THE circulation time is the shortest time taken by an injected substance to travel through the circulatory system to a designated site where it produces its characteristic physiologic or physical response.1

In recent years, the measurement of the circulation time has been employed widely in the diagnosis of cardiac disease and in the evaluation of cardiac function. Modern methods of estimating the velocity of blood flow are both simple and safe. Consequently, an imposing volume of data has accumulated during the past 3 decades that substantially has increased our knowledge.

The purpose of this communication is to review the more important advances in the measurement of the circulation time and in the understanding of its significance.

HISTORICAL REVIEW

Harvey's2 discovery in 1628 that blood moves in a circuit first awakened interest in the problem of the velocity of blood flow. More than a century passed, however, before the next significant contribution was made in this field. In 1733, Stephen Hales3 computed the velocity of blood flow in the aorta of the horse. This he did by estimating the capacity of the left ventricle, measuring the diameter of the base of the aorta, and measuring the pulse rate.

In 1827, Eduard Hering4 measured the velocity of blood flow in horses by injecting a solution of potassium ferricyanide at the right external jugular vein, and determining its time of arrival at the left jugular vein by testing samples of blood for prussian blue. Various modifications of Hering's method were introduced during the next century. Vierordt5 developed a more efficient means of collecting the blood samples and Hermann and Heinz6 experimented with other chemical substances.

The introduction of flow-measuring devices into blood vessels first was attempted by Volkman in 1850, and in the latter part of the nineteenth century by Cybulski and Frank. These methods were crude and the results difficult to interpret accurately.7 In 1892 Meyer8 used blood containing methemoglobin as a test substance in animals and determined its time of arrival by spectroscopy.

A notable advance appeared in 1893 when Stewart8 introduced methods that obviated the collection of samples from an opened blood vessel. He injected hypertonic saline solution into a jugular vein and recorded its arrival at other points in the vascular circuit. By placing a blood vessel between 2 nonpolarizable electrodes, he detected a change in the electric conductivity of the vessel when the injected material arrived. He also used methylene blue, observing by transillumination the time at which the dye appeared in the common carotid artery.

The injection of peptone solution into the femoral artery was employed by Noll9 in 1902. He accepted the interval between the local and general lowering of blood pressure as the minimal circulation time of the animal. The marked alteration in hemodynamics produced by such measures obviously vitiated his results.

In 1906 Heinz9 measured the circulation time of horses and dogs by injecting into their jugular veins lethal doses of strychnine or potassium nitrate. He estimated that the time elapsing between the injection and the death of the animal represented the circulation time.

Steinhau (1907), Langlois and Desbouis (1912), Romm (1924), and Mendolesi (1925) suggested improvements of Stewart's electric method.6 Most of these were extremely ingenious, but impractical.

In 1912, Bornstein10 described a method for measuring the circulation time in man by the inhalation of a mixture of carbon dioxide and air. The moment of first deep inspiration was considered the end point. The average lung-to-medulla time in normal individuals was 12 seconds.

Another clinical circulation time method was suggested in 1922 by Koch.11 He injected a solution of fluorescein into one antecubital vein and collected blood samples from the other at 5-second intervals. The formation of clots and the alteration of flow by the introduction of a needle for collecting samples interfered with the trustworthiness of such a method.
A simple means of estimating the velocity of blood flow in animals was devised by Loevenhart and his associates in 1922. They showed that small doses of sodium cyanide could be employed with safety and that a characteristic alteration in depth of respiration consistently signaled the end point. The arm-to-carotid sinus circulation time thereby was measured.

Using radium C, the active deposit of radium emanation as the test substance, Blumgart and his associates measured the circulation time in normal subjects and in a wide variety of pathologic states. These studies, begun in 1924, were among the earliest to utilize radioactive materials as biological tracers. After injection of a minute amount of sodium chloride solution containing radium C, the times of arrival of the active deposit in the right chambers of the heart and in the arteries about the elbow of the arm were detected by suitably placed Geiger counting chambers and were automatically registered on paper tape. The arm-to-heart and pulmonary circulation times thereby were measured.

In the following years, many other methods were devised and reported. Of particular interest were the contributions of Winternitz and co-workers and Hitzig, who introduced Decholin and ether, respectively, for the measurement of the circulation time. Several other excellent methods in current use are discussed below.

Theoretical Physics of the Velocity of Blood Flow and the Significance of the “Circulation Time”

The fundamental characteristics in a hydraulic system that determine the velocity of flow are, of course, well known. The mean velocity of a stream through a rigid tube is directly proportional to its cross-sectional area and the difference in pressure from point to point. These relations have been expressed by Poiseuille’s Law with the formula 

$$\frac{(P_1 - P_2)r^2}{8LN},$$

where $P_1 - P_2$ is equal to the difference in pressure, $r$ is the radius of the tube, $L$ is the length of the tube and $N$ is the coefficient of viscosity. Formulation of the factors by such a law is valuable in focusing attention on the determinants of velocity, but the futility of exact application of such a law to biological phenomena becomes apparent when one considers the constant flux of circumstances within the body. The peripheral vascular bed is constantly varying, not only because of the delicate flexibility of the vasomotor arteriolar control, but also because, as Krogh and as Richards have shown, certain capillaries may temporarily close. It must, moreover, be borne in mind that a certain change, such as peripheral vasodilatation, may influence the velocity of flow simultaneously in 2 opposing directions. The velocity of flow varies inversely as the resistance; therefore, vasodilatation by lowering the resistance tends to increase the velocity. On the other hand, vasodilatation by increasing the cross-sectional area of the flowing stream tends to decrease the velocity. Many continually varying relationships like these serve thoroughly to confuse theoretical calculations.

For the study of the velocity of blood flow in animals or man, direct measurements therefore must be made. Direct methods can be only approximations, however, because of what may be termed the “stringing-out effect.” By the time the test substance reaches the site at which the time of arrival is ascertained, considerable dilution has occurred. This dilution results from several factors. The innumerable vessels in the body are constantly changing in size and elasticity. There is considerable turbulence of the blood stream due to the faster movement of the axial portion of the flowing stream and due to the tortuous course with many branchings and changes in caliber of arteries, arterioles, capillaries, venules, and veins. Moreover, with every heartbeat discontinuous pulsatile waves are produced with outward expansion and inward vibratory rebound of the arteries and by variable respiratory changes in pressure in the veins. Because of these many influences, the concentration of the first portion of the test substance is greatly diluted and is often below what can be detected by the end organ or by the detecting device. An error of several seconds is readily produced thereby. Very sensitive methods employing radioactive substances probably have the least error.

The “circulation time” measures the velocity of blood flow in a given segment of the circulation. The arm-to-tongue, arm-to-face, arm-to-carotid sinus, or arm-to-medulla time measures the circulation time in the veins of the arm, the superior vena cava, the right heart, the lungs, the left heart, and a short arterial segment. The arm-to-lung time measures the
circulation time in the veins of the arm, the superior vena cava, the right heart, and the pulmonary arterial segment. Various other pathways such as arm-to-perineum and arm-to-foot have been studied.

Obviously the circulation time is the sum of the times during which the test substance traverses the successive segments of a given pathway. Factors that influence one or more of the segments are reflected in the total circulation time. A reduction of blood velocity in one segment therefore could readily be counterbalanced by an increase of velocity in another portion of the pathway.

Physical obstruction (e.g., mediastinal tumor) to the entry of blood into the superior vena cava would tend to lengthen the circulation time. Although an elevated venous pressure per se does not alter the circulation time, the consequent venous distention with the increased cross-section area of the flowing stream tends to slow the velocity of blood flow.

In the heart, a number of factors influence the circulation time. Congenital cardiac anomalies with a significant right-to-left shunt usually produce a short circulation time. A decrease in cardiac output tends to lengthen the circulation time, congestive heart failure being the best example. A heart that is expelling a greatly increased volume of blood generally is associated with a swift velocity of blood flow (short circulation time).28, 29

The size of the heart is regarded by many to influence greatly the circulation time.20-24 The prolonged circulation time in patients with cardiac enlargement has been ascribed to excessive dilution of the test substance by the increased residual blood in the dilated heart.22 It is difficult however to visualize sufficient intracardiac stagnation to account for the prolonged circulation time in a heart that is beating 80 to 120 times a minute and expelling liters of blood during this time.35 The correlation between cardiac dilatation and increased circulation time probably represents association more than an etiologic relationship. Circulation times in the high normal range have been recorded in patients with enormous hearts.29

In isolated right ventricular failure, the velocity of blood flow from arm-to-lung is retarded, whereas the speed of flow from lung to tongue is relatively unimpaired.36 Isolated left ventricular failure is suggested by a relatively normal arm-to-lung circulation time with a prolonged lung-to-tongue time.37-39

Abnormalities of the great vessels, e.g., trunci aberrant and patent ductus arteriosus with reversed flow, frequently produce rapid circulation times. On the other hand, left-to-right shunts in the great vessels may occasionally delay the arrival of an effective concentration of the test substance at the receptor organ.

Diseases of the lung may influence the velocity of blood flow. Pulmonary disease that has not produced secondary cardiac changes or compensatory polycythemia seldom causes prolongation of the circulation time.19, 36, 40 The latter is normal or slightly accelerated in a variety of lung diseases. The acceleration, when present, is due presumably to compensatory increase in cardiac output. The addition of pulmonary congestion to a patient already compromised by a reduced cardiac output causes further lengthening of the circulation time because of the increased cross-sectional diameter of the stream of blood flowing through the lungs.41-42 Pulmonary arteriovenous fistulae shorten the circulation time.

After leaving the left ventricle, the test substance must traverse the arterial segment before arriving at the reaction site. Mention has already been made of left-to-right shunts in the great vessels. Obstructions of the thoracic or abdominal aorta may severely impede blood flow and produce an abnormally long circulation time. In coarctation of the aorta the arm-to-tongue time frequently is normal but the arm-to-leg time is prolonged.

Lastly, inaccuracies may arise at the receptor site because the end point depends upon subjective sensations. For example, impaired taste, whatever the cause, may result in an abnormally long circulation time when Decholin or saccharin is used. A clouded sensorium similarly can vitiate a subjective end point.

Extrinsic factors may influence the circulation time markedly.

Age. The velocity of blood flow is somewhat rapid in childhood.13 A slower circulation time45 with increasing age has been reported although
some observers have failed to corroborate this observation.46, 47

Emotion. Apprehension and anxiety by increasing cardiac output tend to shorten the circulation time.41, 48

Position of the Patient. Several studies have been carried out to determine the influence of posture upon the velocity of blood flow in man with extremely variable conclusions.49-53 In a recent report44 no alteration in circulation time was noted in patients in whom the test was carried out both in the vertical and horizontal positions.

Basal State. Formerly it was thought necessary to perform the circulation time test under rigid basal metabolic conditions.13 Although this no longer applies, care is taken to insure that the subject has not eaten for at least 3 hours,44 nor exercised within 1 hour of the performance of the test.54, 41, 55

Dose of Injected Material. Convincing evidence demonstrates that the circulation time may be shortened by increasing the dose of the test substance. With smaller doses, the dilution in the blood stream leads to low concentrations of the oncoming head of the material that are not detectable. Once the optimal dose is reached, further increase fails to produce further reduction of circulation time. The wide scatter and high range of “normal” values may be due in large part to this fact.44 The optimal dosage of test substances varies widely in different individuals. Ideally, the correct dose should first be discovered empirically before recording the circulation time in a given subject.

Volume of Injected Material. A substantial increase44 in the volume of injected material shortens the circulation time by a few seconds.

Rate of Injection. Most of the methods in common use advocate very rapid injection of the test drug. Obviously, an unusually slow injection would give a falsely prolonged circulation time.

Criteria for an Ideal Substance for Measuring Circulation Time in Man

The following requirements should be met by any substance used to measure circulation time in man.

1. It must not be toxic in the amounts utilized.
2. It should not be present previously in the body in amounts that would interfere with the test.
3. It must not in any way disturb the very phenomena under investigation.
4. It should disappear from the body quickly enough to permit repeated measurements.
5. It must be readily detectable in relatively minute amounts.
6. It must be readily detectable by objective methods.
7. These objective methods must not involve the use of complicated, bulky, or expensive apparatus.

An ideal substance has not yet been discovered.

Substances Used for Circulation Time Measurements and Normal Values Obtained

These are tabulated under the name of the test substance utilized.

Aminophyllin (Theophylline ethylene diamine).46 One milliliter of solution containing 0.24 Gm. of aminophyllin is injected rapidly into an antecubital vein. The end point is a marked increase in the depth of respiration. Normal circulation times vary from 6.8 to 22.0 seconds with an average of 12.1 seconds.47 Characteristic reactions to this test are transient dizziness, flushing, and hyperpnea, disappearing within a few minutes, and vomiting and severe hypotension. Emotional upsets in neurotic subjects have been reported after receiving aminophyllin intravenously.47

Amyl Nitrile. The patient inspires deeply 4 minims of amyl nitrite, the end point being a sensation of heat in the face. The lung-to-face circulation time in normal subjects varies between 14 and 25 seconds, the average being 19.5 seconds.46 In the majority of cases in which this method was used, the heart rate increased 40 to 50 beats per minute. Any method that alters circulatory dynamics must be regarded as of doubtful value. Moreover, dizziness, flushing of the face, and lacrimation were fairly frequent sequelae.

Calcium Gluconate. Two and a half milliliters of a 20 per cent solution of calcium gluconate61...
are injected into an antecubital vein. A hot sensation in the pharynx signifies the end point. The circulation time in normal individuals varies between 10 and 16 seconds, with an average value of 12.5 seconds.

It is reported that calcium gluconate produces inaccurate results when used in patients with congestive heart failure.57 Although the intravenous administration of calcium salts to a patient receiving digitalis is usually innocuous55, 59 an element of danger exists.60, 61 Many patients in whom circulation time tests are carried out are digitalized. Furthermore, the intravenous injection of 10 ml. of 20 per cent calcium gluconate produced changes in the electrocardiograms of 26 normal individuals.62 A much smaller dose of calcium chloride administered intravenously to a British physician produced cardiac and respiratory arrest.63 Fortunately, he recovered and laconically reported that “no residual effects were noted.” A preparation containing calcium gluconate, magnesium sulfate, and copper sulfate dissolved in saline has been reported favorably by some investigators.29, 33, 64

Carbon Dioxide. A modification of Bornstein’s method was introduced in 1939.65 The patient inhales a 50 per cent mixture of carbon dioxide and air, the end point being a feeling of warmth in the head and rapid and deep respiration. Normal values range from 5 to 10 seconds. This simple and apparently harmless procedure appears to enjoy little popularity.

Sodium Cyanide. This test is performed by injecting intravenously 0.25 to 0.50 ml. of a 2 per cent solution of sodium cyanide. The sharp end point is indicated by a gasp or a cough. The average circulation time is 15.6 seconds with normal values ranging from 9 to 21 seconds.66 Unfortunately, in dyspeptic patients the end point may be difficult to observe.1 The side effect of vomiting is very rarely encountered.67 The possible hazard of the test has prevented widespread use.

Decholin (sodium dehydrocholate). This is the most widely used method of estimating the circulation time in man, no doubt due to its simplicity, safety, and clear end point. Five milliliters of 20 per cent Decholin solution are quickly injected intravenously, the end point being a bitter taste in the tongue. Values of 8 to 17 seconds may be considered within normal range.26, 68 Three deaths have occurred following the intravenous administration of sodium dehydrocholate.69, 70 In addition, a substantial number of unpleasant reactions to this drug have been reported.71-75 These have included gastrointestinal disturbances, cardiac arrhythmias, shock, respiratory embarrassments, and hypersensitivity states.

Ether. This substance is extensively employed for the measurement of the arm-to-lung circulation time.27, 36, 38, 76 A mixture of 5 minims of ether and 3 minims of normal saline is injected rapidly into an antecubital vein. The end point is recorded when the patient first smells ether. An observer in a position close to the subject can perceive the ether odor almost as rapidly as the patient. The normal arm-to-lung time varies from 3.5 to 8.0 seconds with an average of 5.4 seconds. About 25 per cent of patients complain of transient pain along the course of the vein, and venous thrombosis is not an infrequent complication.29 Sudden death has been reported.77

Fluorescein. Several modifications of Koch’s method have been suggested in recent years.46, 78, 79, 80 All require a darkened room and some type of ultraviolet light to excite fluorescence. One simple method consists in the injection of 3 ml. of 15 per cent sodium fluorescein intravenously and the determination of the onset of fluorescence of the tongue under ultraviolet light.80 Fluorescein produces nausea and vomiting in a small percentage of patients. Burning on urination occasionally is encountered.

Histamine. This method utilizes the intravenous injection of 0.001 mg. or less of histamine phosphate per kilogram of body weight. A marked flushing of the face denotes the end point. Normal circulation times vary between 13 and 30 seconds with a mean of 23 seconds.81 This test cannot be used in Negroes or very anemic patients. In one series, headache was experienced in 25 per cent of the subjects tested.13 Severe reactions and 1 death have been attributed to this substance.82, 83

Lobeline. Three to 6 mg. of alpha-lobeline are injected rapidly; a cough or tickling in the
throat signals the end point. The average normal circulation time is considered to be between 10.3 and 13.4 seconds. A few patients have developed moderate dyspnea during the test, vomiting is encountered rarely. Alpha-llobeline has been described as having "emphatically disadvantageous effects on the heart and circulation" and being "a pharmacologically active alkaloid with an unclear seat of action and unpleasant side reactions." 

Magnesium Sulfate. Six milliliters of a 10 per cent solution of magnesium sulfate are injected; a feeling of sudden heat in the pharynx indicates the end point. Normal values range from 7.0 to 17.8 seconds, with an average of 12.9 seconds. In 1 report, 579 magnesium sulfate circulation times were carried out in 274 patients without evidence of toxicity. Many hypertensive and some normotensive individuals showed a marked drop of systolic and diastolic pressures immediately after injection. However, circulation times repeated within 2 to 3 minutes in these patients showed satisfactory duplicate values.

Papaverine. Forty milligrams of papaverine hydrochloride are administered intravenously. The end point is a sudden deep inspiration. The range of normal values is from 15.4 to 27.0 seconds, the average circulation time is 20.8 seconds. Frequent side effects are a sensation of throbbing in the temples and mild dizziness; a less frequent occurrence is tachycardia. In one series, papaverine failed to produce satisfactory end points in the majority of patients in whom it was used.

Paraldehyde. This is an arm-to-lung method. Rapid intravenous injection of 1.4 ml. of paraldehyde produces the end point of a sharp cough. The normal range is 3.0 to 9.5 seconds, the calculated mean is approximately 6.0 seconds. The disadvantages are (1) transitory dizziness, which may take several minutes to pass away; (2) rarely, complete hypnosis for a few minutes; (3) cough usually lasting for 1 to 3 minutes; (4) venous thrombosis and pulmonary embolus that occasionally follow its use.

Radium C. A cloud chamber or Geiger-Mueller counter for detecting the test substance at the receptor area and lead shields are required for this test. One to 10 mc. of radium C are injected into an antecubital vein and the end point is determined by the appearance of characteristic tracks in the cloud chamber placed over the other antecubital fossa. The values to be expected in normal individuals are 14 to 24 seconds, averaging 18 seconds. No toxic effects resulted from the use of this material in several hundred patients. Unfortunately, this method requires the use of expensive and complicated apparatus. These factors have limited its widespread adoption.

Saccharin. This is one of the simpler methods. Four milliliters of solution containing 2.5 Gm. of saccharin are injected intravenously. The end point is signaled when the patient suddenly experiences a sweet taste. Normal values range from 9 to 16 seconds with an average of 12 seconds. A careful search of the literature has uncovered only a single report of complications following a saccharin circulation time; paravenous injection resulted in the development of an abscess in the arm of a young woman.

Radioactive Sodium. This method has been advocated especially for measuring the circulation time in children. A dose of 2 to 5 mc. of radioactive sodium per Kg. of body weight is injected into an antecubital vein of one arm. The end point is detected by a Geiger counter held close to the other hand. Normal values for children between 2 and 12 years are 5 to 17 seconds with the average of 11 seconds. This test material must be produced by cyclotron bombardment and is therefore not generally available. The gamma rays produced by it are highly penetrating and present problems in adequate shielding of the detector.

Thiamine. The intravenous injection of 300 mg. of thiamine hydrochloride produces a nutlike taste and smell. This end point normally occurs within 5 to 13 seconds after the beginning of the injection. The parenteral administration of thiamine hydrochloride occasionally may produce severe hypersensitivity reactions. Sudden death has followed the intravenous injection of 100 mg. of this drug.

Less Common Substances. In addition to the substances listed above the following drugs also have been used to determine the velocity of blood flow in man: acetylene, allyl sulfide,
benzyl acetate,74 brilliant vital red,49 ethyl iodide,97 guaiacol,76 methyl salicylate,76 nikethamide,55 perfumes,56 sodium cacodylate,76 stron-
tium bromide,88 and radioactive thorium.99

Technic of Measuring Circulation Time

Circulation time measurements should preferably be performed under standard conditions, particularly if a series of tests is to be done on different days for comparative purposes. The patient should be recumbent and at rest for 30 minutes prior to the test and should have eaten no food for at least 3 hours. He should be told exactly what he is about to experience and every effort should be directed toward allaying his anxiety. He is instructed to say "now" the moment he experiences the first unusual sensation, be it a hot sensation in the pharynx, a bitter or sweet taste on the tongue, etc.

With the patient lying comfortably supine in bed or on a couch, one arm is abducted to about 45 degrees and is supported on a firm pillow. The antecubital fossa should be approximately at the level of the right atrium. If the subject is orthopneic, he is permitted to sit upright supported on pillows. An 18- or 19-gage needle is securely attached to a syringe containing the correct dose of the test substance. Where the method permits, a double dose of the substance is drawn into the syringe, making a change of syringes unnecessary. The needle is introduced into an antecubital vein in the usual manner. An interval of at least 15 seconds must elapse from the release of the tourniquet before the start of the injection. A single dose of solution is injected as rapidly as possible, usually in 1 to 2 seconds. An assistant starts a stopwatch at the commencement of injection and stops it promptly when the patient says "now." If no assistant is available, the operator starts the watch and places it in a convenient position. He waits until the second hand reaches the zero mark and then injects the test material. Observing the watch carefully, he notes the exact time at which the patient signals his reaction. Where applicable, the test is repeated within a couple of minutes without disturbing the needle in the vein. If an objective method is utilized, the aid of an assistant is usually essential.

Choice of Method. We have already stated that an ideal substance for measuring the circulation time has not yet been discovered. The principal criterion for a method is that it should be free from toxic side effects. Obviously, many of the patients in whom one wishes to perform circulation times are suffering from cardiovascular embarrassment. An untoward reaction in such a patient could have very serious consequences.

We believe that the saccharin method is one of the most desirable.29 The end point is clear and not unpleasant for the patient. Saccharin is very soluble so that only a small quantity of solution is required. Furthermore, the test may be repeated within a few minutes with a sharp end point. Venous thrombosis at the site of injection occurs occasionally and one instance of abscess after paravenous injection has been reported.77 The important fact is that no generalized reactions have been recorded following the use of this drug.

Where an objective method is indicated, one utilizing fluorescein appears to be preferable. There are several variations but that of Lubic and Sissman80 probably is the simplest. In this technic, the end point is signaled by the sudden fluorescence of the tongue under ultraviolet light. However, it is necessary to perform this test on several occasions before one becomes skilled in timing the first appearance of fluorescence at the tip of the tongue.

In institutions where the necessary apparatus is available, radium C¹⁰ or radioactive sodium⁵¹ may be recommended, especially when extremely accurate results are desired.

Undoubtedly, Decholin will continue to enjoy wide popularity. Possibly the reason more untoward reactions to this drug have been reported than with any other substances used for circulation time determinations is that it is by far the most commonly employed. Nevertheless, 3 deaths⁶⁹,⁷⁰ have occurred shortly after the intravenous injection of sodium dehy-
drocholate and several alarming reactions also have been reported.⁷⁹, ⁷²-⁷⁵ For the arm-to-lung circulation time, ether is preferable to paraalde-
hyde.

Circulation Time in Various Diseases

Congestive Heart Failure. The distinction between low and high output failure must be
kept in mind. In the former, the circulation time tends to be prolonged; in the latter, it is within the usual normal limits or is somewhat shortened. The lengthened circulation time in low output failure is a reflection of myocardial insufficiency irrespective of its etiology.

In those conditions such as thyrotoxicosis or beriberi heart disease, in which high output failure tends to develop, the velocity of blood flow is increased and the circulation time is shorter than normal. With the development of cardiac failure the blood flow is slowed but usually not enough to produce a circulation time longer than normal.

**Right and Left Heart Failure.** The circulation time is of little value in diagnosing preponderantly right ventricular failure such as cor pulmonale. The characteristic findings are reported as being a prolonged arm-to-lung time with a relatively normal lung-to-tongue time. However, normal arm-to-lung times were found in 34 patients suffering from general heart failure with presumably right and left heart failure. Moreover, typical circulatory findings were not present in 2 patients with primary pulmonary hypertension who exhibited the purest form of isolated right heart failure.

Isolated failure of the left ventricle may be suspected when a normal arm-to-lung time is found in association with a lengthened lung-to-tongue time.

**Congenital Heart Disease.** Circulation time measurements have been used to differentiate certain types of congenital heart disease. In atrial or ventricular septal defects with left-to-right shunts, the circulation time remains within the normal range. In the cyanotic group with a large proportion of blood passing directly from the right ventricle into the aorta, the circulation time is shortened. But when marked polycythemia is present, the circulation time may be normal. In pure pulmonic stenosis, in Lutembacher’s syndrome, and in patent ductus arteriosus there is no alteration in the circulation time. When a right-to-left shunt is suspected, ether must be used with extreme caution, if at all. In some clinics, circulation time measurements are rarely employed. It is considered that in those cases that would show abnormal circulation times, other more direct diagnostic signs are clearly evident.

**Pericarditis.** Although the cardiac output is decreased in chronic constrictive pericarditis, the Decholin circulation time is not unduly prolonged. Stewart and associates reported 6 patients with this disease who were carefully evaluated both before and after surgery. No correlation was demonstrated between the cardiac output and the circulation time. In massive pericardial effusion without congestive failure, the circulation time usually is within normal limits. This clinical test has been used to differentiate between the enlarged cardiac silhouettes of pericardial effusion and cardiac dilatation due to congestive heart failure.

**Pulmonary Emphysema.** Severe chronic pulmonary emphysema does not necessarily obstruct the circulation sufficiently to interfere with the normal velocity of blood flow through the lungs. On the contrary, in some patients with emphysema the velocity of blood flow is increased. This increase may reflect a compensatory response of the circulatory system to deficient pulmonary ventilation. In a recent study of 25 patients with uncomplicated pulmonary emphysema, the lung-to-tongue and arm-to-tongue circulation times were significantly shorter than normal.

**Bronchial Asthma.** The respiratory dynamics during an asthmatic attack resemble those of chronic emphysema with the additional factor of bronchial obstruction. In this disease, normal or somewhat shortened circulation times have been obtained by numerous observers.

A severe attack of bronchial asthma occasionally may closely mimic acute pulmonary edema due to left ventricular failure. In the rare instance where a history cannot readily be obtained, a circulation time may quickly decide the issue, for the patient with left ventricular failure usually has a considerably prolonged circulation time.

**Pneumothorax.** The arm-to-lung time is decreased initially following the production of artificial pneumothorax. This change is thought to be due to the decrease in the pulmonary vascular bed and an increase in the heart rate.

**Pneumonia.** The circulation time in pneumonia is normal or decreased. In those instances in which a decreased circulation time is found,
fever may be an important cause. Again, the reduction in the pulmonary vascular bed may play a part in the acceleration of blood flow.

**Thyrotoxicosis.** The velocity of blood flow is strikingly increased in this disease. In 1 report of 9 patients with thyrotoxicosis but without circulatory failure, the basal metabolic rate averaged 33 per cent above the normal, while the velocity of blood flow through the lungs averaged 83 per cent above normal.²⁹ It has been demonstrated that the increase in the velocity of blood flow in thyrotoxicosis is greater than that which occurs in normal persons with a similarly increased oxygen consumption due to work.¹¹ If congestive heart failure ensues, the circulation time may still be shorter than normal or within normal limits. When thyrotoxicosis is treated successfully the circulation time returns to normal. In patients with basal metabolic rates elevated by dinitrophenol, the circulation times are normal.

**Myxedema.** The circulation time in myxedema is considerably longer than normal. The slowing in blood flow is due to the diminished cardiac output. With adequate thyroid therapy, the circulation time returns to normal. Here again there is evidence that the velocity of blood flow is not directly related to the basal metabolic rate but to the decreased cardiac output. A group of 12 patients with low metabolism and normal blood cholesterol was studied.⁶⁹ Most of these patients had previously been operated upon for hyperthyroidism. The average basal metabolic rate was minus 25 per cent, the average Decholin circulation time was 12.4 seconds. It is of interest that the circulatory changes are the converse of those in thyrotoxicosis. The velocity of the blood flow and the cardiac minute volume output are disproportionately lowered; the latter is reflected in the increased blood arteriovenous oxygen difference.

**Anemia.** In patients with normal cardiovascular systems anemia may significantly shorten the circulation time. This change reflects the compensatory increase in cardiac output, which is inversely proportional to the hemoglobin level; vasoconstriction may also contribute to the increased velocity of blood flow.²⁵ With hemoglobin concentrations of less than 10 Gm., the circulation time tends to shorten considerably.

**Polycythemia.** In polycythemia vera, the circulation time usually is prolonged, more as a result of the greatly increased blood volume and vasodilatation than because of the increased blood viscosity.¹

**Peripheral Vascular Disease.** Kvale and Allen²⁸ used a solution of magnesium sulfate, calcium gluconate, and copper sulfate to measure arm-to-tongue, arm-to-hand, arm-to-perineum, and arm-to-foot circulation times. In normal individuals they obtained a wide range of values, especially in the arm-to-foot times. They reported that in Buerger’s disease and obliterative atherosclerosis the speed of the blood flow to the hands and feet generally was diminished, usually depending upon, and evidently related to, the degree of vascular obliteration. Inconsistent results, however, led them to believe that the method could not be used to diagnose occlusive arterial disease.

Elkin and associates¹¹² used radioactive sodium to measure circulation time to the extremities and were unimpressed with the results obtained. They stated, “The variations in the circulation time to the extremities found in normal individuals is so wide as to render these results valueless in the diagnosis of circulatory disorders.”

**Indications for Circulation Time Measurements**

The circulation time is not a diagnostic test. It reflects the influence of many variable factors, but affords valuable information that may aid in diagnosis and in evaluating the clinical progress of a patient. Specifically, the finding of a short circulation time in a patient with overt congestive heart failure would be of importance, especially since the basal metabolic rate tends to be inaccurate in such circumstances, and I¹²³ uptake studies are not always available and require several days. If thyrotoxicosis were ruled out, then other causes of high output failure obviously would merit investigation. Under such circumstances the circulation time may contribute significantly to the evaluation of the patient.
Circulation times may be helpful in distinguishing the dyspnea of pulmonary disease from that of cardiac origin. The most striking example is an acutely dyspneic and stuporous patient with a chest filled with musical rales. In such circumstances a normal circulation time generally indicates that bronchial asthma is the more likely diagnosis. It is important to note that ether and Decholin should be used with extreme caution in patients suspected of bronchial asthma or other allergic states.

Rarely, the circulation time aids in differentiating the hepatomegaly of liver disease from that of congestive heart failure. Usually the clinical examination and specific liver function tests are adequate. However, both conditions may coexist and under such circumstances circulation time measurements may be particularly valuable in estimating the circulatory component. Similarly, the anasarca of nephritis with hypoproteinemia may on occasion be distinguished from that due to congestive heart failure.

The routine employment of circulation time estimations in all patients entering hospital with cardiac disease is unwarranted. Although the percentage of untoward reactions to the drugs commonly employed is extremely small, the induction of further cardiovascular embarrassment in a seriously ill patient, could, in rare instances produce unfortunate results.

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