of the first or second molars was affected. No milkiness was observed in any teeth of the control rats. No difference could be seen in the enamel when the teeth were sectioned by the method of Cox and Dixon.[3]

This discovery of mottled enamel in the third molars of rats makes it possible to produce preferential decay in a rat mouth if the protective action of fluorine[4] is exerted by such late inclusion in the diet. On the other hand, failure to prevent caries in the third molar would indicate that fluorine exerts its protective action earlier in tooth life. Similarly, other substances, for example, Vitamin D, can be used in a study of their relation to dental caries.

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Circulation Time Under Conditions of Work and Rest in Subjects with Normal and Abnormal Hearts.*

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The work of Blumgart, Weiss, and their associates on circulatory dynamics gave impetus to the investigation of the circulation time.[1] Since publication of their reports, it has been shown that the circulation time is influenced by exercise, the basal metabolism, digestion, the viscosity of the blood, the number of red blood corpuscles, the condition of the respiratory organs, the functional state of the myocardium, and many vasomotor factors.[2] Lucia and Aggeler[3] have shown that the intramuscular injection of adrenalin markedly shortens the circulation time. These factors cause fluctuations sufficient to cast doubt on the value of a single observation or uncontrolled measurements of the circulation time.

The substances in most common use for the subjective determination of the circulation time are calcium gluconate, decholin, saccharin, and ether; those for the objective determination include radioactive

3 Cox, G. J., and Dixon, S. F., *J. Dent. Res.*, 1939, **18**, 153.

4 Cox, G. J., Matuschak, M. C., Dixon, S. F., Dodds, M. L., and Walker, W. E., in press.

* Assisted by a grant from the Christine Breon Fund.

1 Blumgart, H. L., *et al.*, *J. Clin. Invest.*, 1927, **4**, 1, 15, 149, 173, 199, 389, 555.

2 Kunkel, P., Stead, E. A., and Weiss, S., *J. Clin. Invest.*, 1939, **18**, 225.

3 Lucia, S. P., and Aggeler, P. M., unpublished data.

substances and fluorescein. Perhaps alpha-lobelin, sodium cyanide and paraldehyde belong to this latter group.

The values usually accepted for the circulation time of normal and abnormal subjects fluctuate through wide ranges.[4] The variation in circulation time for a given disease condition is as great as the variations between different individuals. Master's work[5] on exercise tolerance suggested to us that perhaps the changes in circulation time induced by exercise might give some clue to the state of the myocardial reserve. Accordingly, we devised a method whereby a subject is given a measured amount of exercise, and the circulation time is obtained before and after the exercise. This study was carried out in normal and pathologic subjects before and immediately after exercise, and also before and after a given period of rest.

Method. With the patient in the supine position, 5 cc of 20% calcium gluconate† were injected rapidly through an 18-gauge needle into an antecubital vein at the level of the midaxilla. The time elapsing between the end of injection and the subjective sensation of warmth at the base of the tongue (the circulation time) was meas-

TABLE I.
Circulation Time of Normal Subjects Before and After Exercise.

Case No.	Circulation Time (in sec)		Difference (in sec)
	before	5 min after	
1	13.0	11.6	—1.4
2	16.8	13.8	—3.0
3	15.2	10.1	—5.1
4	12.6	10.4	—2.2
5	14.4	12.4	—2.0
6	13.0	9.5	—3.5
7	15.0	12.4	—2.6
8	17.0	15.4	—1.6
9	15.0	13.0	—2.0
10	15.2	14.2	—1.0
11	13.7	13.9	+0.2
12	11.7	13.0	+1.3
13	13.2	11.1	—2.1
14	10.6	9.9	—0.7
15	11.1	8.3	—2.8
16	16.4	14.5	—1.9
17	10.0	9.0	—1.0
18	14.8	9.8	—5.0
19	12.2	10.0	—2.2
20	15.6	9.6	—6.0
Mean	13.8	11.6	—2.03

[4] Baer, S., and Slipakoff, B. G., *Am. Heart J.*, 1938, **16**, 29.

[5] Master, A. M., *Am. Heart J.*, 1935, **10**, 495.

† We wish to acknowledge with thanks the cooperation of the Sandoz Chemical Company in furnishing to us the Neo-Calglucon (brand of calcium gluconate) used in these experiments.

TABLE II.
Circulation Time of Abnormal Subjects Before and After Exercise.

Case No.	Circulation Time (in sec) before	Circulation Time (in sec) 5 min after	Difference (in sec)	Diagnosis
1	13.9	12.4	—1.5	Hypertension
2	15.9	13.2	—2.7	"
3	17.4	15.5	—1.9	Auricular Fibrillation, Hypertension
4	14.6	11.3	—3.3	Hypertension
5	13.8	10.8	—3.0	Artscl. Heart Disease
6	8.1	7.0	—1.1	? Hyperthyroid
7	19.0	16.0	—3.0	Artscl. Heart Disease
8	19.1	15.1	—4.0	Luetic Heart Dis., Aortic Insuf.
9	10.3	9.5	—0.8	Hypertension
10	18.3	11.1	—7.2	Bundle Branch Block
11	20.1	16.4	—3.7	Artscl. Heart Disease
12	23.0	18.7	—4.3	Hypertension
13	18.0	13.3	—4.7	"
14	25.9	16.3	—9.3	Auric. Fibrillation, Hypertension
15	20.3	13.4	—6.9	Luetic Heart Disease
16	13.6	11.5	—2.1	Hypertension
17	23.0	19.4	—3.6	Hypertensive
18	28.9	22.9	—6.0	Artscl. Heart Disease
19	12.5	9.8	—2.7	Rheumatic Heart Disease
20	18.4	13.3	—5.1	Artscl. Heart Disease
21	16.1	14.3	—1.8	" " "
22	17.3	15.3	—2.0	" " "
23	13.7	9.9	—3.8	Hypertension
24	31.4	17.0	—14.4	" Auric. Fibrillation
25	19.5	17.4	—2.1	Undiagnosed
26	14.6	10.6	—4.0	Luetic Heart Disease
27	14.6	16.5	+1.9	Artscl. " "
28	19.8	19.0	—0.8	Rh. Ht. Dis., Mit. Sten., Aur. Fib.
29	14.5	14.5	—0.0	Hypertension
30	11.1	11.5	+0.4	Undiagnosed
31	22.1	22.0	—0.1	Luetic Ht. Dis., Aortic Insuf.
32	14.6	14.5	—0.1	Undiagnosed
33	19.0	19.0	—0.0	Hypertension
34	22.8	23.5	+0.7	Luetic Ht. Dis., Aortic Insuf.
35	17.3	21.4	+4.1	Artscl. Heart Disease
36	14.6	15.2	+0.6	Undiagnosed
37	14.6	15.8	+1.2	"
38	14.6	14.5	—0.1	Artscl. Heart Disease
39	12.6	10.0	—2.6	Hypertension
40	14.8	12.4	—2.4	Luetic Heart Dis., Aneurysm
41	15.2	13.8	—1.4	Artscl. Heart Disease
42	17.8	16.0	—1.8	Hyperten. Ht. Dis., Auric. Fib.
43	20.0	18.6	—1.4	Artscl. Heart Disease
44	14.8	13.2	—1.6	" " "
45	17.0	26.8	+9.8	" " " , Angina
46	14.4	11.4	—3.0	" and Hyperten. Ht. Dis.
47	13.0	11.0	—2.0	" Heart Dis., Angina
48	14.8	12.2	—2.6	? Coronary Occlusion
Mean	16.9	14.6	—1.9	

ured with a stop watch. Subsequent determinations were made following injection at the site of the original venipuncture.

Those patients who were subjected to work were directed to make

25 round trips over a two-step lift[5] in a period of 5 minutes, the speed being controlled by a metronome. With few exceptions, all subjects had the same amount of exercise. Patients in the control groups were maintained at rest in the initial position for 5 minutes.

Data: Normal subjects before and after exercise. (Table I.) After exercise, the circulation time was shortened, the mean value being 2.03 seconds, indicating a more rapid circulation. In terms of the fluctuations within the group, the mean value is apparently insignificant.

Abnormal subjects before and after exercise. (Table II.) The subjects were a heterogeneous group of patients suffering from various illnesses associated with slight to severe alteration of cardiac function. After exercise, the circulation time was shortened, the mean value being 1.9 seconds, indicating a more rapid circulation. In terms of the fluctuations within the group, this value is also insignificant. Inspection of Table II reveals that the circulation time is not characteristic of the type of disease, with the possible exception of auricular fibrillation. This fact, we believe, may account in part for the wide fluctuations within the group. This conclusion is further borne out by the data of Hamilton and Cannon,[6] who used radio-

TABLE III.
Circulation Time of Normal Subjects Before and After Rest.

Case No.	Circulation Time (in sec)		Difference (in sec)
	before	5 min after	
1	14.4	13.0	—1.4
2	12.2	10.8	—1.4
3	11.4	11.2	—0.2
4	11.4	10.4	—1.0
5	9.0	7.4	—1.6
6	12.6	10.2	—2.4
7	11.2	12.3	+1.1
8	12.0	11.8	—0.2
9	8.5	9.6	+1.1
10	14.8	14.2	—0.6
11	12.4	12.0	—0.4
12	14.8	14.0	—0.8
13	11.8	11.0	—0.8
14	11.2	8.0	—3.2
15	10.6	8.2	—2.4
16	13.0	15.6	+2.6
17	11.4	16.4	+5.0
18	9.4	12.0	+2.6
19	9.6	10.6	+1.0
20	12.5	10.0	—2.5
21	7.0	6.6	—0.4
Mean	11.6	11.2	—0.28

[6] Hamilton, J. G., and Cannon, E. F., unpublished data.

TABLE IV.
Circulation Time of Abnormal Subjects Before and After Rest.

Case No.	Circulation Time (in sec) before	Circulation Time (in sec) 5 min after	Difference (in sec)	Diagnosis
1	10.2	11.2	+ 1.0	Rh. Ht. Dis., Aortic Insuf.
2	51.3	56.8	+ 5.5	Auric. Fib. ? Etiology
3	14.4	14.6	+ 0.2	Rh. Ht. Dis., Aortic Insuf.
4	11.2	11.0	— 0.2	Artscl. Heart Disease
5	42.0	49.8	+ 7.8	Coronary occlusion
6	12.2	13.0	+ 0.8	Artscl. Heart Disease
7	8.6	7.8	— 0.8	Hyptertension
8	53.2	52.2	— 1.0	Artscl., Hyperten. Ht. Dis.
9	30.6	28.0	— 2.6	Artscl. Ht. Dis., c mild fail.
10	9.6	8.6	— 1.0	Aortic coaretation
11	19.6	19.4	— 0.2	Artscl., Hyperten. Ht. Dis.
12	11.4	11.4	— 0.0	" " " "
13	10.5	9.6	— 0.9	" " " "
14	10.2	10.4	+ 0.2	" " " "
15	11.2	11.0	— 0.2	Ht. Disease, ? etiology
16	12.2	15.0	+ 2.8	Artscl. Hyperten. Ht. Dis., Auri. Fib.
17	17.8	16.6	— 1.2	Paroxysmal Aur. Fib.
18	54.0	39.6	—14.4	Artsl. Ht. Dis., Aur. Fib.
19	17.2	13.4	— 3.8	Ht. Dis., ? etiology
20	8.4	8.6	+ 0.2	Artscl. Heart Disease

sodium and decholin for a comparison of the circulation times of these substances in the same individual. A comparison of the mean values of Groups I and II reveals no significant variations, with the exception that on the average the circulation time of patients with heart disease was prolonged. Insofar as these subjects are concerned, no information of value was obtained by means of this test.

Normal subjects before and after rest. (Table III.) The circulation time for this group remained practically unchanged, the mean difference between tests performed before and after a 5-minute rest period was 0.28 seconds.

Abnormal subjects before and after rest. (Table IV.) In this group there were marked fluctuations between individual values; however, the mean difference between tests performed before and after a 5-minute rest period was only 0.38 seconds. On the average the circulation time was relatively prolonged in these subjects with

TABLE V.
Summary of Mean Circulation Time in Normal and Abnormal Subjects Before and After a 5-Minute Period of Work or Rest.

	No. of Subjects	Circulation Time (in sec) before	Circulation Time (in sec) 5 min after	Difference (in sec)
Normal subjects with work	20	13.8	11.6	2.03
Abnormal " " "	48	16.9	14.6	1.90
Normal subjects at rest	21	11.6	11.2	0.28
Abnormal " " "	20	20.8	20.0	0.38

heart disease, when contrasted with normal subjects. A summary of the significant data is given in Table V.

Summary. The circulation time is characteristic for the subject rather than for the type of heart disease. On the average, the circulation time for individuals with heart disease is prolonged. The difference between the circulation time before and after 5 minutes of exercise is greater than that before and after a 5-minute period of rest. The difference between the circulation time before and after 5 minutes of exercise in the diseased group is similar to that of the normal group. The difference induced in the circulation time after exercise is not significant as a test of cardiac efficiency.

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Comparison of Different Types of Central Stimulation from Analeptics.*

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In a study of the analeptic potency of the sympathomimetic amines,[1] a simple and rapid method has been developed in this laboratory for graphic registration of one kind of central stimulation. In order to establish standards of comparison for this study, observations have been made on 5 unrelated analeptics, to determine whether the method will demonstrate differences between the various compounds, which could serve as a basis for analysis of their actions. The present report gives the results on the stimulant actions of metrazol, picrotoxin, coramine, caffeine, and cocaine, as revealed by this procedure. Later, results of the application of this same method to the sympathomimetic amines will be reported.

After testing a considerable variety of methods for measuring the total activity of animals, one was devised which utilizes well known principles, although somewhat differently applied. It has the advantage of graphically integrating total activity, without the necessity of laboriously measuring marks of a lever on a drum, as is done

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1 Tainter, M. L., Whitsell, L. J., and Dille, J. M., *J. Pharm. Exp. Therap.*, **1939, 67**, 56.