# STUDIES ON THE EFFECT OF THE ACTION OF DIGITALIS ON THE OUTPUT OF BLOOD FROM THE HEART. III.[1, 2]

## PART 1. THE EFFECT ON THE OUTPUT IN NORMAL HUMAN HEARTS

## PART 2. THE EFFECT ON THE OUTPUT OF HEARTS IN HEART FAILURE WITH CONGESTION, IN HUMAN BEINGS

BY HAROLD J. STEWART AND ALFRED E. COHN

*(From the Hospital of the Rockefeller Institute for Medical Research, New York)*

(Received for publication May 31, 1932)

## PART I

### THE EFFECT ON THE OUTPUT IN NORMAL HUMAN HEARTS

The action of digitalis when given to human beings is still incompletely understood. Investigations, in recent years (1, 2, 3, 4), which have been directed toward elucidating its influence on the behavior of the heart have led to a certain degree of confusion. The analysis of the results which have been obtained shows that inferences which were drawn were in part inexact, due to utilizing the results obtained in one situation, in the normal hearts of dogs for example or in those of human beings, in an explanation of the condition of disease. But beside difficulties in interpretation of this sort, error has also resulted from the use of insufficiently tested methods. This defect in the case of human beings applies, it seems, to the use of the method of Field, Bock, Gildea and Lathrop (5) by certain investigators (1, 6), and to that of Henderson and Haggard (7) by others (8). The opportunity is still open, therefore, to study the minute volume output[3] of human hearts under the influence of digitalis when they are normal and also when they are the subjects of heart disease. This study is the more important since the result, observed in analyzing the effect on normal hearts, differs, as it turns out, so profoundly from that which supposedly obtains in enlarged diseased ones. If the two are really the same, fundamental conceptions concerning the circulation in heart failure require radical revision.

In this study digitalis was given to six normal individuals on seven occasions. Observations were made of its effect on cardiac output, on

[1] A preliminary report of these observations appeared in the Proc. Soc. Exp. Biol. and Med., 1931, xxix, 207 and 209.

[2] An abstract of these studies was read before the American Society for Clinical Investigation, May 2, 1932.

[3] It is always the volume output of blood per minute to which reference is made when the word "output" is used.

cardiac size, on arterial blood pressure, on venous blood pressure, on vital capacity, on cardiac rate, and on the electrocardiogram.

Measurements of cardiac output were made by the acetylene method of Grollman (9) which, so far as can now be judged, gives reasonably reliable results, for the cardiac output in man measured by it agrees with the amount estimated simultaneously by a direct method (10, 11). Our results, at all events, agree with those reported by Grollman (12).[4] Estimations of oxygen consumption for use in calculating the cardiac output were made with a Benedict-Roth spirometer. The diastolic size of the heart was traced from x-ray photographs taken at a distance of 2 meters, the subject being placed in a standing position, on thin paper and its area measured with a planimeter as suggested by Levy (13). Estimations of blood pressure were made by the auscultatory method. The three standard leads of the electrocardiogram were taken. Measurements of venous pressure were made by direct methods which will be described later. The vital capacity was measured in a spirometer.

## PLAN OF OBSERVATIONS

After eating a moderate supper the subjects went to bed in the hospital the night before the observations began, and remained there at rest until 24 hours after the administration of digitalis. To assure their being in a basal metabolic state they were given small carbohydrate meals. The volume output was measured at 2, 4, 9, 12 and 15 hours after giving digitalis. The meals were taken just after the 4 and 15 hour measurements. Since from Grollman's observations three hours are required to return to a basal minute volume output (14), though the basal metabolic rate may still be elevated 1 or 2 per cent (15), this distribution made it certain that the measurements were proper. No water was given for three hours before each observation in order to avoid the effect of ingestion of fluid (16). The Gatch frame of the bed was raised one half-hour before observations so that subjects reclined at an angle of 135 degrees because Grollman found that mixing the gases during rebreathing takes place more satisfactorily in this position. Patients suffering from heart failure, moreover, often find it difficult or impossible to lie flat. We wished the two sets of investigations to be comparable from this point of view.

Counts of the pulse rate were made at intervals of a few minutes. At the end of a half-hour, subjects rebreathed from a bag containing a mixture of acetylene and air. Two proper samples of gas were taken for analysis and for calculation of the arteriovenous oxygen difference. The oxygen consumption was then estimated. Electrocardiograms were

[4] We wish to express our thanks to Dr. E. K. Marshall for his kindness in placing at the disposal of one of us (H. J. S.) the facilities of his laboratory to learn this method, and to Dr. Arthur Grollman for his kindness in teaching him his method and discussing our data with him.

taken, followed by measurement of arterial and venous pressures and of vital capacity. Subjects were then wheeled in a chair to the roentgen laboratory to secure x-ray photographs of the heart. After being weighed they returned to bed to await taking the next observations. Records were made of the body temperature (rectal). The temperature of the room in which the studies were made was kept approximately constant (17). Analysis of the samples of gas for concentrations of carbon dioxide, oxygen and acetylene was made in a modified Haldane apparatus (9).

Observations were made immediately before the administration of digitalis, at the intervals stated during the first 24 and at 24 hour intervals until the return of the initial cardiac output. The subjects had been made familiar with the procedures and were not disturbed by them. After the first 24 hours they attended to their usual daily routines except on days of observation when they remained in bed to assure their being in a basal metabolic state. The initial cardiac output in all except one was normal (Subject 4) and agreed with previous measurements in each case.

### *Observations*

Digitalis in the form of digitan (Merck) 0.8 to 1.0 gram was given by mouth in a single dose. No one experienced nausea or vomiting.

*Effect on cardiac minute volume output.* The initial cardiac output in Subject 1 measured 3.84 liters per minute or 2.17 liters per minute per square meter of body surface (Table 1, Figure 1). Two hours after taking digitalis 0.9 gram the output remained unchanged; 4 hours afterward it fell to 3.68 liters per minute. Progressive decrease followed. The lowest point was recorded 24 hours later when it measured 2.54 liters per minute or 1.44 liter per minute per square meter of body surface, equal to 66 per cent only of its initial value. Twenty-four hours later still, the output was 3.01 liters per minute, that is to say, 81 per cent of the initial amount. From this time it returned slowly toward normal; one week later it was 3.40 liters per minute (88 per cent of normal) and after another it was still low.

The results in the 5 other persons were similar (Tables 1 and 2, Figures 2, 3 and 4), with this exception, that the effect of the drug was of shorter duration. The earliest effects were found after 4 to 12 hours; the maximum ones in 4 to 24 hours. At the time of the maximum effect the output was reduced to 60 to 85 per cent of the initial amount.

The normal resting arteriovenous oxygen difference in Subject 1 was 58.4 cc. per 100 cc. blood. Two hours after the administration of digitalis 0.9 gram it remained unchanged; four hours afterward a slight increase occurred (Table 1). Progressive increase took place so that 24 hours later it was 88.0 cc. per 100 cc. blood. The arteriovenous oxygen difference then returned slowly toward its initial value, although at the end of two weeks this had not been attained.

TABLE 1

*Effect of giving digitalis on cardiac output and cardiac size in normal individuals*

| Subject number | Age | Date | Weight | Height | Body surface | Oxygen consumption | Arteriovenous oxygen difference | Cardiac output | Cardiac output per cent of initial | Cardiac output | Cardiac area | Cardiac area per cent of initial | Cardiac rate | Cardiac output | Arterial pressure | Summary of effect on electrocardiogram | Digitan | Time with reference to digitalis administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *years* | *1931* | *kgm.* | *cm.* | *sq. m.* | *cc. per minute* | *cc.* | *liters per minute* | *per cent* | *liters per sq. m. per minute* | *sq. cm.* | *per cent* | *minutes* | *cc. per beat* | *mm. Hg* | | *grams* | |
| 1 ♂ | 34 | March 4 | 66.9 | 168.5 | 1.77 | 224 | 58.4 | 3.84 | 100 | 2.17 | 105.8 | 100 | 80 | 48 | 112/68 | | 0.9 | Before |
| | | | | | | 226 | 58.5 | 3.87 | 100 | 2.20 | 103.4 | 98 | 73 | 53 | 120/72 | T-waves became of lower voltage but remained positive. P-waves changed form. The ventricular rate became slower. | | 2 hours after |
| | | | | | | 224 | 60.9 | 3.68 | 92 | 2.08 | 102.3 | 96 | 72 | 51 | 122/74 | | | 4 hours after |
| | | | | | | 224 | 74.0 | 3.03 | 81 | 1.71 | 102.8 | 97 | 72 | 42 | 132/64 | | | 9 hours after |
| | | | | | | 219 | 78.4 | 2.79 | 72 | 1.58 | 102.6 | 96 | 66 | 42 | 126/66 | | | 12 hours after |
| | | | | | | 217 | 75.1 | 2.89 | 75 | 1.63 | 97.2 | 91 | 72 | 40 | 120/70 | | | 15 hours after |
| | | March 5 | 66.4 | | 1.76 | 224 | 88.0 | 2.54 | 66 | 1.44 | 97.7 | 92 | 78 | 33 | 130/78 | | | 24 hours after |
| | | March 6 | 66.2 | | 1.76 | 221 | 73.4 | 3.01 | 81 | 1.71 | 100.4 | 94 | 78 | 39 | 130/80 | | | 48 hours after |
| | | March 7 | 66.7 | | 1.77 | 219 | 67.6 | 3.24 | 87 | 1.83 | 100.4 | 94 | 77 | 42 | 128/80 | | | 3 days after |
| | | March 8 | 67.2 | | 1.77 | 218 | 67.6 | 3.23 | 87 | 1.82 | * | | 78 | 41 | 134/80 | | | 4 days after |
| | | March 9 | 67.2 | | 1.77 | 226 | 65.5 | 3.45 | 89 | 1.95 | 104.7 | 98 | 74 | 44 | 122/84 | | | 5 days after |
| | | March 11 | 66.3 | | 1.76 | 245 | 72.2 | 3.40 | 88 | 1.93 | 102.2 | 96 | 80 | 42 | 134/80 | | | 7 days after |
| | | March 20 | 66.1 | | 1.76 | 226 | 74.3 | 3.11 | 82 | 1.77 | 102.8 | 97 | 82 | 38 | 126/76 | | | 16 days after |
| 2 ♂ | 31 | February 16 | 73.9 | 175.5 | 1.89 | 239 | 62.2 | 3.84 | 100 | 2.03 | 110.5 | 100 | 58 | 66 | 95/60 | | 0.8 | Before |
| | | | | | | 242 | 64.7 | 3.74 | 98 | 1.98 | 107.4 | 97 | 58 | 64 | 108/70 | $T_2$ became negative and was still diphasic on March 26, 1931. The ventricular rate became slower | | 4 hours after |
| | | | | | | 258 | 66.2 | 3.89 | 101 | 2.06 | 105.2 | 95 | 58 | 67 | 100/60 | | | 9 hours after |
| | | | | | | 251 | 74.1 | 3.38 | 88 | 1.78 | 101.5 | 91 | 59 | 57 | 100/65 | | | 12 hours after |
| | | February 17 | 73.9 | | | 234 | 71.2 | 3.28 | 85 | 1.73 | 103.4 | 93 | 54 | 60 | 95/55 | | | 24 hours after |
| | | February 18 | 74.1 | | | 233 | 59.1 | 3.94 | 103 | 2.08 | 112.5 | 101 | 58 | 68 | 90/50 | | | 48 hours after |
| | | February 19 | 74.1 | | | 231 | 58.5 | 3.95 | 103 | 2.08 | 114.4 | 103 | 64 | 71 | 90/55 | | | 3 days after |
| 3 ♂ | 29 | February 24 | 82.0 | 183.0 | 2.04 | 230 | 58.9 | 3.93 | 100 | 1.92 | 119.8 | 100 | 54 | 73 | 100/65 | | 0.8 | Before |
| | | | | | | 256 | 64.1 | 3.99 | 101 | 1.95 | 104.2 | 87 | 54 | 74 | 95/70 | $T_3$ became of lower voltage but remained positive. The ventricular rate became slower | | 2 hours after |
| | | | | | | 224 | 53.7 | 4.17 | 106 | 2.04 | 110.5 | 92 | 50 | 83 | 90/70 | | | 4 hours after |
| | | | | | | 246 | 82.6 | 2.97 | 75 | 1.45 | 106.5 | 88 | 50 | 59 | 95/70 | | | 9 hours after |
| | | | | | | 230 | 56.6 | 4.06 | 103 | 1.99 | 104.6 | 87 | 50 | 81 | 90/60 | | | 15 hours after |
| | | February 25 | 81.4 | | 2.03 | 254 | 62.6 | 4.05 | 103 | 2.00 | 115.6 | 96 | 64 | 67 | 100/70 | | | 23 hours after |
| | | February 26 | 82.0 | | 2.04 | 229 | 53.8 | 4.23 | 108 | 2.07 | 112.7 | 94 | 60 | 71 | 100/75 | | | 48 hours after |
| | | February 27 | 82.2 | | 2.04 | 240 | 51.6 | 4.65 | 118 | 2.28 | 109.3 | 91 | 52 | 93 | 110/80 | | | 3 days after |
| 4 ♂ | 31 | June 16 | 61.6 | 165.5 | 1.69 | 169 | 63.8 | 2.65 | 100 | 1.57 | 136.3 | 100 | 70 | 38 | 120/90 | | 1.0 | Before |
| | | | 61.6 | | 1.69 | 143 | 68.9 | 2.08 | 79 | 1.23 | 124.0 | 90 | 66 | 32 | 135/90 | $T_{123}$ which were positive at beginning became $-T_1$ and diphasic $T_{23}$. The ventricular rate became slower. $P_3$ became negative and then diphasic | | 12 hours after |
| | | June 17 | 60.9 | | 1.68 | 163 | 87.6 | 1.86 | 70 | 1.11 | 120.0 | 88 | 60 | 31 | 120/90 | | | 24 hours after |
| | | June 18 | 60.9 | | 1.68 | 166 | 60.5 | 2.74 | 103 | 1.63 | 128.7 | 95 | 70 | 39 | 110/70 | | | 48 hours after |

* Patient was not in true posterior-anterior position.

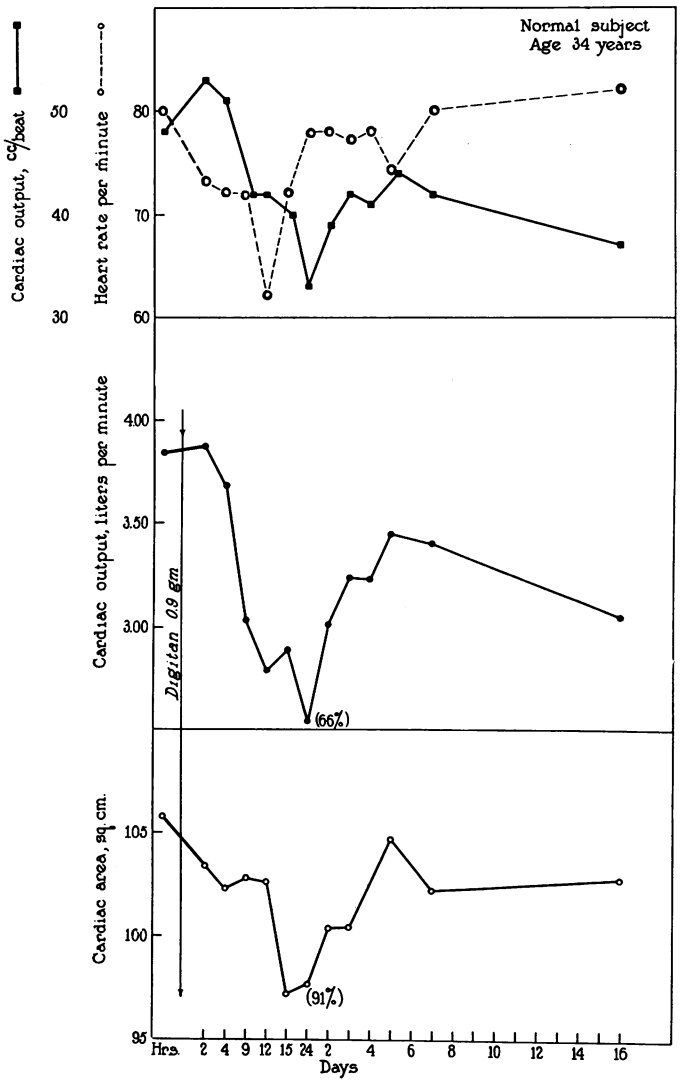



FIG. 1. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND CARDIAC RATE PER MINUTE IN SUBJECT NUMBER 1.

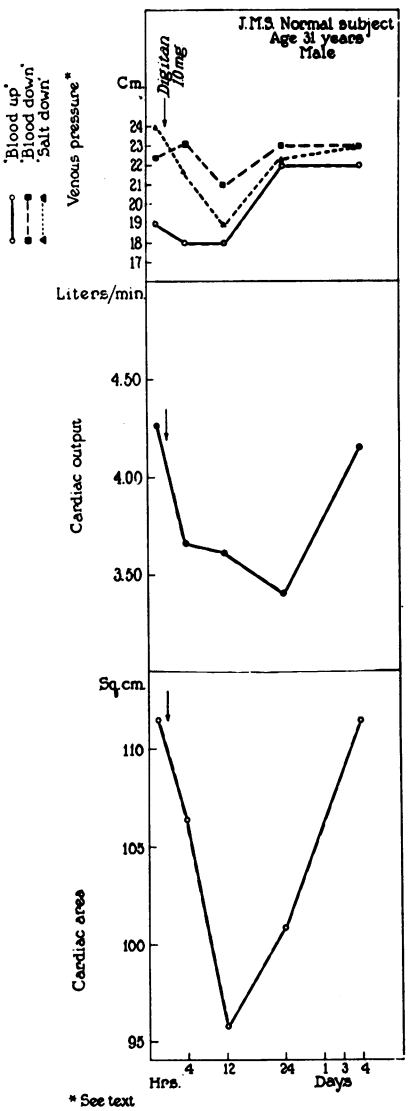



FIG. 2. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND VENOUS PRESSURE IN SUBJECT NUMBER 2.

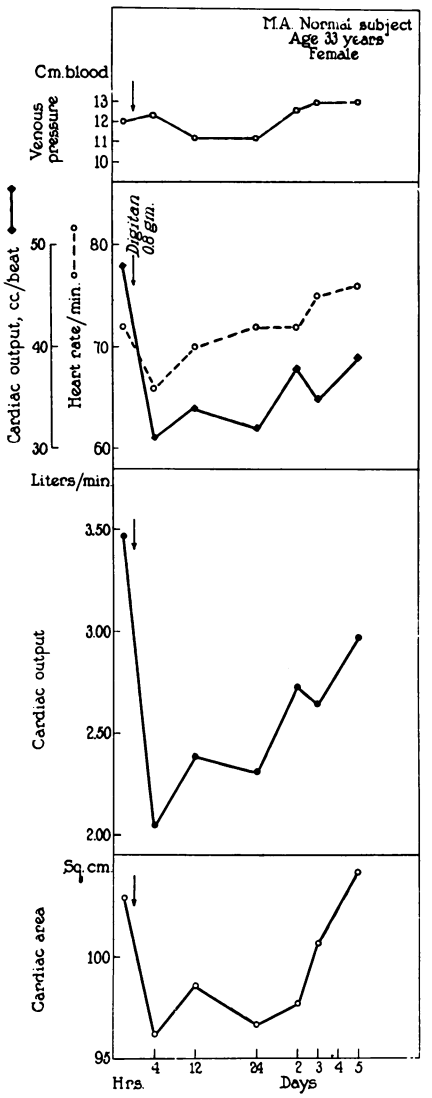



FIG. 3. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE, CARDIAC RATE AND VENOUS PRESSURE IN SUBJECT NUMBER 6.

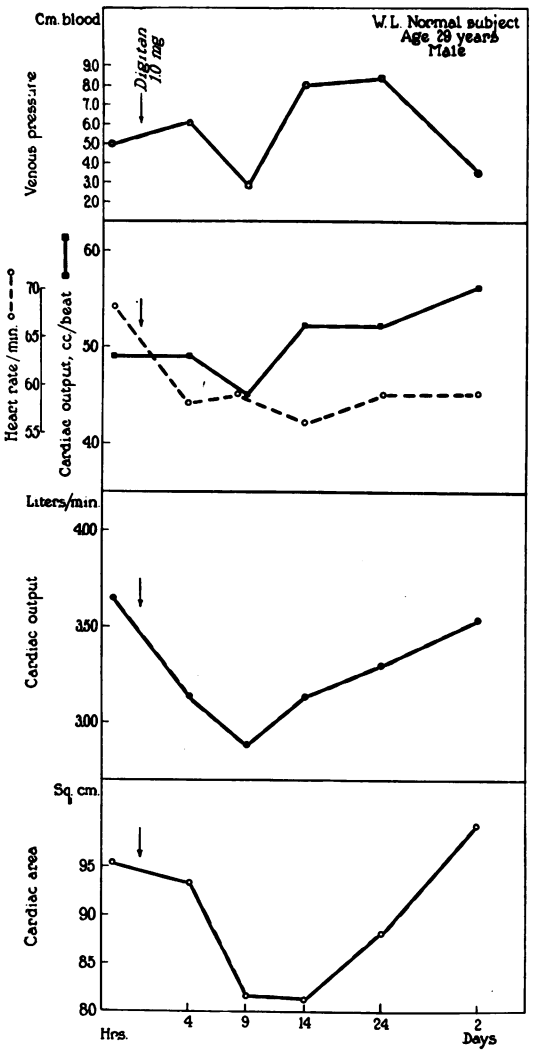



FIG. 4. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND VENOUS PRESSURE IN SUBJECT NUMBER 5.

TABLE 2

*Effect of giving digitalis on cardiac output, cardiac size, venous pressure and vital capacity in normal individuals*

| Subject number | Age | Date | Weight | Height | Body surface | Oxygen consumption | Arteriovenous oxygen difference | Cardiac output | Cardiac output per cent of initial | Cardiac output | Cardiac area | Cardiac area per cent of initial | Heart rate | Cardiac output | Arterial pressure | Venous pressure | | | Vital capacity | Body temperature (rectal) | Digitan | Summary of effect on electrocardiogram | Time with reference to digitalis administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *years* | *1932* | *kgm.* | *cm.* | *sq. m.* | *cc. per minute* | *cc.* | *liters per minute* | *per cent* | *liters per sq. m. per minute* | *sq. cm.* | *per cent* | *minutes* | *cc. per beat* | *mm. Hg* | *cm. blood* | | | *cc.* | *° F.* | *grams* | | |
| 5 ♂ | 29 | January 26 | 68.7 | 170.7 | 1.79 | 238 | 60.3 | 3.65 | 100 | 2.04 | 95.6 | 100 | 68 | 54 | 108/70 | 5.0 | | | 4300 | 98.8 | 1.0 | | Before |
| | | | | | 1.79 | 231 | 73.5 | 3.14 | 86 | 1.75 | 93.8 | 98 | 58 | 54 | 100/50 | 6.0 | | | 4350 | 98.8 | | $T_{123}$ became of lower voltage | 4 hours after |
| | | | | | 1.79 | 223 | 77.2 | 2.89 | 79 | 1.61 | 82.8 | 86 | 59 | 49 | 105/60 | 2.8 | | | 4200 | 99.2 | | | 9 hours after |
| | | | | | 1.79 | 226 | 73.0 | 3.14 | 86 | 1.75 | 81.4 | 85 | 56 | 56 | 100/50 | 8.0 | | | 4300 | 99.0 | | | 14 hours after |
| | | January 27 | 68.5 | | 1.79 | 231 | 69.9 | 3.30 | 90 | 1.84 | 88.3 | 92 | 59 | 56 | 120/80 | 8.3 | | | 4350 | 98.8 | | | 24 hours after |
| | | January 28 | 68.6 | | 1.79 | 230 | 65.0 | 3.54 | 97 | 1.98 | 99.4 | 105 | 59 | 60 | 105/60 | 3.5 | | | 4350 | 98.6 | | | 48 hours after |
| 6 ♀ | 33 | April 8 | 52.5 | 157.0 | 1.50 | 195 | 56.1 | 3.47 | 100 | 2.31 | 102.9 | 100 | 72 | 48 | 80/45 | *blood* 12.0 | | | 2700 | 98.8 | 0.8 | | Before |
| | | | | | | 194 | 94.8 | 2.05 | 60 | 1.37 | 96.2 | 93 | 66 | 31 | 85/50 | 12.3 | | | 2700 | 99.2 | | $T_{12}$ became of lower voltage and $T_3$ isoelectric | 4 hours after |
| | | | | | | 187 | 78.2 | 2.39 | 69 | 1.59 | 98.6 | 96 | 70 | 34 | 85/50 | 11.2 | | | 2700 | 98.6 | | | 12 hours after |
| | | April 9 | 52.7 | | 1.51 | 198 | 85.9 | 2.31 | 67 | 1.53 | 96.7 | 93 | 72 | 32 | 85/45 | 11.2 | | | 2700 | 98.6 | | | 24 hours after |
| | | April 10 | 52.7 | | 1.51 | 186 | 68.0 | 2.73 | 79 | 1.81 | 97.7 | 94 | 72 | 38 | 100/60 | 12.6 | | | 2660 | | | | 48 hours after |
| | | April 11 | 53.2 | | 1.51 | 201 | 76.0 | 2.65 | 77 | 1.76 | 100.7 | 97 | 75 | 35 | 98/60 | 13.0 | | | 2690 | | | | 72 hours after |
| | | April 13 | 53.4 | | 1.51 | 202 | 68.0 | 2.97 | 86 | 1.97 | 104.2 | 101 | 76 | 39 | 100/55 | 13.0 | | | 2650 | | | | 120 hours after |
| | | | | | | | | | | | | | | | | "Blood up" | "Blood down" | "Salt down" | | | | | |
| 2 ♂ | 32 | April 18 | 72.2 | 179.5 | 1.89 | 258 | 60.6 | 4.26 | 100 | 2.25 | 111.5 | 100 | 58 | 73 | 80/45 | 19.0 | 22.3 | 23.5 | 4500 | 97.7 | 1.0 | | Before |
| | | | | | | 254 | 69.4 | 3.66 | 86 | 1.95 | 106.4 | 95 | 55 | 67 | 80/45 | 18.0 | 23.0 | 21.7 | 4700 | | | $T_3$ became diphasic and then negative | 4 hours after |
| | | | | | | 259 | 71.7 | 3.61 | 85 | 1.91 | 95.8 | 86 | 56 | 64 | 90/50 | 18.0 | 21.0 | 19.0 | 4700 | | | | 12 hours after |
| | | April 19 | 71.7 | | 1.89 | 249 | 73.2 | 3.40 | 80 | 1.80 | 100.9 | 90 | 50 | 68 | 80/40 | 22.0 | 23.0 | 22.2 | 4700 | | | | 24 hours after |
| | | April 22 | 71.6 | | | 260 | 62.6 | 4.15 | 98 | 2.20 | 111.5 | 100 | 58 | 72 | 80/40 | 22.0 | 23.0 | 23.0 | 4600 | | | | 4 days after |

The results in the 5 other cases are similar to these except that the effect of the drug was of shorter duration and passed off within a shorter time (Tables 1 and 2). The maximum decrease in the arteriovenous oxygen difference was observed 4 to 24 hours after giving digitalis.

*Effect on cardiac size.* In Subject 1 the size of the heart measured 105.8 sq. cm. (Table 1, Figures 5 and 6). It decreased gradually after the administration of digitan 0.9 gram; it was smallest (97.2 sq. cm.) at the end of 15 hours measuring 91 per cent of its initial size. It was still small at the end of 24 hours, when the output was only 66 per cent of what it was at the beginning. It returned gradually toward its initial size although, as in the case of the cardiac output, this was not reached more than two weeks later.

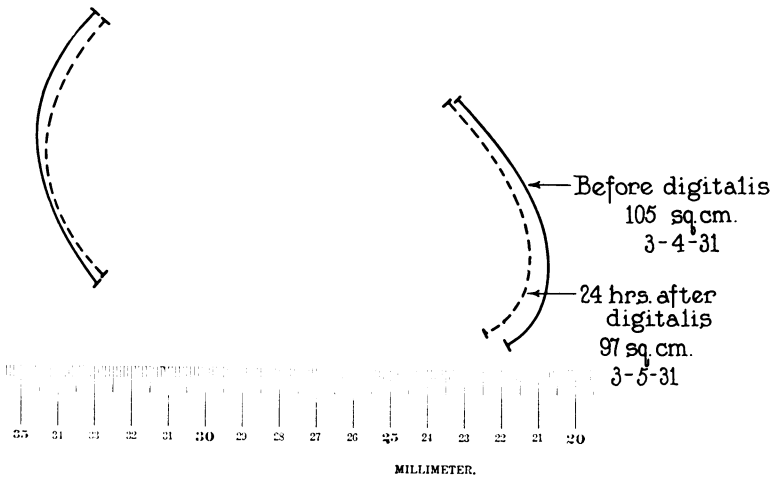



FIG. 5. IN THIS FIGURE IS REPRESENTED THE CHANGE IN SIZE OF THE HEART FOLLOWING THE ADMINISTRATION OF DIGITAN 0.9 GRAM IN SUBJECT NUMBER 1.

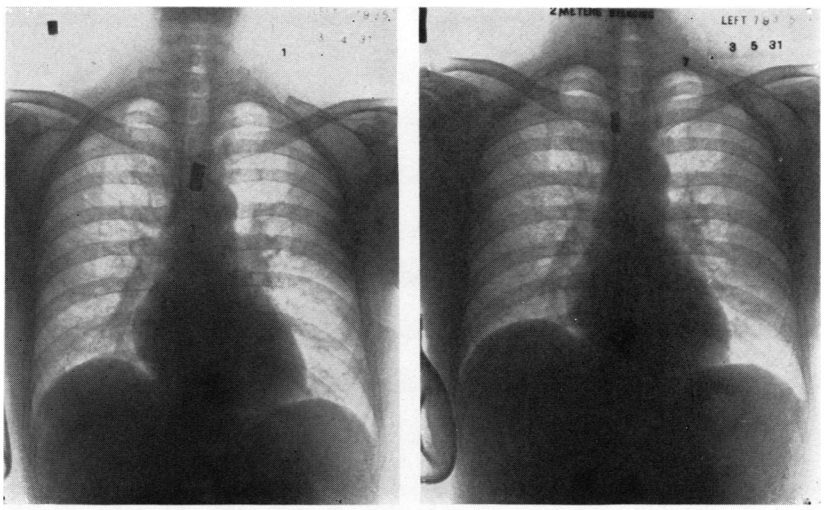
The outlines of the heart were traced from the x-ray photographs taken on March 4 and 5 on thin paper and superimposed in the manner shown.

The results in the 5 other cases corresponded to this one (Tables 1 and 2, Figures 2, 3 and 4). The decrease in size varied between 7 and 15 per cent (to 93 and 85 per cent of the initial measurement) and was recorded 4 to 24 hours after the drug was given. As the effect of the drug wore off the heart regained its original size.

*Effect on cardiac rate.* In all six subjects the cardiac rate fell 4 to 14 beats per minute, counted at the time the cardiac output was measured (Tables 1 and 2, Figures 1, 3 and 4). In each instance it returned toward the initial count as the effect of digitalis disappeared.

*Effect on the electrocardiograms.* In all instances change in form of the *T*-waves of the electrocardiograms occurred (Tables 1 and 2). In one

instance (Subject 4) $T_2$ and $T_3$ which had been positive became diphasic and $T_1$, positive at the beginning, became negative (Table 1). In another instance (Subject 2) $T_3$ which was positive became negative; as the effect decreased it became diphasic and was diphasic still 38 days later when the last record was made (Table 1, Figure 7). It was upright one year later; when the observations were repeated $T_3$ was similarly affected




A B

FIG. 6. IN THIS FIGURE IS REPRESENTED THE CHANGE IN SIZE OF THE HEART FOLLOWING THE ADMINISTRATION OF DIGITAN 0.9 GRAM IN SUBJECT NUMBER 1.

Photograph *A* was taken on March 4, 1931, immediately before and *B* on March 5, twenty-four hours after the administration of the drug.

(Table 2, Figure 7). In the four other subjects (Subjects 1, 3, 5 and 6) positive $T_{123}$ became either smaller or isoelectric (Tables 1 and 2). Alterations of the T-waves occurred as early as two and a half hours after administration of the drug (Figure 7).

Increase in auriculoventricular conduction time did not occur nor did abnormal rhythms or premature contractions develop. In one instance (Subject 4) $P_3$ became negative, to resume its earlier form as the effect of digitalis declined and in another instance (Subject 1) the form of the *P*-waves was altered.

*Effect on oxygen consumption.* The oxygen consumption of each individual remained constant (Tables 1 and 2). The changes in cardiac output which were observed are, therefore, not attributable to alterations of oxygen consumption, but to changes in arteriovenous oxygen difference. The normal oxygen consumption of one subject (Subject 4) was diminished (Table 1) and remained approximately unchanged in estimations

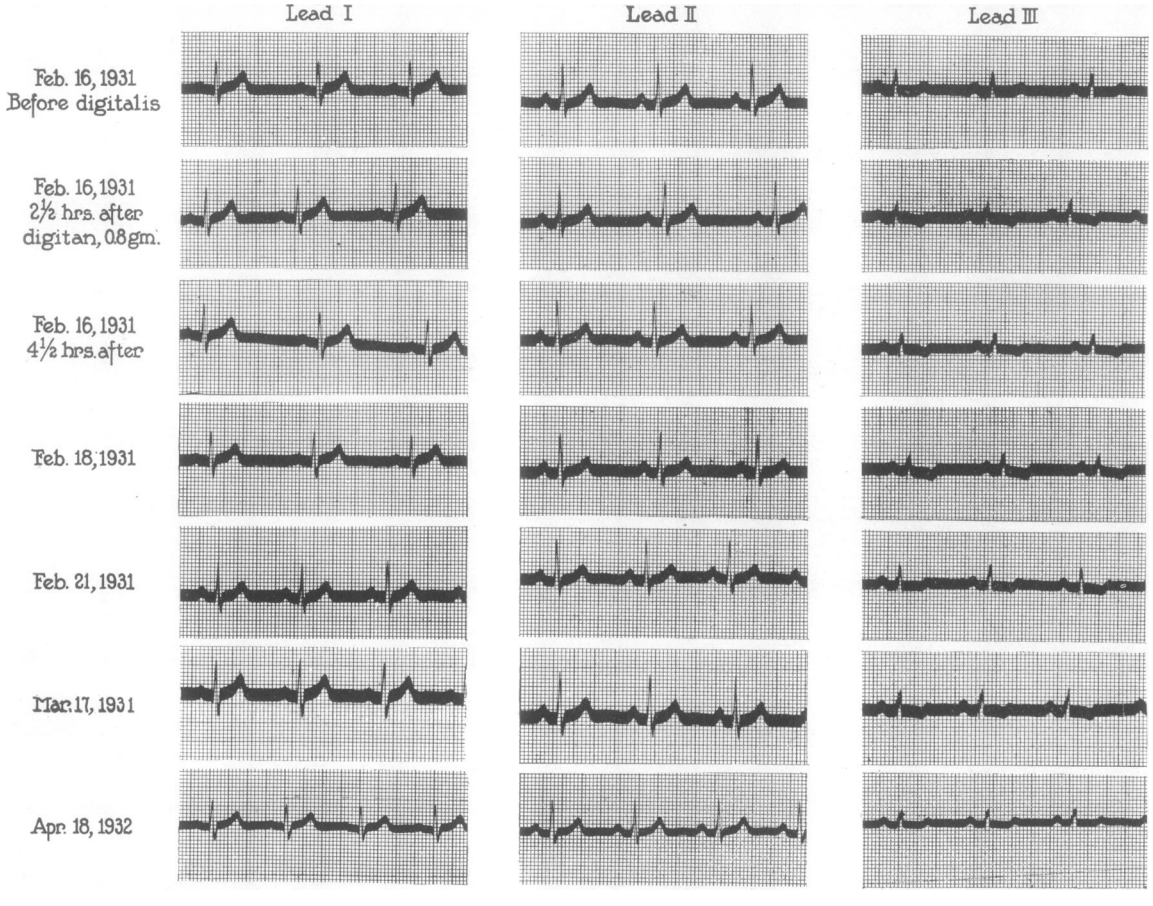



FIG. 7. THE EFFECT OF GIVING DIGITAN 0.8 GRAM ON THE ELECTROCARDIOGRAM OF SUBJECT NUMBER 1 IS SHOWN IN THIS FIGURE

Alterations of the T-waves in Lead III were present $2\frac{1}{2}$ hours after digitalis was given and were still present at the end of 38 days (March 17), when the observations were discontinued. It had, however, regained its usual contour one year later (April 18, 1932). Divisions of the ordinates equal $10^{-4}$ volts. Divisions of the abscissae equal 0.04 of a second. The original curves are sharply contrasted black and white; no half tones are lost by this method of reproduction. The electrocardiograms are reduced to one-half their natural size.

which were made later. There appeared to be no adequate explanation for his low basal metabolic rate. Since the arteriovenous oxygen difference was normal, the initial cardiac output was less than it should have been for his height and weight (Grollman (12)). But after taking digitalis, as in the other subjects, decrease in cardiac output and in cardiac size took place.

*Effect on vital capacity.* Significant alterations did not occur in the vital capacities of the three individuals in whom it was measured (Table 2).

*Effect on arterial and venous pressures.* Significant alterations either in the systolic or diastolic level of the arterial blood pressure did not occur (Tables 1 and 2).

Estimations of venous pressure whether by direct or indirect methods are unsatisfactory especially from the point of view of comparing the results over long periods of time. Errors arise due to the method but also due to difficulty in selecting a level to represent that of the opening of the venae cavae into the right auricle, and in finding this again in making subsequent estimations. For these reasons the venous pressure was measured in two subjects (Subjects 5 and 6) by the method of Taylor, Thomas and Schleiter (18), but in a third (Subject 2) three methods were compared. In the former method the dry wall of the glass tube apparently hinders the rise of blood. An attempt to learn the pressure in the right auricle by taking the pressure elsewhere in the body is, of course, beset with difficulty. The changes which occur in any given region, independent of those elsewhere, make it impossible to be certain that a usual relation continuously exists between the pressures in two veins. It is reasonable to suppose, however, that the direction of change will not be uniformly different. In the absence of a direct method which gives the pressure in the right auricle, the one that has been used yields perhaps the best approximation.

The third subject lay flat on a wide board without pillows at least 15 minutes, his arms at his sides. His venous pressure was measured with the following apparatus. The two arms of a Y tube supplied near their origins with stopcocks were bent at right angles to form manometers; the third one was connected to a needle (Figure 8). The apparatus was sterilized. One of the tubes having a funnel at its upper end was filled with warm sterile normal saline solution, its stopcock being closed. The needle was inserted into a vein. Blood flowed into the open tube. The height of the column was measured from the level of the board ("blood up"). By manipulation or by using a tourniquet, more blood was forced into the manometer. On flowing back into the vein the column came to rest ("blood down"). This stopcock was then closed and the one connected to the tube containing salt solution opened. When this column came to rest, its height also was measured ("salt down"). The needle was always inserted at the same point in the same vein.

Venous pressure estimated in these three ways showed wide variations

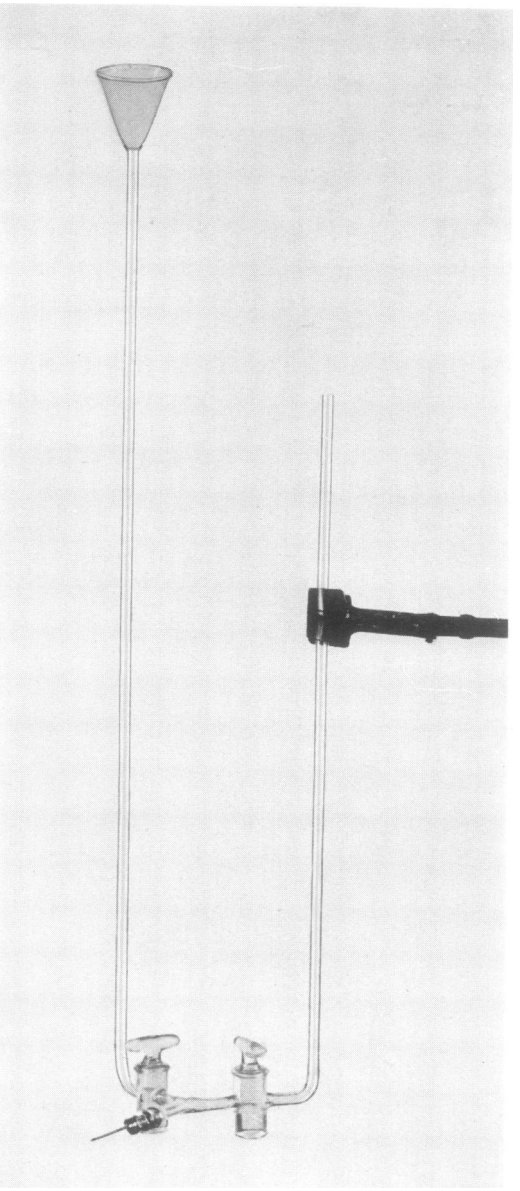


FIG. 8. IN THIS FIGURE IS REPRESENTED A PHOTOGRAPH OF THE APPARATUS WHICH WAS USED IN THE MEASUREMENT OF VENOUS PRESSURE IN SUBJECT NUMBER 2 (TABLE 2).

(Table 2, Figure 2). The height taken by the "blood up" method was usually lower than by the "blood down," and "salt down" greater than the "blood up," but sometimes it was greater and sometimes less even than the "blood down" measurement. All measurements were made from the level of the board on which the subject lay. To find the correct pressure, a correction must be made to allow for the height of the caval openings above the board. To learn this, x-ray photographs are taken at 2 meters, the subject lying flat on his back (Figure 9). It appears that the height sought is approximately 11.0 to 12.0 cm. This, or a similar appropriate figure (found in each case), must be subtracted from the manometric value. If the initial "blood up" measurement is selected, the venous pressure is 19.0 cm.; if the "blood down," 22.3 cm.; if the "salt down," 23.5 cm. (Subject 2).

Detailed attention was given to the matter of the level of venous pressure because it has attained importance from the position taken by Tainter and Dock (4) who believe that decrease in cardiac output in normal dogs after giving digitalis is due to constriction of the hepatic veins. The venous pressure, they found, was low. In the three human cases studied when alterations in cardiac minute output are correlated with the

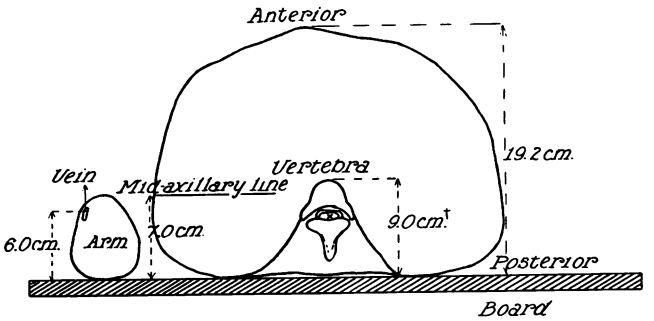



FIG. 9. IN THIS FIGURE IS SHOWN THE POSITION OF THE ARM DURING MEASUREMENTS OF VENOUS PRESSURE IN SUBJECT NUMBER 2 (TABLE 2). The anatomical distances are given.

† This measurement was made from an X-ray photograph of the chest (lateral view) taken at a distance of 2 meters.

height of the venous pressure, it appears from estimations made that no consistent change was observed.

In one instance (Subject 5) the minute output diminished to 86 per cent of its normal amount four hours after giving digitalis (Table 2, Figure 4), the venous pressure having increased 1.0 cm. (from 5.0 to 6.0 cm.). At the end of nine hours when the output fell to 79 per cent, the venous pressure measured 2.8 cm., although fourteen hours afterward when the output was again 86 per cent the pressure was high (8.3 cm.). Forty-eight hours afterward, when the minute output was normal (97 per cent), the venous pressure was low (3.5 cm.). In a second patient

(Subject 6) (Table 2, Figure 3), the variations of venous pressure were smaller, ranging from 0.8 cm. below to 1.0 cm. above the initial measurement, though the output fell to 60 per cent. In a third patient (Subject 2, Table 2, Figure 2), the three methods of taking venous pressure gave inconsistent readings at the four hour period. When the output was near its lowest point, the pressure by all methods was low, but when it was actually lowest, they were again high, two of them above their initial values.

*The effect on symptoms.* The symptoms of one individual (Subject 1) deserve detailed description. Twelve to fifteen hours after taking digitalis he became conscious that his heart was beating slowly and forcefully, so that he felt distress in his cardiac region. There was moderate dyspnea while lying in bed on two pillows. These symptoms were relieved slightly when he sat in a half-reclining position. The cardiac minute output at this time had fallen to 70 per cent. Twenty-four hours afterward, when he began again to walk about, more than the slightest exertion was impossible without creating severe dyspnea. He was, in fact, comfortable only when sitting upright at rest. At this time the output was 66 per cent and the size of the heart smaller than at the beginning. At thirty-six hours, dyspnea became much more severe, so that walking as slowly as possible elicited severe dyspnea and distinct cardiac pain. The pain did not radiate. The sensation was as if the heart were being squeezed. He was forced to rest two or three times in walking the length of a city block to recover from shortness of breath and to allow the cardiac pain to pass off. The next day these symptoms were still present but to a less extent. They persisted for several weeks. The duration of the symptoms corresponded to the period of diminished cardiac output. Associated with diminished cardiac output, decrease of the volume flow of blood through the coronary arteries must, in all probability, have occurred, and in consequence a degree of anoxemia on the part of the muscle. Were this the train of events, the inference is not unjustified that pain, which was experienced in so prominent a form, was the result of cardiac ischemia, in accordance with the view which has recently been revived by Keefer and Resnik (19).

Three other subjects complained of lassitude in the second twenty-four hours after digitalis was given. They were able to engage, in spite of low outputs, in their usual activities. One (Subject 2) complained of dyspnea on climbing a flight of stairs when his output was low, but recovered when it returned to normal. The other two complained of no disagreeable symptoms.

## SUMMARY AND CONCLUSIONS

The effect of giving digitalis to six normal individuals was studied with particular reference to its effect on cardiac output, on cardiac size and on venous pressure. The following phenomena were observed: (1)

The output of blood from the heart decreased. (2) The size of the heart diminished. (3) Slight decrease in cardiac rate occurred. (4) These effects were at a maximum four to twenty-four hours after giving the drug. (5) Significant changes did not occur in the levels of arterial and venous pressure. (6) Changes in form, sometimes slight, of the T-waves of the electrocardiogram occurred in each instance and were present as early as 2½ hours after the drug was given. (7) As the effect of digitalis wore off (48 hours to 3 weeks), output, size, rate, and the T-waves of the electrocardiogram returned toward their initial values. (8) A correlation was not established from these data between decrease in cardiac output and change in the level of venous pressure.

## PART II

### THE EFFECT ON THE OUTPUT OF HEARTS IN HEART FAILURE WITH CONGESTION, IN HUMAN BEINGS

It has been demonstrated as a fact that giving digitalis decreases the cardiac output and cardiac size in normal human beings. What the effect of its administration is when hearts are in a state of failure is still unknown. Investigations to discover this have, therefore, been undertaken and are now reported.

Seven patients exhibiting signs and symptoms of heart failure were studied. Although Grollman, Proger and Dennig (11) have shown that the acetylene method is adequate for the analysis of cardiac patients exhibiting pulmonary stasis, since the gases in a rebreathing bag come into equilibrium with the blood leaving the lungs within a prescribed time, only such cases were selected as were to all intents and purposes free of pulmonary congestion. The lungs were usually clear at the time the measurements were made. Rarely, at the extreme bases behind, a very few râles were heard on deep breathing.

### METHODS

All the patients when studied were at rest in bed. They were taking ward diet, free of salt except that used in cooking. The intake of fluid was, except in the case of one patient, limited to 1200 cc. a day. In the excepted case it was not limited. Measurements of cardiac output were made as in normal persons by the acetylene method (9, 10, 11). Owing to the difficulty cardiac patients experience in breathing when recumbent, all observations were made one half-hour after assuming the sitting position (20) at an angle of 135 degrees, the legs being fully extended. They were made familiar with the procedures beforehand. The vital capacity of the patients was estimated and the volume of gas in the bag adjusted to that amount which each, within a given time, could mix completely (9, 10, 11). This adjustment is necessary because it is impossible, during dyspnea when the vital capacity is diminished, for patients to manage an amount of gas (2400 cc.) as great as can normal individuals.

The size of the heart, in x-ray photographs, was measured as before (13). Electrocardiograms were made; the heart rate was counted; the arterial blood pressure and the vital capacity were estimated. In certain instances venous blood pressure was measured by the method of Taylor, Thomas and Schleiter (18). The observations were made in the following order: the patients, in a *basal metabolic state*, rested in the sitting position while the radial pulse (and cardiac rate in the case of patients exhibiting fibrillation of the auricles) was counted at intervals of five minutes. At the end of one half-hour they rebreathed the acetylene-air mixture. Samples of gas were taken for estimation of the arteriovenous oxygen difference, the first after rebreathing 7 to 8 times within fifteen seconds, the second after 3 to 4 additional rebreathings within ten seconds, the samples being taken during expiration. Shortly afterward the oxygen consumption was measured with a Benedict-Roth spirometer. After a pause of a few minutes the arterial and venous pressures and the vital capacity were measured in succession, and electrocardiograms were taken. Then x-ray photographs were secured.

Observations were made immediately before the administration of digitalis and at frequent intervals afterward. Digitalis in the form of digitan (Merck) 1.0 gram was given either in a single dose or within ten hours; in one instance, the dose was 0.8 gram, and in another 1.3 gram. Nausea and vomiting did not occur.

## OBSERVATIONS

Four patients exhibiting normal cardiac mechanism in the presence of signs and symptoms of heart failure comprise the first group.

*Case 1.* D. T. T. (Hospital number 7696), a Negro, 47 years of age, was admitted to the hospital on March 12, 1931. He was the subject of high systolic pressure (195 mm. Hg), discovered at the age of 43 years during a physical examination to which he submitted because of the occurrence of temporal headaches. At the age of 46 years he suffered from an attack of rheumatic fever and pericarditis. Two months later dyspnea appeared. Three months later still, he began to suffer from attacks of noctural dyspnea occurring at intervals of two weeks. Two months before admission dyspnea became constant and six weeks later, edema of the legs first appeared. On admission he complained of palpitation. He was dyspneic. A few râles were heard at the bases of the lungs posteriorly but disappeared within three days. There was general arteriosclerosis; the systolic blood pressure measured 170 mm. Hg, the diastolic 100 mm. Hg; pulsus alternans was present; the heart was enlarged; its rhythm was normal; there were signs of mitral insufficiency. The liver was enlarged and there was ascites; edema of the extremities, although present on admission, disappeared after resting in bed three days. The *etiological* diagnosis [5] was: rheumatic fever, arteriosclerosis, arterial

[5] The diagnoses in this paper conform to the nomenclature for cardiac diagnosis recommended by the Heart Committee of the New York Tuberculosis and Health Association. "Criteria for the classification and diagnosis of heart disease." 2d ed. New York Tuberculosis and Health Association, New York. 1929.

hypertension; the *anatomical:* cardiac hypertrophy, mitral insufficiency, left ventricular preponderance; the *physiological:* normal sinus rhythm, heart failure of the congestive type (first attack), pulsus alternans.

His cardiac output during the period of heart failure measured 2.90 liters per minute [6] on March 17, and 2.88 liters, three days later (March 20) (Table 3, Figure 10A). The area of the heart equalled 198.3 sq. cm. (Table 3, Figures 11 and 12). When digitalis (digitan 1.0 gram) was given (March 20) diuresis occurred (Figure 10A), he lost weight, became free of dyspnea and palpitation, and the liver became smaller (March 25). On March 21, 15 hours after taking the drug, the cardiac output increased to 3.54 liters per minute and the size of the heart decreased to 180.2 sq. cm. (March 22); slowing of the cardiac rate and alterations of the form of the T-waves of the electrocardiograms occurred (Table 3, Figures 10A, 11 and 12). As the effect of digitalis wore off the signs of heart failure reappeared (dyspnea, palpitation, enlargement of the liver). Two weeks later (April 6) the cardiac output fell to 2.62 liters per minute and the size of the heart increased to 193.6 sq. cm. When digitalis was given on three other occasions, April 6, May 11, and June 12, results similar to those just described were observed; increase in diuresis and in cardiac output, and decrease in cardiac size. As the effect of digitalis declined, the signs of heart failure reappeared; output decreased and cardiac size increased (Table 3, Figures 10A and 10B).

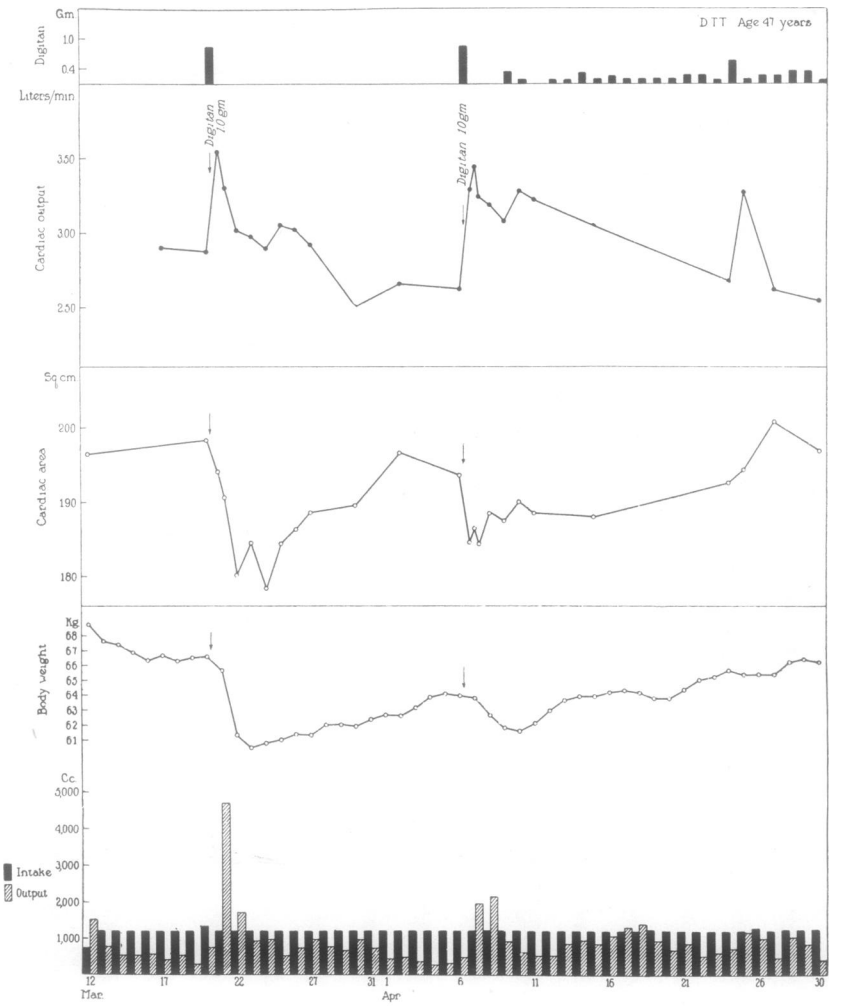
*Summary.* In this patient exhibiting normal cardiac mechanism in the presence of signs and symptoms of heart failure of the congestive type, the volume output of blood from the heart was diminished and the heart was large. On administering digitalis on each of four occasions, output increased and the size of the heart diminished. Changes in the reverse fashion occurred as the effect of digitalis disappeared. Giving digitalis induced diuresis on each occasion and was followed by amelioration of his signs and symptoms.

*Case 2.* M. R. (Hospital number 7852), a Negro aged 33 years was admitted to the hospital on September 22, 1931. He enjoyed good health until he "caught cold" four months before admission and suffered from shortness of breath for a few days. This experience was repeated two months later. On admission he complained of shortness of breath. The heart was enlarged; there were signs of mitral insufficiency and aortic roughening. There were a few râles at the bases of the lungs posteriorly. X-ray photographs of the chest showed that there was a small collection of fluid in the space between the upper and lower lobes of the right lung. The liver was enlarged. Ascites and edema of the extremities were present. The systolic blood pressure measured 150 mm. Hg; the diastolic, 100 mm. Hg. The Wassermann reaction in the blood was positive. The *etiological* diagnosis was syphilis; the *anatomical:* cardiac hypertrophy, mitral insufficiency, aortic roughening, left

[6] In the description of events and in the figures, the total cardiac output per minute is recorded. Calculation of the cardiac output on the basis of the surface area of the body (liters per minute per square meter of body surface) frequently showed the changes in a more striking manner, especially if diuresis occurred and the patient lost weight. These measurements are included in the tables (Tables 3 and 4).

ventricular preponderance; the *physiological:* normal sinus rhythm, slight arterial hypertension, heart failure of the congestive type (first attack).

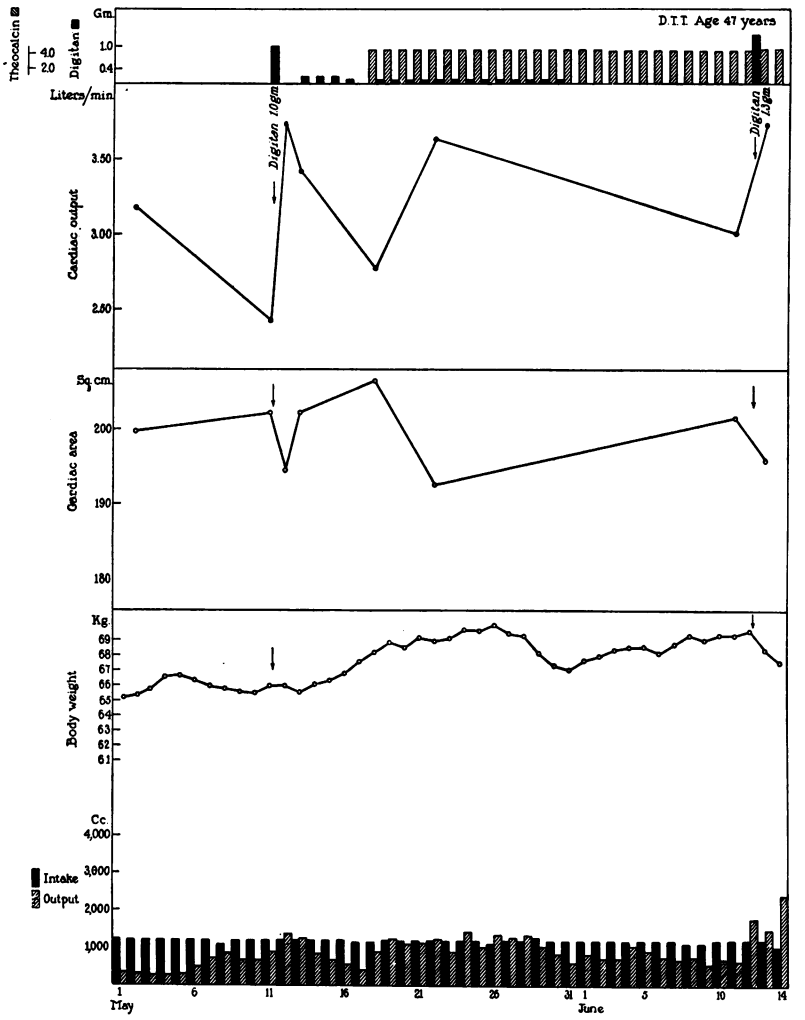
Diuresis occurred promptly when digitalis (digitan 1.0 gram) was administered on September 23. He lost weight, edema, ascites and râles disappeared, the liver became smaller, dyspnea became less and the interlobar fluid diminished. The cardiac output which had been less than normal, 2.05 liters per minute, increased in 24 hours to 2.73 liters, and the size fell to 130.4 sq. cm. from having been 143.4 sq. cm. (Table 3, Figure 13). Vital capacity increased and cardiac rate became slower; alterations in the T-waves of the electrocardiogram occurred. On September 29 the output measured 2.77 liters per minute and the heart was smaller than in the state of decompensation. As the effect of digitalis wore off he became dyspneic, the interlobar fluid re-collected,




*A*

See legend on opposite page.

the liver increased in size. Ten days later (October 5) the cardiac output was only 1.44 liter per minute and the heart was larger, 134.2 sq. cm. Digitan 1.0 gram was given a second time (October 6), but diuresis failed to occur. He became, however, less dyspneic. Next day there was a temporary rise in the cardiac output (2.21 liters per minute) and decrease in cardiac size (125.8 sq. cm.). He became more dyspneic, the liver increased in size, ascites appeared and on October 13 the output fell to 1.63 liter, and cardiac size rose




*B*

FIG. 10 *A* AND *B*. IN THESE FIGURES IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE, AND VOLUME OF URINE IN D. T. T. (CASE 1).

The cardiac mechanism was normal during heart failure.

TABLE 3

*Effect of giving digitalis on cardiac output and cardiac size in patients exhibiting normal cardiac rhythm in the presence of signs and symptoms of heart failure*

| Case and hospital number | Age | Date | Weight | Height | Body surface | Oxygen consumption | Arteriovenous oxygen difference | Cardiac output | Cardiac output | Cardiac area | Cardiac rate | Cardiac output | Arterial pressure | Vital capacity | Theocalcin | Effect on T-wave of electrocardiogram | Digitan | Time with reference to digitalis administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *years* | *1931* | *kgm.* | *cm.* | *sq. m.* | *cc. per minute* | *cc.* | *liters per minute* | *liters per sq. m. per minute* | *sq. cm.* | *minutes* | *cc. per beat* | *mm. Hg.* | *cc.* | *grams* | $T_1$ $T_2$ $T_3$ | *grams* | |
| 1. D.T.T. 7696 ♂ | 47 | March 17 | 66.5 | 165.3 | 1.74 | 306 | 105.3 | 2.90 | 1.66 | 195.4 | 88 | | ¶ | | | − − 0 | | Before |
| | | March 20 | 66.5 | | 1.74 | 295 | 102.2 | 2.88 | 1.65 | 198.3 | 108 | 27 | 180–150/125 | | | − − ∓ | | |
| | | March 20 | | | | | | | | | | | | | | | 1.0 | |
| | | March 21 | 65.6 | | 1.73 | 292 | 82.5 | 3.54 | 2.00 | 194.1 | 88 | 40 | 175–160/120 | | | ∓ ∓ ∓ | | 15 hours after |
| | | | 65.6 | | 1.73 | 327 | 99.0 | 3.30 | 1.91 | 190.7 | 108 | 31 | | | | + ∓ − | | 22 hours after |
| | | March 22 | 61.4 | | 1.67 | 292 | 97.1 | 3.01 | 1.80 | 180.2 | 104 | 29 | 180–145/120 | | | + ∓ − | | 2 days after |
| | | March 23 | 60.5 | | 1.66 | 271 | 90.9 | 2.98 | 1.80 | 184.5 | 98 | 30 | 160–140/110 | | | + ∓ − | | 3 days after |
| | | March 24 | 60.8 | | 1.67 | 273 | 94.0 | 2.90 | 1.74 | 178.4 | 88 | 33 | 165–135/110 | | | ∓ ∓ − | | 4 days after |
| | | March 25 | 61.0 | | 1.67 | 258 | 84.5 | 3.05 | 1.83 | 184.4 | 103 | 30 | 140–130/110 | | | ∓ ∓ − | | 5 days after |
| | | March 26 | 61.3 | | 1.68 | 247 | 81.6 | 3.03 | 1.80 | 186.4 | 92 | 33 | 145–140/110 | | | ∓ ∓ 0 | | 6 days after |
| | | March 27 | 61.3 | | 1.67 | 264 | 90.5 | 2.92 | 1.75 | 188.6 | 92 | 32 | 150–135/110 | | | ∓ ∓ + | | 7 days after |
| | | March 30 | 61.9 | | 1.68 | 259 | 103.6 | 2.50 | 1.50 | 189.5 | 100 | 25 | 170–130/110 | | | − ∓ + | | 8 days after |
| | | April 2 | 62.6 | | 1.69 | 297 | 111.7 | 2.66 | 1.57 | 196.5 | 96 | 23 | 180–130/120 | | | − ∓ + | | |
| | | April 6 | 64.0 | | 1.71 | 304 | 115.8 | 2.62 | 1.53 | 193.6 | 96 | 25 | 175–140/130 | | | − ∓ + | | Before |
| | | April 6 | | | | | | | | | | | | | | | 1.0 | |
| | | April 7 | 63.8 | | 1.71 | 286 | 87.0 | 3.29 | 1.92 | 184.5 | 100 | 33 | 175/130 | | | ∓ ∓ − | | 9 hours after |
| | | | 63.5 | | 1.71 | 289 | 84.0 | 3.44 | 2.01 | 186.5 | 96 | 36 | 175–140/120 | | | ∓ ∓ − | | 15 hours after |
| | | | 63.6 | | 1.71 | 231 | 89.8 | 3.24 | 1.89 | 184.3 | 96 | 34 | 160–140/120 | | | + ∓ − | | 23 hours after |
| | | April 8 | 62.6 | | 1.69 | 303 | 95.1 | 3.19 | 1.89 | 188.5 | 84 | 38 | 150–130/105 | | | + ∓ − | | 2 days after |
| | | April 9 | 61.8 | | 1.68 | 296 | 96.4 | 3.07 | 1.83 | 187.5 | 98 | 31 | 175–140/118 | | | ∓ ∓ ∓ | | 3 days after |
| | | April 10 | 61.6 | | 1.68 | 290 | 88.4 | 3.28 | 1.95 | 190.0 | 100 | 33 | 175–150/120 | | | ∓ ∓ ∓ | 1.0 | 4 days after |
| | | April 11 | 62.2 | | 1.68 | 278 | 86.0 | 3.23 | 1.92 | 188.7 | 98 | 33 | 152–135/110 | | | ∓ ∓ ∓ | | 5 days after |
| | | April 15 | 63.9 | | 1.71 | 256 | 84.2 | 3.05 | 1.78 | 188.0 | 94 | 32 | 170–140/115 | | | ∓ ∓ ∓ | | |
| | | April 16 | | | | | | | | | | | | | | | 1.1 (April 16–23) | |
| | | April 24 | 65.6 | | 1.74 | 287 | 107.1 | 2.67 | 1.53 | 192.4 | 104 | 25 | 178–130/120 | | | ∓ ∓ ∓ | 0.6 | |
| | | April 25 | 65.4 | | 1.73 | 311 | 95.1 | 3.27 | 1.89 | 194.3 | 96 | 34 | 180–150/115 | | | ∓ ∓ ∓ | | |
| | | April 27 | 65.4 | | 1.72 | 265 | 101.7 | 2.61 | 1.51 | 200.7 | 96 | 27 | 170–140/120 | | | ∓ ∓ + | 1.2 | |
| | | April 30 | 66.2 | | 1.73 | 264 | 103.7 | 2.54 | 1.47 | 196.5 | 96 | 26 | 190–150/120 | | | ∓ ∓ 0 | | |
| | | May 1 | | | | | | | | | | | | | | | discontinued | |
| | | May 2 | 66.4 | | 1.74 | 296 | 93.4 | 3.17 | 1.82 | 199.7 | 94 | 33 | 180–150/115 | | | ∓ ∓ ∓ | | |
| | | May 11 | 67.0 | | 1.74 | 263 | 108.1 | 2.43 | 1.39 | 202.2 | 97 | 25 | 160–130/110 | | | + − − | 0.7 | |
| | | May 12 | 67.0 | | 1.74 | 265 | 70.9 | 3.74 | 2.15 | 194.6 | 92 | 40 | 150–145/110 | | | + ∓ − | | |
| | | May 13 | 66.6 | | 1.74 | 277 | 81.1 | 3.41 | 1.96 | 200.2 | 104 | 32 | 175–155/115 | 2200 | | | 0.7 (May 13–16) | |
| | | May 18 | 69.2 | | 1.76 | 308 | 111.0 | 2.77 | 1.57 | 206.6 | 110 | 25 | 170–140/120 | 2375 | 4.5 | ∓ ∓ + | 0.1 q.d. | |
| | | May 22 | 70.0 | | 1.77 | 290 | 79.6 | 3.64 | 2.05 | 194.7 | 100 | 36 | 160–150/110 | 2400 | q.d. | ∓ ∓ + | (May 18–30) | |
| | | May 30 | | | | | | | | | | | | | | discontinued | | |
| | | June 11 | 70.4 | | 1.77 | 300 | 99.6 | 3.00 | 1.69 | 201.5 | 98 | 30 | 160/120 | 1940 | | − − 0 | | Before |
| | | June 12 | | | | | | | | | | | | | | 1.3 | | |
| | | June 13 | 69.4 | | 1.76 | 307 | 82.4 | 3.72 | 2.11 | 195.9 | 91 | 40 | 140–120/110 | 2000 | | − − − | | 24 hours after |

TABLE 3 (*continued*)

| Case and hospital number | Age | Date | Weight | Height | Body surface | Oxygen consumption | Arteriovenous oxygen difference | Cardiac output | Cardiac output | Cardiac area | Cardiac rate | Cardiac output | Arterial pressure | Vital capacity | Theocalcin | Effect on T-wave of electrocardiogram | Digitan | Time with reference to digitalis administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *years* | *1931* | *kgm.* | *cm.* | *sq. m.* | *cc. per minute* | *cc.* | *liters per minute* | *liters per sq. m. per minute* | *sq. cm.* | *minutes* | *cc. per beat* | *mm. Hg.* | *cc.* | *grams* | $T_1$ $T_2$ $T_3$ | *grams* | |
| 2. M.R. 7852 ♂ | 33 | September 23 | 49.8 | 156.0 | 1.47 | 224 | 109.4 | 2.05 | 1.39 | 143.4 | 74 | 28 | 150/100 | 1200 | | + ∓ ∓ | 1.0 | Before |
| | | September 23 | | | | | | | | | | | | | | | | |
| | | September 24 | 49.3 | | 1.46 | 203 | 74.3 | 2.73 | 1.87 | 130.4 | 64 | 43 | 170/90 | 1275 | | + ∓ ∓† | | 24 hours after |
| | | September 25 | 49.0 | | 1.46 | 200 | 81.9 | 2.44 | 1.67 | 134.9 | 62 | 40 | 150/100 | 1325 | | ∓ ∓ ∓‡ | | 48 hours after |
| | | September 29 | 46.4 | | 1.42 | 185 | 66.7 | 2.77 | 1.95 | 132.4 | 70 | 40 | 150/100 | 1300 | | − − − | | |
| | | October 5 | 45.7 | | 1.42 | 186 | 128.8 | 1.44 | 1.01 | 134.2 | 76 | 20 | 160/100 | 1300 | | ± − − less negative | | |
| | | October 6 | | | | | | | | | | | | | | | 1.0 | |
| | | October 7 | 45.4 | | 1.41 | 197 | 89.1 | 2.21 | 1.57 | 125.8 | 74 | 30 | 165/100 | 1300 | | + ∓ ∓ | | 24 hours after |
| | | October 8 | 45.4 | | 1.41 | 203 | 101.3 | 2.00 | 1.42 | 134.4 | 76 | 26 | 165/100 | 1275 | | + ∓ ∓ | | 48 hours after |
| | | October 9 | 45.3 | | 1.41 | 202 | 123.0 | 1.64 | 1.16 | 139.6 | 76 | 22 | 160/100 | 1250 | | ± ∓ ∓ | | 3 days after |
| | | October 13 | 46.1 | | 1.42 | 194 | 118.7 | 1.63 | 1.15 | 144.5 | 84 | 20 | 160/100 | 1125 | | Change in reverse direction | | |
| | | October 14 | | | | | | | | | | | | | 2.0 | | | |
| | | October 15 | 46.0 | | 1.42 | 173 | 71.3 | 2.42 | 1.70 | 136.4 | 72 | 34 | 145/95 | 1450 | 4.5 | | | |
| | | October 16 | 44.6 | | 1.41 | 202 | 65.8 | 3.07 | 2.17 | 128.8 | 70 | 44 | 145/95 | 1325 | q.d. | | | |
| | | October 19 | 43.9 | | 1.38 | 197 | 64.8 | 3.04 | 2.20 | 135.2 | 66 | | 140/90 | 1500 | | | | |
| | | October 20 | 44.1 | | 1.40 | 205 | 60.3 | 3.40 | 2.43 | 132.3 | 66 | 52 | 140/90 | 1700 | | | | |
| 3. W.N. 7712 ♂ | 32 | March 27 | 62.5 | 178.0 | 1.78 | 303 | 122.9 | 2.46 | 1.38 | | 116 | 21 | 120/80 | | | + + + | | |
| | | March 28 | 62.1 | | 1.78 | 290 | 111.1 | 2.61 | 1.46 | 248.9 | 108 | 24 | 120/80 | | | + + + | | |
| | | March 30 | 62.5 | | 1.79 | 283 | 104.1 | 2.72 | 1.52 | 252.7 | 122 | 22 | | | | + + + | | Before |
| | | March 30 | | | | | | | | | | | | | | | 1.0 | |
| | | March 31 | 63.1 | | 1.79 | 273 | 103.0 | 2.65 | 1.48 | 247.7 | 80* | 33 | 125/60 | | | + + + | | 13 hours after |
| | | | 63.4 | | 1.78 | 260 | 103.0 | 2.52 | 1.41 | 247.7 | 74** | 34 | 125/60 | | | − + + | | 23 hours after |
| | | April 1 | 63.4 | | 1.78 | 278 | 109.1 | 2.55 | 1.42 | 237.4 | 88§ | 28 | 120/70 | | | ± + + | | 2 days after |
| | | April 2 | 63.7 | | 1.79 | 276 | 147.7 | 1.87 | 1.04 | 236.7 | 88* | 21 | 125/70 | | | − + + | | 3 days after |

TABLE 3 (*continued*)

| Case and hospital number | Age | Date | Weight | Height | Body surface | Oxygen consumption | Arteriovenous oxygen difference | Cardiac output | Cardiac output | Cardiac area | Cardiac rate | Cardiac output | Arterial pressure | Vital capacity | Theocalcin | Effect on T-wave of electrocardiogram | Digitan | Time with reference to digitalis administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *years* | *1931* | *kgm.* | *cm.* | *sq. m.* | *cc. per minute* | *cc.* | *liters per minute* | *liters per sq. m. per minute* | *sq. cm.* | *minutes* | *cc. per beat* | *mm. Hg.* | *cc.* | *grams* | $T_1$ $T_2$ $T_3$ | *grams* | |
| 4. C.M. 7779 ♀ | 21 | June 1 | 39.5 | 162.0 | 1.38 | 179 | 81.8 | 2.19 | 1.59 | 141.4 | 84 | 26 | 100/55 | 2200 | | + + + | | Before |
| | | June 1 | | | | | | | | | | | | | | | 1.0 | |
| | | June 2 | 39.6 | | 1.38 | 191 | 63.5 | 3.00 | 2.17 | 133.7 | 80 | 40 | 80/50 | 2300 | | + + + all lower voltage | | 24 hours after |
| | | June 3 | 39.2 | | 1.37 | 207 | 75.5 | 2.74 | 2.00 | 134.8 | 80 | 38 | 98/55 | 2300 | | + + + all lower voltage | 0.2 | 48 hours after |
| | | June 4 | 39.1 | | 1.37 | 189 | 70.6 | 2.68 | 1.96 | 129.9 | 84 | 32 | 105/50 | 2425 | | + + + all lower voltage | | 72 hours after |

¶ Pulsus alternans was present; the two systolic readings represent the levels at which the alternate beats came through.

† Incomplete heart block; occasional 2 : 1 block; conduction time increased.

‡ Incomplete heart block has disappeared.

* Coupled rhythm due to ventricular premature contractions, right; ventricular premature contractions were felt in the radial pulse.

** Not coupled.

§ Ventricular premature contractions every 2d, 3d or 4th beat; ventricular premature contractions were felt in the radial pulse.

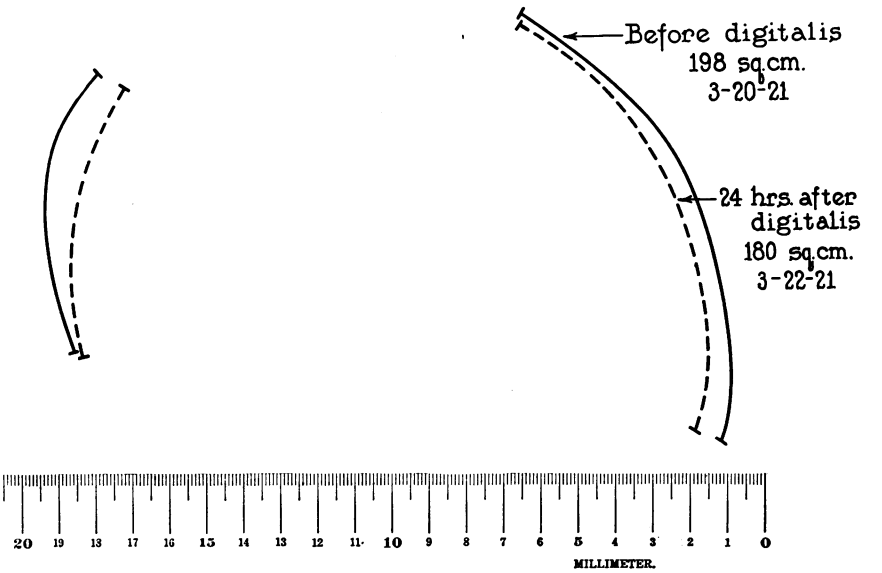



FIG. 11. IN THIS FIGURE IS DEMONSTRATED THE DECREASE IN SIZE OF THE HEART WHICH OCCURRED FOLLOWING THE ADMINISTRATION OF DIGITAN 1.0 GRAM IN D. T. T. (CASE 1).

The outlines of the heart were traced on thin paper from the x-ray photographs.

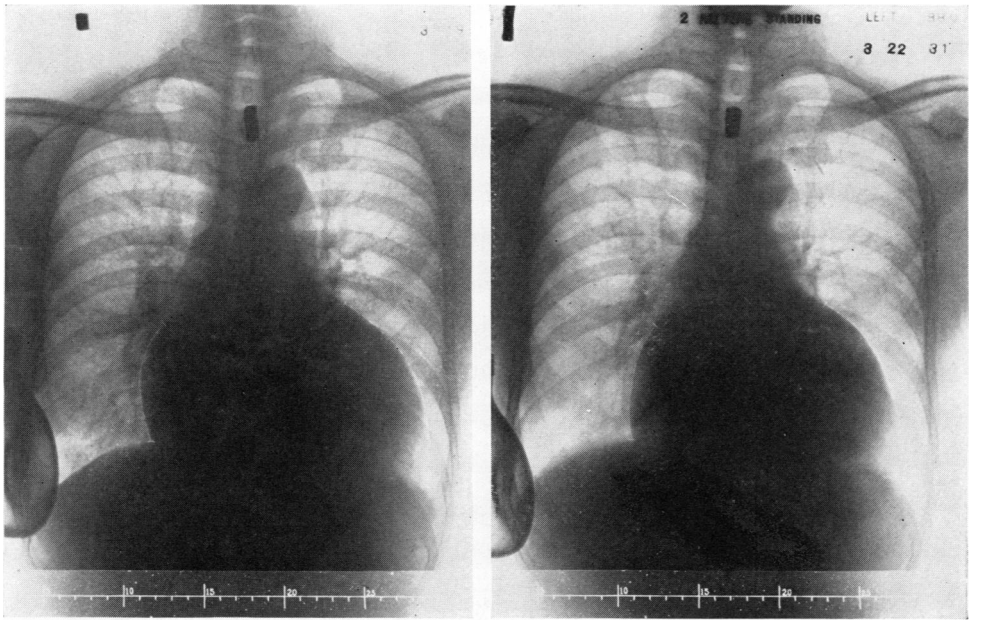


FIG. 12. IN THIS FIGURE ARE REPRODUCED X-RAY PHOTOGRAPHS OBTAINED IN THE CASE OF D. T. T. (CASE 1)

*A* was taken on March 20, before, and *B* on March 22, twenty-four hours after digitalis had been given.

to 144.5 sq. cm. Administration of theocalcin was then begun. Diuresis occurred promptly and he became free of edema. Increase in cardiac output occurred again (2.42 liters per minute, October 15) as well as decrease in cardiac size (128.8 sq. cm.), and increase in vital capacity. These relations remained unchanged for the next five days. Observations were then discontinued.

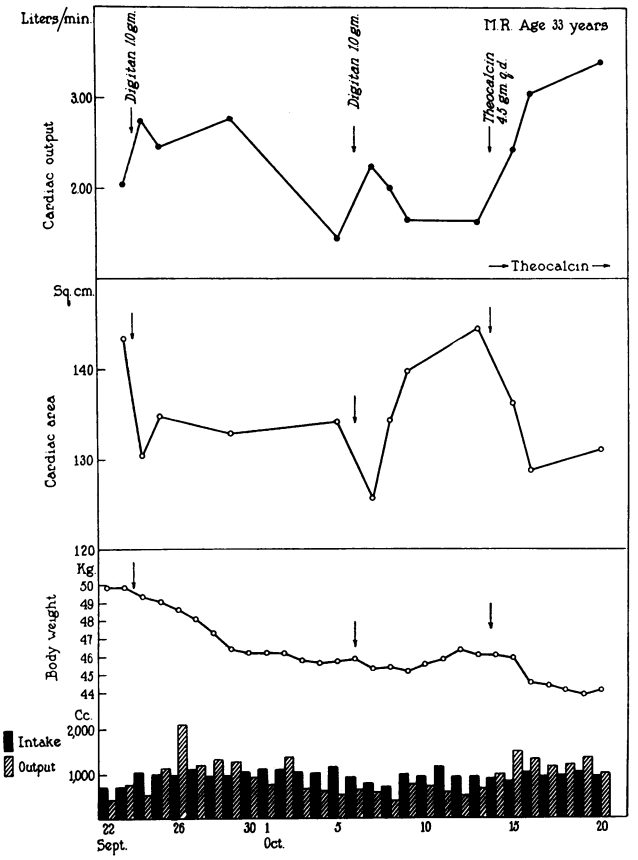



FIG. 13. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND VOLUME OF URINE IN M. R. (CASE 2).

The rhythm was normal during heart failure.

*Summary.* The cardiac output in this patient exhibiting normal cardiac mechanism was diminished during heart failure and the heart was larger than in the state of compensation. On the administration of digitalis, cardiac output increased, cardiac size diminished, vital capacity increased slightly, alterations in the form of the T-waves of the electrocardiograms occurred, and the patient became free of the signs of heart failure. Changes occurred in the reverse fashion as the effect of the drug

wore off. These events were repeated to a lesser degree on a second administration of digitalis though diuresis did not occur. But when theocalcin was given, diuresis took place, the output increased and the size of the heart decreased to an amount greater than resulted from giving digitalis.

*Case 3.* W. N. (Hospital number 7712), a white man aged 32 years, was admitted to the hospital on March 26, 1931. He suffered from attacks of rheumatic fever at 17, 18 and 29 years of age. His heart was affected during the first attack. Shortness of breath beginning suddenly when he was 28 years of age incapacitated him for two weeks; afterward dyspnea was present on exertion. Four months before admission dyspnea increased and edema of the extremities appeared. One month later he stopped work. Digitalis was prescribed and he became free of edema. Recently, taking the drug induced ventricular premature contractions; coupled rhythm resulted. He discovered that breathing deeply or coughing usually relieved him of this rhythm. On admission he was cyanotic, there were a few râles at the bases of the lungs posteriorly, the pleural cavities were free of fluid, ascites and edema of the extremities were present and the liver was swollen. The heart was enlarged, its rhythm regular. There were signs of mitral stenosis and insufficiency and of aortic insufficiency. The *etiological* diagnosis was: rheumatic fever; the *anatomical:* cardiac hypertrophy, aortic insufficiency, mitral stenosis and insufficiency, right ventricular preponderance; the *physiological:* regular sinus rhythm, ventricular premature contractions, heart failure of the congestive type (first attack).

On March 30, the heart's output was low (2.72 liters per minute) and its size large (252.7 sq. cm.) (Table 3). On administration of digitalis (digitan 1.0 gram) (March 30) coupled rhythm due to ventricular premature contractions occurred and persisted. Diuresis did not take place. He gained weight. Twenty-four hours after taking digitalis (March 31) the cardiac output remained approximately unchanged but the size of the heart decreased slightly. Seventy-two hours later, the cardiac output fell to 1.87 liter per minute. The rhythm was still coupled.

*Summary.* In this instance digitalis was without diuretic effect. Although the size of the heart became smaller, cardiac output was at first unchanged, though it diminished later. Coupled rhythm occurred after digitalis was given, and persisted. Alterations in the form of the T-waves of the electrocardiograms occurred.

The effect of giving digitalis when the rhythm of the heart is normal and when there are *no signs* of heart failure of the congestive type was shown in the case of C. M. (*Case 4*, Hospital number 7779), a white girl who was admitted to the hospital May 22, 1931, complaining of dyspnea. She suffered attacks of rheumatic fever at ages 5, 6, 7, 8, 9 and 12 years. When first examined at this hospital at 9 years of age, involvement of the heart had already occurred. Dyspnea first appeared when she was 13 years of age. On admission to the hospital at the age of 21 years the heart was enlarged; there were signs of mitral stenosis and aortic insufficiency. Dyspnea was present. There were *no signs* of heart failure of the congestive type. The *etiological* diagnosis was: rheumatic fever; the *anatomical:* cardiac hypertrophy, mitral stenosis, aortic

insufficiency, right ventricular preponderance; the *physiological:* normal sinus rhythm, ventricular premature contractions, cardiac insufficiency.

The cardiac output increased from 2.19 liters per minute to 3.00 liters, and cardiac size fell from 141.1 sq. cm. to 133.7 sq. cm. when digitan 1.0 gram was given (Table 3, Figure 14). Dyspnea disappeared. Although there was no evidence of accumulation of fluid, the output of urine increased slightly. The vital capacity increased. Alterations in the form of the T-waves of the electrocardiograms occurred.

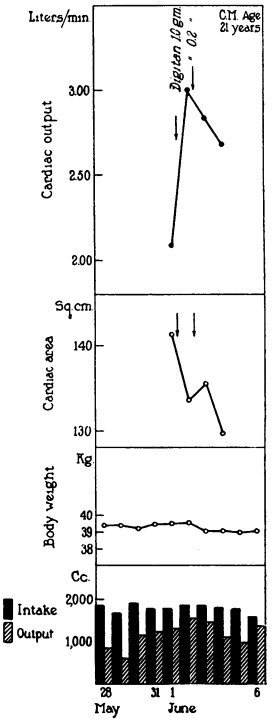



FIG. 14. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT AND CARDIAC SIZE IN C. M. (CASE 4).

The rhythm of the heart was normal. Dyspnea was the only symptom of heart failure.

*Summary.* In this patient who exhibited no signs of heart failure but whose cardiac output was nevertheless diminished, the administration of digitalis resulted in increase in cardiac output and diminished cardiac size.

In the second group are three patients suffering from auricular fibrillation who exhibited signs and symptoms of heart failure of the congestive type.

*Case 5.* S. G. (Hospital number 7902), a white man 31 years of age, was admitted to the hospital on November 9, 1931. He suffered from an attack

of rheumatic fever at 26 years of age; involvement of the heart occurred at that time. Dyspnea and palpitation began 16 months before admission following over-exertion. He took digitalis irregularly. On admission the heart was enlarged. Auricular fibrillation was present. There were signs of mitral stenosis and insufficiency and of aortic insufficiency. Cyanosis was present. There were a few râles at the bases of the lungs posteriorly which disappeared within twenty-four hours. Edema of the extremities and ascites were not present; the liver was palpable. The *etiological* diagnosis was: rheumatic fever; the *anatomical:* cardiac hypertrophy, mitral stenosis and insufficiency, aortic insufficiency, left ventricular preponderance; the *physiological:* auricular fibrillation.

When admitted to the hospital he was under the influence of digitalis; the ventricular rate was slow, the pulse deficit small. On November 11, the cardiac output measured 2.58 liters per minute, the cardiac size, 154.9 sq. cm., and the vital capacity, 2200 cc. (Table 4, Figure 15). As the effect of digitalis wore off the ventricular rate became more rapid and the pulse deficit wider. Body weight increased and dyspnea became more severe. He complained of palpitation and cardiac pain. The liver became larger. On November 28, the cardiac output fell to 2.23 liters per minute, the size of the heart rose to 159.7 sq. cm. and the vital capacity fell to 1600 cc. On the administration of digitalis in the form of digitan 1.0 gram after measurements were made on November 28, diuresis occurred promptly, the ventricular rate became slower and the patient felt better. Twenty-four hours later his output increased to 3.40 liters per minute, the size of the heart fell to 153.6 sq. cm., and the vital capacity rose to 1800 cc. The administration of digitalis was continued until December 4. Diuresis continued, he lost weight and became free of the signs and symptoms of heart failure. As before, when the drug was no longer given, its effect wore off. Heart failure (cyanosis, dyspnea, palpitation, cardiac pain, enlargement of the liver, rapid ventricular rate, gain in body weight, decrease in vital capacity) reappeared. The cardiac output fell to 1.67 liter per minute (January 5) and the size of the heart increased to 164.6 sq. cm. Venous pressure measured 11.6 cm. of blood. Digitan 1.0 gram was given a second time. Diuresis again occurred promptly and the ventricular rate again became slow. The output increased to 2.47 liters per minute and the size of the heart fell to 144.5 sq. cm. The venous pressure fell to 3.0 cm. of blood and the vital capacity increased to 1900 cc. Diuresis continued until the patient became free of heart failure.

*Summary.* In this case the volume output was less and the size greater during heart failure than during the state of compensation. On administration of digitalis, cardiac output increased, cardiac size diminished, vital capacity increased, venous pressure decreased, ventricular rate became slower, and the patient became free of the signs and symptoms of heart failure. As the effect of digitalis wore off, changes occurred in the reverse direction.

*Case 6.* M. C. (Hospital number 7489), a woman 51 years of age was admitted to the hospital on May 6, 1931. Dyspnea appeared first when she was 46 years of age. A first attack of heart failure occurred two years later. On admission she was suffering from a fourth attack of heart failure. She had been complaining of shortness of breath and swelling of the feet and

TABLE 4

*Effect of giving digitalis on cardiac output, cardiac size, vital capacity and venous pressure in patients exhibiting auricular fibrillation during heart failure*

| Case and hospital number | Age | Date | Weight | Height | Body surface | Oxygen consumption | Arteriovenous oxygen difference | Cardiac output | Cardiac output | Cardiac area | Ventricular rate | Arterial pressure | Venous pressure | Vital capacity | Effect on T-wave of electrocardiogram | Theocalcin | Digitan | Time with reference to digitalis administration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *years* | *1931* | *kgm.* | *cm.* | *sq. m.* | *cc. per minute* | *cc.* | *liters per minute* | *liters per sq. m. per minute* | *sq. cm.* | *minutes* | *mm. Hg* | *cm. blood* | *cc.* | | *grams* | *grams* | |
| 5. S.G. 7902 ♂ | 31 | November 11* | 61.0 | 165.5 | 1.68 | 242 | 84.0 | 2.58 | 1.50 | 154.9 | 64 | | | 2200 | $-T_{12}, \mp T_3$. | | | |
| | | November 28 | 62.8 | | 1.70 | 245 | 109.5 | 2.23 | 1.31 | 159.7 | 100 | | | 1600 | $T_{12}$ less neg., $+T_3$. | | 1.0 | Before |
| | | November 28 | | | | | | | | | | | | | | | | |
| | | November 29 | 62.9 | | 1.70 | 255 | 75.0 | 3.40 | 2.00 | 153.6 | 68 | | | 1800 | $T_{12}$ more neg., $\mp T_3$. | | | 24 hours after |
| | | November 30 | 62.4 | | 1.68 | 240 | 95.9 | 2.50 | 1.50 | 156.5 | 68 | | | 1700 | | | | 48 hours after |
| | | December 1 | 61.4 | | 1.68 | 245 | 91.9 | 2.67 | 1.59 | 157.7 | 65 | | | 1800 | | | 0.5 | |
| | | December 3 | 59.3 | | 1.66 | 213 | 89.7 | 2.37 | 1.43 | 155.4 | 67 | | | 1900 | | | (Dec. 1–8) | |
| | | December 10 | 56.8 | | 1.63 | 222 | 89.0 | 2.50 | 1.53 | 160.8 | 66 | | | 2200 | | | | |
| | | *1932* | | | | | | | | | | | | | Change in reverse direction. | | | |
| | | January 5 | 58.4 | | 1.64 | 218 | 130.7 | 1.67 | 1.02 | 164.6 | 100 | | 11.6 | 1700 | $T_{12}$ less neg., $+T_3$. | | | Before |
| | | January 5 | | | | | | | | | | | | | | | 1.0 | |
| | | January 6 | 58.3 | | 1.64 | 230 | 93.0 | 2.47 | 1.51 | 144.5 | 60 | | 3.0 | 1950 | $T_{12}$ more neg., $\mp T_3$. | | | 24 hours after |
| | | January 7 | 57.2 | | 1.63 | 212 | 83.7 | 2.53 | 1.55 | 161.3 | 53 | | 4.9 | 2100 | | | | 48 hours after |
| | | January 9 | 55.9 | | 1.62 | 214 | 86.9 | 2.46 | 1.52 | 160.3 | 60 | | 4.0 | 2150 | | | 0.1 | |
| | | January 10 | | | | | | | | | | | | | | | 0.3 | |
| | | January 11 | 55.2 | | 1.61 | 209 | 92.3 | 2.27 | 1.40 | 170.6 | 52 | | 2.5 | 2300 | | | | |
| | | *1931* | | | | | | | | | | | | | | | | |
| 6. M.C. 7489 ♀ | 51 | May 20 | 59.0 | 163.0 | 1.63 | 199 | 81.5 | 2.44 | 1.50 | 185.3 | 91† | 140/110 | | 1650 | $+T_1, \mp T_{23}$. | | 1.0 | Before |
| | | May 20 | | | | | | | | | | | | | | | | |
| | | May 21 | 58.1 | | 1.62 | 208 | 74.6 | 2.79 | 1.72 | 170.5 | 56 | 160/110 | | 1800 | $\mp T_1, -T_{23}$. | | | 24 hours after |
| | | May 22 | 56.6 | | 1.61 | 214 | 62.0 | 3.45 | 2.14 | 167.3 | 60 | 130/110 | | 1825 | $\mp T_1, -T_{23}$. | | | 48 hours after |
| | | May 27 | 56.4 | | 1.60 | 212 | 66.0 | 3.21 | 1.99 | 167.4 | 82 | 130/110 | | 1710 | $\mp T_1, -T_{23}$. | | | |
| | | *1932* | | | | | | | | | | | | | | | | |
| 7. M.J. 5783 ♀ | 38 | January 19 | 84.3 | 164.0 | 1.89 | 284 | 158.9 | 1.78 | 0.94 | ‡ | 108 | | 9.5 | 1600 | $+T_{123}$. | | | Before |
| | | January 19 | | | | | | | | | | | | | | | 0.8 | |
| | | January 20 | 83.1 | | 1.88 | 275 | 110.8 | 2.48 | 1.32 | ‡ | 79 | | 6.5 | 1600 | $-T_{12}, \mp T_3$. | | | 24 hours after |
| | | January 21 | | | | | | | | | | | | | | 2.0 | | |
| | | January 22 | | | | | | | | | | | | | | 4.5 | | |
| | | January 23 | 82.3 | | 1.87 | 306 | 75.5 | 4.05 | 2.17 | ‡ | 81 | | 3.5 | 1500 | | (daily) | | |
| | | January 30 | 77.0 | | 1.82 | 295 | 89.2 | 3.31 | 1.82 | ‡ | 96 | | 4.4 | 1700 | $\mp T_1, +T_{23}$. | | | |

* Patient was under the influence of digitalis on admission to hospital.

† The radial pulse rate was counted in this patient.

‡ The size of the heart could not be measured; see text.

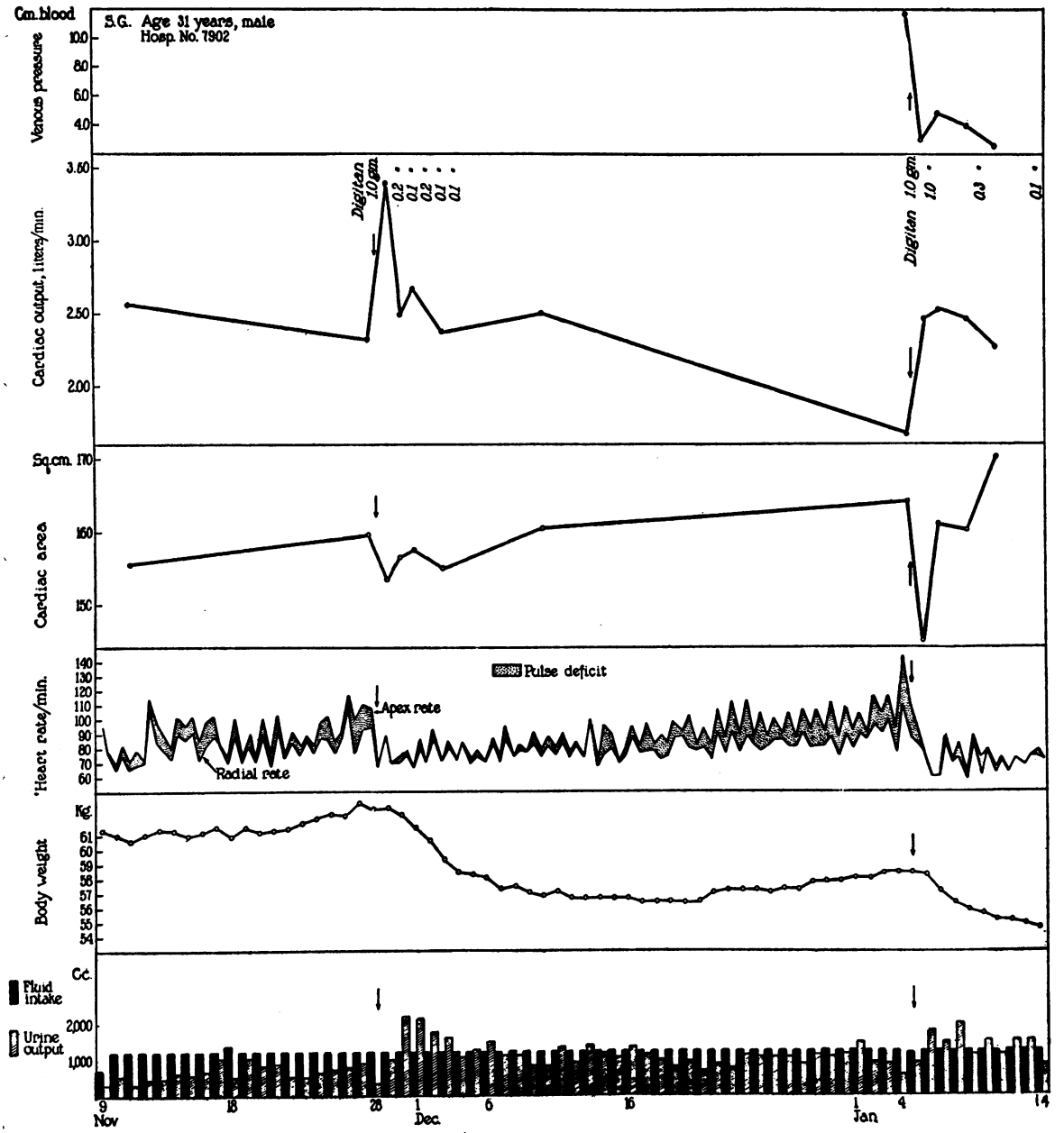



FIG. 15. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND VOLUME OF URINE IN S. G. (CASE 5), THE SUBJECT OF AURICULAR FIBRILLATION.

abdomen for four weeks. The *etiological* diagnosis was: unknown; the *anatomical:* enlargement of heart, chronic myocarditis, right ventricular preponderance, mitral insufficiency; the *physiological:* auricular fibrillation, ventricular premature contractions, heart failure of the congestive type (fourth attack).

The cardiac output was 2.44 liters per minute on May 20, and the size of the heart 185.3 sq. cm. (Table 4, Figure 16). She had not taken digitalis

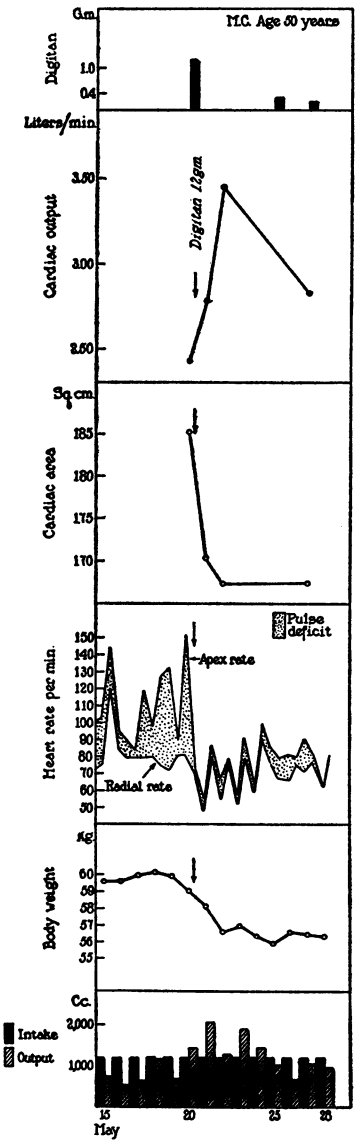



FIG. 16. IN THIS FIGURE IS REPRESENTED THE EFFECT OF GIVING DIGITALIS ON CARDIAC OUTPUT, CARDIAC SIZE AND VOLUME OF URINE IN M. C. (CASE 6) EXHIBITING AURICULAR FIBRILLATION.

since admission to the hospital. The ventricular rate was rapid, the pulse deficit was great, there were a few râles at the bases of both lungs posteriorly; there was edema of the extremities; ascites was present, the liver was enlarged. On the same day she was given digitalis (digitan 1.0 gram). The ventricular rate became slower, diuresis occurred, she lost weight, râles, edema and ascites disappeared, and the liver became smaller. Two days later (May 22) the cardiac output rose to 3.45 liters per minute and the size of the heart fell to 167.3 sq. cm. The vital capacity rose from 1650 to 1825 cc.

*Summary.* In this patient exhibiting auricular fibrillation, the cardiac output was diminished and the size of the heart large during heart failure. On the administration of digitalis the output rose, the size diminished and the patient became free of edema.

*Case 7.* M. J. (Hospital number 5783), a white woman, 38 years of age, was admitted to the hospital on January 11, 1932. Hypertension had been present for five years and auricular fibrillation for three years. On admission, suffering from a seventh attack of heart failure, she exhibited marked edema of the extremities and enlargement of the liver. There were a few râles at the bases of the lungs posteriorly. The heart was large, the ventricular rate rapid. The systolic blood pressure measured 180 mm. Hg, the diastolic, 140 mm. Hg. The *etiological* diagnosis was: arterial hypertension; the *anatomical:* enlargement of heart, left ventricular preponderance; the *physiological:* auricular fibrillation, intraventricular heart-block, heart failure of the congestive type.

The cardiac output measured 1.78 liter per minute on January 19, and the venous pressure, 9.5 cm. blood (Table 4, Figure 17). The heart was enlarged to such an extent that its left border, in the x-ray photographs, could not be distinguished from the shadow of the chest wall; for this reason its size was not measured. Digitalis (digitan 0.8 gram) was given; the ventricular rate decreased and 24 hours later (January 20) the cardiac output rose to 2.48 liters per minute, and the venous pressure fell to 6.5 cm. blood. As diuresis did not occur at once, the administration of theocalcin was begun on January 21. Cardiac output increased to 4.05 liters per minute and the venous pressure fell to 3.5 cm. of blood. Diuresis occurred and persisted until the patient became free of edema.

*Summary.* In this patient exhibiting auricular fibrillation with a rapid ventricular rate, the cardiac output was diminished during heart failure. Following the administration of digitalis, output increased, venous pressure fell, and ventricular rate became slower. The administration of theocalcin was more effective than digitalis in the relief of heart failure. It resulted also in greater increase in cardiac output.

## SUMMARY

The experience gained from a study of these patients makes it clear that (1) the volume output of blood per minute from the heart in human beings is diminished during heart failure, both when the cardiac mechanism is normal and when auricular fibrillation is present.

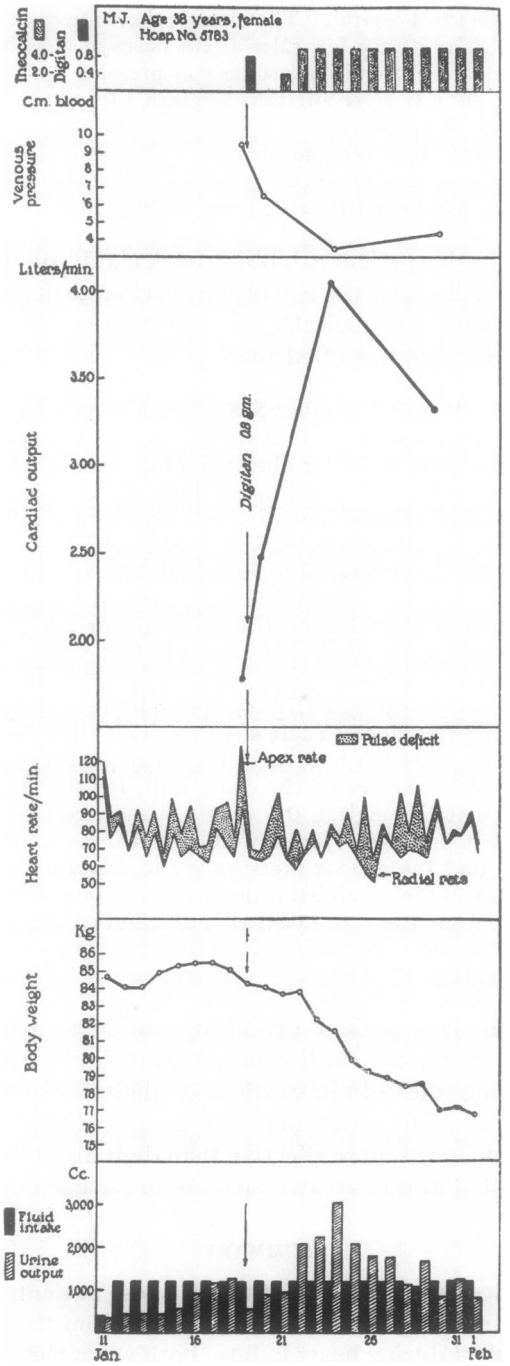



FIG. 17. IN THIS FIGURE IS SHOWN THE EFFECT OF GIVING DIGITALIS AND THEOCALCIN ON CARDIAC OUTPUT, CARDIAC SIZE AND OUTPUT OF URINE IN M. J. (CASE 7), THE SUBJECT OF AURICULAR FIBRILLATION.

(2) During heart failure the size of the heart is larger than it is when in a state of compensation.

(3) When improvement results, the administration of digitalis occasions: (*a*) *increase* in cardiac output; (*b*) *decrease* in cardiac size; (*c*) *decrease* in venous pressure; (*d*) increase in vital capacity; (*e*) slowing of the ventricular heart rate. (*f*) Changes in the form of the electrocardiogram are observed at this time.

(4) The administration of theocalcin was more effective in the relief of heart failure than digitalis in two patients. Giving it occasioned (*a*) increase in cardiac output, greater in amount than resulted from giving digitalis; (*b*) decrease in cardiac size; and (*c*) decrease in venous pressure.

## DISCUSSION

In all subjects, normal as well as those suffering from heart failure, alterations in form of the $T$-waves of the electrocardiograms followed the administration of digitalis. They were frequently the earliest effects observed. The alterations were not uniform; the most characteristic and usual one was negativity of $T_3$ (21); in certain cases $T_1$ and $T_2$, however, also became negative; $T_1$ or $T_2$ or $T_3$ sometimes became diphasic. On the other hand, waves which were negative became positive, and finally changes in amplitude only, occurred. The point to be emphasized is that *change* in form of the waves *always* took place.

There is ample experience with theocalcin in the treatment of heart failure to show that it is often useful in the relief of edema when digitalis fails (22). The new experience, although limited to observations in two patients, supplies evidence that in addition its action is accompanied by increase in cardiac output and decrease in cardiac size and in venous pressure. What the mechanism is by which theocalcin accomplishes these results is still unknown. Various possibilities suggest themselves, a xanthin effect on the rate of coronary flow, a calcium ion effect on heart muscle, or still another form of calcium action.

It has already been shown in Part I of this paper that the results of the administration of digitalis to normal individuals differ in several respects from those just described in patients. These differences include: (*a*) *decrease* in cardiac output; (*b*) *decrease* in cardiac size; (*c*) no significant alteration in the level of venous blood pressure; (*d*) no change in vital capacity.

A matter of major importance which has emerged from conducting these researches is the paradox that one and the same drug, digitalis, when given to human beings has, in normal persons, one effect, and in persons the subjects of heart disease, another; decrease in the output of blood in the former, increase in the latter, as Burwell, Neighbors and Regen found (1). In parallel situations in dogs (normal (23) and pathological (24)) the results resemble those now reported. Is the difference in

result due to an essential difference in action or is it due to a difference in the essential conditions which are being investigated?

In both normal and diseased hearts, in human beings and in dogs the action of digitalis has, at least in one respect, an identical consequence; in both, the size of the heart becomes smaller. It has also another consequence; the vigor of its action increases. If this consequence were not known from former experience (Cohn and Stewart (24, 25, 26)) it would have become apparent from the present ones in which the output of blood in diseased persons increases. The difference in the effect in the two types of heart, normal and pathological, results, so we think and as we have formerly stated, from the fact that normal hearts when under its influence become smaller but, being smaller pumps, expel smaller volumes, though contraction is more effective. The net result of its action, if it depends upon an effect on the hepatic veins, does so to a minor, perhaps to a negligible, degree only. Pathologically enlarged hearts likewise become smaller, but not so small that their cavities shrink to dimensions less than normal; in point of fact, though they decrease, their final dimensions are larger perhaps than when they were in their healthy state. They attain, due to the action of digitalis, sizes commensurate with ejecting larger volumes than were possible in the state of failure. Whether decrease in size to the extent to which it occurs facilitates the result, the expulsion, namely in heart failure, of larger quantities than before; or whether the increase in contractile capability brings it about, the fact is nevertheless clear that the heart has become smaller and that the circulation which was insufficient before, has become sufficient. The evidence for improvement is to be found in the amelioration of the symptoms and in changes in the other physical signs.

The explanation of these events may perhaps be found in Starling's theory dealing with the length of the muscle fibers of the heart (27). The theory is too well known to require repetition. It is not a wide stretch to believe that it is applicable in these cases in which there is such clear evidence of change in size of the heart and of increase in its functional capacity.

There is required still, consideration of that aspect of the problem which Dock and Tainter (3, 4) have brought forward. The major part of the argument which deals with their contention and the evidence which leads us to take a different view, is contained in a former paper (28). It is necessary to discuss one more phase of the matter. In cases where the output becomes smaller, as in the normal heart, the point has been made (3, 4) that this is due, not to a change in diastolic size of the heart, a change in tone, but to decrease in inflow, a result of constriction of the hepatic veins, indicated by the fact that the venous pressure is low. Low venous pressure is, on the latter assumption, regarded as the sign of

a small volume of blood available for inflow into the heart. Low venous pressure was found by Dock and Tainter in dogs, which they studied, for a maximum of two hours after the injection of a digitalis substance.

The plain result of the measurement of the venous pressure in normal human beings is that a change in pressure parallel with the volume of the output does not occur. Based on these observations, and in view of the anatomical arrangement in the liver of human beings, the mechanism proposed by Dock and Tainter seems untenable. A reason for the difference in interpretation can be given to the last statement, depending on a difference in the times when their observations and ours were made—theirs after an interval varying from a few minutes to two hours, ours after many hours and as a matter of fact after several days. The duration of their observations was, as has been pointed out, brief. If the course of the entire subsequent action in dogs is determined by events in these early minutes, we have no counter argument to offer. But it seems unlikely in healthy human beings that, if the outflow is small and the venous pressure normal or even elevated, as in several instances, the level of the venous pressure can be responsible for the result, in the sense in which Dock and Tainter wish to attribute to it a deciding influence. The venous pressure, far from being low, is too inconstant in its behavior to bear the burden of responsibility for so conspicuous an action as the decrease in output. What the venous pressure is in healthy intact dogs, after hours or days, is still unknown. Information on this point is desirable.

On the other hand we have demonstrated again, and it is an observation which is now well known, that fall in venous pressure is not an infrequent occurrence following the administration of digitalis to patients suffering from heart failure and edema. *Increase* in cardiac output occurs in such cases, as these observations show, at a time when venous pressure falls; venous pressure, in short, is high when the output is small and falls as output increases. The venous pressure is high under these circumstances not because the venous return is great but because the heart is incapable of propelling through its cavities all the blood which comes to it.

It seems necessary, therefore, in the case of normal hearts, the evidence being what it is, to hold belief in the theory that decrease in outflow is due to increase, expressed as decrease beyond the natural, perhaps optimal length, in tone of the heart muscle.

## CONCLUSIONS

1. A consequence of the action of digitalis is to decrease the volume output of blood per minute from the heart in normal human beings and to decrease its size.

2. The volume output of blood per minute from the heart which is in failure is diminished and its size larger than when it is in a state of compensation.

3. Following the administration of theocalcin in patients during heart failure, cardiac output increases and cardiac size and venous pressure diminish.

4. Giving digitalis increases the volume output of blood per minute from failing hearts and decreases their size.

5. Digitalis, we think, has similar, perhaps identical, actions both in normal and in diseased hearts; it *decreases* cardiac size and *increases* the extent of ventricular contraction (23). The consequence of these actions is that the volume of the cardiac output which results differs, depending on an initial difference in size of the ventricular cavities, in the two situations. In the one, the normal heart, it becomes too small, in the other, the diseased heart, it develops a suitable size.

## BIBLIOGRAPHY

1. Burwell, C. S., Neighbors, De. W., and Regen, E. M., J. Clin. Invest., 1928, v, 125. The Effect of Digitalis upon the Output of the Heart in Normal Man.
2. Harrison, T. R., and Leonard, B. W., J. Clin. Invest., 1926, iii, 1. The Effect of Digitalis on the Cardiac Output of Dogs and Its Bearing on the Action of the Drug in Heart Disease.
3. Dock, W., and Tainter, M. L., J. Clin. Invest., 1929–30, viii, 467. The Circulatory Changes after Full Therapeutic Doses of Digitalis, with a Critical Discussion of Views on Cardiac Output.
4. Tainter, M. L., and Dock, W., J. Clin. Invest., 1929–30, viii, 485. Further Observations on the Circulatory Actions of Digitalis and Strophanthus with Special Reference to the Liver and Comparisons with Histamine and Epinephrine.
5. Field, H., Bock, A. V., Gildea, E. F., and Lathrop, F. L., J. Clin. Invest., 1924, i, 65. The Rate of the Circulation of the Blood in Normal Resting Individuals.
6. Weiss, S., and Ellis, L. B., J. Clin. Invest., 1929–30, viii, 435. Circulatory Measurements in Patients with Rheumatic Heart Disease Before and After the Administration of Digitalis.
7. Henderson, Y., and Haggard, H. W., Am. J. Physiol., 1925, lxxiii, 193. The Circulation and Its Measurement.
8. Ringer, M., and Altschule, M., Am. Heart J., 1929–30, v, 305. Studies on the Circulation. II. Cardiac Output in Diseases of the Heart and Under the Influence of Digitalis Therapy.
9. Grollman, A., Am. J. Physiol., 1929, lxxxviii, 432. The Determination of the Cardiac Output of Man by the Use of Acetylene.
10. Baumann, H., und Grollman, A., Ztschr. f. klin. Med., 1931, cxv, 41. Über die theoretischen und praktischen Grundlagen und die klinische Zuverlässigkeit der Acetylenemethode zur Bestimmung des Minutenvolumens.
11. Grollman, A., Proger, S., and Dennig, H., Arch. f. exp. Path. u. Pharm., 1931, clxii, 463. Zur Bestimmung des Minutenvolumens mit der Azetylenemethode bei Arbeit, bei normalen und kranken Menschen.
12. Grollman, A., Am. J. Physiol., 1929, xc, 210. Physiological Variations in the Cardiac Output of Man. VI. The Value of the Cardiac Output of the Normal Individual in the Basal, Resting Condition.

13. Levy, R. L., Arch. Int. Med., 1923, xxxii, 359. The Size of the Heart in Pneumonia. A Teleroentgenographic Study, with Observations on the Effect of Digitalis Therapy.
14. Grollman, A., Am. J. Physiol., 1929, lxxxix, 366. Physiological Variations in the Cardiac Output of Man. III. The Effect of the Ingestion of Food on the Cardiac Output, Pulse Rate, Blood Pressure, and Oxygen Consumption of Man.
15. Soderstrom, G. F., Barr, D. P., and Du Bois, E. F., Arch. Int. Med., 1918, xxi, 613. Clinical Calorimetry. XXVI. The Effect of a Small Breakfast on Heat Production.
16. Grollman, A., Am. J. Physiol., 1929, lxxxix, 157. Physiological Variations in the Cardiac Output of Man. II. Changes in the Cardiac Output, Metabolism, Blood Pressure, and Pulse Rate of Man Following the Ingestion of Fluids.
17. Steele, J. M., Effect of Digitalis on Body Temperature. (To be published.)
18. Taylor, F. A., Thomas, A. B., and Schleiter, H. G., Proc. Soc. Exp. Biol. and Med., 1930, xxvii, 867. A Direct Method for the Estimation of Venous Blood Pressure.
19. Keefer, C. S., and Resnik, W. H., Arch. Int. Med., 1928, xli, 769. Angina Pectoris; a Syndrome Caused by Anoxemia of the Myocardium.
20. Grollman, A., Am. J. Physiol., 1928, lxxxvi, 285. The Effect of Variation in Posture on the Output of the Human Heart.
21. Cohn, A. E., Fraser, F. R., and Jamieson, R. A., J. Exp. Med., 1915, xxi, 593. The Influence of Digitalis on the T-wave of the Human Electrocardiogram.
22. Stewart, H. J., J. Clin. Invest., 1930, viii, 389. The Use of Theocalcin in the Treatment of Heart Failure of the Congestive Type.
23. Stewart, H. J., and Cohn, A. E., J. Clin. Invest., 1932, xi, 897. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. II. The Effect on the Output of the Hearts of Dogs Subject to Artificial Auricular Fibrillation.
24. Cohn, A. E., and Stewart, H. J., J. Clin. Invest., 1928, vi, 53. The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Normal Dogs.
25. Cohn, A. E., and Stewart, H. J., J. Clin. Invest., 1928, vi, 79. The Relation Between Cardiac Size and Cardiac Output per Minute Following the Administration of Digitalis in Dogs in Which the Heart is Enlarged.
26. Cohn, A. E., and Stewart, H. J., J. Clin. Invest., 1924, i, 97. Evidence that Digitalis Influences Contraction of the Heart in Man.
27. Starling, E. H. The Linacre Lecture on the Law of the Heart, given at Cambridge, 1915. Longmans, Green and Co., London, 1918.
28. Cohn, A. E., and Steele, J. M., J. Clin. Invest., 1932, xi, 871. Studies on the Effect of the Action of Digitalis on the Output of Blood from the Heart. I. The Effect on the Output of the Dog's Heart in Heart-Lung Preparations.