15086

# Influence of Dosage and Volume on the Circulation Time.

ARTHUR RUSKIN AND PAUL ROCKWELL. (Introduced by George M. Decherd, Jr.)
*From the Department of Medicine, University of Texas Medical School, and the Heart Station of the John Sealy Hospital, Galveston, Texas.*

While using the subjective nut-like taste and smell which follows the intravenous injection of thiamine as a method of determining the circulation time,[1] we found that our figures for normal individuals ranged from 5 to 12 seconds, the great majority being between 7 and 9 seconds. Other subjective methods involving taste (Table I) give variable but, in general, higher figures, according to the literature. This is also true of most of the so-called objective methods (Table I), involving detection of radioactive substances, dyes, or deep inspiration caused by stimulation of the carotid sinus or the respiratory center in the medulla. The papaverine method of Elek and Solarz,[2] presumably involving the stimulation of the medullary respiratory center, gives figures for normals of 15.9 to 27 seconds, which seem to be much too long. On the other hand, the improved lobeline method, utilizing the perception of "tickling" in the throat as well as carotid sinus stimulation of respiration, in the hands of Piccione and Boyd[3] gave results in normals entirely comparable to ours, 5 to 12 seconds. The results would have been somewhat higher had they included the time of injection. Bernstein and Simkins[4] stated that 7-17.8 seconds were the normal circulation times for their routine dose, 6 cc of 10% magnesium sulphate, but mentioned that in "sensitive patients" doses of as little as 2 cc gave circulation times as low as 6 seconds. We have obtained similar low values in some normal individuals, especially with one gram doses of magnesium sulphate as well as the usual doses of intravenous arsenicals used in the treatment of syphilis.[5] Different points of detection alone cannot explain the marked differences in circulation times obtained by the various methods in comparable patients (Table I), or the same patients.[1-6] It must be remembered, however, that the velocity of blood flow is considerably greater in the arteries than in the arterioles, capillaries and venules, and that the latter channels are perhaps variably involved in all of the above methods.

The diodrast method of Robb and Steinberg[7] for visualization of the heart and great vessels may be considered an objective method for the determination of circulation time. The left ventricle has been visualized by the authors in 6 to 9 seconds, and sometimes longer. If approximately 1 second is added for further transmission to the tongue,[8] the resulting circulation time is closer to our figures than to most other published in the literature (Table I), including the authors' own sodium cyanide circulation times. Because this method employs large volumes (35 cc), injected under pressure through a large bore needle, with the arm held up and the body vertical, it was felt necessary to study the effect of varying volumes, and of the position of the body and arm, especially since it is generally assumed that large volumes give too high a reading because of the delay in injection. As early as 1922, Loevenhart

1 Ruskin, A., and Decherd, G., *Federation Proc.*, 1945, **4**, 62.

2 Elek, S. R., and Solarz, S. D., *Am. Heart J.*, 1942, **24**, 281.

3 Piccione, F. V., and Boyd, L. J., *J. Lab. and Clin. Med.*, 1941, **26**, 766.

4 Bernstein, M., and Simkins, S., *Am. Heart J.*, 1939, **17**, 218.

5 Ruskin, A., Rockwell, P., and Decherd, G., unpublished observations.

6 Hussey, H. H., Cyr, D. P., and Katz, S., *Am. Int. Med.*, 1942, **17**, 849.

7 Robb, G. P., and Steinberg, I., *Am. J. Roentgenol.*, 1939, **41**, 1.

8 Blumgart, H. L., and Weiss, S., *J. Clin. Invest.*, 1927, **4**, 15.

TABLE I.
Normal Human Circulation Times by Various Methods.

| Substance | Effect at | Circ. time (sec.) | References |
|---|---|---|---|
| Radium-C | other arm | 12 -23 | Blumgart and Weiss, 1927 |
| Thorium-X | " " | 10 -20 | Gerlach *et al.*, 1943 |
| Radioactive sodium | " " (children) | 5 -17 | Hubbard *et al.*, 1942 |
| Fluorescein (ultra violet) | conjunctiva | 7 -15.6 | Fishback, 1941 |
| | lip | 15 -20 | Lange and Boyd, 1942 |
| Methylene blue (photoelect.) | skin | 7 -21.6 | Jablons *et al.*, 1942 |
| Lobeline | carotid sinus | 5 -12 | Piccione and Boyd, 1941 |
| Sodium cyanide | " " | 9 -21 | Robb and Weiss, 1933 |
| Aminophylline | medulla | 7.1-20.4 | Koster and Sarnoff, 1943 |
| Papaverine | medulla? | 15.4-27 | Elek and Solarz, 1942 |
| Histamine | skin | 13 -30 | Weiss *et al.*, 1929 |
| Decholin | tongue | 10 -16 | Tarr *et al.*, 1933 |
| Saccharin | " | 9 -16 | Fishberg *et al.*, 1935 |
| Calcium chloride | " | 9 -15 | Kahler, 1930 |
| Calcium gluconate | " | 10 -16 | Goldberg, 1936 |
| Magnesium sulphate | " | 7 -17.8 | Bernstein and Simkins, 1939 |
| Magnes. Sulph. comp. (Macasol) | " | 5 -24 | Kvale and Allen, 1939 |
| Diodrast | left ventricle | 6 - 9 | Robb and Steinberg, 1938 |
| Thiamine | tongue and nose | 5 -12 | Ruskin *et al.*, 1945 |

*et al.*,[9] using sodium cyanide for the determination of circulation time in animals, found that sub-optimal doses gave no, or false high, readings. We[5] have noted the same effect in patients, particularly those in cardiac failure, when employing either magnesium sulphate or thiamine. It seemed likely that variation in volume, dosage, and possibly position of the patient might explain in part the highly variable data thus far obtained by different workers.

*Method.* The effect of dosage was determined by injecting thiamine hydrochloride* in doses from 5 to 900 mg (0.1 cc to 3 cc, diluted as needed), magnesium sulphate 0.05 to 1.0 g (0.1 to 2 cc of the 50% solution), sodium dehydrocholate (decholin) 0.05 to 1.0 g (0.25 to 5 cc of the 20% solution, diluted as needed), and theophylline-ethylenediamine (aminophylline) 0.01 to 0.48 g (0.05 to 2 cc of the 24% solution). Various doses of the same drug were injected in the same patients, using those confined to bed but without demonstrable heart disease, on different days, in approximately the same near-basal condition, either before breakfast, or during the day before meals. Our observations agree with those of other workers,[10–13] that no perceptible error is thus introduced. Rapid injection into the antecubital vein required 2 seconds or less, with the stop watch timed from the beginning of the injection. The majority of the observations were done in duplicate and the curves (Fig. 1-5) were drawn from their averages.

The effects of volume, pressure and posture, were studied by using thiamine hydrochloride in a constant dose of 300 mg, a supra-optimal dose for the 5 patients studied (Fig. 6). This amount, diluted with normal saline solution to volumes varying from 1 to 30 cc, was injected through a 14 gauge needle. In one instance (patient C.F.), the dose was injected repeatedly in 1 and 30 cc volumes on different days with the results shown. In 2 other instances the 1 and 20 cc volumes were injected in the antecubital vein in the direction opposite the venous flow as well as in the same direction (Fig. 6). In 2 other instances 20 cc volumes were also injected with the patient standing upright and the arm elevated as in the clinical diodrast method.

*Results. Effect of Dosage.* When the circu-

[9] Loevenhart, A. S., Schlomovitz, B. H., and Seybold, E. G., *J. Pharm. and Exp. Therap.*, 1922, **19**, 221.

* Kindly supplied to us by Dr. H. S. Newcomer, E. R. Squibb and Sons, in 10 cc rubber-capped vials, containing exactly 300 mg per cc.

[10] Reingold, I. M., Neuwelt, F., and Necheles, H., *J. Lab. and Clin. Med.*, 1942, **28**, 289.

[11] Tarr, L., Oppenheimer, B. S., and Sager, R. V., *Am. Heart J.*, 1933, **8**, 766.

[12] Goldberg, S. G., *Am. J. Med. Sc.*, 1936, **192**, 36.

[13] Kvale, W. F., and Allen, E. V., *Am. Heart J.*, 1939, **18**, 519.

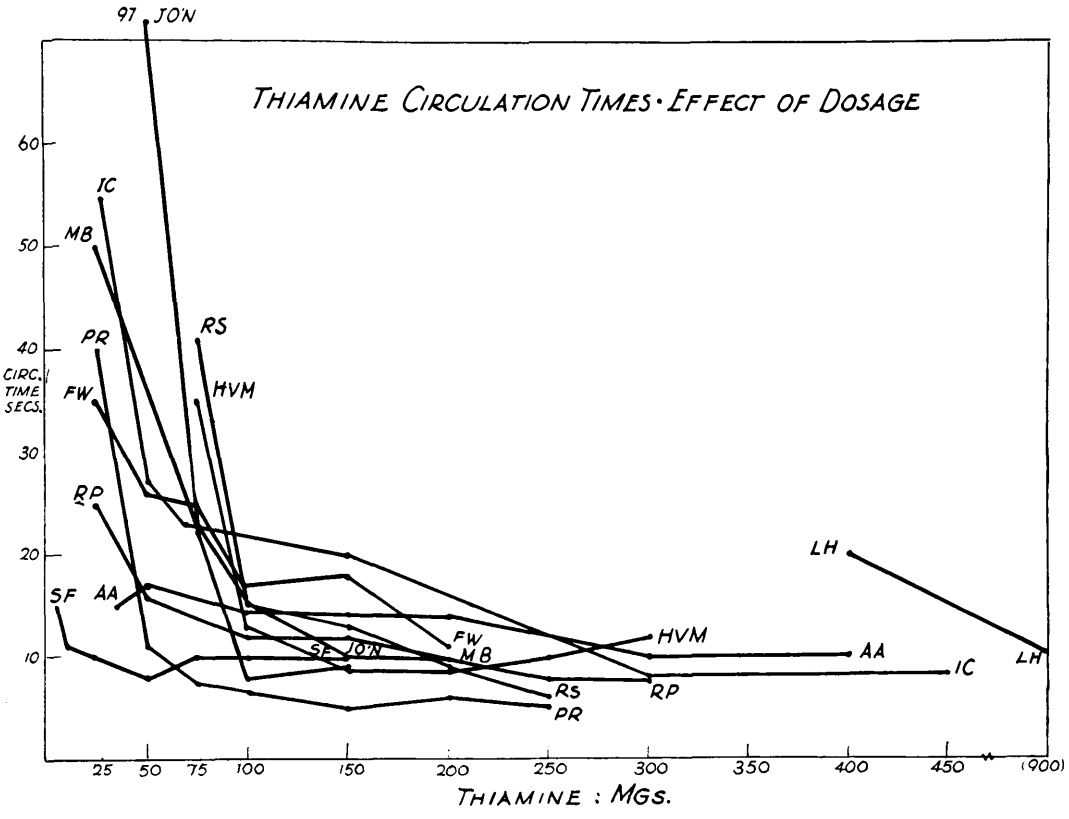


FIG. 1.
Effect of various dosages of thiamine hydrochloride upon the circulation times of 11 patients free from demonstrable heart disease.

lation time in seconds was plotted against dosage, logarithmic curves were obtained in most instances. (Fig. 1-5). For thiamine low doses gave rather higher readings than for decholin and magnesium sulphate; aminophylline showed the narrowest span of circulation times for varying doses. It will be seen that the lowest dose of any drug first producing a response varied in different individuals. Likewise the optimal dose reaching the asymptotic level, or producing the shortest circulation time, varied similarly. Thus, one individual (S.F., Fig. 1) could taste and smell thiamine with a dose as low as 5 mg, and 25 mg was his optimal dose, higher doses not shortening the circulation time appreciably. Another (L.H. Fig. 1) gave no response until 400 mg was injected and gave a much lower reading of the circulation time with 900 mg. This patient was a rare exception, who with a standard dose of 300 mg would have been classified as a nonreactor. The asymptotic or optimal doses obtained were, in general at least 100-300 mg for thiamin, 0.24-0.48 g for aminophylline, 1.0 g for magnesium sulphate, and 1.0 g for decholin. This would indicate that dosages previously used in investigative and clinical work may have been too low and, hence, the readings so obtained too high.

*Effect of Volume and Position.* Fig. 6 shows the effect of volume on the circulation time, and it will be seen that when 300 mg of thiamine was injected in 5 cc of solution instead of 1 cc the circulation time was shortened by 1-2 seconds. The 20 cc and 30 cc volumes, as compared to 1 cc, shortened it by 3-5 seconds. 1 cc volumes injected up or down the vein made no difference in circulation time in two instances. Twenty cc volumes, however, injected in a direction opposite the venous flow, actually lengthened the circulation time by 1-2 seconds. Whether the 20 cc volumes were injected in horizontal or

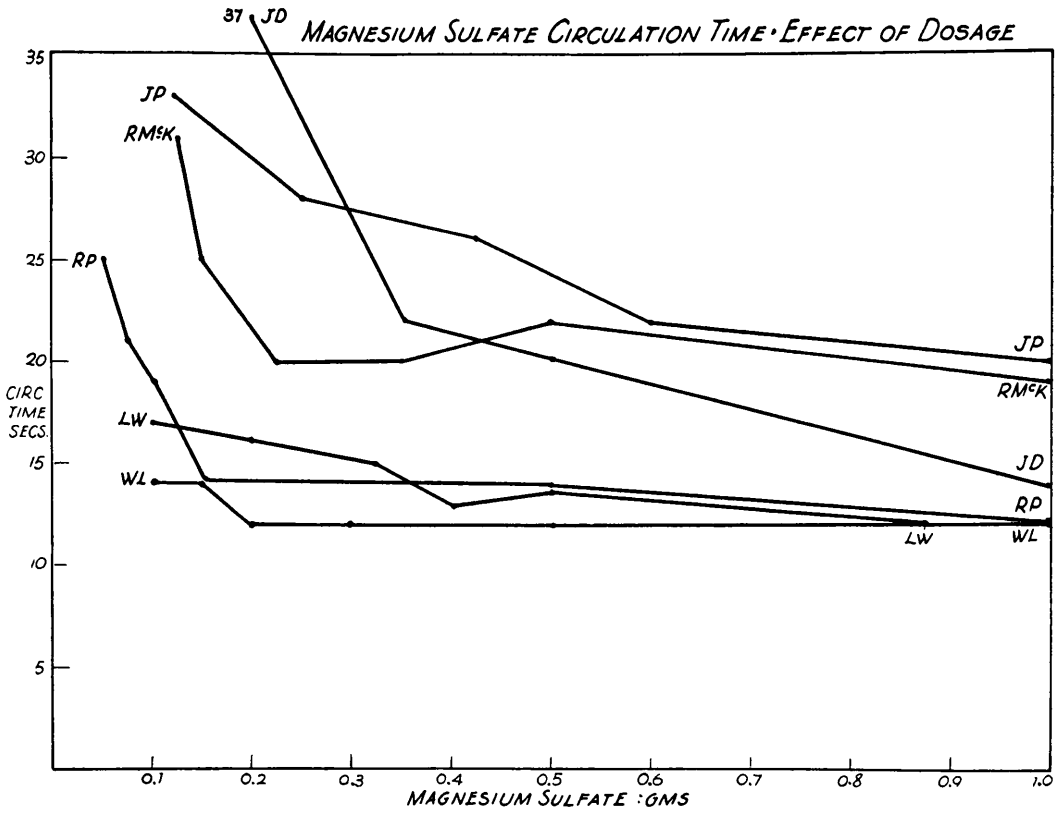


FIG. 2.

Effect of various dosages of magnesium sulphate upon circulation times of 6 patients, free from demonstrable heart disease.

vertical body and arm positions made no difference in circulation times.

*Comment.* The optimal dose of any agent used for determining the circulation time is that dose which gives values in the asymptotic portion of the curve (Fig. 1-5). Our study shows that the optimal dosage of at least 4 drugs used in the measurement of circulation time varies with the individual and the drug; that low or suboptimal doses give no end-points or end-points that are too high, and that these also vary with the individual and the drug. It follows that in any study, clinical or experimental, the use of a standard dosage will result in some failures to obtain an end-point, and this is probably true, contrary to some claims[2,4,11,12,14] of almost any drug in clinical usage.[1,3,5,6] It also follows that the wide scatter and high range of "normal" circulation times by various methods may be due to disregard of the logarithmic variation of circulation time with dosage. This is even more true of patients in congestive heart failure.[4,5] Failures or unduly high and variable readings are also obtained especially for distant points of detection, such as the feet, hands and perineum.[5,13] In other words, either slowing of the circulation as in congestive heart failure, or greater distance to the points of detection result in dilution, or, in effect, lower the amount of the drug actually reaching the place of detection; the end result is that of a suboptimal dose. In congestive heart failure a higher threshold of stimulation or perception may also be present and different optimal doses for the estimation of circulation times in various stages of heart failure may be required for this reason as well. We have attempted[5] to study the effect of dosage in patients with congestive heart failure, and the results have

[14] Robb, G. P., and Weiss, S., *Am. Heart J.*, 1933, **8**, 650.

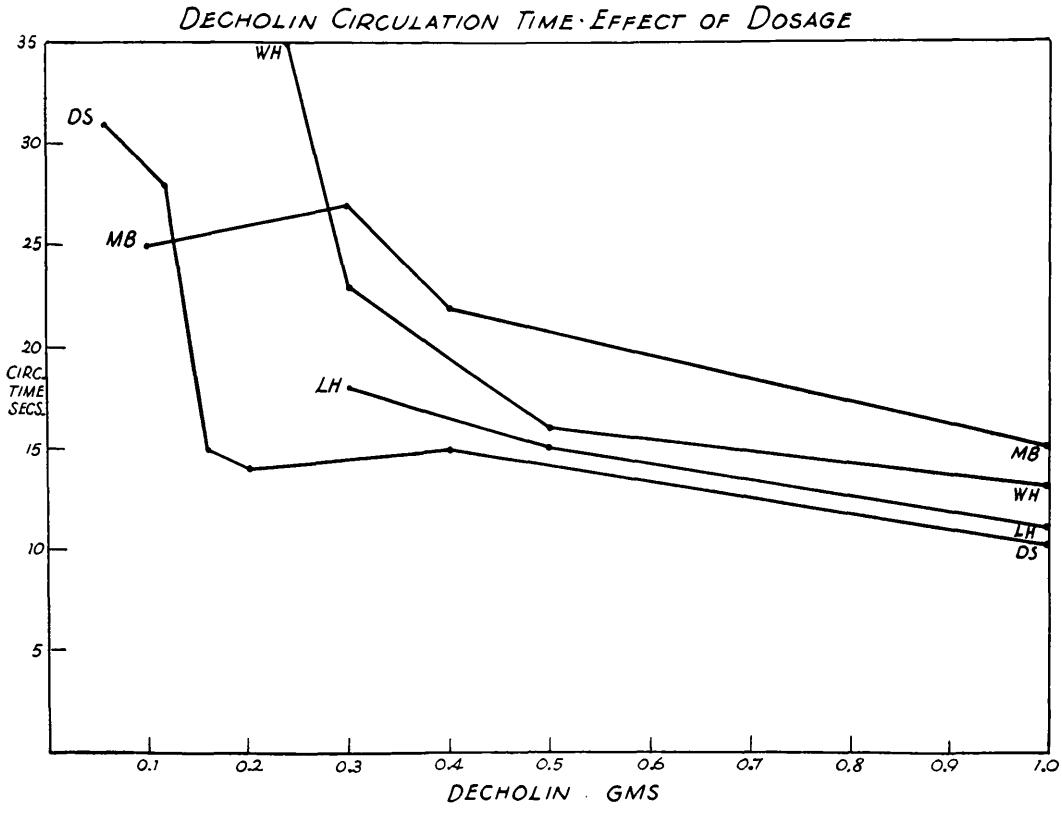


FIG. 3.

Effect of various dosages of decholin upon the circulation times of 4 patients, free from demonstrable heart disease.

shown the same trends as in the present study, but have been too variable for graphic representation.

Our findings are in essential agreement with the evidence obtained in animals by Loevenhart *et al.*[9] of prolonged circulation times when subminimal doses of sodium cyanide were used. Robb and Weiss[14] likewise stated that relatively low doses of sodium cyanide gave circulation times in patients from 3 to 10 seconds longer than those obtained from larger doses, and presented a case showing a reduction of the circulation time from 22 to 16 seconds upon increasing the dose from 5 to 10 mg. Elek and Solarz[2] likewise tried the effect of increasing the dosage of papaverine from 32 to 56 mg in 2 cases, with corresponding reduction of the circulation time from 25 to 21 seconds, which they interpreted, however, to be of no significance.

It would be of great interest to determine whether the same logarithmic curves hold for varied dosage of radioactive substances and dyes now used (Table I) as objective measurements of circulation time. We have noted that the trend holds for one objective method —the aminophyllin one, and we have mentioned above that two groups of workers pointed it out for another one—the sodium cyanide method.

In a review of the subject Blumgart[15] defined circulation time as the interval of time necessary for the fastest particle of a foreign substance to traverse the shortest possible path between the point of injection and the place of detection. Our experiments indicate that it takes not one but a certain concentrated number of particles per unit time to be detected by the taste buds of the tongue, or the sensory nerves of the throat, or to stimulate the respiratory center enough to produce an easily detectable inspiratory gasp.

15 Blumgart, H. L., *Medicine*, 1931, **10**, 1.

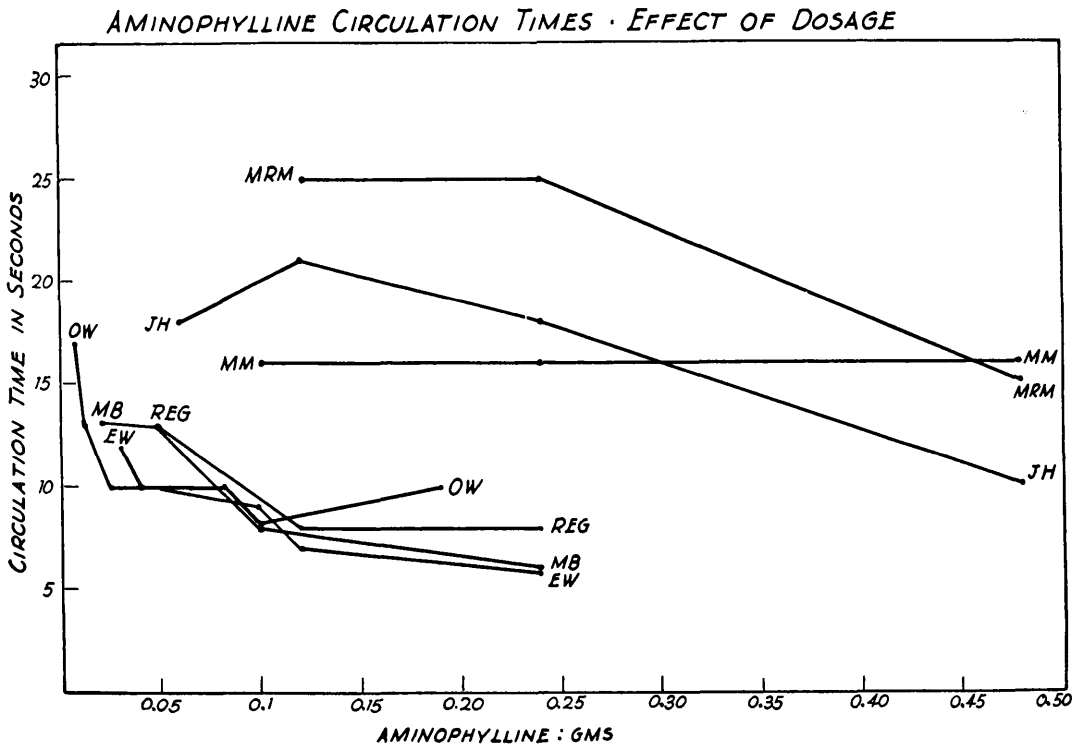


FIG. 4.
Effect of various dosages of aminophylline upon the circulation times of 7 patients free from demonstrable heart disease.

In other words, strength and duration of the stimulus have to be considered in actual practice. It was our impression, without pneumographic evidence, that suboptimal doses of aminophylline produced a poorly defined and more gradual as well as late inspiration, if they gave an end-point at all. With magnesium sulphate, decholin, and thiamine we have noted, too, that the degree of sensation of heat or taste, was, in general, in proportion to the dose used. Similar observations have been made for sodium cyanide,[10] lobeline,[3] and papaverine.[2] While proof is not now available, it is reasonable to believe that the same statements probably held for the detection of radioactive substances by the Geiger counter or dyes by the photoelectric cell and galvanometer, or ultraviolet light fluorescence. It was noted that suboptimal doses of aminophylline produced less lengthening of circulation time than did those of the subjectively appreciated drugs. This may be true of other objective methods, and the shorter the span of circulation time with dosage, the flatter the curve, the more dependable should that method be. On the other hand, the safest maximum dosage of the various drugs listed in Table I, with the exception of thiamine and a few others, may not give the shortest or asymptotic circulation times in individual cases. Our observations[5] indicate that the sensory nerves of the tongue and throat are apparently depressed in some patients by smoking, old age, and previous strong tastes, with resulting failure or undue prolongation of the circulation times when subjective methods involving taste or heat perception are used. Such is the frequent effect, for instance, of repeating the drug injection within several minutes of the previous test, contrary to the claims of other observers[4,11,12] that comparable duplicate measurements may be thus always obtained. A higher threshold of stimulation, thus, may act just as a suboptimal dose. This criticism may not hold for the so-called objective methods;[2,5,16] further study is necessary.

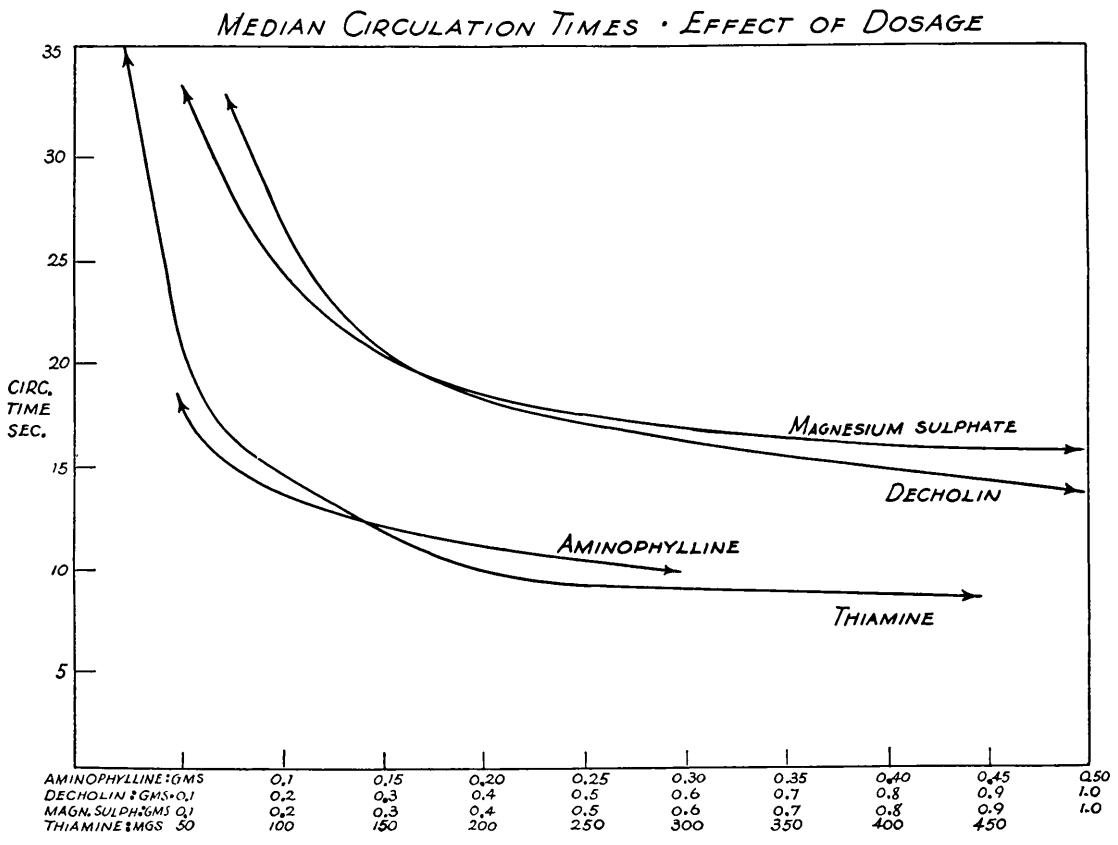


FIG. 5.
Curves showing median circulation times as dependent on dosage of thiamine, magnesium sulphate, decholin, and aminophylline.

Another limiting factor, particularly true of decholin, 10% magnesium sulphate or calcium salts, and especially, diodrast, is volume of solution. Loevenhart *et al.*[9] showed for sodium cyanide in animals, and most subsequent investigators implied, that duration of injection over one second will prolong the circulation time. Efforts had been made, therefore, to limit the volume of solution and inject it as rapidly as possible, if necessary through a large bore needle. Winternitz *et al.*[17] noted, without explanation, that dilution of the dose of histamine recommended by Weiss *et al.*,[18] to 5 cc gave shorter and more constant circulation times than had been reported by the latter group. The results of Winternitz's group are not comparable, however, with those of other observers because their measurements were begun at the end, rather than at the beginning, of injection. Our results show that volumes of 5 cc shorten the thiamine circulation time by 1-2 seconds, and volumes of 20-30 cc by 3-5 seconds. Preliminary observations indicate that this is apparently also true of other methods.[5] Other variable factors, however, are involved in this shortening. One is the great pressure exerted, which mechanically propels the larger volumes forward to the heart, since the capacity of the venous channels up to the right auricle is not much greater than the volumes of fluid injected. That pressure as well as volume is involved is also shown by the fact that injection in the direction opposite the venous flow actually lengthens circulation time despite the over-

16 Koster, H., and Sarnoff, S. J., *J. Lab. and Clin. Med.*, 1943, **28**, 812.

17 Winternitz, M., Deutsch, G., and Brüll, Z., *Med. Klinik.*, 1931, **27**, 986.

18 Weiss, S., Blumgart, H. L., and Robb, G. P., *Am. Heart J.*, 1929, **4**, 664.

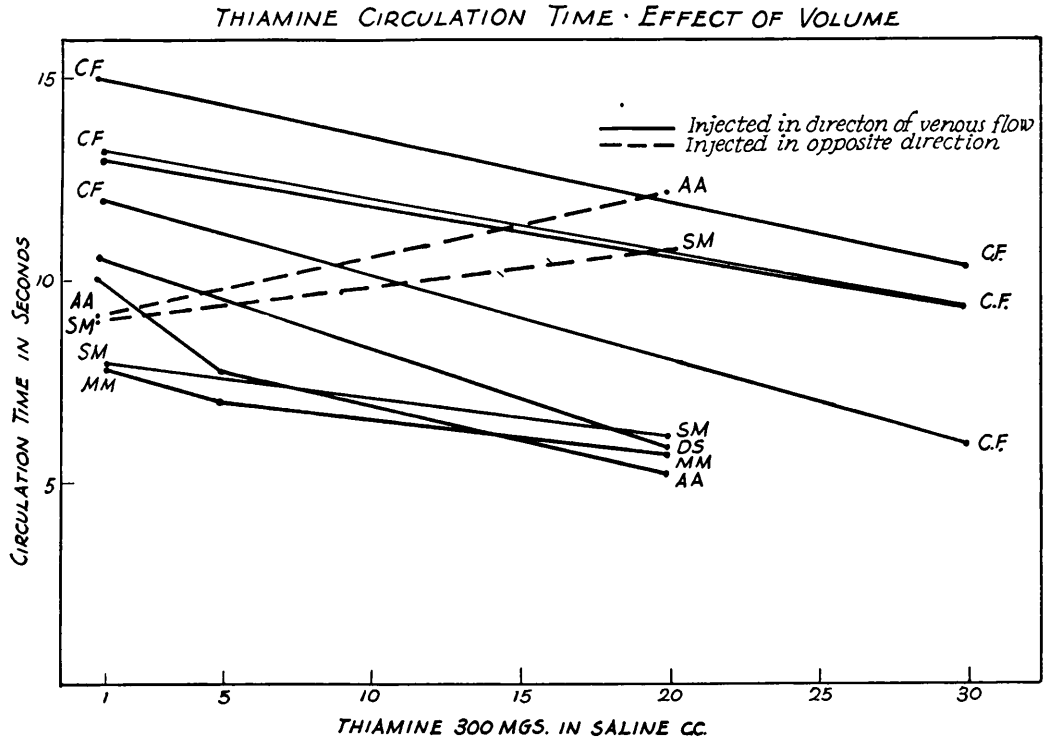


FIG. 6.

Effect of injection of 300 mg of thiamine hydrochloride in volumes of saline varying from 1 to 30 cc on the circulation times. Dotted lines represent effect of injecting the various volumes in patients A.A. and S.M. in the direction opposite the venous flow.

filling of the veins. We have not attempted to study the effects of quantitated pressures. Despite the slowness of injection of the larger volumes in some cases, up to 3-4 and even 5 seconds, the circulation time, measured from the beginning of injection was always shortened. In other words, the effect of dilution of the drug by slow injection, which has been shown to act in opposite fashion,[9] was counterbalanced by the factors of volume and pressure. Other factors, such as the effects of streamline versus turbulent flow, the former of which is known to double the speed of flow in the central portion of the stream as compared with average velocity,[19] are impossible to evaluate from our data.

19 Vennard, J. K., *Elementary Fluid Mechanics*, 1940, p. 113, John Wiley & Sons.

*Summary.* 1. By the use of various dosages of thiamine, magnesium sulphate, decholin and aminophylline, it was shown that lower doses are either ineffective or produce prolonged circulation times. 2. Logarithmic curves express this relationship of circulation time to dosage. These vary from person to person. 3. Beyond a certain dose, varying in different individuals, further increase in dosage causes no appreciable decrease in circulation time. This may be called the optimal or asymptotic dose, and the time the shortest or "true" circulation time. 4. Increasing the volumes containing the same doses of thiamine to 5 cc or more, shorten the circulation times markedly enough to affect clinical measurements.