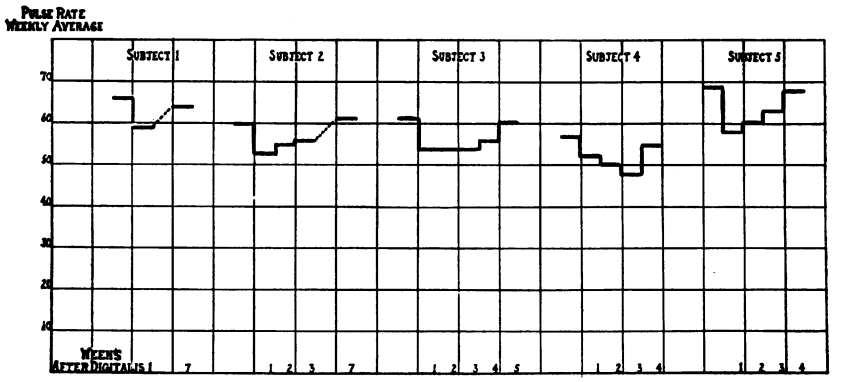

FIG. 7. THE EFFECT OF DIGITALIS ON THE BASAL PULSE RATE

per minute toward the normal level and the continued slow pulse was sometimes associated with an output per beat in excess of the one usual for the individual. The secondary drop in cardiac output, however, was accompanied by a corresponding fall in the volume expelled by the heart per beat.

The electrocardiogram

The galvanometric tracings showed in each case a flattening of T-waves in all leads. In one case T_3 became diphasic. Sinus arrhythmia became more marked. The P-R interval was not prolonged more than 0.02 second in any tracing.

Subjective effects

Each individual experienced nausea, lasting in different instances from 1 to 10 days. None vomited; all suffered a greater or less degree of anorexia. All complained of a curious and indescribable depression of spirits and activity, which outlasted the nausea. None had diarrhea.

Blood pressure

No consistent changes in either systolic or diastolic blood pressure were observed.

Basal metabolic rate

As is usually the case when trained subjects are studied the basal metabolic rates were uniformly low. In several cases the lowest rates observed were obtained during the period of maximum digitalis effect but the changes were too slight to have significance.

DISCUSSION

The output of the heart per minute under ordinary conditions of life is a constantly changing value. It changes with position, with temperature, and it changes tremendously with increased oxygen consumption during exercise. It is therefore somewhat surprising that digitalis, which affects cardiac activity both by direct myocardial action and through the nervous system, should produce such relatively small changes in the output per minute. Certainly if the drug may produce an increase in the output of the normal heart one might expect unmistakable evidence of it in such experiments as these. Such an increase was not, however, observed; on the contrary there was in each case a definite decrease, and that decrease was observed in a group of subjects whose cardiac output was already as low as rest, fasting, and training could bring it. The decrease was not large but strikingly consistent when the normal variation in cardiac output and the possibilities of technical error are considered.

It is difficult to reconcile these observations and those of Harrison and Leonard with the cardiodynamic studies of Wiggers. This in-

vestigator, using optical methods of registration, studied the effect of digitalis upon the intraventricular pressure curves under carefully controlled conditions. He concludes that digitalis acts as a cardiac stimulant, that is, it improves the contractile force of the ventricular beat and increases the systolic discharge. The possibility must be considered, however, that even the same pharmacological effect upon cardiac muscle might produce a different effect upon the output of the heart of an animal which has been subjected to severe operative procedures and upon the output of the heart of a normal human subject. If the same pharmacological effect upon heart muscle can produce different effects upon cardiac output in different states of heart muscle, it is then unsafe to apply our conclusions directly to an analysis of the effect of digitalis upon the cardiac output of patients suffering from heart failure. For example, a drug which by increasing the tonus of heart muscle diminishes the output per beat of a normal heart might by an exactly similar action on the muscle increase the output per beat of a dilated and insufficient heart. Therefore, until some method for the determination of cardiac output has been shown to be trustworthy in patients with heart failure the most important application of this concept of digitalis action must be made, if made at all, upon the basis of indirect evidence.

The experiments of Cohn and Stewart (1924) present indirect evidence that the output of the heart is increased by digitalis, as their x-ray observations demonstrate an increased amplitude of the ventricular excursions following the administration of digitalis. Since there was no measurable diminution in the total size of the hearts studied this is evidence of increased output although the changes are very small. Their subjects, however, were patients with heart disease, and that introduces complications which make their experiments not comparable with ours.

Reliable current methods such as those devised by Plesch (1909); Krogh and Lindhard (1912); Douglas and Haldane (1922); Field, Bock, Gildea and Lathrop (1924); Burwell and Robinson (1924); all depend upon equilibrium between a gas or gases in the alveolar air and those in the pulmonary capillaries. Under the conditions imposed by pulmonary congestion such an equilibrium may be impossible to attain (Peters and Barr (1921)).

Blumgart (1927) has studied the *velocity* of blood flow before and after the administration of digitalis to normal men, and finds that there is no substantial change. This observation, whether compared with the concept of digitalis as increasing or as decreasing cardiac output, suggests that velocity and volume do not necessarily vary together. They need not vary together, of course, if there is a coincident change in the volume of the circulatory fluid. Such changes in volume might be brought about by the effect of digitalis upon the vessels, an effect which Gottlieb (1924) and others believe to be of great importance.

The significance of the change in cardiac output associated with nausea is not known. During the period of nausea three subjects had also a slight average increase in the basal metabolic rate. Both changes may be associated with the discomfort of the sensation.

SUMMARY

In a small series of normal men the administration of from 1.4 to 2.7 grams of digitalis leaf was followed by a diminution in the output of the heart per minute and per beat, and in the basal pulse rate. This diminution was comparable to that found by Harrison and Leonard (1926) after the administration of digitalis to normal dogs.

When nausea was produced by digitalis there was a tendency for the cardiac output per minute to return toward the normal level. The pulse rate remained slow at this time so that the output per beat often increased to above the amount usual for the individual. The subsidence of nausea was accompanied by a second period of diminished cardiac output.

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