ESTIMATION OF THE BLOOD CIRCULATION TIME IN HEALTH AND DISEASE : AN EVALUATION OF THE THEOPYLLINE-ETHYLENEDIAMINE METHOD.

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Introduction.

In recent years,and more especially since the recognition of isolated left ventricular failure as a common clinical entity, it has been realised that a knowledge of the velocity of blood flow through the heart and lungs is of definite value in the differentiation of cardiac and broncho-pulmonary disorders. However,measurement of blood velocity - the distance travelled by a particle of blood in a unit of time - presents so many practical difficulties that the clinician prefers to measure the time taken for a particle of blood to travel between two fixed points,and this measurement - which is inversely proportional to the blood velocity - he calls the "blood circulation time".

This report describes the selection and clinical trial of a method of blood circulation time measurement which does not appear to have been used previously in this country.

SECTION ONE.

REVIEW OF PREVIOUS WORK ON THE SUBJECT.

Review of Previous Work on the Subject.

There are many methods of estimating the blood circulation time, but all are based on the same principle - the introduction into the bloodstream at one point of a substance which may be detected at another point by one or more of its physical or pharmacological properties.

The first recorded investigation was that of Hering (1827), who injected potassium ferrocyanide into the right external jugular vein of a horse, withdrew blood from the corresponding vein on the left side and tested it for the Prussian blue reaction.

Many years later, Stewart (1894), made an intravenous injection of 2.5% saline, the volume varying with the size of the animal and the distance between the injection and recording points, and detected its arrival by means of a galvanometer coupled to a pair of unpolarizable electrodes which were applied directly to a blood vessel at the recording point. In this way he measured the circulation time through the lungs, liver, kidneys and other organs of various experimental animals.

The first practicable means of measuring the circulation time in Man was devised by Bornstein (1912), who made the subject inhale a mixture of 5 - 7% carbon dioxide and air.

The carbon dioxide entered the blood through the lungs and was carried through the left side of the heart to the arteries and so the brain, where it stimulated the respiratory centre. The resultant increase in the depth of respiration constituted the end-point, and the circulation time was calculated from a tracing of the respiration on a revolving drum. This method gives the circulation time through the left heart unit only, and the result includes the lung - head circulation time proper plus the reaction time of the respiratory mechanism. Although his clinical trials were few, Bornstein found that the circulation time was reduced in anaemia, and increased in cardiac failure.

Ten years later Koch (1922), presented the results of an extensive investigation in which he made use of the properties of fluorescein. He prepared a solution of fluorescein and sodium bicarbonate in distilled water, and injected 1.0 c.c. into a right arm vein: through a cannula in a left arm vein he collected blood in oxalated tubes. The blood was left to sediment, a few drops of potassium hydroxide added, and a note made of the earliest tube in which fluorescence appeared. He found that fluorescein disappeared from the circulating blood within 30 minutes, so that the test could be repeated in the same individual after that time. In a series of 119 normal cases, he found that the mean "arm - arm" circulation time was 20.75 seconds and that duplicate tests gave results within one

second of the original. Patients with cardiac failure had increased circulation times - up to 65 seconds in one instance - and it was noticed that 6 out of 7 cases having readings over 50 seconds died within a few weeks. This method is simple and safe, it has an objective end-point, hence it may be used in unconscious or unco-operative individuals, but the necessary canalization of a vein makes it inconvenient, disturbing to the patient and unsuitable for routine use in the consulting room or busy out-patient department.

In order to avoid the inconvenience of bleeding the patient to find the end-point, Blumgart and Yens (1927), devised the ingenious "radium C" method, in which a radioactive substance is injected at one point and detected on its arrival at another point by a special instrument. The radioactive substance is prepared by exposing sodium chloride to radium emanation for an appropriate time - during which radium C is deposited upon the salt. The sodium chloride is dissolved in sterile distilled water and its radioactivity is measured by means of a gamma ray electroscope: it is not injected for at least 20 minutes after it has been removed from exposure to the emanation - to allow alpha ray activity to diminish to 4% of its initial value. Since the active deposit gives out radiations which penetrate tissues and air, but not lead, a shield of lead is fitted round the patient's left side, except at the bend of the left elbow where there is placed the cylinder of the detecting device which is a complicated "cloud chamber of the C.T.R. Wilson type".

The solution is injected rapidly into a right arm vein and when the first traces of it arrive in the arteries at the bend of the left elbow, the cloud chamber indicates their presence. The circulation time is measured on a stopwatch.

In clinical trials of this method, Blumgart and Weiss (1927a), injected 0.1 - 0.2 c.c. of the radioactive solution and found that the circulation times of 53 subjects, who were free from disorders of the blood, heart or endocrine organs, ranged from 14 - 24 seconds, with a mean value of 18 seconds. Duplicate tests, which may be made three hours after the inital trials, showed only slight differences - the maximum difference in any one case being 3 seconds, and the average difference 2 seconds. Continuing their trials in patients with valvular disease of the heart, the same authors (1927b), found that the circulation time was increased in cardiac failure, but in proportion to the functional disability of the myocardium and not according to the extent of the valvular lesion. Investigating the velocity of blood flow in arteriosclerotic heart disease, they found (1927c) the circulation time increased to 30 seconds in subjects with regular rhythm and no history of dyspnoea or signs of congestive failure, and increased to 50 seconds in others with auricular fibrillation, a history of dyspnoea and signs of congestive failure. In order to facilitate further investigations in this field, these workers (1927d) adapted the radium C method

to measure the pulmonary circulation time: this they did by fitting over the patient's heart a lead shield with a central hole over the right auricle. A recording device was applied to the aperture in the shield, and it was now possible to measure the "right arm - right auricle time", which they called the "venous velocity time", and the "right auricle - left arm artery time", which they called the "crude pulmonary circulation time". In a series of 62 measurements, they found that the average "venous velocity time" was 6.7 seconds and the average "crude pulmonary circulation time" was 10.8 seconds.

Using this amended method in patients with pulmonary emphysema, they found (1927e) that 21 out of the 25 cases had normal values for the arm - arm and pulmonary circulation times: the other 4 had an average arm - arm circulation time of 28.5 seconds and an average pulmonary circulation time of 18.9 seconds, from which it was considered that they had early cardiac failure in addition to emphysema.

In applying the radium C methods to a study of the circulatory response to thyrotoxicosis, Blumgart with Gargill and Gilligan, (1930a) showed that the arm - arm and crude pulmonary circulation times were markedly reduced in their 13 cases: studying 7 cases of untreated myxoedema they found the circulation times as markedly increased (1930b). When the same workers (1931) studied their findings in blood diseases they found that the circulation time tended

to decrease as anaemia became more severe, and that, on the other hand, polycythaemia produced a definite prolongation of circulation time.

There is no doubt that this radium C method gives extremely accurate results, but it requires such expensive equipment that other workers had to look for a method more suitable for routine use.

Reverting to Koch's principle, Thompson and his colleagues (1928) injected 3 c.c. of a 4 to 5% solution of brilliant vital red and collected peripheral venous blood in small tubes which were changed at 15 second intervals. The clotted blood was centrifuged and in the appropriate specimens the serum was coloured by the dye: in this way, they estimated the arm - arm circulation time to be from 30 to 45 seconds.

Using a 7.5% solution of the same dye, and taking more frequent samples, Moore and Kinsman (1936) found that the arm - leg circulation time in ten normal subjects ranged from 7.5 to 26.0 seconds, with an average of 12.2 seconds. Hamilton and others (1928) injected up to 700 mgm. of phenol - tetraiod - phthalien sodium, in 1.0 - 1.5 c.c. of physiological saline, into the jugular vein, collected blood samples through a needle in the radial artery, and estimated their content of the dye. They quote a "jugular vein" - radial artery" circulation time of 23.0 seconds.

These dye injection tests had the same disadvantages

as Koch's fluorescein technique, and were superseded by methods which did not require the withdrawal of blood samples, but used substances capable of producing an end-point which could be recognized readily by the unaided senses of the subject or the investigator.

The earliest example of this group was the "histamine flush test" introduced by Weiss and others (1929). Allowing 0.001 mgm. per kilogramme of body weight, they injected intravenously histamine phosphate in 1: 5,000 or 1: 10,000 solution, which produced a dilation of the minute vessels of the face - noticeable to the observer as a flush. In 65 normal subjects, the circulation time ranged from 13-30 seconds, with a mean value of 23 seconds: in 26 patients with congestive heart failure the range was 21 - 82 seconds with a mean of 47 seconds, and, in 7 patients with severe anaemia, it was 9-16 seconds with a mean of 11.5 seconds. Estimations made in parallel with the radium C method showed close similarity in results, with the histamine times some 5.0 seconds longer on average - due, they say, to the fact that the circulation time is longer in the smaller vessels. In addition to the flush, the injection of histamine produces side effects, including a subjective sensation of heat in the face, general weakness and pulsating headache lasting for a few minutes: these are "not serious" according to Weiss and his associates.

In an English trial of the test, Bain (1934) obtained an adequate response in 90% of his 300 cases, but found differences of up to 10.0 seconds in duplicate readings, and encountered more serious side effects. A quarter of his patients complained of headache, six developed dyspnoea, and alarming reactions occurred in three others - of whom one died. The fatal case was given two minims of adrenaline intravenously, as an antidote to histamine, and Bain considers that this was the immediate cause of death in that, in all probability, it produced ventricular fibrillation. The frequency and severity of these reactions contraindicate the routine use of the histamine test, in spite of the fact that it has an objective end-point.

A series of tests, based on the power of certain salts to produce a subjective sensation of warmth, began with the use by Kahler (1929) of calcium chlorate in 10% solution. He injected 5 c.c. intravenously and found that this produced as an end-point a feeling of heat - first noticed in the mouth, then, in turn, in the neck, thorax, perineum, arms and legs. Goldberg (1936) preferred to use calcium glueonate, also in 10% solution, and found that it produced a most intense end-point in the throat and tongue - the hot sensation welling up rapidly "like a gush of steam". His readings for the arm-throat circulation time averaged 12.5 seconds in 60 normal subjects, with extremes of 10 and 16 seconds; in 15 cases of cardiac failure they averaged

26.7 seconds with extremes of 20 and 40 seconds: in 17 cases of hyperthyroidism they averaged 9.9 seconds with extremes of 7 and 11 seconds, whereas in 4 cases of myxoedema they averaged 20 seconds with extremes of 19 and 22 seconds. He performed duplicate tests in 156 cases and found that the second readings usually checked closely with the first. However, in a later trial of this test, Wall (1939) found that it was unreliable and might give no end-point at all in patients who had a long circulation time.

Calcium gluconate was used also - in a compound solution with magnesium sulphate, sodium chloride and copper sulphate - by Spier, Wright and Saylor (1936) who found that it produced a good end-point in the tongue, and later in the perineum, hands and feet. Testing 40 normal subjects, they obtained arm-tongue circulation time results ranging from 7-22 seconds, with a mean of 14.6 seconds. They hoped that the end-point obtainable in the hands and feet would enable them to measure the circulation time to the extremities, and thus help in the diagnosis of peripheral vascular diseases, but Kvale and Allen (1939) showed that the arm-foot circulation time results were not constant enough to be of value in the recognition of such disorders. The compound solution is difficult to prepare - since it must be kept at a constant pH - and deteriorates rapidly, so the method is of limited worth.

Magnesium Sulphate alone was used by Bernstein and Simkins (1939) in 10% solution, of which they injected 6.0 c.c. intravenously: this produced a hot feeling in the tongue and pharynx, and later in the face, perineum and extremities. The average result of 91 "arm-tongue" tests in normal subjects was 12.9 seconds, which is near Goldberg's average with calcium gluconate, and no untoward reactions occurred in the series of 579 tests on 274 individuals. The test, therefore, is safe and inexpensive, but, both the magnesium and calcium salt methods produce subjective sensations in various parts of the body in quick succession - with the result that, as Speir and his colleagues (1936) state, "occasionally the confusion of the rapid action renders the first test unsatisfactory."

Shortly after the introduction of the first of the calcium salt methods, Winternitz and his colleagues (1931) described a new method which they had tried extensively in their clinic in Prague. They made an intravenous injection of 5 c.c. of a 20% solution of sodium dehydrocholate - "decholin" - and when this reached the tongue it produced an intensely bitter taste which was very readily appreciated by the patient. They found that the normal arm-tongue circulation time lay between 8 and 14 seconds, but that the readings of up to 60 seconds occurred in congestive cardiac failure. The test could be repeated within a few minutes,

and as many as five successive injections were made in one individual without harmful effects; indeed, out of 1,200 tests there were only 4 or 5 unpleasant reactions - in sensitive individuals in whom the bitter taste caused sickness or vomiting. (Winternitz at alii, 1932). In the United States, Tarr and his co-workers (1932) were attracted by the simplicity of the method and gave it a thorough trial. In their series of 60 normal subjects, the circulation time ranged from 10-16 seconds, with a mean value of 13 seconds; in 100 subjects with congestive heart failure the range was 17-47 seconds with a mean of 26 seconds, and in 68 cases of hyperthyroidism the range was 6.5 - 12.0 seconds with a mean of 9 seconds. Duplicate results in the same individual agreed closely as a rule, and there was never more than 5 seconds of a difference. They record that the bitter taste was followed occasionally by a feeling of nausea, with actual vomiting in odd cases, and that about 1% of their patients complained of pain in the gall bladder region after the injection, due to distension of that organ. Their conclusion that the test was simple and reliable was supported by Gargill (1933), who found that three successive measurements in the same subject usually "checked within one second". Thereafter the method was used extensively in medical clinics, and its safety was not doubted until Macy and his colleagues

(1936) reported a fatal result in a middle aged woman with intractable asthma: just over 2.0 c.c. of decholin had been given when she was "seized with a severe asthmatic state and died within three minutes". Several years later, Leys (1944) reported three instances of a toxic reaction: one was "distinctly unpleasant", another "slightly alarming", and the third fatal - the patient collapsed immediately after the injection, was revived by nikethamide, but after an hour had a second circulatory collapse and died within a few minutes. Replying to Leys, Winternitz (1944) declared that out of 2,000 injections he knew of only three cases of collapse, and none had been fatal: he added, however, that he himself had almost abandoned the decholin method.

In contrast to the bitter taste produced by decholin, a sweet taste is produced by saccharin and this was the basis of the method introduced by Fishberg, Hitzig and King (1933). They chose saccharin - sodium benzosulphinid - because it stimulates the taste buds in high dilution and it is very soluble, hence only a small volume of solution need be injected to produce a sharply defined end-point. In the routine test they injected intravenously 2.5 gm. of soluble saccharin dissolved in 2.0 c.c. of distilled water, and found that this produced a good end-point in 99 out of 100 cases. The arm-tongue circulation time in normal subjects was between 9 and 16 seconds, with an average of 12 seconds,

and in subjects with cardiac failure there were higher readings, some over 40 seconds. The test can be repeated in the same subject within a few minutes, and the authors claim that the results "check closely", but later workers do not support this entirely. Esser and Berliner (1943) made a careful comparison of duplicate measurements by this method and found that, in normal subjects, the average difference between first and second tests was 2.3 seconds under basal conditions (as for B.M.R. estimation) and 4.5 seconds under ordinary ward conditions - these results correspond to differences of 12.6% and 21.8% respectively: in subjects with heart failure the average difference was 4.1 seconds under basal, and 11.3 seconds under ward conditions - corresponding to differences of 15.9% and 41.0%. Nevertheless, this method has been used as a routine by many physicians and has given apparent satisfaction - probably because of its simplicity and safety. No dangerous reactions have been reported after a saccharin test, and even the perivascular infiltration of the solution is said to be harmless - but Leinoff (1935) describes an atypical inflammatory reaction of some severity following such an infiltration: however, the patient was jaundiced at the time, and he considers that this may have contributed to an obscure chemical inflammation.

In a recent paper, Ruskin and Decherd (1945) described

a method of measuring the arm-tongue circulation time with thiamine solution, which produces as an end-point a nut-like taste and smell. The dose of thiamine varies from 50-300mgm. and the test, which failed in 8% of cases, appears to be inferior to the saccharin method.

In the arm-tongue tests, the end-point is entirely subjective, so that the results are unreliable when the subject is physically or mentally incapable of co-operating fully in the investigation.

An interesting group of tests with an objective end-point is that in which the injected substance is a respiratory stimulant, and produces a sharp increase in the depth of breathing, readily noticed by the observer. The first substance to be used in this way was sodium cyanide, which was introduced by Loevenhart and his colleagues (1922) as a means of estimating the circulation time in animals, after they had noticed, in the course of other studies, that a latent period occurred between the injection of the drug and the increase in respiration. (Loevenhart et alii, 1918). Later, Heymans, Bouckaert and Dautrebaud (1931) proved that cyanide acted through the carotid sinus, so that Loevenhart's test was a measurement of the vein-carotid sinus circulation time. Adapting the method for use in Man, Robb and Weiss (1933) used a 2% aqueous solution and injected from 5 to 10 mgm. of sodium cyanide -

according to the patients' bodyweight - into an antecubital vein; the response was a sudden increase in the amplitude of respiration, which constituted a sharp end-point. The phase of increased respiration lasted for only 20 seconds or so, and, apart from a temporary increase in the heart-rate of 10-15 beats per minute, there were no side effects. In a series of 35 normal subjects, the results for the "arm to carotid circulation time" ranged from 9-21 seconds, with a mean of 15.6 seconds, and in duplicate tests the average difference between first and second measurements was 2 seconds. The reading obtained from this test is the sum of the true circulation time and the reaction time of the carotid sinus-respiratory mechanism, but Robb and Weiss, by parallel measurements with cyanide and radium C methods, showed that the reaction time proper is negligible in comparison with the total circulation time. Sodium cyanide in doses up to three times the optimal amount has been used without untoward reaction, but it is a poison of such toxicity that very few clinicians care to risk errors in the dispensing or injection of the solution; consequently the test has never been favoured in this country.

A similar method was tried by Berliner (1940) using alpha lobeline which also gives a measurement for the arm-carotid sinus circulation time. In the test, 5.0 mgm. of alpha lobeline hydrochloride is injected into an arm vein as 0.5 c.c. of a 1% solution, and produces a choking sensation

in the throat, followed by a cough and hyperpnoea: the end-point is the onset of coughing. The first injection may fail to produce an end-point, and a higher dose may be necessary for a successful result: where duplicate readings are obtained, they differ considerably (Lilienfeld and Berliner, 1942). In view of the variability of results and the unpleasant reactions - including faintness, violent coughing and severe bronchospasm - which may follow the injection of alpha lobeline, the test is unsuitable for general use.

A trial of papaverine as a respiratory stimulant for the measurement of circulation time was made by Elek and Solarz (1942), who injected 40 mgm. of the hydrochloride in 1.25 c.c. of water. The end-point was a sudden, deep inspiration, often followed by a visible flushing of the face and a subjective sensation of facial warmth, throbbing in the temples and mild dizziness. The results stated, when compared with the decholin or the calcium gluconate circulation times in the same subjects, do not inspire confidence in the method, and since Berk and Sapeika (1945), in a further trial, obtained a good end-point in only 13 out of 50 cases and found that no satisfactory differences in circulation time occurred in patients with thyrotoxicosis, congestive heart failure or anaemia, their conclusion that papaverine is unsuitable for the determination of circulation time seems

justified.

In an effort to prevent atelectasis occurring in surgical cases as an early post-operative complication, Sperling, Weisman and Papermaster (1942) gave intravenous injections of theophylline-ethylenediamine, and found that these produced a sudden increase in the rate and depth of respiration. Koster and Sarnoff (1943) observed that this increase in respiration was so marked that it amounted in many cases to a gasp, and they decided to use theophylline-ethylenediamine as a means of estimating the circulation time from the arm to the respiratory centre. They injected 1.0 c.c. of aminophylline, containing 0.24 gm. of theophylline-ethylenediamine, and found that this amount was always effective. Since the gasp was preceded occasionally by swallowing movements, a "change in facial expression from subjective sensations", or a sharp catch in the breath during expiration, the first observable change was taken as the end-point. They describe the characteristic reaction of the patient as "a transient dizziness, flushing and a hyperpnoea": this passed off in a few minutes, and no untoward effects were observed. Their series of 72 cases consisted of post-operative patients of both sexes and of all ages between 12 and 82 years: the results for the arm-head circulation time ranged from 7.1-20.4 seconds, with a mean of 12.4 seconds, and in only one case was there any

difficulty in recognising the end-point. Duplicate readings were not taken, and the test was not performed in patients with cardiovascular, metabolic or blood diseases, hence its reliability cannot be assessed: however it has apparent advantages in that it entails the injection of only a small volume of theophylline-ethylenediamine solution which is non-toxic and readily available in proprietary form.

In recent years, several workers have described tests in which an objective end-point is determined by direct visual or photometric changes. Fishback (1941), working on rabbits, found that the intravenous injection of a fluorescein solution was followed in a few seconds by the sudden appearance of a yellow coloration of the conjunctiva and mucous membrane of the lips when these were exposed only to ultra-violet light. He tried the same method in man with promising results, and found that 5.0 c.c. of a 20% solution of fluorescein was sufficient to produce a brilliant yellow colour on the palpebral conjunctiva, when ultra-violet light was directed upon it-from a Kromayer lamp with a Woods filter - in a dark room. Later, with his colleagues, he found (Fishback, Guttman and Abramson, 1942) that the results for the "arm-eye" circulation time ranged from 7•0-15.6 seconds in normal subjects, and were in close agreement with subjective calcium gluconate test results in the same patients. Lange and Boyd (1943),

using 5.0 c.c. of a 5% solution of fluorescein and taking as their end-point the greenish-yellow colour appearing on the lips, obtained higher readings, with a range of 15-20 seconds, in their series of 216 normal subjects: in hyperthyroidism and anaemia the average circulation time was reduced, and in hypothyroidism and cardiac failure it was increased. Out of 600 tests, the only untoward reaction was slight nausea, lasting for a minute or so, in three instances. The same authors had suggested in an earlier paper (Lange and Boyd, 1942) that the intravenous injection of fluorescein might help to check the adequacy of the circulation in localised areas, since they had observed that incarcerated bowel did not become fluorescent. To facilitate such investigations, Lange and Krewer (1943) introduced their "dermofluorometer" - an instrument consisting of a lamp, suitable filters, and a photocell-photometer unit - which permits quantitative measurement of the fluorescence at the recording point. A less elaborate method of estimating the adequacy of the peripheral circulation was devised by Nathanson and Merliss (1943) : since normal skin does not show fluorescence, they produced a wheal on the skin of the arm or leg, by the injection of histamine, and then injected the fluorescein solution intravenously. In due course, examined under ultra-violet light, a brilliant fluoreseence appeared " about the wheal and in the wheal itself" and this allowed them to

measure the arm-arm or arm-leg circulation time. In 32 normal subjects, the average arm-leg circulation time was 20.1 seconds, whereas in 20 subjects with "arteriosclerosis obliterans" it was increased to 52.9 seconds, so the test may have some value in the diagnosis of peripheral vascular disease. The chief objection to these modifications of Koch's original fluorescein method is that the end-point can be detected only under ultra-violet light in a dark room. A photometric method was described by Jablons (1943), based on the principle that light can be transmitted through animal tissues to influence a photo-electric cell, and the intensity of illumination reaching the cell may be dimished by dyes injected intravenously. A recording unit, somewhat similar to the Lange and Krewer dermofluorometer, is arranged with a light source behind the lobe of the ear, and a photo-electric cell in front coupled to a galvanometer - the instrument is, in fact, a photo-electric colorimeter with the lobe of the ear taking the place of the cup or test tube. From 2-5 c.c. of a 1% solution of methylene blue is injected into an arm vein, and when the dye reaches the lobe of the ear there is a deflection of the galvanometer needle. Using this test, Jablons and his colleagues found that the arm-ear circulation time measurements in 36 normal subjects ranged from 8.4-21.6 seconds, with a mean of 13.8 seconds, and in 15 subjects with cardiac failure, they ranged from 20-45 seconds. (Jablons and Cohen, 1943:

Jablons, Cohen and Swirsky, 1944). These visual and photometric methods are of considerable value, but require too much apparatus to be suitable for the average practioner.

Recently, the Swedish workers Nylin and Malm (1944) have described a method based on a different principle - they withdraw blood from the patient, "label" it with radioactive phosphate and inject it into an arm vein: from an artery in the other arm, they obtain blood samples and estimate the radioactivity of them. Although the method is unsuitable for routine use, it may have some value for research workers.

In addition to the many methods of measuring the circulation time through the right heart, lungs and left heart, some tests have been devised to measure the circulation time through only one side of the heart. The right heart circulation time was measured by Hitzig (1934,1935), who introduced the ether method, in which a solution of 0.33 c.c. of ether in the same volume of saline is injected into an arm vein. The solution passes through the right auricle and ventricle to the pulmonary capillaries where the ether volatilises into the alveoli and rises through the air passages to the nose, where its typical odour is recognised by the patient. The observer can smell the ether almost as soon as the patient, so that the end-point is both subjective and objective. Hitzig found that, in 164 normal

cases, the right heart or "arm-lung" circulation time measurements ranged from 3.5-8.0 seconds, with a mean of 5.5 seconds, whereas in 18 cases of frank right heart failure they ranged from 9-27 seconds. By subtracting the arm-lung time from the arm-tongue (saccharin) time, he obtained a figure for the "lung-tongue" time, which corresponds roughly to the circulation time through the left heart unit. Hitzig states that the injection of the ether solution was not followed by any severe reaction, although in a third of the cases there was a transient cramp-like pain in the region of the puncture, but Leinoff (1935) describes the death of an asthmatic subject from an apparent hypersensitivity to the ether in the test solution.

As an alternative to ether, Miller (1934) injected a solution of benzyl or linalyl acetate, and found that these perfume ingredients produced a distinctive odour in the subject's breath.

The arm-lung test described by Candel (1938) uses paraldehyde, which volatilises into the air passages and produces a cough as the end-point: however the test has several disadvantages, since the drug may produce hypnosis or paroxysms of violent coughing lasting for several minutes and followed by dizziness.

The circulation time through the left heart unit was measured by Gubner, Schnur and Crawford (1939) who used a

modification of the first clinical method described by Bornstein in 1912. After a maximal expiration, the subject takes two rapid full inspirations of a 50% mixture of carbon dioxide and air, the beginning of the first inspiration being the starting-point: the end-point consists of a subjective feeling of warmth passing over the head, often with slight giddiness, and an objective quickening and deepening of respiration. Individual sensitivity to carbon dioxide varies greatly, but the double inspiration is almost always effective. In over 30 tests in normal subjects, Gubner and his colleagues obtained readings in the 5-10 seconds range, most of the results being between 7 and 8 seconds, and found that duplicate results were within one second of the original measurements.

Another method, said to measure "the functional capacity of the left ventricle", was introduced by Gross (1945), using amyl nitrite: an ampoule is crushed, the patient inhales the vapour through the nose, and indicates when he feels a well-marked sensation of heat in the face. The inhalation may be followed by unpleasant side-effects, including headache, faintness and giddiness, and by an increase in the heart rate of 40 or 50 beats per minute. The results of tests in 100 normal subjects ranged from 14-25 seconds, and the mean was 19.5 seconds - which is high in comparison with the carbon dioxide results and the

average figure derived from arm-lung and arm-head measurements. A disadvantage of the test is that the intensity of the heat sensation in the face decreases as the circulation time increases: as a result, in cases of severe cardiac failure where the circulation time is greatly increased, the end-point is indefinite.

Although the measurement of the circulation time through only one side of the heart is of considerable value in certain cases, that value is enhanced when the total circulation time also is known: the right and left heart circulation time tests, therefore, cannot replace those which measure the total circulation time.

A method of circulation time measurement, if it is to be used to anyone, must be safe and efficient: in addition, if it is to be of use to the general practitioner, it must be simple and speedy and should not require expensive or elaborate equipment. Reliability is essential, and most workers now agree that this cannot be obtained from tests which have a subjective end-point. Our attention was confined, therefore, to that group of tests in which the objective end-point is determined without the use of any special apparatus - the group in which an obvious and dramatic change in respiration is produced by the injected substance. Previous work on the alphalobeline and papaverine tests, quoted above, did not suggest that these were likely

to be satisfactory, hence we were left with a choice between the cyanide and theophylline-ethylenediamine methods, neither of which had been given an extensive trial in this country. Since the cyanides are such notorious poisons, it seemed unwise to use one of them for intravenous injection, in a routine test, while there was a reasonable alternative, so it was decided to select theophylline-ethylenediamine, which had the additional advantage of being available commercially in sterile solution in convenient ampoules.

As we have shown, Koster and Sarnoff tried their new method in a relatively small number of normal cases only: it was necessary, therefore, before adopting the test for routine use, to give it a thorough trial in a larger number of normal subjects and in others suffering from these disorders which are known to affect the blood circulation time.

SECTION TWO.

CLINICAL TRIALS OF THE THEOPHYLLINE-ETHYLENEDIAMINE TEST.

CLINICAL TRIALS OF THE THEOPHYLLINE-ETHYLENEDIAMINE TEST.

In this investigation, theophylline-ethylenediamine solution was used in the form of the proprietary "cardophylin", which is available in ampoules of 2.0 c.c., containing 0.48 gm. of the drug: since the dose is 1.0 c.c., an ampoule is often sufficient for two tests.

PROCEDURE: The syringe is charged, a tourniquet is applied to the right upper arm of the recumbent patient and an antecubital vein is entered: the tourniquet is released and, after a delay of a few seconds for the re-adjustment of the venous bloodflow, the syringe plunger and stopwatch cap are pressed simultaneously. The watch is stopped whenever the end-point occurs.

In order to avoid discrepancies, a 10.0 c.c. syringe was used always with a guage 1 needle for these make it possible for the 1.0 c.c. of solution to be injected very rapidly, and since the piston stroke is only about 0.5 cm. the syringe is easy to control. After some practice, the investigator finds no difficulty in manipulating the syringe with his right hand and the stopwatch with his left, but an assistant may take the watch - although this means that the recorded "circulation time" includes the reaction times of both the investigator and his assistant.

A. THE CIRCULATION TIME IN NORMAL SUBJECTS.

In this part of the trial, the routine test was performed on 150 subjects who were "normal" in that they did not suffer

from diseases of the heart, of the blood or of metabolism: they were typical adult hospital patients, of all ages, from the wards and out-patient clinics. The results, which are detailed in Table 1, ranged from 6.8 - 22.0 seconds, with a mean of 12.1 seconds and a standard deviation of 2.3.

In order to find if the circulation time is reasonably constant in the same individual, duplicate measurements were made in a further group of 50 normal subjects. Although maximum accuracy could be had only by performing each test under strictly basal conditions, these are unobtainable in general practice, hence the tests were made under normal ward conditions, with an interval of several days between the two. The results, which appear in Table II show that the differences between first and second measurements range from 0-2.6 seconds, with a mean difference of 1.1 seconds.

In the 250 tests on 200 normal subjects there was no evidence of any constant relationship between blood circulation time and the subject's age, weight, pulse rate or blood pressure: these details are omitted, therefore, from the tables for the sake of simplicity.

With regard to the end-point, it must be emphasised that, although it is usually a sharp, deep inspiration amounting to a gasp, this may be preceded by a swallowing movement, a sudden change in facial expression denoting anxiety, or a catch in the breath during expiration. There is a

temptation to wait for the dramatic gasp, but since it does not occur in a small percentage of tests, it is imperative that the first observable change should be regarded as the definitive end-point. Of the 250 tests in normal subjects, the end-point was an inspiratory gasp in 224 (89.6%), a swallowing movement in 15 (6%) a change in expression in 9 (3.6%) and a catch in the breath during expiration in 2 (0.8%). In no case was there any dangerous reaction, but most subjects spoke of a feeling of warmth over the face and of a "light-headedness" lasting for about half-a-minute: these side-effects were more prominent in excitable individuals, usually women, and in 8 cases - all confirmed psychoneurotics - they produced a violent emotional upset, with weeping, trembling and tachycardia. Local reactions occurred only in the very few cases in which there was some perivenous leakage of the solution: this caused severe pain at the site of the leakage but was not followed by necrosis or thrombosis.

B. THE BLOOD CIRCULATION TIME IN METABOLIC DISTURBANCES DUE TO DISORDERS OF THE THYROID GLAND.

Under normal ward conditions, since basal conditions cannot be obtained in general practice, 31 tests were made in 21 cases of hyperthyroidism, and 1 test was made in a case of myxoedema.

The detailed results appear in Table III and show that, in the 15 tests in these cases of hyperthyroidism which were free from auricular fibrillation and cardiac failure, and

in which treatment had not begun, the circulation time measurements ranged from 5.6-13.6 seconds, with a mean of 7.1 seconds. If case No. 259, with a circulation time of 13.6 seconds, were excluded, the range would be reduced to 5.6-8.5 seconds and the mean to 6.7 seconds: the physician in attendance on this case was of the opinion, which the circulation time tended to confirm, that cardiac failure was developing as a complication. In the cases in which thiouracil treatment had already begun the measurements were appreciably higher, and the successive tests showed that clinical improvement was paralleled by a rise in the circulation time unless in the presence of auricular fibrillation and cardiac failure.

The case of myxoedema, which was under treatment for a mild relapse, had a circulation time above the normal average.

C. THE CIRCULATION TIME IN DISORDERS OF THE BLOOD.

The results of 39 tests in 29 cases of anaemia, and 4 tests in 3 cases of polycythaemia, appear in Table IV. These show that the blood circulation time is roughly parallel to the haemaglobin percentage, and the successive tests confirm that an increase in the haemoglobin percentage is usually accompanied by an increase in the circulation time and vice versa.

D. - THE CIRCULATION TIME IN CARDIOVASCULAR DISEASE.

In this series, 108 tests were performed in 85 cases which were classified into four groups according to functional and structural disturbance.

The first group consisted of 8 cases of hypertension uncomplicated by cardiac failure: the results of 9 tests, which are shown in Table V, ranged from 10.0 - 17.0 seconds, with a mean of 12.8 seconds.

The second group consisted of 22 cases of organic heart disease, 14 being examples of uncomplicated valvular lesions and 8 being examples of apparently cured subacute bacterial endocarditis: of the 23 tests made, the results, in Table VI, show a range of 6.2 - 16.4 seconds, with a mean of 12.4 seconds.

The third group contained 7 cases of rheumatic carditis, in various stages of activity, described in Table VII: the results of 11 tests ranged from 7.6 - 17.0 seconds, with a mean of 10.4 seconds.

The fourth and largest group consisted of 48 cases of cardiac failure, which was predominantly left ventricular in 19, and right ventricular in 29: the details appear in Table VIII and show that the results of 25 tests in left ventricular failure ranged from 15.8 - 35.0 seconds, with a mean of 21.0 seconds, and the result of 40 tests in right ventricular failure ranged from 13.0 - 58.0 seconds, with the same mean of 21.0 seconds.

TABLE I.

ARM-HEAD CIRCULATION TIME MEASUREMENTS IN 150 "NORMAL" PATIENTS.

DIAGNOSIS.	C.T. in secs.	DIAGNOSIS.	C.T. in secs.
Pleural effusion	6.8	Spastic paraplegia	9.1
Anxiety neurosis	7.0	(Convalescent) rheumatism	9.2
N. A. D.	7.4	Rheumatoid arthritis	9.2
Anxiety neurosis	7.6	N. A. D.	9.4
Anxiety neurosis	7.9	N. A. D.	9.4
Pulmonary emphysema	8.0	N. A. D.	9.5
(Convalescent) pneumonia	8.0	Cardiac Neurosis	9.5
Anxiety neurosis	8.0	Hysteria	9.6
Sciatic neuritis	8.6	Stomatitis	9.6
Cerebral concussion	8.6	Spondylitis	9.6
Subacute nephritis	8.9	Rheumatoid arthritis	9.8
Meningioma	8.9	Bronchial asthma	9.8
Carcinoma of liver	9.0	Duodenal Ulcer	10.0
N. A. D.	9.0	Cardiac neurosis	10.0
N. A. D.	9.0	Rheumatoid arthritis	10.0

TABLE I. (contd.)

DIAGNOSIS.	C.T. in secs.	DIAGNOSIS.	C.T. in secs.
Infective arthritis	10.0	Emphysema and silicosis	11.0
Duodenal ulcer	10.0	Cerebral concussion	11.0
Pleural effusion	10.0	Anxiety neurosis	11.0
Rheumatoid arthritis	10.0	Infective arthritis	11.0
Pleural effusion	10.0	Duodenal ulcer	11.0
N. A. D.	10.1	Effort syndrome	11.0
Cerebral concussion	10.2	Chronic nephritis	11.0
Anxiety neurosis	10.2	Effort syndrome	11.0
Polyneuritis	10.2	Gastric ulcer (healed)	11.0
Anxiety neurosis	10.4	Functional Dyspepsia	11.0
Cardiac neurosis	10.4	Rheumatoid arthritis	11.0
Rheumatoid Arthritis	10.4	N. A. D.	11.2
Cardiac neurosis	10.4	Hepatic cirrhosis	11.2
Anxiety neurosis	10.8	Aortic aneurysm	11.2
(Convalescent) pyelitis	10.8	Pituitary tumour	11.2
Rheumatoid arthritis	11.0	Infective hepatitis	11.3

TABLE I. (contd.)

DIAGNOSIS.	C.T. in secs.	DIAGNOSIS.	C.T. in secs.
Bronchiectasis	11.4	Cardiac neurosis	12.0
N. A. D.	11.4	Effort syndrome	12.0
Cerebral concussion	11.4	N. A. D.	12.0
Rheumatoid arthritis	11.4	(Convalescent) rheumatism	12.0
Anxiety neurosis	11.5	N. A. D.	12.0
Tuberculosis (spinal)	11.6	N. A. D.	12.0
N. A. D.	11.6	Pulmonary emphysema	12.0
Effort syndrome	11.6	Cardiac neurosis	12.0
Mental deficiency	11.6	Cerebral tumour	12.0
Rheumatoid arthritis	11.6	Rheumatoid arthritis	12.1
Infective arthritis	11.8	Infective arthritis	12.2
Disseminated sclerosis	11.9	Infective hepatitis	12.2
N. A. D.	12.0	Carcinoma (colon)	12.2
Chronic bronchitis	12.0	Haematomyelia	12.4
Anxiety neurosis	12.0	N. A. D.	12.6
Anxiety neurosis	12.0	Osteo arthritis	12.6

TABLE I. (contd.)

DIAGNOSIS.	C.T. in secs.	DIAGNOSIS.	C.T. in secs.
Gastric ulcer	12.7	Pulmonary emphysema	13.5
Subacute nephritis	12.8	Nephritis (healed)	13.6
Post-encephalitic Parkinsonism	12.8	N. A. D.	13.6
(Convalescent) pneumonia	12.8	Gastric ulcer	13.8
Pulmonary tuberculosis	12.8	Effort syndrome	14.0
Duodenal ulcer	12.8	Pellagra	14.0
Pulmonary tuberculosis	12.9	Anxiety neurosis	14.0
N. A. D.	12.9	CO poisoning	14.0
Aortic aneurism	13.0	Erythema nodosum	14.0
Polyneuritis	13.0	Hysteria	14.0
Diabetes mellitus	13.0	Cerebral concussion	14.2
N. A. D.	13.0	N. A. D.	14.6
Trigeminal neuralgia	13.2	Gout	14.6
Acromegaly	13.2	Myasthenia gravis	14.6
Rheumatoid arthritis	13.2	Anxiety neurosis	14.8
Pulmonary emphysema	13.4	N. A. D.	14.8

TABLE I. (contd.)

DIAGNOSIS.	C.T. in secs.	DIAGNOSIS.	C.T. in secs.
Meningioma	15.0	Bronchiectasis	16.0
N. A. D.	15.0	Diabetes mellitus	16.0
Cerebral thrombosis	15.0	Simple goitre	16.0
Pleural effusion	15.0	Diabetes mellitus	16.0
Pulmonary emphysema	15.0	Diabetes mellitus	16.0
Diabetes mellitus	15.1	Rheumatoid arthritis	16.4
Pulmonary emphysema	15.2	(Convalescent) malaria	16.8
Arteriosclerosis	15.4	Cerebral arteriosclerosis	17.0
Gastric ulcer	15.4	Diabetes mellitus	17.4
Pulmonary emphysema	15.6	Gastric ulcer	17.6
Erythema nodosum	15.6	Fibrositis	18.0
Gastric ulcer	15.8	Pulmonary emphysema	22.0

Mean reading 12.07 seconds = 12.1 seconds.

Standard deviation 2.3 seconds.

TABLE II.

DUPLICATE MEASUREMENTS IN 50 "NORMAL" PATIENTS.

DIAGNOSIS	Circulation Time in seconds.	
	(1)	(2)
Appendicular abscess	7.8	6.8
Duodenal ulcer	8.1	9.0
Erythema nodosum	8.6	7.0
Pneumococcal arthritis	8.8	7.8
Infective hepatitis	9.0	9.6
Gastric Ulcer	9.4	8.5
Amoebic hepatitis	9.4	9.4
Cerebral tumour	9.4	10.5
Pleural effusion	9.8	9.6
Diabetes mellitus	10.0	9.6
Cerebral malaria	10.2	10.8
Tabes dorsalis	10.2	11.4
N. A. D.	10.2	11.0
(Convalescent) Glandular fever	10.3	11.6

TABLE II. (contd.)

DUPLICATE MEASUREMENTS IN 50 "NORMAL" PATIENTS.

DIAGNOSIS.	Circulation Time in seconds.	
	(1)	(2)
Gastric ulcer	10.4	10.2
Subacute nephritis	10.8	12.2
Hepatic cirrhosis	10.9	10.4
Tabo - paresis	11.0	10.8
N. A. D.	11.0	13.2
Acute gastritis	11.0	10.8
Subacute nephritis	11.1	9.8
Gastric ulcer	11.2	11.0
Trigeminal neuralgia	11.2	11.0
Subacute nephritis	11.4	10.4
(Convalescent) pneumonia	11.8	10.6
Gonococcal arthritis	11.8	10.4
N. A. D.	11.8	12.4
Tonsillitis	12.0	11.0
Carcinoma (stomach)	12.0	10.0
Functional dyspepsia	12.0	9.8

TABLE II. (contd.)

DUPLICATE MEASUREMENTS IN 50 "NORMAL" PATIENTS.

DIAGNOSIS.	Circulation Time in seconds. (1)	(2)
Diabetes mellitus	12.0	12.0
N. A. D.	12.2	11.8
Functional dyspepsia	12.4	12.0
Pleural effusion	12.6	11.6
Duodenal ulcer	13.2	14.8
Epilepsy	13.8	11.8
Aortic aneurysm	14.0	12.8
Cerebral concussion	14.0	13.8
Aortic aneurysm	14.4	15.2
Subacute nephritis	14.8	17.0
Gastric ulcer	15.4	17.4
Diabetic gangrene (toe)	15.4	16.1
Tabes dorsalis	15.4	12.8
(Resolved) pneumonia	15.8	13.8
Erythema nodosum	16.6	15.0

TABLE II (contd.)

DUPLICATE MEASUREMENTS IN 50 "NORMAL" PATIENTS.

DIAGNOSIS.	Circulation Time in seconds.	
	(1)	(2)
Duodenal ulcer	16.8	14.2
Gastric ulcer	16.8	18.6
Tabes dorsalis	18.6	17.0
Diabetes mellitus	18.9	20.2
Cerebral thrombosis	19.6	20.8

Differences range from 0-2.6 seconds.

Average difference between first and second tests 1.09 seconds = 1.1 seconds.

TABLE III.

CIRCULATION TIME IN DISORDERS OF THE THYROID GLAND.

Case No.	Sex and age	REMARKS.	C.T. in secs.
		(A) Single tests before Treatment.	
251	F42	Typical thyrotoxicosis	5.6
252	F52	Typical thyrotoxicosis	6.0
253	F44	Typical thyrotoxicosis	6.0
254	F53	Thyrotoxicosis superimposed on long-standing "simple goitre".	6.2
255	F24	Mild hyperthyroidism	6.8
256	F38	Thyrotoxicosis superimposed on long-standing "simple goitre".	7.0
257	F34	Mild hyperthyrodism	7.0
258	F27	Mild hyperthyroidism	8.5
259	F42	Early thyrotoxicosis superimposed on long-standing "simple goitre"	13.6
		(B) Single tests after Treatment has begun.	
260	M42	Thyrotoxicosis: considerable clinical improvement after 12 days on thiouracil	13.6
261	F57	Thyrotoxicosis: some improvement after 14 days on thiouracil -	

TABLE III. (contd.)

Case No.	Sex and age.	REMARKS.	C.T. in secs.
261 ctd	F57	thiouracil: auricular fibrillation still present but no evidence of cardiac failure.	13.6
262	M48	"Masked hyperthyroidism" after 8 days on thiouracil: auricular fibrillation still present	13.8
263	F21	Thyrotoxicosis: considerable clinical improvement after 2 months on thiouracil	14.2
264	F55	Thyrotoxicosis after 4 days treatment with thiouracil and digoxin: auricular fibrillation and congestive cardiac failure still present.	14.4
		(C) Successive Tests.	
265	F38	Mild hyperthyroidism (as an out-patient).	7.2
		Duplicate test on admission but without treatment	7.1
266	F42	Typical thyrotoxicosis: before treatment	5.9
		After 10 days on methyl thiouracil, definite clinical improvement: 5 lbs. gain in weight	6.9
267	F18	Thyrotoxicosis superimposed on "simple goitre":	
		before treatment	6.0

TABLE III. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
267 ctd	F18	After 12 days on thiouracil, clinical improvement: 3 lbs. gain in weight	7.0
268	F54	Typical thyrotoxicosis: before treatment	7.0
		After 11 days on thiouracil, considerable clinical improvement: 7 lbs. gain in weight	9.0
269	F64	Typical thyrotoxicosis: before treatment	7.0
		After 14 days on thiouracil: clinical improvement	10.0
		After a further 3 months on thiouracil as an out-patient: great clinical improvement	12.2
270	M57	"Masked hyperthyroidism" with auricular fibrillation and congestive cardiad failure, before treatment	17.4
		After 14 days on thiouracil and digitalis: no evidence of congestive failure but auricular fibrillation still present: 2 lbs. gain in weight (in spite of loss of oedema fluid)	14.2
		After a further 6 months treatment as an out-patient : auricular fibrillation -	

TABLE III. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
270 ctd	M57	auricular fibrillation still present but no failure: additional 5 lbs. gain in weight	14.0
271	M52	"Masked hyperthyroidism" and auricular fibrillation but no evidence of cardiac failure, before treatment	16.0
		After 11 days on methyl thiomacil: clinical improvement: 4 lbs. gain in weight: auricular fibrillation still present	15.8
		After a further 24 days treatment: clinical improvement but auricular fibrillation still present	14.4
272	F61	Myxoedema: treated with thyroid extract at intervals for 15 years	15.6

TABLE IV.

CIRCULATION TIME IN DISORDERS OF THE BLOOD.

Case No.	Sex and Age	REMARKS.		C.T. in secs.
		Single Tests.		
273	M45	Hypochromic anaemia in monocytic leukaemia		
			Hb 52%	6.0
274	M48	Hypochromic anaemia following melaena from		
		duodenal ulcer:	Hb 64%	6.0
275	F42	Microcytic hypochromic anaemia:	Hb 50%	6.9
276	M56	Microcytic hypochromic anaemia:		
		carcinoma of stomach:	Hb 30%	7.0
277	F71	Pernicious anaemia (relapsed):	Hb 76%	7.0
278	F19	Hypochromic anaemia: ulcerative		
		colitis:	Hb 70%	7.6
279	M39	Hypochromic anaemia in Hodgkin's		
		disease:	Hb 70%	7.6
280	F26	Microcytic hypochromic anaemia:	Hb 80%	7.6
281	F31	Hypochromic anaemia: healed		
		pulmonary tuberculosis:	Hb 82%	7.6
282	M35	Hypochromic anaemia following		
		haematemesis	Hb 72%	7.8
283	F39	Microcytic hypochromic anaemia:	Hb 80%	8.0
284	F24	Microcytic hypochromic anaemia:	Hb 86%	8.2

TABLE IV. (contd.)

Case No.	Sex and Age	REMARKS.		C.T. in secs.
285	M54	Hypochromic anaemia following haematemesis:	Hb 78%	8.6
286	F23	Microcytic hypochromic anaemia:	Hb 80%	8.6
287	M27	Hypochromic anaemia following haenatemesis:	Hb 88%	9.2
288	M62	Hypochromic anaemia following haematemesis:	Hb 64%	10.4
289	M53	Hypochromic anaemia following haematemesis:	Hb 62%	11.0
290	M63	Hypochromic anaemia following haematemesis:	Hb 64%	11.2
291	F61	Pernicious anaemia:	Hb 62%	13.2
292	F37	Polycythaemia: congenital heart disease:	Hb 122%	17.6
293	M66	Polycythaemia vera:	Hb 109%	19.0

Successive Tests.

294	F45	Pernicious anaemia (relapsed):	Hb 32%	6.0
		After 18 days treatment:	Hb 66%	8.4

TABLE IV. (contd.)

Case No.	Sex and Age	REMARKS.		C.T. in secs.
295	M52	Hypochromic anaemia following haemoptysis: bronchiectasis:	Hb 65%	7.0
		After 10 days treatment:	Hb 80%	8.8
296	M36	Hypochromic anaemia following haematemesis:	Hb 65%	7.2
		After 11 days treatment:	Hb 70%	8.1
297	M33	Hypochromic anaemia: ulcerative colitis:	Hb 68%	7.6
		After 2 months treatment:	Hb 74%	8.2
298	M53	Hypochromic anaemia following haematemesis:	Hb 68%	8.6
		After 15 days treatment:	Hb 82%	10.7
299	F20	Hypochromic anaemia in anorexia nervosa:	Hb 64%	8.8
		After 6 days:	Hb 60%	6.4
300	M51	Hypochromic anaemia: haemorrhoids:	Hb 44%	10.0
		After 7 days treatment:	Hb 65%	11.2
301	M33	Hypochromic anaemia: ulcerative colitis:	Hb 90%	10.3
		After 7 days:	Hb 85%	9.0
302	M57	Hypochromic anaemia: following haematemesis:	Hb 75%	12.0
		After 10 days treatment:	Hb 87%	15.9

Case No.	Sex and Age	REMARKS.		C.T. in secs.
303	M36	Hypochromic anaemia following		
		haematemesis:	Hb 70%	13.7
		After 11 days treatment	Hb 75%	11.2
304	M41	Polycythaemia vera:	Hb 110%	12.4
		Next day, after venesection:	Hb96%	10.8

TABLE V.

Circulation Time in Hypertension without evidence of cardiac failure.

Case No.	Sex and Age	REMARKS.	C.T. in secs.
305	F57	Hypertensive heart disease with coronary sclerosis and bundle branch block: angina of effort: B.P. 180/120	10.2
306	F57	Hypertensive heart disease: atherosclerosis: angina of effort: B.P. 240/140	11.0
307	F52	Essential hypertension: headache the sole symptom: B.P. 180/100	11.8
308	F76	Essential hypertension: arteriosclerosis: B.P. 240/135	13.0
309	M64	Hypertensive heart disease: atherosclerosis: angina of effort: B.P. 180/100	13.4
310	F28	Hypertension following toxaemia of pregnancy: no abnormal signs of symptoms except B.P. 210/140	14.0
		Re-examined 5 months later: B.P. 180/130	10.4
311	F48	Hypertensive heart disease: angina of effort: B.P. 280/150	14.2
312	F64	Hypertensive heart disease: slight cardiac enlargement: B.P. 220/120	17.0

(9 tests in 8 cases, mean reading 12.8 seconds.)

TABLE VI.

Circulation Time in Organic Disease without functional incapacity.

"compensated cardiacs".

Case No.	Sex and Age	REMARKS.	C.T. in secs.
		(a) Uncomplicated valvular lesions.	
313	M9	Rheumatic heart disease: mitral incompetence	6.2
314	M12	Congenital heart disease: patent interauricular septum	8.0
315	M17	Rheumatic heart disease: mitral stenosis	9.2
316	F30	Rheumatic heart disease: mitral stenosis	11.4
317	F44	Rheumatic heart disease: mitral incompetence	12.0
318	F26	Rheumatic heart disease: mitral stenosis	13.0
319	M17	Congenital heart disease: pulmonary stenosis	13.0
320	F47	Rheumatic heart disease: mitral stenosis	13.6
321	F32	Rheumatic heart disease: mitral stenosis	14.0
322	M21	Rheumatic heart disease: mitral incompetence	15.0
323	M62	Rheumatic heart disease: mitral stenosis	15.0
324	M16	Rheumatic heart disease: mitral and aortic incompetence	15.6
325	F48	Rheumatic heart disease: mitral stenosis and aortic incompetence	15.6

TABLE VI. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
326	F21	Rheumatic heart disease; mitral incompetence:	16.4
		(b) Subacute bacterial endocarditis after apparent cure by penicillin.	
327	F29	Mitral stenosis and aortic incompetence; one month after cessation of treatment	9.4
328	F18	Congenital subaortic stenosis; two months after treatment	9.8
329	F24	Mitral incompetence; one month after treatment	10.6
		Two months after treatment	12.0
330	F25	Congenital pulmonary stenosis; three months after treatment	11.8
331	M31	Mitral incompetence; 18 months after treatment	12.0
332	M32	Mitral stenosis and aortic incompetence; 15 months after treatment	12.2
333	M40	Mitral incompetence; 15 months after treatment	12.6
334	F19	Mitral incompetence; 8 months after treatment	16.0

TABLE VII.

Circulation Time in Rheumatic Carditis.

Case No.	Sex and Age	REMARKS.	C.T. in secs.
335	M20	Acute rheumatism 4 months previously with polyarthritis but no clinical evidence of carditis: re-examined and found to have loud mitral systolic murmur and increased sedimentation rate: subacute rheumatic carditis: apyrexial	7.6
336	M15	Acute rheumatism in quiescent phrase of polycyclic course: central systolic murmur and increased sedimentation rate: subacute rheumatic carditis: apyrexial	9.0
		13 days later: reactivation of carditis: mild pyrexia (99°)	7.2
337	F14	Acute rheumatism in quiescent phase: soft mitral systolic murmur: slight increase in sedimentation rate: subacute rheumatic carditis: apyrexial	9.0
		4 days later: reactivation of carditis: mild pyrexia (98.8)	7.6
338	M12	Recurrence of acute rheumatism: aortic and mitral incompetence: nodules on elbows and ankles: sedimentation rate slightly increased: subacute rheumatic carditis: apyrexial	10.2
339	F14	Convalescent from acute rheumatic carditis: mitral systolic murmur: sedimentation rate normal: apyrexial	10.3
340	M18	Convalescent from acute rheumatic carditis: aortic incompetence and mitral systolic murmur: sedimentation rate normal; apyrexial	13.6

TABLE VII. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
341	M30	Recurrence of acute rheumatism: aortic incompetence and mitral systolic murmur: high sedimentation rate: auricular fibrillation but no congestive failure: apyrexial	17.0
		After 10 days digitalisation	12.0
		After a further 3 days digitalisation	10.4

TABLE VIII.

CIRCULATION TIME IN CARDIAC FAILURE.

Case No.	Sex and Age	REMARKS.	C.T. in secs
		(A) Predominantly left ventricular failure.	
342	M52	Exertional dyspnoea: aortic incompetence: specific aortitis	15.8
343	M63	Exertional dyspnoea since an attack of retrosternal pain a month previously: arteriosclerosis: hypertensive heart disease: left bundle branch block	16.1
		After a week's rest, no dyspnoea	12.6
344	M55	Orthopnoea since coronary thrombosis 10 days previously	16.8
345	M52	Orthopnoea: hypertrophy of left ventricle: chronic nephritis: hypertensive heart disease	16.9
346	M56	Exertional dyspnoea: oedema of ankles: malignant hypertension: hypertensive heart disease with failure spreading to right ventricle also	18.0
347	M71	Exertional dyspnoea and intermittent claudication: arteriosclerosis: myocardial ischaemia	18.6

TABLE VIII. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
348	M67	Dyspnoea of increasing severity for past year, now orthopnoea: B.P. 180/110: hypertensive heart failure.	19.0
		After 9 days rest: orthopnoea less marked: B.P. 150/95	18.0
		After a further 6 days: up a little without dyspnoea: general improvement: B.P. 150/100	15.2
349	M60	Dyspnoea and dysphagia: aneurysm of the ascending arch of the aorta: cardio-aortic syphilis: left ventricular failure. B.P. 165/70	19.0
		After 7 days rest: I. S. Q.	20.2
350	F53	Exertional dyspnoea: B.P. 170/105: hypertensive heart failure	20.0
351	M75	Exertional dyspnoea: B.P. 150/80: left ventricular failure following coronary thrombosis	20.0
352	M55	Exertional dyspnoea and retrosternal pain: B.P. 115/75: arteriosclerotic heart disease	22.0
353	F58	Orthopnoea: cardio-venal disease: B.P. 260/145: hypertensive heart failure	22.4
		After 6 days treatment: no orthopnoea: B.P. 220/130: general improvement	18.4
354	M50	Exertional dyspnoea: B.P. 220/130: hypertensive failure.	23.0
355	M25	Exertional dyspnoea: aortic incompetence: B.P. 120/70: left ventricular failure	23.4

TABLE VIII. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
356	M57	Dyspnoea of increasing severity for several years: arteriosclerotic heart disease	26.5
		After 11 days rest: I. S. Q.	25.5
357	F53	Exertional dyspnoea: B.P. 140/80: arteriosclerotic heart disease	26.8
358	M55	Exertional dyspnoea: B.P. 200/130: hypertensive heart failure	27.0
359	F71	Exertional dyspnoea: B.P. 190/130: past coronary thrombosis: left ventricular failure	30.0
360	M48	Exertional dyspnoea: B.P. 200/160: hypertensive heart failure	35.0
		(B) Predominantly right ventricular failure.	
361	M62	Oedema of legs: B.P. 200/110: right heart failure following hypertensive failure	12.3
		After 14 days: oedema more severe: ascites: oligura: B.P. 160/110	16.8
362	F68	Previous dyspnoea much improved but oedema of legs increasing: cervicalveins full: B.P. 160/110: right heart failure following hypertensive failure of left heart	13.0
363	F63	Exertional dyspnoea: oedema of ankles and lumbar pad: cervical veins full: B.P. 210/140: Hb 68%: right heart failure following hypertensive failure: anaemia	14.0
364	M50	Oedema of legs: moderate ascites: B.P. 150/90: myocardial failure from previous coronary sclerosis	14.4

TABLE VIII. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
364 ctd	M50	After 11 days treatment: oedema gone: B.P. 140/90: general improvement	9.8
365	M49	Exertional dyspnoea: oedema of legs much diminished after treatment but still present: B.P. 160/110: right heart failure following hypertensive failure	14.6
366	M18	Residual hepatic enlargement from old pericarditis: test after pericardiectomy	15.0
367	F45	Exertional dyspnoea: oedema of ankles: liver slightly enlarged: rheumatic heart disease	16.0
368	M50	Exertional dyspnoea: sacral oedema: early ascites: cardiac enlargment on X-ray: emphysema: right heart failure: "cor pulmonale"	17.0
369	F59	Exertional dyspnoea: oedema of ankles: cervical veins full: auricular fibrillation: B.P. 160/90 right heart failure following hypertensive failure	17.5
370	F25	Exertional dyspnoea: convalescent from congestive failure: no oedema now: rheumatic heart disease	18.0
371	M59	Exertional dyspnoea: oedema of legs: ascites: liver enlarged and pulsating: emphysema: right heart failure: "cor pulmonale"	18.2
		After 7 days treatment: oedema diminished: liver moderately enlarged still	15.8
372	M43	Orthopnoea: oedema of ankles: cervical veins full: auricular fibrillation: rheumatic heart disease	18.6
		After 7 days treatment: no oedema: heart rate controlled by digitalis	12.2

TABLE VIII. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
373	M54	Exertional dyspnoea: lumbar oedema: cervical veins full: bronchiectasis: right heart failure "cor pulmonale"	20.2
		After 11 days treatment: general improvement	13.0
374	M23	Orthopnoea: lumbar oedema: cervical veins full: auricular fibrillation: rheumatic heart disease	21.2
375	F35	Exertional dyspnoea: oedema of legs: sacral pad: cervical veins full: liver enlarged: rheumatic heart disease	21.5
		After 7 days treatment: less oedema	18.2
		After a further 7 days: no oedema: liver much smaller: general improvement	12.9
376	M38	Exertional dyspnoea: oedema of ankles: enlarged liver: auricular fibrillation: controlled by digoxin: rheumatic heart disease	22.5
377	F43	Exertional dyspnoea: oedema of legs: cervical veins full: auricular fibrillation: rheumatic heart disease	23.4
378	F52	Recovering from congestive failure: liver still moderately enlarged: no oedema: auricular fibrillation partially controlled by digitalis: rheumatic heart disease	23.8
		After a further 4 days treatment	20.0
379	M65	Exertional dyspnoea: oedema of ankles: cervical veins full: congestive failure in relapsed pernicious anaemia: Hb 80%	24.0
		After 3 weeks at work, (refused to enter ward) oedema more severe: liver greatly enlarged	25.0

TABLE VIII. (contd.)

Case No.	Sex and Age	REMARKS.	C.T. in secs.
380	M38	Ascites: cervical veins full: auricular fibrillation: rheumatic heart disease:	24.2
381	M57	Oedema of legs: sacral pad: cervical veins full: liver moderately enlarged: rheumatic heart disease	25.0
382	F38	Exertional dyspnoea: cervical veins full: liver moderately enlarged: B.P. 210/140: rheumatic heart disease and hypertensive failure	25.2
383	F36	Oedema of legs: cervical veins full: subacute bacterial endocarditis with congestive failure	26.4
384	F29	Exertional dyspnoea: oedema of legs: auricular fibrillation: rheumatic heart disease	29.0
385	M50	Oedema of ankles: cervicalveins full: auricular flutter changed to auricular fibrillation as a result of treatment	29.0
		After 7 days: return to normal rhythm	22.0
386	F24	Exertional dyspnoea: oedema of legs: sacral pad: cervical veins full: oliguria: auricular fibrillation: rheumatic heart disease	30.8
		After 3 weeks treatment: no oedema: urinary output normal: heart rate controlled by digitalis	12.0
387	M49	Orthopnoea: cervical veins full: no oedema: auricular fibrillation: rheumatic heart disease	33.0
388	M48	Orthopnoea: oedema of legs: cervical veins full: specific aortitis with aortic incompetence: right heart failure following left ventricular failure	35.0
389	M70	Orthopnoea: oedema of legs: cervical veins full: myocardical failure from previous coronary thrombosis	58.0

SECTION THREE.

COMMENTARY AND CONCLUSIONS.

COMMENTARY.

In selecting theophylline-ethylenediamine as an agent for the measurement of blood circulation time, Koster and Sarnoff (1943) did so because it appeared to satisfy their basic conditions, which were:-

1. The injected substance must be non-toxic in the dosage used.
2. The injection of a small volume of solution should be sufficient to produce a good end-point, so that the injection time is negligible in comparison with the total circulation time.
3. The end-point should be sharp and reliable.
4. The end-point should be objective in order to eliminate errors in unreliable or unco-operative patients.
5. The end-point should be detectable without the use of elaborate apparatus.
6. The agent itself should be readily available.

In view of the extensive trial which has been described in the preceding section, it is now possible to justify the selection of this method insofar as it meets these basic requirements. Out of 433 tests in 339 cases, there was no dangerous reaction, but a few excitable subjects were somewhat upset by the test, and eight confirmed psychoneurotics showed signs of a violent emotional disturbance lasting for about ten minutes. The recommended dose of 1.0 c.c. of

cardophylin can be injected within one second, so that the injection-time is almost constant, and this dose produces a good end-point in almost every case. The adequacy of the dosage was confirmed by Ruskin and Rockwell (1945), who were investigating the influence of dosage in several methods of blood circulation time measurement: they found that doses of theophylline-ethylenediamine between 0.12 - 0.24 gm. (corresponding to 0.5 - 1.0 c.c. of cardophylin) produced almost constant results, and also that suboptimal doses of this substance produced less lengthening of circulation time than did those of subjectively appreciated drugs. It has been emphasised that the first observable change must be taken as the end-point, for the dramatic gasp, although it is usual, is not always seen: a swallowing movement, a sudden change in facial expression or a sharp catch in the breath during expiration constitutes an equally reliable end-point - and is confirmed by a gasp, a second or two later, in the majority of such cases. In only 4 out of the 433 tests recorded was there any difficulty in recognising the end-point, and only one test had to be discarded because an end-point could not be obtained.

In addition to meeting the requirements enumerated by Koster and Sarnoff, the test, if it is to be considered to be reliable, must give consistent results in any one normal individual, and appropriate results in individuals suffering

from disorders which are known to affect the circulation time.

The results of duplicate tests in a group of 50 normal subjects showed very close agreement, the maximum difference between any two tests was 2.6 seconds, and the average difference was only 1.1 seconds: this is within physiological limits, as shown by Stewart (1921), because the injected substance may enter the right ventricle immediately after systole and be held there for almost a second, if the heart rate is 60, and there may be a similar delay in the left ventricle, so that the total delay may be close on two seconds.

There is considerable difference of opinion in the literature on the influence of age on the blood circulation time, but, as a result of a careful investigation, Gibson and Evans (1937) conclude that there is no significant relationship between the two, and our results support this view for adult patients. However, we found a reduction in circulation time in children and adolescents: this may be due, in part, to a probable overdosage of cardophylin - since it is difficult to measure accurately fractions of 1.0 c.c. of solution - and, in part, to the increased relative strength of the pulmonary circulation in childhood.

Apart from disease, the circulation time is influenced by exercise, a fact which has been confirmed by many workers including Boothby and Rynearson (1937): inaccuracies from this source may be eliminated by resting the patient before performing the test. Posture also affects the result, and

Wilburne (1942) has shown that the normal subject has a higher circulation time when sitting with the legs dependent than when recumbent, whereas the subject with congestive heart failure has a lower reading when sitting with the legs dependent; such discrepancies were avoided in the cardophylin trial by making each measurement with the patient recumbent. Reingold, Neuwelt and Necheles (1942), using the cyanide method, found that the measurement varied appreciably with fasting and the taking of meals; in our investigation an attempt was made to minimise such variations by performing the test, in ward patients, between two and four hours after a meal: the same conditions probably applied to most tests in out-patients, and the close agreement between duplicate readings suggests that the attempt was successful.

The diseases which are most likely to affect the circulation time are fevers, disorders of the blood, disorders of the thyroid gland affecting metabolism, and cardiovascular conditions.

In a study of blood velocity in hyperpyrexia, Kissin and Bierman (1933) found that the circulation time diminished as the body temperature increased, and that there was a rough inverse relationship between the two: Kopp (1936 a and b) had similar findings and also observed (1936 a) that for the same temperature increase, a patient with aortic incompetence, but without heart failure, suffered a greater reduction in

circulation time than a similar patient with a normal heart. Since the advent of intensive chemotherapy, pyrexia of any appreciable degree is seldom seen in an ordinary hospital, hence it was impossible to test the cardophylin method in this condition; however, two cases in the rheumatic carditis group had mild elevations of temperature (Table vll) which may have contributed to their low circulation time readings. The reduction of the circulation time in anaemia has been described by almost every worker quoted in section one, and the reduction is to be expected on physiological grounds, for the compensatory mechanism whereby the deficiency of haemoglobin is minimised by an increase in the minute output of the heart necessitates an increase in blood velocity and hence a reduction in the circulation time. The results of our tests in anaemia and polycythaemia, shown in Table lV, confirm that the circulation time is roughly proportional to the haemoglobin content of the blood. Although the test is normally of little value in the diagnosis of anaemia, it may be helpful on occasion, for an unexpectedly low reading - in cardiac failure, for example, as in No.363 in Table Vlll - may be due to anaemia which has not been appreciated clinically.

The decrease in circulation time in hyperthyroidism also has been described by many workers, and our results are in agreement. A typical case of thyrotoxicosis, untreated, has a cardophylin circulation time of 7.0 seconds or less, and this increases with treatment, in parallel with clinical improvement; however, if such a case is complicated by auricular

fibrillation, the circulation time may be normal, and if obvious cardiac failure is present also, the measurement may be appreciably increased. In complicated cases, therefore, the circulation time may be regarded as the sum of two hypothetical measurements - a low reading due to hyperthyroidism, and a high reading due to cardiac failure: since the cardiac condition responds to treatment more rapidly than the primary disorder, the second hypothetical measurement falls faster than the first one rises, so that the net result is a slight fall in the recorded circulation time.

In mild or early cases of hyperthyroidism, the reduction in circulation time is less marked, and the results obtained in our trials might be considered as low normal readings, similar to those obtained, for example, in cases of anxiety neurosis. This is particularly unfortunate, since early hyperthyroidism and anxiety neurosis are often difficult to distinguish clinically: nevertheless we must agree with King and Sohval (1939) that, in such borderline cases, the circulation time is not a reliable aid to diagnosis.

However, the test has a definite place in the study of thyroid disorders, for it may give the first indication of developing cardiac failure in an apparently straightforward case of thyrotoxicosis, and conversely it may suggest a diagnosis of "masked hyperthyroidism" in an obscure case of cardiac failure. Moreover, since the introduction of thiouracil and

and its derivatives has led to the treatment of many cases of hyperthyroidism as out-patients, the test may be used as an adjunct to clinical examination in the assessment of the patient's progress, and is much more convenient than the estimation of his basal metabolic rate. The test may be used similarly in cases of myxoedema.

Measurement of the blood circulation time is of greatest value in the diagnosis of cardiovascular disease, hence in our investigation we gave particular attention to cases in this category. Out of a total of 108 tests in subjects with definite cardiovascular disease, 65 were made in those who presented clinical evidence of cardiac failure, and 43 in those who presented no such evidence. Our first group of patients suffered from hypertension, with various signs and symptoms of which none suggested cardiac failure; the results in Table V, were within normal limits and confirm the findings of Kvale, Allen and Adson (1939). Our second group consisted of patients with organic disease of the heart but without heart failure; in some, the valvular lesions were uncomplicated, and in others they had been aggravated by subacute bacterial endocarditis: once again the results were within normal limits, as shown in Table Vl, and were similar to those of Wood (1936).

Our third group consisted of patients with rheumatic carditis in various stages of activity, and the results in Table Vll show that the circulation time was roughly inversely proportional to the degree of activity except in case No.341,

in which the occurrence of auricular fibrillation produced a high reading, which was reduced to normal by effective digitilisation. The reduction in circulation time in the active phase is due probably to the increase in metabolism caused by the infection, and to the mild anaemia which is usual in these cases.

The final group consisted of patients with clinical evidence of cardiac failure, and was subdivided into two sections - the first contained all cases in which failure was predominantly left ventricular in type, and the second contained all in which it was predominantly right ventricular. Although the average reading was the same in each section, the range was much greater in the second owing to the very high reading in case No.389 in which there was severe failure of both right and left ventricles following myocardial in farction. The low readings obtained in some of the cases, in which right ventricular failure had occurred as a sequel to failure of the left ventricle, are surprising, but they may correspond to the brief clinical improvement which occurs when a patient, with orthopnoea from left ventricular failure, develops right ventricular failure and finds that he can breathe comfortably. The results in Table Vlll show that, although the circulation time is prolonged in most cases of cardiac failure, the actual reading does not bear, in general, any definite relationship to the degree of failure as judged by clinical standards: on the other hand, in any one particular case, serial readings

do reflect the degree of failure or of recovery, and may give prognostic help.

However, it is as an aid to diagnosis that circulation time tests have won a place in clinical medicine, and they have done so because they enable the physician to assess the functional ability of the heart in cases where this is in doubt. In a typical case of right ventricular failure, from rheumatic heart disease, with peripheral venous congestion, ascites, gross oedema and enlargement of the liver, a circulation time is not a necessary preliminary to diagnosis: but a case of cirrhosis of the liver with ascites might well have an old valvular lesion in his heart, in which case the circulation time measurement would have some value. In pregnancy, slight oedema of the ankles is not uncommon in a patient with a normal heart, but if oedema occurs in a patient with rheumatic heart disease, the circulation time test may be of appreciable help in determining its significance. In this connection, although Cohen and Thomson (1956) found the circulation time in healthy pregnant women to be within the normal non-pregnant range, and Greenstein and Clahr (1937) found it to increase as pregnancy advances without signifying cardiac insufficiency, it should be recorded that Manchester and Loube (1946) describe a careful investigation, involving fortnightly tests throughout pregnancy in 48 normal women, which showed that the circulation time diminishes significantly in both the

second and third trimesters, and they conclude that a reading near the upper limits of the accepted "normal" range may be an early sign of cardiac decompensation.

The diagnosis of early left ventricular failure is difficult at times, because the usual presenting symptom of dyspnoea on exertion may be found also in effort syndrome, anaemia, and such pulmonary diseases as emphysema and tuberculosis; paroxysmal dyspnoea may be due to bronchial asthma as well as to more advanced failure of the left ventricle. Our results, have shown that the circulation time is normal in the effort syndrome, and the decreased readings in anaemia have been discussed above: the results in the relatively few cases of pulmonary disease are consistent with the findings of other workers who have concentrated on the investigation of such cases. Oppenheimer and Hitzig (1936) found that the circulation time in 25 cases of emphysema, uncomplicated by cardiac failure, was normal or slightly reduced, and Plotz (1939) had the same findings in 37 cases of bronchial asthma: Hurst and Brand (1937) examined 153 cases of pulmonary tuberculosis and discovered that the circulation time was within normal limits, irrespective of the extent of the disease and of the presence or degree of collapse of the lungs. In contrast, we have shown that the circulation time is greatly increased in left ventricular failure, and Epstein and Young (1943) have demonstrated that the increase is accompanied

usually by radiological signs of pulmonary congestion although clinical signs in the chest may be lacking. Hitzig, King and Fishberg (1955) found that in early failure, especially if due to malignant hypertension, the circulation time may be prolonged even before the occurrence of dyspnoea as a symptom, and Selzer (1945) showed that an increase in circulation time may be the earliest indication of the development of left ventricular failure in acute myocardial infarction. It is evident, therefore, that the circulation time may be increased before clinical signs or symptoms of left ventricular failure appear, and this supports the suggestion of Webb, Sheinfeld and Colin (1936) that the test should be used in surgery for the recognition of patients who are poor "operative risks" because of incipient heart failure.

CONCLUSIONS.

The theophylline-ethylenediamine method of blood circulation time measurement requires the minimum of apparatus, and in normal subjects gives consistent and reliable results, which are comparable with those obtained by the widely used decholin and saccharin methods, when allowance is made for the extra second or two which is necessary for the injection of the larger volume of solution of the latter substances.

The end-point, which is entirely objective, takes the form of a marked inspiratory gasp in about 90% of cases, and is readily recognisable, although less dramatic, in the other 10%.

No dangerous reaction occurred in 433 tests in 339 patients, but unpleasant side-effects were noted in a few excitable subjects and in others with pyschoneurotic disorders.

In disorders of the blood, the circulation time is roughly proportional to the haemoglobin level, showing a decrease in anaemia and an increase in polycythaemia, and approaches the normal value in parallel with that level.

In uncomplicated hyperthyroidism, the circulation time is considerably decreased, and returns towards normal in parallel with clinical improvement; where cardiac failure is present as a complication, the circulation time is normal or slightly increased, and tends to decrease with treatment, which influences the complication more rapidly than the primary condition.

In cardiovascular disease, the circulation time is normal in hypertension and in organic valvular disease provided that there is no evidence of cardiac failure; when cardiac failure is present, the circulation time is increased but fluctuates in the individual patient according to the course of the disease, and is modified by concomitant anaemia or thyrotoxicosis. The chief value of circulation time measurement is in the differentiation of early cardiac failure and broncho-pulmonary disease, and the theophylline-ethylenediamine method is eminently suitable for this purpose.

S U M M A R Y.

The commoner methods of blood circulation time measurement have been reviewed, and the theophylline-ethylenediamine test, which has not been used previously in this country, was selected for clinical trial, since it appeared suitable for routine use in general practice and in a busy hospital out-patient department.

Extensive clinical trials - involving 433 tests in 339 cases - are described, and the results indicate that the theophylline-ethylenediamine method is safe, simple and reliable, is suitable for use in the control of the treatment of thyrotoxicosis, and is a valuable aid to the diagnosis of cardiac failure.

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