A CLINICAL STUDY OF THE ACTION OF 10 COMMONLY USED DRUGS ON CARDIAC OUTPUT, WORK AND SIZE; ON RESPIRATION, ON METABOLIC RATE AND ON THE ELECTROCARDIOGRAM

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The possession of a technique which permitted rapid estimations of cardiac output and which, demanding no intelligent cooperation, seemed especially suitable for use on ward patients, has permitted an extensive study on the action of common drugs on the heart and circulation in clinical conditions. This study contains about 450 estimations of cardiac output performed on 85 patients.

Coincidentally with these estimations the action of drugs on pulse rate, on blood pressure, on respiratory rate and volume, and on metabolic rate was observed. Orthodiagrams and electrocardiograms were secured also. Therefore, certain parts of our study dealt with effects already well known.

The results of such estimations have permitted the calculation of heart work, of peripheral resistance, of arteriovenous oxygen difference, and of the ratio of heart work to heart size, the latter a factor of decisive importance in our conception of cardiac stimulation and depression. Therefore our study demonstrates the effect of drugs on these functions also.

Most of the drugs selected are commonly used in cases of cardiac and circulatory disease. We have studied the actions of digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerine, pitressin, quinidine, morphine and strychnine. We have studied the effects of drugs in those clinical conditions in which physicians are accustomed to employ them. But when suitable cases were not available the effects were studied in other conditions.

Almost without exception our results support the general conceptions of drug action derived from animal experiments.

PROCEDURE

All estimations were performed in the morning. The patients received no food after their evening meal and no water after midnight. They were taken from the ward in bed or in a wheel chair. An electrocardiogram and an orthodiagram were obtained first. Then the subjects lay down for at least 45 minutes. Duplicate estimations of cardiac output and metabolism were then made, together with repeated determinations of pulse rate, blood pressure, respiratory rate and volume.

If the study concerned a rapidly acting drug, this was administered soon after the control estimations. The patient was watched until evidence of the drug's action became manifest objectively. Duplicate estimations of cardiac output and metabolism were then made, the purpose being to make these determinations at the height of action. Orthodiagrams and electrocardiograms were secured immediately afterward.

Cardiac output was estimated by the method of Starr and Gamble (1), the analyses being performed by the katharometer method of Donal, Gamble and Shaw (2). Metabolism was estimated from samples of expired air drawn from a mixing bottle containing a fan.

Respiratory volume was obtained by reading the spirometer at frequent intervals. Respiratory rate was counted repeatedly during the period of observations. It is well known that subjects breathing from a spirometer under 3 mm. H_2O negative pressure, and through valves, tend to breathe somewhat deeper and more slowly than under normal conditions.

The left ventricular work was calculated as described before (3). The peripheral resistance was calculated from the formula used by Bazett et al. (4).

The volume of the heart was estimated from Kahlstorf's formula (5).

The analyses concerned with estimating cardiac output were performed by Donal, those concerned with metabolism by Joseph, Donal or Eagle. The orthodiagrams were made by Margolies. Starr selected the patients from the wards and decided on the drug and dosage suitable for them. Gamble or Starr administered the drugs and, with Joseph, made clinical observations. The statistical analysis was carried out by Starr and Joseph with the assistance of Dr. H. A. Schroeder.

We are indebted to Dr. L. H. Collins for clinical help in the spring of 1934, to many of the staff and interns of the University Hospital for assistance in securing patients and in adopting the therapy employed to assist this study, and especially to our many patients who so willingly cooperated.

Conclusions from results obtained by cardiac output methods

Before the results can be discussed with profit certain conceptions fundamental to our viewpoint must be set forth. The first concerns our method of drawing conclusions from our results. A second group has to do with basic conceptions of cardiac physiology in relation to which our results will be presented. Our approach to this problem differs from that of certain other workers in this field and this difference must be discussed in detail.

Grollman (6) describes his method as accurate to 10 per cent, i.e. changes of less than this amount might be accounted for by errors inherent in technique and analysis. This conception is supported chiefly by a long series of estimations made on a normal subject who gave results varying within this limit. That changes of less than 10 per cent are not significant is thus rendered probable, but one should not conclude that all changes greater than 10 per cent are significant. To give a patient a drug and to attribute to its action any change of cardiac output of over 10 per cent would be highly hazardous. Duplicate estimations of cardiac output by the acetylene method differ by far more than 10 per cent in many patients. Our method shows similar variations. Standards derived from the best subjects under ideal conditions cannot be used with safety to estimate the significance of differences in clinical work. It is not sufficient to estimate variability due to errors inherent in the method. There is a large variability inherent in subjects, who may change their cardiac outputs due to apprehension and excitement, or induce irregular errors due to poor cooperation. Unless this type of error is considered the conclusions drawn may be highly erroneous.

We have, therefore, employed statistical procedures to estimate the significance of our differences. The method is not a perfect one for our purpose, but it provides the best criterion for the significance of quantitative data. A detailed discussion of the means employed follows.

In order to estimate the significance of average results obtained on a number of patients given a single drug we have followed exactly the procedure given by Fisher (7, page 104) and made use of his Table IV, to obtain the probabilities. We have defined significance in the customary manner, i.e. a probability larger than 95 in 100 that the result obtained was not due to chance. But we wish to point out that this definition is arbitrary and probably too rigid for clinical work in which physicians constantly are being forced to make important decisions based on data whose probability of error is enormously greater than 5 in 100. Therefore when, after the administration of certain drugs, we have not demonstrated changes of sufficient magnitude and constancy to merit the term significant, we do not imply that these smaller changes should be neglected. They often represent a better picture of the drug's action in clinical conditions than was available before, although not as perfect as one would like. When data become more ample the significance of the smaller changes may be established.

Since no two patients are identical, the question might be raised whether it was proper to draw conclusions from an average of the results obtained. The answer is that we are doing the best we can with the data at our disposal. In the future when series of more similar conditions and dosages are available, more accurate conclusions can be drawn concerning the action of drugs under special circumstances.

Something must be said concerning our ideas of the conclusions which should be drawn from the results obtained from one or two estimations of cardiac output, made on one patient before and after the administration of a drug or other agent. The discussion which follows probably applies to results obtained by Grollman's acetylene method also, for the variation of duplicate estimations found by Nylin (8) on patients by this method agrees closely with that we obtain on patients by our method.

Single estimations, before and after the administration of a drug, give one no knowledge of the spontaneous variability inherent in method and subject, and this makes accurate conclusions im-

possible unless other data on variability are available.

Duplicate estimations, before and after, provide one with a very imperfect measure of the inherent variability, and the data can be handled statistically. They may be considered as two experiments and handled, as we have handled the larger series, according to Fisher (7, Section 24). A very steady subject will have to be used or a very large change found before significance can be attained.

However, long experience with a method permits one to set up other criteria. We have proceeded as follows. A sample was taken consisting of the last 65 pairs of duplicate estimations made on patients in this investigation. The standard deviation computed from the deviation of each of the duplicates about the mean of each pair was found to be 5.6 per cent.

An example will make our procedure clear. Below we calculate a testing standard deviation from two pairs of duplicates in the same manner as was employed for the 65 pairs.

Patients	Duplicate cardiac outputs	Mean of duplicates	Deviation from mean	Deviation from mean of deviations squared
	liters per minute		*per cent*	
A	3.0, 3.2	3.1	+3.2 −3.2	10.2 10.2
B	4.0, 4.6	4.3	+7.0 −7.0	49.0 49.0
		mean of deviations = 0		Σ118.4

$$\sigma = \sqrt{\frac{118.4}{4}} = 5.4 \text{ per cent}$$

If one has duplicate estimations before and after the condition inducing change: standard deviation of difference between the means $= \sqrt{\frac{\sigma^2}{2} + \frac{\sigma^2}{2}}$.

If one has only one observation before and after: standard deviation of difference between individual estimates $= \sqrt{\frac{\sigma^2}{1} + \frac{\sigma^2}{1}}$.

Estimates of the probabilities for any difference may be obtained from Fisher's Table (7, p. 139). In actual practice it is more convenient to think in terms of differences between the results of two estimates, expressed in percentage of their mean, than in the deviations from their means. The first is, of course, twice the second. In the text the conclusions have been expressed in terms of differences.

At the suggestion of Dr. J. H. Austin this standard deviation, 5.6 per cent, was checked by an estimation from the median divided by 0.955,

a figure derived from Pearson (9), which gave an identical value. We propose to use this figure, 5.6 per cent, as a testing standard deviation, a measure of the variability to be expected in the method applied to an average subject.

Employing this figure we find that when we have made one estimation before and one after the agent inducing change, differences between the results of 32, 30, 25, 20 and 10 per cent of their mean have probabilities of 95, 94, 88, 60 and 45 to 100 that they are not due to chance. Differences of over 32 per cent are significant.

If one has results of duplicate estimations before and after the agent studied, differences between the means of each pair of 22.4, 20, 15, 10 and 5 per cent have probabilities of 95, 92, 82, 63 and 45 to 100 that they are not due to chance. In this case differences of over 23 per cent are significant.

Obviously, when estimations are made on the same patient under the same conditions but on different days, the inherent variation is likely to be larger than in duplicate estimations on the same day. In order to make a basis for interpretation of prolonged experiments with drugs we have estimated the variability of the average of duplicate determinations obtained on one day with the same value found on a subsequent day. Discarding the trained subjects and also those patients whose clinical conditions had changed materially between the observations, the needed data were available on 18 patients, and the standard deviation was 7.7 per cent. Therefore, if the difference between the means of duplicate estimations was 30, 20 or 10 per cent the probabilities would be 92, 75, and 44 in 100 that the difference was not due to chance. Differences of over 35 per cent are significant.

This use of a testing standard deviation has disadvantages which should be obvious; for example, some subjects, as cases of hyperthyroidism, are notoriously unstable, undergoing far larger fluctuations in cardiac output than the average subject. To use our testing standard deviation in such a case would be hazardous. Excessive divergence of duplicate estimates would aid in identifying some such cases but there is no way to protect oneself against the occasional error. We are chiefly concerned with recording the exact method by which we draw conclusions

from our data. Then, if improvement in this method occurs to us or to others, correction of our conclusions will be easy. For this reason we have not increased our testing standard deviation by adding multiples of its standard error as is the practice of some statisticians in somewhat similar situations.

Cardiac stimulation and depression

In recent years drugs have been classified as cardiac stimulants or depressants when they increased or diminished contractility of cardiac muscle, as measured by levers attached in animal experiments. Soon after techniques for measurement of cardiac output were available, it became evident that the administration of these drugs was not always followed by a change in cardiac output in the direction which their action on preparations of cardiac muscle had led one to expect. In our opinion, results obtained by the two types of experiments can be reconciled if certain well known facts of circulatory physiology are kept in mind.

Most drugs which affect the heart act elsewhere on the circulation also and changes in the latter may cause secondary changes in cardiac behavior. Before a drug can be spoken of as stimulant or depressant to cardiac function the nature of the secondary changes must be carefully considered.

It seems obvious that the cardiac output is not dependent on the heart alone and that it should not be used as a test of cardiac capacity (10). The normal behavior of the heart, when its inflow and the resistance against which it works are changed, has been described by Starling (11) as follows: the work per beat of the normal heart is related to its size. This " Law of the Heart " also holds for clinical conditions, as closely as the relation between basal metabolic rate and body surface, and more closely than any similar relationship studied (12). From it has been derived a satisfactory definition of cardiac stimulation and depression. A heart is stimulated when its work per beat, in proportion to its diastolic size, increases. It is depressed when the reverse occurs (13). When one applies this definition to the drugs that we have studied the supposed dis-

crepancies between the results obtained on man and in animal experiments largely disappear.

Therefore, we have estimated cardiac stimulation and depression by plotting our results in diagrams (Figures 1 and 2) showing the normal relationship between left ventricular work per beat and heart volume, derived from formula 2, Table V, of a previous paper (12). If the values are changed by the administration of drugs so that the point representing them moves upward or to the left we conclude that stimulation has occurred, for the heart's work in proportion to its size has increased. Movement to the right or down indicates cardiac depression. Movement parallel to the line AB defines neither stimulation nor depression but represents the response a normal heart would make to changes elsewhere in the circulation, such as diminished venous return, increased arterial pressure, etc.

Difficulties in the clinical study of cardiac work are obvious. Only the work of the left ventricle can be estimated. There is some evidence from animal experiments that the work of the right ventricle is proportional to that of the left, but this could not be expected to hold in certain clinical conditions. Fortunately, the right ventricle's work is only a fraction of that of the left so that large percentage changes in right ventricular work would make but a small percentage change in the total cardiac work. There being no known method of estimating in the clinic the blood pressure in the pulmonary artery we have ignored the work contributed by the right ventricle in our calculations, although we are fully conscious of the errors which may be involved in certain instances such as mitral stenosis.

Bay (15) has suggested an ingenious method for estimating the amount regurgitated in aortic insufficiency. This gives accurate results on his schema, but it is not intended for use in the clinic. However, he has recalculated the left ventricle's work in three of our published cases and concludes that our estimate is far too small. Bay points out that, before his formula would yield an accurate result, the following conditions would have to obtain: (1) the usual blood flow to the tissues must be maintained, (2) the peripheral resistance must be unaltered, (3) elasticity must be normal. But there is evidence that peripheral resistance is reduced in aortic regurgitation (16),
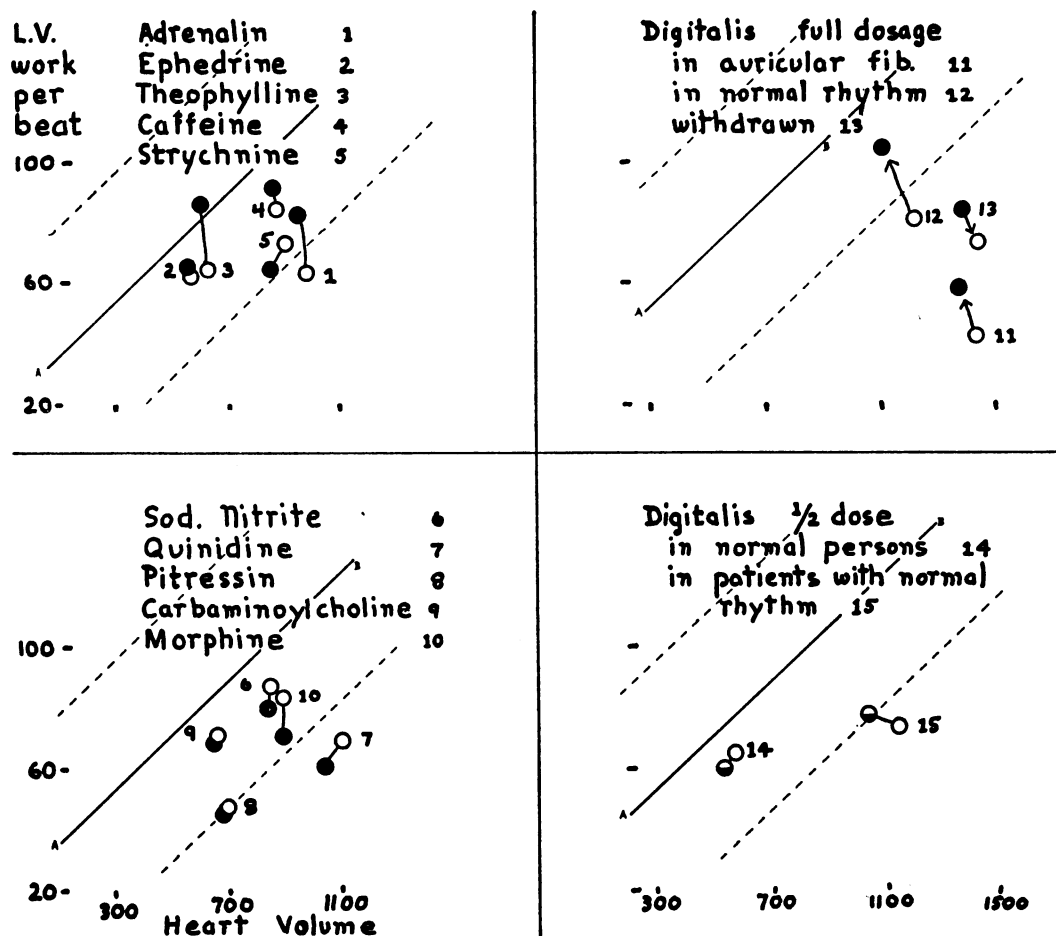
FIG. 1. EVIDENCE OF CARDIAC STIMULATION OR DEPRESSION BY DRUG ACTION—AVERAGE RESULTS

The solid lines AB are the calculated best line for persons without heart disease. The outlying dotted lines have been placed at twice the standard deviation from AB and define the normal zone, as in Figure 3 (12). According to our definition movement of points at right angles to AB, upwards and to the left, indicates cardiac stimulation, the reverse movement depression. The circles indicate the position of average values before drug administration, the solid dots are average values on the same patients during drug action.

Ordinates in grammeters per beat. Abscissae in cm^3. The graphs are not absolutely identical with Figures 3, 4 and 5 (12) because a different method of calculating heart volume was used.

that distensibility decreases with age and in disease (17), and that normal blood flow is not always maintained (12). We also question the assumption that blood flow varies as the square root of the pressure applied, a condition well known to occur in hydraulics, and which doubtless holds for Bay's schema, but apparently not for the circulation (18). The expected deviation of most of these items from the basic assumptions of the formula would make the actual aortic leak far smaller than that calculated by Bay. The difficulties involved can be illustrated by pointing out

that the formula as it stands will calculate the amount of " aortic leak " when applied to data from any case with a large pulse pressure, quite irrespective of evidence of the presence of aortic regurgitation. For these reasons we have not changed our method of calculating work in the cases of aortic regurgitation in this series. We gladly admit, as Bay points out, that each result is too small by the amount of the leak and welcome Bay's study as the first attempt to improve the estimation. Complete data have always been given in our tables to permit any one interested
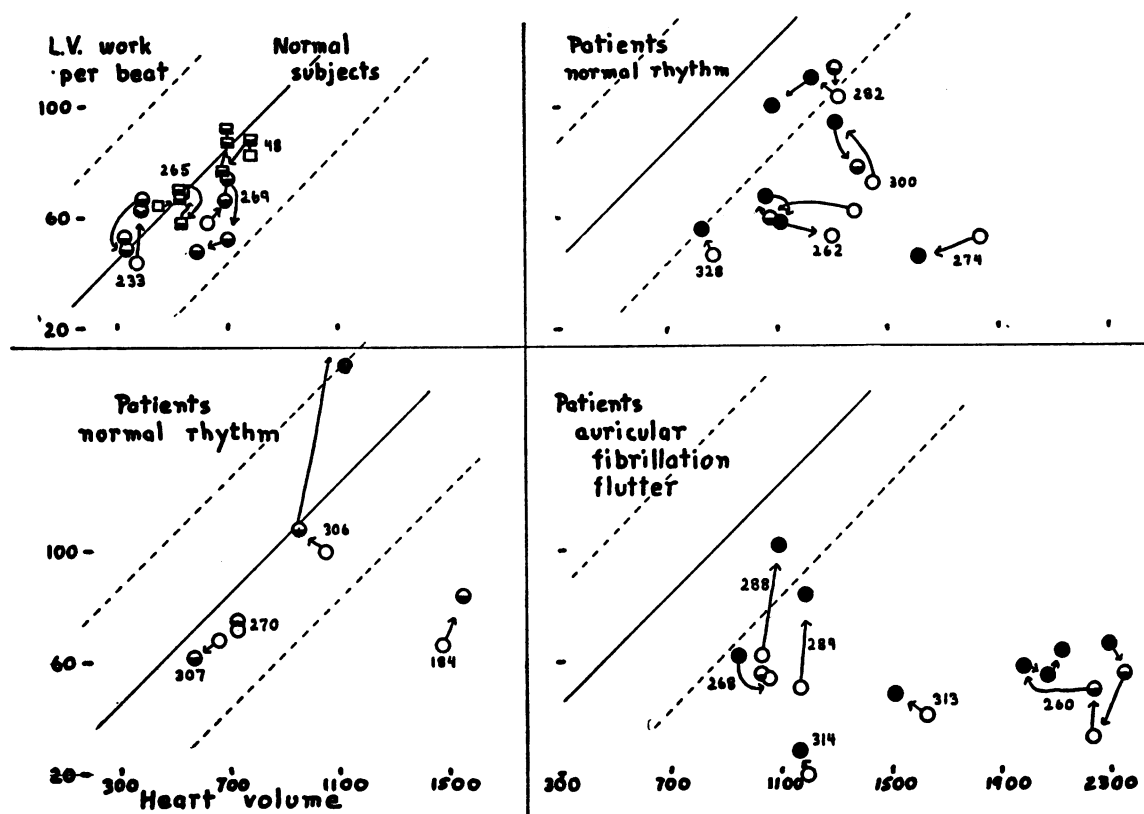
FIG. 2. EVIDENCE OF CARDIAC STIMULATION BY DIGITALIS. RESULTS IN INDIVIDUAL CASES

Coordinates and lines as in Figure 1. Empty symbols indicate values in cases who had received no digitalis for 2 weeks or longer. Dots indicate values obtained during full digitalis action. Symbols half filled indicate the intermediate state, e.g. values obtained after half doses of digitalis, or in patients, previously exhibiting full action, who received no digitalis for one week. Case numbers correspond to data in Table III.

to recalculate the work according to newer and better methods as they become available. Being concerned with changes, the absolute values are of minor importance in this study.

RESULTS

The diagnoses, dosages, and other clinical data, together with the results on each case, have been assembled in Tables II and III at the end of the paper. The figures given for metabolic rate are averages of duplicate estimations, those for pulse rate, respiration, and blood pressure are averages of more numerous results.

The results of the statistical analyses have been summarized in Table I also at the end of the paper. The probabilities are given as the next higher figure in Fisher's table, e.g.; 0.209 is recorded as 0.3 etc.

In Figure 3 the results have been presented in a graphic form which has been found useful for teaching medical students.

Digitalis

Every patient given this drug had severe cardiac disease; some had recently recovered from congestive failure, others were considered threatened with it, but none had constant râles at the lung bases or the other classic signs of this condition when our tests were made.

As several days must elapse before the effects of digitalis can be secured in the clinic, and about two weeks pass before such effects disappear after discontinuing the drug, the investigator is faced with the problem whether changes detected are due to action of the drug, or to changes in the patient's condition, either spontaneous or induced
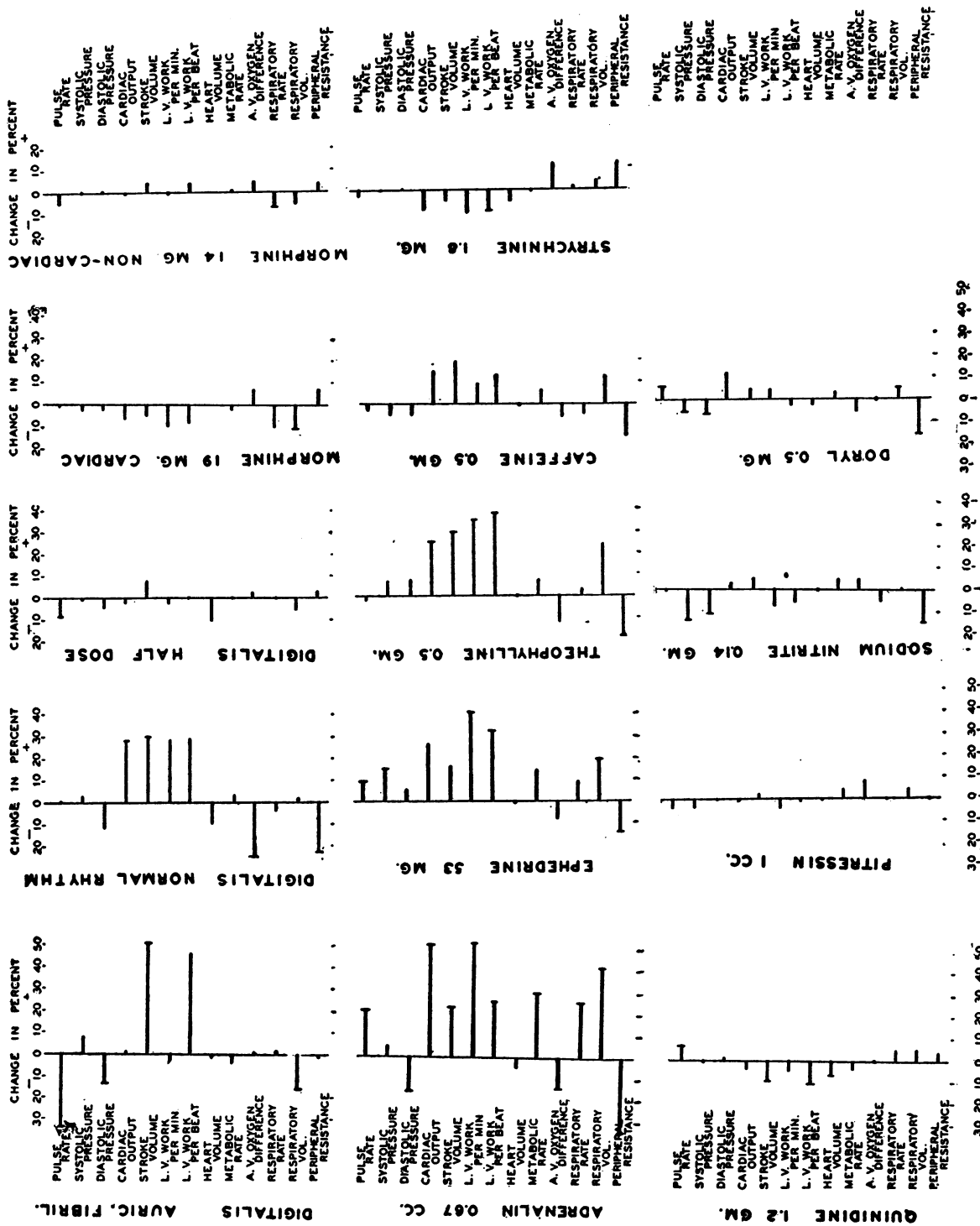
FIG. 3. GRAPHIC PRESENTATION OF THE AVERAGE RESULTS TO PERMIT EASY COMPARISON BETWEEN THE ACTIONS OF THE DRUGS STUDIED
A cross bar at the end of any main bar indicates that the change is statistically significant.

by rest, diet, and routine hospital care, factors quite sufficient to bring about improvement in most cardiac cases admitted to the wards. Therefore, we have attempted to safeguard our conclusions by two methods: (1) We have studied not only the effect of giving digitalis but also the effect of withdrawing it, when this maneuver did not conflict with the patient's well being. (2) We have questioned any change of cardiac output as evidence of digitalis action when it could be explained by a corresponding change of basal metabolic rate.

All the results are set forth in Table II. The well known digitalis effects on the electrocardiogram were seen in our cases and are indicated in Table II for comparison with the other data.

The results must be divided into three main groups, viz: those obtained on normal persons, in patients with auricular fibrillation, and in patients with cardiac disease with normal rhythm.

Digitalis action in normal persons

The four young or middle aged adults were given one-half the " therapeutic dose " of U. S. P. Tr. digitalis (0.075 cc. per pound of body weight). They came to the laboratory without breakfast and rested in bed over an hour before the first group of estimations were made. Next day they took the drug by mouth at 8:00 a.m. and the procedure of the first day was repeated. Then they ate a light carbohydrate meal and a similar group of tests was made about 10 hours after the administration of the drugs. They returned to the laboratory fasting next morning, and on later mornings for the same studies. No subject had any very definite symptoms although one experienced malaise which might have been attributed to the drug.

The results show a consistent and significant increase in cardiac output 6 hours after the administration of the drug. Later the results were more irregular, and the averages did not show a significant change at any one time. In each subject, however, the increase was followed by a period in which both heart size and cardiac output were a little smaller than before the drug.

The reduced cardiac output following the administration of digitalis to normal subjects has been found by all who studied the subject and

has had much emphasis (19, 20). The temporary increase we find has been reported before (21), but, not being found consistently, it has had little emphasis.

Action of digitalis in heart disease with auricular fibrillation or flutter

We have had opportunity to study five such cases. The results are given in Table II.

In judging the effects of digitalis we have depended more on the well known clinical evidence than on the dosage given the patient.

Two of the cases were " fully digitalized " when first tested. Digitalis was withdrawn for two weeks and then given until effect on pulse rate was manifest. Two cases received it for the first time in our experiments.

In two instances the experiments were not entirely as we wished. Case 313 had received 0.18 gram of digitalis daily for 5 days before the first test; but he showed no evidence of action at that time and so has been regarded as not under the influence of the drug. Two weeks later, after receiving a much larger amount he became " fully digitalized." Case 268 with hyperthyroidism, after receiving no digitalis for 2 weeks, showed a marked drop in pulse rate after about half the dose usually required for such an effect. The simultaneous diminution in basal metabolic rate may explain the difference in cardiac rate and output, and conclusions concerning digitalis action cannot be drawn with safety. We have compiled statistics both including and excluding these two cases.

Averages compiled from observations made when the demonstrated effect on cardiac output was maximal, Figure 3 and Tables I and II, show that the significant effects of the drug in auricular fibrillation are the diminution of pulse rate, diastolic pressure, and volume of respiration, and the increase of stroke volume. The increase in work per beat escaped significance by the narrowest of margins. The cardiac output per minute was usually but little changed. One patient (Case 260), the sickest of the group, had such a large percentile increase that it balanced the effect of the remainder. Due to a rise of average systolic pressure the average pulse pressure was increased, the mean pressure changed but little.

The exclusion of the two doubtful cases mentioned before does not change the conclusions materially. The average changes in pulse rate and work per beat are still significant. Those of work per beat, stroke volume and respiratory volume are as large as in the whole group but just miss significance because of the reduced number of cases.

Unlike the cases with normal rhythm, the average heart volume did not diminish in patients with auricular fibrillation. This apparent discrepancy may well be due to the marked slowing of heart rate in the latter group which, by allowing more time for filling during diastole, would increase the observed diastolic volume and mask the effect of the drug.

The effects of withdrawing digitalis were studied in Cases 260 and 268. The preceding effects of digitalis on pulse rate and respiratory volume were reversed in both cases. The cardiac output fell significantly in Case 260, it was changed but little in Case 268. Changes in heart volume were not noteworthy in either case.

The one case (Case 289) of auricular flutter available showed a significant increase of cardiac output after digitalis, a slight slowing of the pulse rate (Table II), and the results gave evidence of cardiac stimulation after the drug (Figure 2).

Digitalis in heart disease with normal rhythm

Eight cases fall into this group. In 6 we attempted to ascertain the effect of full doses of digitalis. In the absence of effect on pulse rate we counted chiefly on the electrocardiogram to tell us when the drug was acting. Difficulties were encountered in two cases. Case 274, probably with hyperthyroidism, had an elevated metabolic rate during the preliminary estimations; it was progressively much lower at the later tests so this result has been omitted from the statistics. Case 306, a young colored man accustomed to hard physical labor in spite of advanced rheumatic heart disease, had developed auricular fibrillation together with severe symptoms which brought him to the hospital. The arrhythmia ceased spontaneously and was replaced by persistent bradycardia. Recovery took place with unusual rapidity, beginning before full digitalis action was

expected and continuing during six days when the drug was withdrawn. We suspected, therefore, that other factors than digitalis were at work. But finding no fault with the experiment except the unusual extent and rapidity of improvement under the drug, we have included it in the statistics.

The averages of results in the five best cases (Figure 3) show that the effect of full doses was to cause significant increase of cardiac output and stroke volume, and a significant decrease of A–V oxygen difference and peripheral resistance. The heart volume was diminished markedly in 3 cases and unchanged in 2. The average pulse rate was unchanged.

Attempts were made to test the effects of withdrawing digitalis in 5 cases. In Case 262, tested 12 days after withdrawal of the drug, the previous effects of its action were reversed. In Case 282, 13 days after withdrawal, the cardiac output was slightly smaller but there was little change in the other functions. Seven days after withdrawal, Case 300 showed a slight decrease in cardiac output also. However, in Case 274 the cardiac output increased in spite of withdrawal of the drug for 12 days; doubtless this may be attributed to the general clinical improvement taking place simultaneously.

In 4 cases, all with normal rhythm, tests were made to determine whether small doses had any effect. Cases 262, 306 and 307 were given 0.0075 gram per pound, half the dose calculated to produce full effects; Case 270 was given a still smaller dose. The average reduction in pulse rate was small but significant. Changes in cardiac output were always small, it diminished in 3 cases and was unchanged in one. In Case 270 this fall is coincident with a fall in basal metabolic rate and may not be due to the drug. The heart volume diminished in 3 of the 4 cases but the average change is not significant (Figure 3, Tables I and II).

These " small " doses of digitalis appeared to exert slight effects on pulse rate, heart size, and on the electrocardiogram of these patients. The normal subjects taking a similar dose showed the two latter effects but there was no noteworthy effect on their pulse rates.

The average pulse rate was more slowed by " half " doses than by " full " doses of digitalis.

TABLE I

Statistics on the effect of drugs on heart, circulation, respiration and metabolic rate *

Drug and remarks	Number of cases	Average dose	Pulse rate	Blood pressure Systolic	Blood pressure Diastolic	Cardiac output	Stroke volume	Left ventricular work per minute	Left ventricular work per beat	Heart volume	Metabolic rate	Arterio-venous O₂ difference	Respiration Rate	Respiration Volume	Peripheral resistance
Digitalis (in auricular fibrillation).............	5	Full	−33.0 / 0.01	+ 7.6 / 0.2	−12.2 / 0.05	+ 1.3 / 1.0	+50.5 / 0.05	− 4.1 / 0.8	+45.0 / 0.1	−1.7 / 0.5	− 3.5 / 0.7	+ 0.7 / 1.0	+ 1.8 / 0.8	−15.9 / 0.01	− 1.3 / 1.0
Same, 3 best cases..........	3	Full	−37.1 / 0.05	+15.2 / 0.2	−16.5 / 0.2	+10.3 / 0.8	+69.2 / 0.1	+ 6.9 / 0.8	+68.6 / 0.05	−0.4 / 1.0	+ 4.9 / 0.7	+ 4.0 / 0.9	+ 2.9 / 0.8	−14.1 / 0.2	− 3.3 / 0.9
Digitalis (in normal rhythm)..	5	Full .	+ 0.2 / 1.0	+ 2.8 / 0.8	−10.1 / 0.4	+28.2 / 0.01	+30.0 / 0.05	+27.9 / 0.2	+28.1 / 0.1	−8.0 / 0.2	+ 0.3 / 1.0	−20.5 / 0.01	− 3.3 / 0.4	+ 2.1 / 0.9	−22.9 / 0.01
Digitalis (in normal rhythm)..	4	One-half	− 7.9 / 0.02	− 1.0 / 0.9	− 4.3 / 0.4	− 2.2 / 0.7	+ 7.0 / 0.5	− 4.1 / 0.6	+ 1.3 / 0.8	−9.5 / 0.3	+ 0.9 / 0.9	+ 2.4 / 0.7	− 0.1 / 1.0	− 4.8 / 0.5	+ 2.7 / 0.8
Epinephrine.................	6	0.7 mgm.	+21.0 / 0.02	+ 4.8 / 0.3	−14.5 / 0.01	+51.7 / 0.01	+22.7 / 0.02	+52.4 / 0.01	+26.2 / 0.05	−4.0 / 0.2	+30.4 / 0.01	−13.3 / 0.05	+26.0 / 0.05	+42.0 / 0.01	−35.1 / 0.01
Ephedrine..................	6	53 mgm.	+ 9.7 / 0.02	+14.8 / 0.02	+ 5.2 / 0.2	+27.0 / 0.5	+15.7 / 0.2	+41.2 / 0.02	+32.7 / 0.05	−1.0 / 0.8	+14.2 / 0.1	− 8.6 / 0.1	+ 9.2 / 0.3	+19.4 / 0.02	−12.9 / 0.01
Caffeine...................	4	0.5 gram	− 2.4 / 0.6	− 4.0 / 0.1	− 3.8 / 0.4	+14.8 / 0.3	+19.1 / 0.4	+ 9.3 / 0.5	+13.8 / 0.4	−0.8 / 0.6	+ 6.9 / 0.7	− 6.1 / 0.4	− 4.1 / 0.4	+12.6 / 0.6	−14.3 / 0.3
Theophylline..............	7	0.48 gram	− 1.7 / 0.6	+ 6.8 / 0.2	+ 7.0 / 0.1	+25.8 / 0.01	+29.4 / 0.01	+35.4 / 0.01	+38.0 / 0.01	−0.3 / 0.9	+ 7.8 / 0.2	−12.4 / 0.1	+ 2.7 / 0.7	+23.8 / 0.2	−18.9 / 0.05
Carbaminoylcholine..........	6	0.5 mgm.	+ 7.6 / 0.01	− 6.5 / 0.02	− 7.2 / 0.02	+12.3 / 0.1	+ 3.7 / 0.6	+ 4.9 / 0.5	− 2.6 / 0.7	−2.0 / 0.5	+ 3.5 / 0.4	− 5.5 / 0.6	− 0.2 / 1.0	+ 5.6 / 0.01	−16.6 / 0.01
Sodium nitrite..............	7	0.13 gram	− 0.8 / 1.0	−13.8 / 0.01	−11.5 / 0.01	+ 3.4 / 0.8	+ 5.0 / 0.7	− 8.5 / 0.3	− 6.3 / 0.4	−0.1 / 1.0	+ 5.0 / 0.1	+ 4.9 / 0.6	− 4.6 / 0.3	+ 1.0 / 0.8	−15.4 / 0.05
Pitressin..................	7	20 units	− 3.7 / 0.1	− 3.6 / 0.2	− 0.2 / 1.0	− 1.8 / 0.9	+ 2.0 / 0.8	− 4.5 / 0.6	− 1.9 / 0.9	−1.4 / 0.6	+ 3.3 / 0.5	+ 8.7 / 0.3	− 0.5 / 1.0	+ 3.9 / 0.6	− 1.2 / 1.0
Quinidine.................	8	1.2 grams	+ 7.7 / 0.05	− 1.4 / 0.6	+ 1.2 / 0.7	− 3.6 / 0.5	− 9.5 / 0.05	− 4.3 / 0.5	−10.9 / 0.05	−6.7 / 0.05	− 3.3 / 0.3	+ 0.1 / 1.0	+ 5.7 / 0.4	+ 5.8 / 0.2	+ 3.7 / 0.6
Morphine (cardiacs)..........	8	19 mgm.	− 1.7 / 0.6	− 2.7 / 0.4	− 2.5 / 0.1	− 7.3 / 0.2	− 5.3 / 0.4	− 9.7 / 0.1	− 8.0 / 0.3	—	− 2.3 / 0.5	+ 7.5 / 0.4	−10.0 / 0.1	−10.4 / 0.01	+ 7.0 / 0.2
Morphine (non-cardiacs)......	8	14 mgm.	− 4.9 / 0.1	− 0.1 / 1.0	+ 1.0 / 0.8	− 1.1 / 0.9	+ 4.0 / 0.6	− 0.7 / 1.0	+ 4.3 / 0.6	—	+ 0.4 / 1	+ 4.0 / 0.7	− 7.7 / 0.05	− 6.4 / 0.2	+ 3.6 / 0.8
Strychnine.................	7	1.8 mgm.	− 2.6 / 0.4	− 0.2 / 1.0	+ 0.6 / 0.2	− 9.0 / 0.1	− 5.0 / 0.3	−10.8 / 0.1	− 9.7 / 0.05	−6.3 / 0.2	− 1.6 / 0.8	+11.5 / 0.1	+ 1.8 / 0.8	+ 3.8 / 0.7	+11.9 / 0.1

* Mean percentage changes induced by drug action in Roman type
Probabilities of significance of the means, for P = 1, in italics

In two cases, first given "half," then "full" dosage, the pulse rate first diminished and then returned to its previous level. It is interesting to recall that repeated doses of digitalis, given in acute animal experiments, often cause a primary slowing followed by an increase of heart rate (22).

Effect of atropine on cases receiving digitalis

In two cardiac cases, Numbers 288 and 306, we estimated the effects of a subcutaneous dose of atropine on patients having an abnormally slow heart rate under digitalis. Case 288, with auricular fibrillation, was given 0.6 mgm. atropine. The pulse rate increased 19 per cent, the heart size diminished slightly and the metabolic rate increased a little. The cardiac output was unchanged (Table II).

Case 306 in normal rhythm received 1.2 mgm. of atropine. A marked increase of pulse rate followed but the cardiac output diminished significantly. Pulse pressure diminished in both cases leaving mean blood pressure essentially unchanged.

Obviously the striking effect of atropine is on the pulse rate, the other changes were not constant.

The effect of coupled beats

Purely by accident, we obtained, after Case 260 had received a large dose of digitalis, one set of estimations while coupled beats had supplanted normal rhythm. A few minutes later normal rhythm returned and a similar set of observations was secured. Our confidence in the validity of the differences in cardiac output found is en-

hanced by the fact that we always obtained excellent agreement of duplicate estimations in this patient.

During the period of coupling, the pulse rate was but little faster than in the following normal rhythm but the cardiac output was diminished markedly, the metabolic rate was diminished, and the respiratory rate increased. The change in cardiac output during the coupling was of the magnitude which would be present if the normal beats delivered the same amount as before but the extrasystoles contributed almost nothing to the circulation. Apparently this common complication of digitalis action may cause a profound depression of the circulation. It is of interest that the patient insisted he felt as well during the coupling as before or afterward.

Discussion of digitalis action

That digitalis benefits patients with certain types of heart disease has been known since Withering. The clinical work on this subject has been reviewed recently (24, 25). The mechanism underlying this improvement has been debated (26). Most conspicuous in patients with decompensated fibrillating hearts, the improvement was attributed by Mackenzie to the change in rate of beating. Clinicians have usually believed that the improvement secured in patients with exhausted hearts, beating with regular rhythm, resulted from an increased contraction, and a larger output (24). This belief was supported by the results of Cushny's experiments on mammalian hearts with the cardiometer and the myocardiograph (22).

The discovery that digitalis decreased the output of the heart of normal dogs (20, 26) was therefore unexpected, as was the opinion that digitalis should be regarded as a cardiac sedative (26). Reduction of cardiac output after digitalis was found in normal men by Burwell, Neighbors and Regen (19) and by Stewart and Cohn (20). We find it also.

Studies upon the effect of these drugs on the output of decompensated hearts have been less concordant. Ringer and Altschule (27) and Lauter and Baumann (28) found an increase in output in weakened hearts, while Kininmonth (29) found increases in some subjects and de-

creases in others. Little confidence can be placed in these observations, however, for they were made with methods based on erroneous assumptions. Eppinger, von Papp, and Schwarz (30) and Schwarz and Schimmer (31) using an oxygen method of doubtful accuracy found a decrease of output in cardiac patients with digitalis, while Ewig and Hinsberg (32) with a carbon dioxide method found no change. In contrast, however, Grassmann and Herzog (33) using the acetylene method of Grollman (6) found an increase in most cases when given digitalis. This finding was supported by acute experiments with intravenous injections of strophanthin, in which the cardiac output was deduced by the pulse-wave-velocity and blood pressure method of Broemser and Ranke (34).

Stewart and Cohn (20), employing Grollman's method, with which they had found a decrease in normal cases, discovered an increased output associated with digitalis in patients with signs of heart failure but without pulmonary congestion. They suggested that the drug increased the extent of the contraction in both conditions, and that the accompanying decrease in heart size, which led to a lower output from a normal heart, resulted in a larger output from one which had been dilated initially.

Using a slight modification of the same method, Friedman, Clark, Resnik and Harrison (35) found no such consistent increase in minute volume in decompensated subjects. Administration of digitalis gave an increase in some cases, but no change or a decrease in others. The direction of the change could not be correlated with the presence or absence of clinical improvement. They attributed the divergent results of Stewart and Cohn to the failure of these investigators to secure adequate mixing of the respiratory gases, and considered that in their own work this had been avoided by a slight prolongation of the rebreathing time. If this is the explanation, we are left with the impression that slight differences in technique make such great differences in result that our confidence in the accuracy attained is diminished. The difficulties inherent in the application of the gas methods for estimating cardiac output in patients with varying amounts of pulmonary congestion are obvious. But we ac-

TABLE II *

Original data and diagnoses of individual cases receiving digitalis

Case number	Sex	Age (years)	Height (inches)	Weight (pounds)	Date	Digitalis before and between observations (grams or cc.)	Cardiac output (duplicate determinations) (liters per minute)		Pulse rate (per minute)	Average blood pressure (mm. Hg)	Average O₂ consumption (cc. per minute)	Respiration Rate (per minute)	Respiration Volume (liters per minute)	Heart volume (cc.)	Clinical evidence of drug action	Notes on the form of the electrocardiogram P.R. (seconds)	Notes on the form of the electrocardiogram T waves, etc.	Diagnosis and remarks
											DIGITALIS—NORMAL PERSONS							
48	M.	40	67	153	Oct. 15, 1934	None	3.8	3.6	55	105-74	231	9	5.1	776	None		Normal	Normal
					16	11.5 cc.	4.6	4.1	59	102-74	245	11	5.2	776	None			
					16	No more	3.4	2.9	53	105-79	232	11	5.3	682	None			
					17	No more	4.1	3.3	55	108-75	227	10	4.9	697	None			
					19	No more	3.8	3.9	53	108-82	230	9	5.4		None			
233	F.	47	62	114	Dec. 3, 1934	None	2.7	2.9	59	99-69	154	11	3.2	366	None		Normal T1 isoelectric, T2 up 0.5 mm	Normal
					5	8.5 cc.	3.2	3.3	61	105-71	149	12	3.1	385	None			
					5	No more	3.5	3.5	65	108-74	182	13	3.5		None			
					6	No more	2.3	2.7	57	101-72	153	8	3.6	330	None		T1 diphasic, T2 inverted 3 mm	
					7	No more	2.7	2.5	60	106-65	158	11	3.8		None			
265	M.	26	65	144	Nov. 26, 1934	None	3.1	3.5	64	111-76	191	12	4.8	451	None		Normal Unchanged	Norma
					27	11.0 cc.	3.8	3.4	74	117-86	222	11	5.0	527	None			
					27	No more	4.0	3.1	70	114-84	231	13	5.5		None			
					28	No more	3.1	3.3	71	116-70	211	14	5.3	536	None			
					30	No more	3.0	2.9	65	111-81	196	14	4.5		None			
269	M.	30	68	169	Dec. 10, 1934	None	3.0	3.4	63	108-81	280	9	5.5	629	None		Normal T2 up 2 mm T2 isoelectric	Normal
					11	12.7 cc.	3.5	3.1	59	108-65	283	12	5.6	688	None			
					11	No more	4.3	4.1	67	116-68	263	11	5.6		None			
					12	No more	2.7	2.9	63	115-57	253	12	5.3		None			
					14	No more	2.6	2.4	60	107-62	290	13	6.5	585	None		T2 isoelectric	
											DIGITALIS—PATIENTS WITH AURICULAR FIBRILLATION							
280	M.	27	69	165	Oct. 5, 1934	Full	2.8	3.1	66	141-87	277	21	6.8	2290	Yes		T2 slight diphasic	Rheumatic heart disease, mitral stenosis, formerly decompensation, Class III
					12	No more	2.4	2.6	79	132-87	250	30	9.5	2344	Yes		No change	
					22	No more	1.6	1.9	72	124-98	237	28	9.1	2230	Slight		No change	At 5 p.m. after carbohydrate lunch Nauseated later in day
					22	1.1 grams	2.6	2.4	72	140-71	253	29	9.7		Yes			
					23	0.5 gram	1.9	1.9	49	142-80	220	?	9.3	1990	Yes		T1 deepened	
					25	No more	1.9	1.9	51	144-64	223	31	10.4	2070	Yes			
					29	No more		1.9	58	140-64	257	16	7.7	2107	Yes			
					Nov. 2	No more		2.8	58	132-60	227	28	7.1		Yes			
					Nov. 2, 1934	No more		2.8	50	130-70	261	20	7.3	1996	Yes		No change	
288	M.	50	61	124	Nov. 30, 1934	Full	3.5	3.3	91	147-71	283	25	4.5	944	Yes		T 1, 2, 3 isoelectric T2 slightly higher T2 isoelectric	Coupled beats No coupled beats Diffuse toxic goiter, Class II B
					Dec. 11, 1934	No more	3.3	3.4	87	131-78	285	18	7.3	1067	Slight			
					11	1.8 grams	2.7	2.6	66	131-99	223	19	7.0	1060	Yes			
288	M.	75	65	136	Mar. 19, 1935	None	3.2	3.4	106	176-120	237	10	7.9	1032	None		Occasional ventricular extrasystoles More ventricular extrasystoles	Arteriosclerotic heart disease decompensation 6 months ago. Class II B After 0.6 mgm. atropine
					22	1.8 grams	3.0	3.0	63	227-90	201	14	6.3	1095	Yes			
					22	No more	3.0	3.0	75	215-105	235	19	6.9	1025				
313	M.	38	69	141	Nov. 22, 1935	0.9 gram	2.8	3.0	97	127-70	293	18	8.9	1630	None		T1, 2, 3 isoelectric No change	Rheumatic heart disease, mitral stenosis, recently decompensated, Class II B
					Dec. 13, 1935	3.5 grams	2.6	3.0	68	119-70	262	17	7.0	1520	Yes			
314	M.	58	63	116	Nov. 22, 1935	None	2.0	1.6	130	100-80	178	17	7.0	1200	No		T2 isoelectric T2 inverted 2 mm	Rheumatic heart disease, mitral stenosis, formerly decompensated, Class II B
					Dec. 3, 1935	1.9 grams	1.6	1.6	69	102-75	216	18	6.5	1178	Yes			

						DIGITALIS—PATIENTS WITH AURICULAR FLUTTER												
Case	Sex	Age			Date	Digitalis				B.P.					Effect		ECG / Rhythm	Remarks
289		58	61	189	Apr. 26, 1936 May 1, 1936	None 2.6 grams	2.3 2.7	1.9 2.7	72 60	155-101 177-103	216 234	11 18	6.3 6.9	1171 1210	No Yes		2 to 1, 3 to 1 or 4 to 1 Mostly 4 to 1 flutter	Auricular flutter since 1912
DIGITALIS—PATIENTS WITH NORMAL RHYTHM. FULL DOSAGE																		
262	M.	52	67	147	Oct. 29, 1934 30 Nov. 1, 1934 5 13	None 1.1 grams 1.2 grams No more No more	2.9 2.8 3.4 2.7 2.4	3.1 2.5 3.3 2.4 2.6	79 73 77 60 70	134-104 133-106 126-100 130-70 129-88	227 224 227 224 242	17 18 17 16 16	8.2 8.4 9.1 8.0 8.1	1369 1067 1055 1100 1280	None None Yes Yes No	0.21 0.23 0.22 0.25 0.25	T2 up 2 mm. T2 inverted 1 mm. T2 inverted 2 mm. T2 diphasic T2 diphasic	Rheumatic heart disease? Pulmonary valvulitis. Former paroxysmal cardiac dyspnea. Class II B. Occasional nodal extrasystole. Occasional dropped beat
262	M.	46	63	184	Feb. 19, 1935 Mar. 1, 1935 5 8	0.2 gram daily No more 2.5 grams No more	3.6 3.6 4.8 3.4	4.1 3.4 3.9	59 80 76 69	152-98 159-100 160-98 176-100	230 249 280 268	16 11 10 11	10.0 7.2 9.0 6.3	1303 1315 1217 1070	Some None Toxic Yes	0.20 0.22 0.28 0.28	T2 diphasic T2 same T2 upright T2 diphasic	Hypertensive heart disease formerly decompensated. On digitalis 0.2 gram for 9 days. Class II B. Vomited after 1st run. No more nausea
300	M.	53	66	150	Oct. 1, 1935 4 11	None 2.1 grams No more	3.1 3.0 3.2	2.7 3.8 3.2	78 68 64	205-163 203-158 207-154	252 245 254	20 20 17	7.6 7.9 7.6	1456 1308 1410	None Yes Slight	0.19 0.20 0.20	T2 slightly diphasic RV12 depressed RT2 less depressed	Hypertensive heart disease, formerly decompensated, Class II B
306	M.	33	67	141	Oct. 22, 1935 25 Nov. 1, 1935 1 8	None 1.1 grams No more 1.8 grams	2.9 2.6 4.5 3.3 4.3	3.1 2.9 4.7 3.0	42 40 43 71 45	124-89 130-93 165-95 155-106 154-109	217 199 218 231 205	16 13 12 15 15	6.0 5.4 5.1 6.0 6.3	1050 958 1030 1000 1120	None Yes Yes Yes	0.18 0.24 0.24 0.16 0.21	T2 upright 2.5 mm. T2 same T2 higher T2 upright 2.5 mm. T2 lower	Rheumatic heart disease, former auricular fibrillation, Class II B. Clinical improvement striking. After 1.2 mgm. atropine
328	M.	41	71	160	Feb. 4, 1936 18	None 2.6 grams	2.9 3.2	2.8 4.2	105 87	173-75 139-55	351 353	27 25	12.3 10.0	873 819	None Yes	0.16 0.18	T2 upright 3 mm. T2 upright 2 mm. ventricular extrasystoles	Lues. Slight aortic regurgitation, Class II A
274	M.	54	64	163	Jan. 15, 1935 25 Feb. 6, 1935	None 2.1 grams No more	3.8 2.7 3.4	3.3 2.8 3.2	87 68 68	120-71 112-57 116-59	306 280 239	19 17 18	7.4 6.7 6.3	1520 1261 1557	None Doubtful None		T2 lower still up T2 higher	Multiple hereditary telangiectases, Class II B. (?) Hyperthyroidism, formerly decompensated, on iodides
DIGITALIS—NORMAL RHYTHM. SMALL DOSAGE																		
270	M.	72	66	139	Dec. 17, 1934 21	None 0.5 gram	2.8 2.5	2.8 2.5	56 49	158-55 156-55	216 178	13 12	8.7 6.8	718 720	None None		No change	Arteriosclerotic heart disease; slight aortic regurgitation. Class II A
307	M.	22	68	146	Oct. 25, 1935 29	None 1.1 grams	4.2 4.2	3.1 3.1	78 73	127-86 106-77	294 326	15 14	5.9 6.4	663 578	None Slight	0.16 0.16	Normal T3 inverted	Hyperthyroidism, Class II A
185	M.	48	64	164	Apr. 25, 1933 29	None 1.0 gram	5.4 4.1	5.0 3.5	85 73	182-72 180-71	281 209	15 19	7.2 5.4	1086 1045	None None			Arteriosclerotic heart disease; slight aortic regurgitation. Outpatient Class II A
184	M.	23	73	168	Apr. 25, 1933 May 2, 1933	None 1.5 grams	4.2 4.5	3.7 4.2	74 64	122-57 129-52	314 319	16 17	8.6 6.9	1470 1552	None ?			Rheumatic heart disease; slight aortic regurgitation. Outpatient Class II A

* While any discussion of the value of drugs is outside the scope of this paper, some mention must be made of the beneficial effects of digitalis in our cases as judged by the author in charge of the ward. Of the cases of auricular fibrillation Case 260 was benefitted little if at all, and withdrawal of the drug caused little detectable clinical change. Case 262 with hyperthyroidism was not benefitted. Cases 288 and 314 were greatly, and Case 313 slightly, benefitted. Case 289, the case of flutter, had indefinite cardiac pain after digitalis and it was later abandoned.

Of the patients with normal rhythm Case 262 was much improved and the gain was lost when the drug was omitted. Case 328 was much improved also. In Case 306 the rapid and striking improvement was probably not to be attributed to medication. Cases 274 and 282 were no better after the drug. The cases receiving small dosage showed no improvement certainly due to the drug.

Therefore we do not find any single feature of digitalis action which is invariably correlated with clinical improvement.

cept these results as the best that can be obtained at present under these conditions.

Therefore one might judge from the literature that digitalis exhibited varying cardiac effects in animal preparations, in normal persons, in patients with heart disease and normal rhythm, and in auricular fibrillation. Our results, viewed superficially, would reveal the same thing, for considering all our subjects as one group, the estimated cardiac output after digitalis is diminished in four, increased in eight, varied in four, and was essentially unchanged in four. A similar diversity of results was found by Harrison and his coworkers in congestive heart failure (21).

But by the application of the conception described on page 802 our results can be unified. Utilizing our definition of stimulation and depression, and plotting the average digitalis effects in Figure 1 and the satisfactory individual cases in Figure 2, we find that digitalis stimulates the heart in every instance, i.e. the heart's work per beat, in proportion to its size, increases. Withdraw the drug and the reverse usually occurs. Those cases in which cardiac output diminished after digitalis also have had a diminution of pulse rate, or of heart size, or of both.

We, therefore, support the classic view that digitalis is a cardiac stimulant, a conclusion drawn many times from the results of clinical observation and animal experiment, and we believe that the apparent divergencies of digitalis action can be unified by this conception.

Epinephrine

The second group of estimations was made from 20 to 40 minutes after the subcutaneous injection when tremor of extended hands, and changes in either pulse rate or blood pressure were present. The results, Table III, are similar in most respects to those of our predecessors in this field. Somewhat to our surprise the average mean blood pressure failed to rise after adrenalin in our subjects. The systolic pressure rose in 4 of the 6 subjects but the diastolic pressure fell in every instance. The latter is the usual finding (36) so the effect on mean blood pressure is often small.

Our results (Figure 3 and Table III) show a significant increase in pulse rate, metabolic rate, cardiac output, cardiac work, and respiration after the drug. There was also a great diminution of peripheral resistance. Marked stimulation of the heart muscle is indicated by the data illustrated in Figure 1.

The electrocardiograms showed no noteworthy change except in Case 299, who, showing only occasional ventricular extrasystoles before the drug, developed short periods of bigeminal rhythm, the extrasystoles replacing every second beat.

The usual effects of epinephrine increasing metabolic rate, systolic blood pressure and pulse rate are well known. Euler and Liljestrand (37) first demonstrated effect on cardiac output on two normal subjects. Field and Bock obtained a similar result (38). Lauber and Brauch (39) secured evidence of a similar effect on 3 patients at the height of action, after a small dose, as 0.01 mgm., given intravenously. The latter authors employed Broemser and Ranke's method (34) in which cardiac output is deduced from the blood pressure and pulse wave velocity. This method has been criticized (4), and we have had no experience which permits us to evaluate its results.

It should be emphasized that the effects of epinephrine on heart and circulation far overbalanced the blood pressure effects on our subjects. Indeed, despite the blanching around the site of injection seen in all our subjects, and the facial pallor seen in some, the peripheral resistance markedly diminished in every case, and one is forced to conclude that vessels dilated at some location. Clough deduced this from the fall of diastolic pressure (40) and Grollman points out the same implication in Euler and Liljestrand's data (6).

It seems reasonable to suppose that local vasoconstriction at the site of injection, due to the high concentration of drug at that spot, so impedes absorption that the minute amounts of drug reaching the general circulation dilate vessels as do extremely minute doses injected intravenously in animal experiments. Reflex vasodilatation from increased pressure due to the cardiac stimulation may be a factor also.

Ephedrine

Changes in blood pressure allowed us to identify clearly the height of action in most instances

TABLE III
Original data and diagnoses of individual cases

Case number	Sex	Age	Height	Weight	Cardiac output (duplicate determinations)		Pulse rate	Average blood pressure	Average O₂ consumption	Respiration		Heart volume	Dose	Diagnosis and remarks
										Rate	Volume			
		years	inches	pounds	liters per minute		per minute	mm. Hg	cc. per minute	per minute	liters per minute	cc.		
														EPINEPHRINE
													mgm.	
1	M.	62	73	168	3.3		56	168–75	282		8.1			Diabetes mellitus, peripheral vascular disease
					4.3		62	155–58	308		9.6		0.5	Arteriosclerosis
274	M.	54	64	163	3.4	3.2	68	116–59	239	18	6.4	1587		Multiple hereditary telangiectases. Congestive failure 6 months
					5.3	4.2	67	130–53	312	18	8.8	1425	0.45	before
276	M.	47	71	165	3.3	3.1	78	114–65	213	9	5.3	564		Neurocirculatory asthenia
					6.1	5.4	104	112–57	310	14	8.9	554	0.8	
299	M.	52	72	162	4.0	3.7	92	120–105	379	20	11.8	1157		Hyperthyroidism
					5.6	5.5	110	129–84	543	27	16.5	1150	0.5	
326	M.	50	62	156	3.4	3.6	64	136–87	248	11	5.4	815		Myxedema under thyroid medication
					4.5	5.7	82	155–83	304	15	8.0		1.0	Arteriosclerotic heart disease. Angina pectoris
333	M.	52	65	152	3.0	4.1	57	118–80	176	12	4.3	690		Psychoneurosis
					6.3	6.0	78	128–65	230	14	5.9	666	0.75	
														EPHEDRINE
													mgm.	
233	F.	47	62	114	2.7	2.9	59	99–70	154	11	3.2	366		Normal
					3.7	3.5	67	115–73	158	14	3.7		50	
258	M.	50	67	130	3.4	3.1	62	96–79	121	17	3.5			(?) Myxedema
					5.1	4.6	68	128–89	177	17	3.8		50	
263	M.	43	68	140	4.1	3.2	58	102–79	223	7	5.1	509		(?) Neurasthenia
					3.4	3.9	61	112–79	232	9	5.8	468	50	
265	M.	26	65	144	3.1	3.5	64	111–76	191	12	4.8	451		Normal
					3.0	4.5	72	118–77	209	15	5.4	456	50	
269	M.	30	68	169	3.0	3.4	63	108–61	280	9	5.5	629		Normal
					4.9	4.5	63	115–70	322	7	7.9		50	
332	M.	62	65	189	2.0	3.0	70	116–69	264	22	7.2	750		Gastro-intestinal influenza
					2.8	3.2	83	135–68	287	23	8.8	781	67.5	Convalescent
														CAFFEINE
													grams	
281	M.	23	66	145	4.3	3.9	73	138–49	259	10	5.1	920		Post-encephalitis. Rheumatic heart disease. Aortic regurgita-
					6.0	5.6	65	129–46	262	10	5.4	894	.5	tion. Never decompensated, (?) mitral valvulitis
282	M.	46	63	184	3.6	4.1	59	152–98	230	16	10.0	1303		Hypertensive heart disease. Just out of 2d decompensation.
					3.6	4.1	63	145–91	235	14	9.4	1326	.5	On digitalis
283	F.	32	64	157	3.5	4.2	93	117–75	168	9	4.1	545		Syphilis. Psychoneurosis, (?) neurocirculatory asthenia
					5.5	4.3	92	115–74	239	9	7.1	534	.5	
284	M.	37	70	191	5.3	4.5	67	125–77	268	14	7.5	772		Psychoneurosis. Atypical constant precordial pain
					5.1	3.9	63	123–76	220	14	5.8	772	.5	
														THEOPHYLLINE ETHYLENEDIAMINE
													grams	
303	M.	16	68	129	2.9	3.2	109	123–75	247	23	7.1	373		(?) rheumatic fever. No known cardiac involvement
					4.8	3.9	100	118–82	245	22	7.5	412	0.48	
306	M.	33	67	141			45	155–108	197	15	5.3	1120		Advanced rheumatic heart disease. Paroxysm of auricular fibril-
					4.9	6.2	50	171–118	253	20	10.3	1055	0.48	lation. Now normal rhythm. Fully digitalized
307	M.	22	68	146	4.2	3.1	73	106–77	326	14	6.4	578		Hyperthyroidism. Has received ½ calculated dose digitalis
					4.9	3.7	78	105–77	291	13	6.0	550	0.48	
308	M.	37	68	129	3.2	2.6	85	100–74	211	19	5.8	608		Angina pectoris. Xanthomatosis
					3.0	3.3	76	97–75	243	18	6.6	614	0.48	
309	M.	50	70	136	2.5	2.6	56	88–62	201	10	4.8	571		Low backstrain. Possibly neurocirculatory asthenia.
					2.6	2.8	52	107–75	219	10	5.4	565	0.48	
317	M.	47	67	159	3.1	2.3	91	148–117	224	17	5.8	680		Angina pectoris
					3.4	3.5	88	158–130	238	16	6.3	650	0.48	
329	M.	57	66	116	2.0	1.5	54	117–67	178	17	5.1	528		Angina pectoris
					2.1	3.3	53	137–66	201	17	6.0	542	0.48	(?) Duodenal ulcer
														CARBAMINOYLCHOLINE
													mgm.	
271	M.	39	63	114	2.9	3.4	73	103–69	226	7	5.5	579		Thromboangiitis obliterans
					3.9	3.8	82	87–61	227	7	6.0	555	0.5	
277	M.	44	68	153	3.0	2.9	63	223–127	214	15	5.9	558		Arteriolar nephrosclerosis
					3.0	3.0	71	205–122	235	15	6.0	612	0.4	
315	M.	27	60	166	3.4	3.1	78	125–90	285	17	7.1	755		Headache—no cause found
					4.3	3.3	80	112–86	312	18	7.5	748	0.6	
323	M.	36	60	169	3.0	2.9	52	94–65	230	15	5.8	656		Thromboangiitis obliterans
					3.1	3.8	58	93–64	254	15	6.0	656	0.6	
324	M.	30	74	182	4.3	5.0	73	113–71	308	15	8.4	667		Thromboangiitis obliterans
					3.7	4.0	75	113–61	313	14	8.9	621	0.6	
327	M.	60	66	131	2.1	2.5	64	181–87	232	14	5.2	720		Arteriosclerotic peripheral vascular disease
					3.2	2.9	68	174–81	208	14	5.5	650	0.4	

TABLE III—*Continued*

Case number	Sex	Age	Height	Weight	Cardiac output (duplicate determinations)		Pulse rate	Average blood pressure	Average O₂ consumption	Respiration Rate	Respiration Volume	Heart volume	Dose	Diagnosis and remarks
		years	*inches*	*pounds*	*liters per minute*		*per minute*	*mm. Hg*	*cc. per minute*	*per minute*	*liters per minute*	*cc.*		
SODIUM NITRITE													*grams*	
280	M.	32	71	118	8.3	7.5	71	211–135	247	5	6.2	602		Advanced chronic glomerulonephritis
					5.1	4.7	68	164–112	200	6	9.3	589	0.12	Very nervous. Excited during 1st run
317	M.	47	67	159	2.4	3.0	88	137–107	202	17	5.7	660		Angina pectoris
					3.5	2.5	95	113–92	226	17	5.9	635	0.12	
318	M.	35	63	136	4.2	3.7	72	223–167	201	15	5.7	672		Essential hypertension. Former hemiplegia
					3.0	3.8	73	185–136	195	13	5.4	638	0.12	
319	M.	43	66	157	2.2	2.4	64	187–153	215	15	5.2	912		Essential hypertension. Former hemiplegia
					3.5	3.2	59	145–118	221	13	5.1	850	0.12	
320	M.	56	68	157	2.9	2.8	83	231–127	265	22	7.7	800		Renal arteriolosclerosis with beginning renal failure
					2.5	2.8	80	217–120	279	23	7.8	836	0.12	
321	M.	55	65	141	2.8	2.6	60	166–115	255	13	6.4	1090		Renal arteriolosclerosis with beginning renal failure. Blood urea nitrogen 30
					3.3	3.0	61	161–107	276	14	6.2	1055	0.12	
322	F.	45	64	124	4.6	4.1	122	259–159	266	19	6.1	856		Advanced chronic glomerulonephritis
					3.9	3.0	112	252–155	262	17	6.0	872	0.18	Blood urea nitrogen normal. Died 3 weeks later
330	M.	72	67	193	3.2	2.3	61	141–89	236	14	5.8	955		Arteriosclerotic heart disease. Aortic stenosis?
					2.8	2.5	62	115–85	262	15	6.8	1080	0.12	
NITROGLYCERINE													*mgm.*	
1	M.	62	73	168	1.9		54	145–65	221		6.9			Diabetes mellitus. Peripheral vascular disease
					3.9	3.1	71	114–68	227		12.1		1.2	Arteriosclerosis
2	M.	63	73	170	1.7		78	195–95	195		6.4			Essential hypertension. Left hemiplegia
					2.2	3.9	95	160–97	275		7.3		1.2	
PITRESSIN													*units*	
266	F.	38	65	104	4.3	3.3	79	88–68	163	11	4.0	366		Diabetes insipidus
					2.7	2.2	71	89–64	153	10	3.1	331	30	
266					2.0	2.7	64	87–65	139	9	3.0			5 days after 1st test
					2.2	2.7	68	83–61	144	9	3.3		30	
272	M.	23	70	120	2.2	2.5	74	101–62	184	17	5.1	423		Neurocirculatory asthenia
					2.4	2.5	73	94–64	186	24	5.8	377	8	
272					2.3	2.1	70	94–56	191	22	5.8	423		3 days after 1st test
					2.1	2.0	65	86–58	196	19	5.5	405	16	
274	M.	54	34	163	2.7	2.8	68	112–57	260	17	6.7	1604		Multiple hereditary telangiectases. Fully digitalized
					3.0	2.4	67	115–60	288	18	7.1	1565	10	
312	M.	36	63	137	4.3	4.2	65	94–70	220	11	10.8	548		Diabetes insipidus
					4.4	4.6	62	79–57	263	9	13.3	570	10	
328	M.	41	71	160	3.2	4.1	87	139–55	353	25	10.0	819		Syphilitic heart disease. Aortic regurgitation fully digitalized
					2.8	3.1	80	144–66	293	24	9.6	837	10	
293	M.	23	67	132	2.3	2.5	72	103–64	211	14	4.3	498		Diabetes insipidus
					3.5	3.2	70	103–64	235	13	5.5	514	?	Snuffed pituitary powder up nose
QUINIDINE													*grams*	
260	M.	27	69	165	2.8	3.0	66	141–87	277	21	6.8	2290		Rheumatic heart disease. Advanced valvulitis. Auricular fibrillation. Formerly decompensated. Fully digitalized
					2.4	2.6	71	141–95	269	30	8.0	2280	1.0	
272	M.	23	70	120	2.5	2.0	79	99–52	193	21	5.5	469		Neurocirculatory asthenia
					2.8	2.8	93	102–57	199	22	6.2	424	1.0	
274	M.	54	64	163	3.7	3.3	87	120–71	306	19	7.4	1834		Multiple heriditary telangiectases. Decompensated 5 months before. No digitalis
					3.9	3.6	88	107–64	309	20	8.0	1640	1.0	
275	F.	38	60	112	2.2	2.3	61	137–96	145	12	3.4	715		Rheumatic heart disease; mitral stenosis; auricular fibrillation digitalised
					2.0	1.8	55	137–97	124	14	3.2	661	0.6	
282	M.	46	63	184	3.6	2.4	60	160–100	249	11	7.2	1315		Hypertensive heart disease. Formerly twice decompensated. No digitalis
					3.1	3.5	70	166–107	244	9	7.0	1336	2.0	
282					3.4	3.9	69	176–100	268	11	6.3	1070		7 days after previous test. No digitalis
					3.5	3.5	72	141–90	232	11	6.6	1045	2.0	Improved clinically
285	F.	32	60	127	3.8	3.9	86	196–133	182	16	4.4	551		Arteriolar nephrosclerosis. Nausea and vomiting soon after post-drug run
					4.5	3.3	95	200–137	189	16	4.8	460	1.4	
287	F.	34	63	110	4.1	4.1	97	110–70	187	18	4.9	454		Neurocirculatory asthenia
					3.6	3.0	110	114–69	183	17	5.1	396	0.4	

TABLE III—*Continued*

Case number	Sex	Age	Height	Weight	Cardiac output (duplicate determinations)	Pulse rate	Average blood pressure	Average O₂ consumption	Respiration Rate	Volume	Heart volume	Dose	Diagnosis and remarks
		years	inches	pounds	liters per minute	per minute	mm. Hg	cc. per minute	per minute	liters per minute	cc.		

MORPHINE (NON-CARDIAC CASES)

Case number	Sex	Age	Height	Weight	Cardiac output	Pulse rate	Average blood pressure	Avg O₂	Resp. Rate	Volume	Heart volume	Dose (mgm.)	Diagnosis and remarks
239	M.	17	67	115	5.2 4.4	94	124–80	241	20	6.5			Typhoid fever convalescent
					3.7 3.3	81	121–76	235	18	5.2		10	
240	M.	58	66	139	3.5 3.8	63	100–92	136	14	3.7	567		Duodenitis
					3.2 3.2	60	96–84	160	13	4.3		15	
241 4-3-34	M.	24	64	121	3.7 3.5	83	106–78	204	17	5.2	498		Arthritis, colitis
					4.7 4.4	76	105–84	222	17	4.9		15	
241 4-10-34	M.	24	64	121	3.8 4.4	72	99–77	228	17	4.9	498		Arthritis, colitis
					3.1 3.8	75	107–84	248	15	4.7		15	
242	M.	29	72	163	4.7 5.1	82	109–92	270	11	5.5			Chronic colitis
					5.4 5.0	82	110–91	231	11	5.4		15	
243	M.	35	68	131	4.4 3.7	68	110–95	213	13	4.9	514		Gastric neurosis
					3.9 4.6	62	112–95	191	11	3.8		15	
244	F.	35	63	117	4.0 4.4	72	104–70	182	19	5.3	437		Psychoneurosis
					4.1 4.1	69	100–75	173	16	4.7		15	

MORPHINE (CARDIAC CASES)

Case number	Sex	Age	Height	Weight	Cardiac output	Pulse rate	Average blood pressure	Avg O₂	Resp. Rate	Volume	Heart volume	Dose (mgm.)	Diagnosis and remarks
245	M.	57	69	157	3 5 3.7	46	149–77	212	12	5.1	477		Coronary occlusion. Angina pectoris
					3.6 3.5	51	141–72	193	11	4.4		15	
246	M.	33	66	176	6.0 5.2	66	150–90	247	16	5.4	700		Angina pectoris
					4.1 5.1	62	145–85	250	11	4.8		15	
247	M.	43	70	181	3.5 2.9	75	165–99	283	20	7.6	1240		Hypertensive heart disease. Just out of decompensation
					3.0 4.0	68	180–100	260	15	6.4		15	
248	M.	65	67	140	4.2 4.4	96	124–65	305	14	7.3	1282		Thyroid heart disease. Auricular fibrillation. Never decompensated
					4.0 3.3	86	113–65	270	14	6.0		15	
249	M.	51	66	108	3.5 3.4	72	128–65	239	17	6.6	1345		Arteriosclerotic heart disease. Aortic stenosis (?) Attacks of nocturnal dyspnea
					2.8 3.1	74	129–65	241	13	5.4		30	
250	M.	39	67	119	2.8 3.7	78	115–82	206	20	6.0	1380		Rheumatic heart disease. Decompensated 6 months ago. Mitral stenosis
					2.9 2.4	78	114–81	223	20	5.7	1314	30	
251	M.	59	63	178	2.1 2.6	79	127–72	257	22	5.5	585		Coronary thrombosis 1 month before
					2.3 2.7	77	109–67	229	19	5.4	636	30	
301	M.	22	67	149	7.5 6.3	102	129–59	400	14	8.4	769		Hyperthyroidism
					5.6 6.8	104	132–59	440	14	8.2	644	15	

STRYCHNINE

Case number	Sex	Age	Height	Weight	Cardiac output	Pulse rate	Average blood pressure	Avg O₂	Resp. Rate	Volume	Heart volume	Dose (mgm.)	Diagnosis and remarks
118	F.	47	61	153	2.0 1.4	60	103–69	162	20	4.5	1083		(?) Rheumatic heart disease. Very few physical signs. On digitalis
					1.5 1.7	60	95–62	143	23	4.5	1105	2.0	
291	M.	22	65	132	2.5 2.9	55	119–71	205	20	6.6	1100		Rheumatic heart disease. Mitral stenosis. Former pulmonary hemorrhage
					2.5 2.5	54	122–72	165	15	5.6	990	1.5	
292	M.	14	66	129	5.6 5.1	72	116–68	222	11	5.6	510		Recent rheumatic fever (?) Cardiac involvement
					4.0 3.6	64	120–64	208	10	4.8	464	1.0	
294	M.	28	65	134	4.8 4.1	52	127–24	220	13	6.2	1500		Rheumatic heart disease. Advanced aortic regurgitation with all peripheral signs
					4.7 3.5	52	135–25	278	13	6.8		1.5	
295	M.	30	68	144	3.0 2.6	54	133–83	199	14	5.9	672		Thromboangiitis obliterans
					3.0 3.1	55	132–76	217	14	5.7	548	1.5	
296	M.	27	70	152	4.9 4.8	64	100–67	235	8	5.9	688		Thromboangiitis obliterans
					4.5 4.2	59	98–66	256	8	8.5	669	2.0	
297	M.	51	64	160	6.5 5.7	98	109–85	258	20	11.6	1277		Heart enlarged without obvious cause. Nervous. Poor subject
					5.0 4.1	90	110–85	220	19	8.8	1170	2.0	
316	M.	48	68	171	3.3 2.6	80	160–115	287	12	6.0	986		Arteriosclerotic heart disease. Auricular fibrillation. On digitalis
					2.7 2.3	80	152–110	284	15	6.2	991	3.0	

and it appeared from 15 to 45 minutes after the subcutaneous injection.

The action of ephedrine was rather irregular; some of our subjects responded markedly, others very little, to the same subcutaneous dose. Our results show a significant increase in pulse rate, systolic blood pressure, respiratory volume, cardiac output and cardiac work, and a significant diminution of peripheral resistance. The pattern of the response (Figure 3) closely resembles that found after adrenalin, but ephedrine is less powerful in the dosage given. The stimulant action of ephedrine on the heart is also less than that of adrenalin (Figure 1).

The increase in metabolic rate was irregular, being marked in some subjects, absent in one. This seems to have been the experience of others also (41).

The electrocardiograms of all but one of our subjects showed diminution in height of the T

wave after the drug. In Case 310, who had been clinically much improved by the drug, an upright T wave became biphasic. Changes of this type have been reported on dogs and in an occasional patient after the drug (42).

The action of ephetonine, a synthetic racemic ephedrine, was carefully studied in a single normal subject by Euler and Liljestrand (43). We used the natural *l* rotatory ephedrine which is more active than the racemic. Therefore, our results are not strictly comparable with those of Euler and Liljestrand, but they agree as well as one would expect.

The depressant action of ephedrine on the heart, demonstrated after large doses in animal experiments (42) does not seem to be a factor in the clinic after proper dosage of the drug.

As is the case with epinephrine the diminution in peripheral resistance indicates that vessels have dilated somewhere and that the increased blood pressure is to be entirely explained by increased cardiac output. Such a large increase of cardiac output accompanied by general vasoconstriction would surely cause a dangerous rise of blood pressure. Doubtless the nervous and humeral mechanisms of homeostasis, brought into action by the elevation of pressure overbalance the constrictor action of the drug.

Caffeine and theophylline ethylenediamine

These drugs, belonging to the same group, may be considered together. Both drugs, although injected well into the deltoid muscle gave rise to soreness at the site of injection in every instance. Both drugs had but little effect on the functions usually measured in the clinic—pulse rate, respiratory rate and blood pressure—so that we could do little more than guess at the time of maximum drug effect. We made the second group of estimations from 20 to 40 minutes after the injection.

The averages show a marked increase in cardiac output, work and respiration; and a diminution of peripheral resistance. These changes are significant for theophylline. Figure 3 shows that the average circulatory and respiratory effects of the two drugs have a similar pattern, theophylline being more powerful in the dosage used. Both drugs are cardiac stimulants (Figure 1).

The electrocardiograms of our patients showed no noteworthy change after either drug.

Three of the seven patients given theophylline had angina pectoris. In spite of the increased heart work demonstrated in these cases no cardiac pain followed in any instance.

Our results after intramuscular injections of caffeine correspond in a general way with those obtained by Grollman (6) after giving caffeine by mouth to normal persons. The effect of caffeine on the metabolic rate of our patients is similar to the experience of others (6, 41) in that, while most subjects show no change after the drug, an occasional person shows a marked increase.

In three cases of congestive heart failure, one studied three times, Friedman, Resnik, Calhoun and Harrison (44) made single estimations of cardiac output by the acetylene method before and after the oral administration of from 1.5 to 0.9 grams of theophylline daily for two days. The average of the results showed an increased cardiac output of 9.8 per cent after the drug but the results of individual experiments were irregular and this difference, judged by the standards we have set for ourselves, is not significant. These investigators were chiefly interested in the effect on the circulation of loss of fluid by diuresis, and so they had no need of performing their estimations at the height of drug action. We believe, therefore, these results to be as similar to ours as should be expected.

Our studies indicate that these two drugs rank among the powerful cardiac and circulatory stimulants. We believe that clinicians, basing judgment on their lack of effect on pulse rate, respiratory rate and blood pressure, have underestimated their activity, and possibly their value also.

Carbaminoylcholine

Carbaminoylcholine (doryl) was investigated because of the especial interest of one of the authors (45). It is a representative of the group of drugs whose action is similar to that which follows stimulation of parasympathetic nerves. Of the 6 patients, 4 were subject to peripheral vascular disease and previously had had relief of pain after the drug. All of them had improved to the extent of freedom from pain when these tests

were made. A slight flush with some diminution of blood pressure and increase of pulse rate gave evidence that the drug was acting when the estimations were made, 20 to 40 minutes after the subcutaneous injections.

The average results, Figure 3, show a significant increase of pulse rate and respiration, and a significant diminution of blood pressure and peripheral resistance. The average cardiac output increased 12 per cent but the changes found in individual cases were irregular enough to prevent significance being attained in so small a series.

When plotted in Figure 1 the average results do not indicate any stimulant or depressant effect on the heart.

The electrocardiograms showed no change of form which could be attributed to the drug.

After doses of the size given the effects on the circulation are much similar to those which follow other vasodilators. We find no evidence of any effect like cardiac vagus stimulation.

Nitrites

All but one of the patients tested had a pronounced hypertension. A dose of 0.06 gram of sodium nitrite in solution was given by mouth as soon as the control estimations were over, and repeated about 30 minutes later just before the second inhalation of ethyl iodide began. The change in blood pressure guided us in making the two estimations of cardiac output at the height of the action of the drug. This was usually about 20 or 30 minutes after the second dose.

Case 280 was obviously excited during the control period and its data, included in Table III, have been omitted from the statistical analysis. The results show that a diminution of blood pressure occurred in all but one case, which, although given a third dose, still showed no noteworthy change. The average diminution of blood pressure and peripheral resistance are significant. The average heart work diminished with the fall in blood pressure, but there was enough variation in the individual cases to prevent significance being attained. The averages of the cardiac output and of the other functions measured were not materially influenced by the drug (Figure 3).

The electrocardiograms of Case 280 showed a surprising change. In Lead II the T wave, up-

right less than 1 mm. before the drug, increased to 6 mm. after it; in Lead III the T wave, originally inverted 1 mm., became 4 mm. upright. The electrocardiogram during the drug's action was far more normal than that taken before it. Cases 318 and 322 showed very slight increases in height of the T wave in Lead II during the action, but Case 319 showed a 1 mm. diminution of the T wave in this lead. The electrocardiograms of the other patients were unchanged. The changes found are similar to those described by Evans and Hoyle (46) after amyl nitrite and nitroglycerine.

Our results, Figure 1, indicate that sodium nitrite causes slight depression of the heart, a finding consistent with the results of animal experiments (22).

Sodium nitrite gives effects enduring long enough to permit duplicate estimations of cardiac output during its action. Therefore it was preferable for this investigation to the rapidly acting nitrites whose action may change materially in intensity before such estimations can be completed. However, in two cases of hypertension we obtained single estimations of cardiac output during the period of diminished blood pressure following the administration of nitroglycerine (Table III).

After a single control estimation, tablets totalling 1.2 mgm. of nitroglycerine were placed under the tongue. In the first case the pressure diminished sharply, attaining a minimum 10 minutes after the administration of the drug. A marked increase in cardiac output was present at that time. Forty minutes later, 20 minutes after the blood pressure had returned to its previous level, the estimated cardiac output had fallen, but not to the control level. In the second case, after a slow fall, the systolic blood pressure curve became level and did not regain its previous height during the next 35 minutes. Twenty minutes after the administration of the drug the cardiac output was but little elevated. Fifteen minutes later it was markedly increased. Obviously, there was a significant increase in cardiac output after nitroglycerine in these two cases, and the extent of the change was larger than that usually seen after sodium nitrite.

In general our results are similar to those of our predecessors in this field. Weiss and Ellis

(47) studied 5 cases of hypertension employing the cardiac output method of Field, Bock et al. which gives higher results than the more recent methods. After doses of sodium nitrite larger than those we employed, the average cardiac output diminished 12.6 per cent. If one omits one of their cases with an abnormally high output before the drug, the diminution is only 7 per cent, in contrast to an increase of 3.4 per cent in our series. Neither change is significant and in other respects our results resemble theirs.

Gaisböck and Jarisch (48) using the Krogh and Lindhard method repeatedly on two normal subjects, found an average increase of 44 and 20 per cent in cardiac output after subcutaneous injection of small doses of sodium nitrite although the pulse rate and blood pressure were unchanged. Weiss and Ellis (47) found no change in cardiac output of normal persons after large doses by mouth. On four normal persons Lindhard (49) found a significant increase of cardiac output, averaging 23 per cent, after acute experiments with amyl nitrite. In the same subject, more prolonged inhalation was followed by a smaller effect which, judged by our standards, was not significant.

Lauber and Brauch (39) calculating the cardiac output from the pulse wave form, velocity, and pressure, according to Broemser's method, divide the action of nitroglycerine into two parts. At first output and work are increased, later both are diminished.

In general the results indicate that when the blood pressure is lowered rapidly by a nitrite the cardiac output is regularly increased. If the blood pressure falls slowly or not at all the results are less regular, either an increase or no change being found. In our series cardiac work per minute diminished, not significantly, after sodium nitrite but apparently increased in the two experiments after nitroglycerine.

Pitressin

We made four observations of pitressin action on three patients with diabetes insipidus who were accustomed to take the drug, and on three other patients who had never received it. In the former, pituitary preparations were withdrawn for about 18 hours and polyuria had developed

before the control estimations. These patients' urine was measured before and after they received their usual dose at the time of testing. The polyuria was checked in every instance. Estimations were made 20 to 50 minutes after the drug's administration, usually by subcutaneous injection. Marked facial pallor gave evidence that the drug was acting when the estimations were made.

The results, Table III, do not demonstrate any obvious difference between the response of the patients with diabetes insipidus and the other patients, therefore both sets have been averaged in Table I and Figure 3. The results on Case 293, who inhaled pituitary powder, have been omitted from the statistical calculations because of lack of knowledge of the dose absorbed.

The averages show that no significant change in any item measured followed pitressin. Most of the individual results show the same thing. Case 260 showed a marked diminution of cardiac output after the drug but a second test did not confirm the finding. Case 293 alone showed a decided increase.

The electrocardiograms were unchanged after the drug except in Case 328 whose P waves diminished from 2 to 1 mm. in height in Leads II and III after the drug. We did not observe any prolongation of A–V conduction time as has been observed both in animals and man (52).

When plotted in Figure 1, our averages do not indicate that any depression of the heart resulted from these therapeutic doses of the drug. That relatively larger doses depress the heart in heart-lung and other animal preparations is well known (23).

Pituitrin is known to produce inconstant changes of blood pressure in different patients. Moffat (51) studied 62 cases; in the majority there was little or no change after 1 cc. intramuscularly. The general trend was towards a slight rise immediately after injection, and downward thereafter. Our results with pitressin are quite similar.

Grollman and Geiling (52) studied two normal subjects by the acetylene cardiac output method. Therapeutic doses of pituitrin and pitressin produced a transient diminution of pulse rate, oxygen consumption, and cardiac output, followed by a more prolonged increase. Hartl (53), calculating the cardiac output from blood pressure curves

and pulse wave velocity according to Broemser's method, deduced an increased peripheral resistance and a diminished cardiac output after 10 units of pitressin in one subject. The curve of these results resembles that of Grollman and Geiling but the changes are not so marked and the secondary rise of cardiac output did not reach the initial level.

Our estimations of pulse rate, cardiac output and metabolism, made during the period after administration of the drug in which Grollman and Geiling obtained evidence of an increase of these functions, did not give similar results.

We have not investigated the changes in cardiac output found soon after the injection by the ethyl iodide method, but Dr. H. A. Schroeder made estimations by the acetylene method 10 minutes after the injection of 20 units of pitressin in three patients. The average output was diminished 11 per cent at this time, as found by Grollman and Geiling, but unlike their results, the metabolic rates were essentially unchanged. Varying effects of pituitrin on metabolic rate have been reported by numerous authors (52). It is of interest that in our results the changes average out.

We conclude that pitressin is a drug usually causing little enduring change in the functions we have measured. The more pronounced effects, seen occasionally, vary in their direction so that average changes are not significant.

Quinidine

The quinidine was administered by mouth and the subsequent observations were begun as soon as the action manifested itself by an increase of pulse rate, usually between one and two hours after the drug had been taken. The dosage was larger than that usually given in a single dose in the clinic. Case 285 probably received a slight overdose for she vomited after the estimations although she denied nausea during them.

Two of the cases had auricular fibrillation which persisted in spite of the drug. Two had previously been digitalized and the only instance of diminished pulse rate after quinidine occurred in one of these. In other respects the action of quinidine after digitalis did not seem different.

All the changes demonstrated after quinidine were small but some occurred with such regularity that they were significant. The average pulse rate rose significantly. The stroke volume and work per beat were significantly diminished (Table I, Figure 3).

The average size of the heart diminished significantly and this may well be a reflection of the change in heart rate. A more rapid rate, providing less time for filling, must surely reduce the diastolic size if the inflow remains unchanged.

The electrocardiograms were changed in all cases with normal rhythm, the T wave being from 1 to 2 mm. more upright in two or three leads after the drug. This was very striking in Case 282. In Case 285, Lead III, the QRS complex changed its form, the Q wave originally present disappearing, and the complex becoming M shaped. These results differ from those usually described, for, after patients have been given the drug daily for several days, inversion of the T wave is the common finding (50). In anesthetized dogs soon after intravenous injection of quinidine Lewis et al. (54) described an elevation of the T wave probably analogous to that seen in our acute experiments.

By means of animal experiments quinidine has been proved a strong cardiac depressant. The average results do not demonstrate cardiac depression in our subjects, although they received larger doses than usual. Perhaps clinical experience has set the dosage of quinidine at a point where cardiac depression is minimal.

Morphine

This drug was the first studied, and our data are less complete than in other groups. The size of the heart after the administration of the drug was estimated in only four cases, the electrocardiogram was taken in but one.

Seven determinations were performed on patients without heart disease and not seriously ill. The estimations during morphine action were made as soon as pupillary constriction was manifest, and were performed between ½ and 1½ hours after the subcutaneous injection. The averages (Table I and Figure 3) show little change in heart or circulation. The largest change was in the average pulse rate which diminished about 5 per cent, but even this did not attain signifi-

cance. Changes in respiration were more pronounced, that of the rate being significant.

Eight cases of severe cardiac disease, all severely ill but none of them in congestive failure, were given slightly larger doses. The sedative and pupillary effects were very obvious in each case. Two of the three patients, receiving 0.03 gram, vomited some hours after the test was over but, like the other patients, they denied any nausea or discomfort during it. Again the changes in heart and circulation were slight (Figure 3). The average pulse rate is less affected than in the non-cardiac group, but the metabolism, cardiac output and work were diminished somewhat more. The depression of respiration was again marked, the change in volume was significant.

The effect on heart size was determined on only four patients. When these results are plotted, Figure 1, cardiac depression is suggested, but the change is not significant. Such an effect is in accord with the action of morphine on the isolated heart but the paucity of our data prevents us from placing emphasis on the finding.

The results we obtained on pulse and respiratory rate and on basal metabolic rate were all similar to those of previous investigators (41, 55) who found no change or very small reductions in these functions after morphine. Depression of respiration by morphine, shown in our results, is in accord with expectations from animal experiments and from studies on patients with pneumonia (56).

That morphine benefits patients severely ill with cardiac disease is unquestioned. The usual explanation is that the drug, by quieting the patient, reduces the metabolic rate and so permits a slower circulation maintained by reduced cardiac effort. We regard our results as giving slight support to this conception. The diminution of cardiac work after morphine is somewhat more obvious in our cardiac cases, though absent in the more normal persons. In still more restless patients a greater reduction in both metabolic rate and cardiac work would be expected.

Strychnine

As strychnine was used in the therapy of cardiac disease some years ago we utilized cardiac patients whenever they could be secured. We had no way of assuring ourselves that the drug was acting when the estimations were made. Knowing well that the effects could be expected to pass off rapidly we made the post-drug estimations from 10 to 30 minutes after subcutaneous injection. Case 297 appeared to be excited during the control estimations and these results have been omitted from the statistics although they are consistent with the other findings.

The average results, Figure 3, indicate that only mild effects can be attributed to the drug. No noteworthy stimulation of respiration appeared, except perhaps in Case 296, but we believe that a finding occurring only once is more likely to be an artifact. There was an increase in peripheral resistance and a small diminution of most of the other items measured. The findings in individual cases are quite consistent so that significance is approached in several instances and attained in the case of work per beat.

When plotted on Figure 1, the results do not indicate any stimulant effect on the heart.

The electrocardiograms showed no noteworthy change which could be attributed to the drug.

Attracted by the fact that Margolies found slight diminution in the size of the heart after strychnine in the first six cases not taking digitalis, this part of our study was continued in the outpatient department. Six patients not on digitalis were selected. All had well marked heart disease and four had markedly enlarged hearts. Orthodiagrams, made about 45 minutes after 2 mgm. of strychnine subcutaneously, showed no diminution of heart size in any case.

Our results give no support to the old belief, now generally abandoned, that strychnine stimulates the heart. On the other hand they cannot be dismissed as negative. Slight vasoconstriction with enough diminution of cardiac output to keep the blood pressure constant is suggested. Vasoconstriction in the splanchnic vessels, attributed to stimulation of the vasomotor center, is a well known action of this drug in animal preparations (23). Wenckebach has advocated the clinical use of strychnine in hypotonic cases (57). Our results are of interest in this connection.

GENERAL DISCUSSION

As a general rule our results demonstrate that the effects of drugs on patients are analogous to

comparable results obtained in animal experiments. One exception must be pointed out.

The drugs which give cardiac stimulation in animal experiments cause a similar effect on the patients receiving them in therapeutic dosage. But, in proper clinical doses, the cardiac depressants cause no depression in patients at all comparable with that which may be demonstrated in animal experiments.

In other words, as generally used in the clinic, the stimulants cause marked cardiac stimulation, the depressants are followed by little, if any, demonstrable depression of myocardial function. Doubtless clinical experience has set the proper dose of the depressants at a level at which the heart is but little handicapped by this phase of their action.

SUMMARY

The subjects consisted of 85 patients suffering chiefly from cardiac or circulatory disease but not from congestive heart failure. The number of patients tested for the effects of each drug varied from 2 to 16.

The drugs investigated included digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerine, pitressin, quinidine, morphine and strychnine. As far as possible we studied the action of drugs given under the conditions in which physicians are accustomed to employ them.

The study consisted of a group of estimations made before, during, and sometimes after the drugs' action. This group consisted of duplicate determinations of cardiac output and metabolic rate; and repeated estimations of pulse rate, blood pressure, respiratory rate and volume. Ortho-diagrams and electrocardiograms were secured also.

Based on a conception derived by Starling and his associates from the behavior of the dog's heart-lung preparation, a method has been devised for estimating the extent of myocardial stimulation or depression occurring during drug action in the clinic.

A statistical analysis of the data affords a basis for describing the action to be expected after the administration of these drugs in clinical conditions. With but few exceptions our results support the general conceptions of drug action derived from animal experiments.

The tables contain data on the basal cardiac output and its related functions in many common diseases of the heart and circulation.

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