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VISUALIZATION OF THE CHAMBERS OF THE HEART, THE PULMONARY CIRCULATION, AND THE GREAT BLOOD VESSELS IN MAN*†

A PRACTICAL METHOD

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HERETOFORE there has been no method of visualizing the left chambers of the heart and the superior vena cava and no practical procedure for outlining the right chambers of the heart, the pulmonary circulation and the thoracic aorta in man. Gross changes in size and shape have been detectable by roentgen examination but precise information concerning the individual chambers of the heart, the pulmonary artery, the vena cava and the aorta could not be obtained. Contrast roentgenography has made such information available in other regions of the body, notably the central nervous system, the bronchi, the gastrointestinal tract, the genitourinary system, and the peripheral arteries and veins; but this method has had limited success when applied to the cardiovascular structures in the thorax. Forssmann[11] in 1931 tried unsuccessfully to visualize the chambers of the heart by the injection of an iodide preparation into the right auricle through a catheter which he had introduced into a vein at the elbow and advanced to the heart. In the same year Egas Moniz, Lopo de Carvalho and Almeida Lima[9] succeeded in visualizing the pulmonary blood vessels by the use of a concentrated solution of sodium iodide and Forssmann's technique of injection. Since then, this method of pulmonary arteriography or modification has been used by Lopo de Carvalho and his associates,[25,26,27,28] Conte and Costa,[5] Heuser,[15] Ravina,[37] and others. Ameuille and his associates[1] also outlined the right chambers of the heart in this way in a few instances. Although reputedly harmless, the difficult nature of cardiac catheterization has precluded general use of this method. Nuvoli[33] recently made the thoracic aorta opaque by injecting sodium iodide after puncturing the left ventricle in one patient and the ascending aorta in another; this technique obviously is not suitable for routine use. In the past year, Castellanos, Pereiras, and Garcia[4] visualized the right side of the heart and the pulmonary artery by the peripheral intravenous injection of organic iodide compounds. Their method, however, was effective only in children under six years of age and it failed to outline the left chambers of the heart and the aorta.

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Intravenous injection of the radiopaque substance for visualization of the pulmonary blood vessels in adults has been tried and discarded.[26] Despite these failures, it was believed that opacification of the heart and the lungs could be accomplished in this way because of the relatively high concentration with which brilliant vital red dye traverses these structures in the dye injection cardiac output method.[29,50] In order to test this belief it was necessary, first, to develop a technique which would permit injection of the radiopaque substance rapidly enough to make the blood stream opaque, and then to find a contrast solution which would be freely miscible with the blood, pharmacologically inert, nonirritating to the vascular system, nontoxic in the dosage used, and rapidly inactivated or eliminated by the body. The use of a large bore needle and syringe tip permitted the ejection of 30 cc. of water per second, a rate which later was found sufficient to satisfy the first requirement. The relatively innocuous organic iodide compounds used for intravenous pyelography offered a possible solution for the other problem. Preliminary study in rabbits begun in January, 1936, showed that visualization could be obtained by the use of several of these compounds in amounts comparable to those which could be given safely to man, and that the addition of glucose[3] or sodium iodide[5] was unnecessary. Clinical trial then proved the feasibility of this procedure[39]; the first successful visualization of the right side of the heart and the pulmonary circulation was obtained on January 30, 1937, and the first visualization of the left chambers and the aorta on May 23, 1937.

METHOD

The method consists of two essential parts: the injection of enough radiopaque substance into the blood entering the heart to make the chambers and important thoracic blood vessels opaque to the roentgen ray during the first circulation; and the making of roentgenograms of these structures at the time of opacification.

The procedure is carried out in two stages. In the first, a large transfusion needle is inserted into the basilic or cephalic vein of the arm. The patient then is seated before the casette in the position giving the best view of the structures to be visualized; this position should be determined beforehand by roentgenoscopic examination. The arm used for the injection is extended upward and the radiopaque solution is injected rapidly into the vein. Roentgenograms are made after appropriate intervals. The intervals between injection and the arrival of the contrast substance in the superior vena cava, the right chambers of the heart, and the pulmonary blood vessels are short and fairly constant. Longer and more variable periods are required for it to reach the left chambers of the heart and the thoracic aorta, but they may be learned before injection by determining the circulation time to these regions.

Low power roentgen-ray equipment can be used although a power unit with high capacity gives better results and is therefore desirable. A fast moving stereoscopic casette shifter is advisable because it provides two roentgenograms per exposure, and also stereoscopic films if desired. Two operators are required: the physician, who makes the injection, and the technician, who makes the roentgenograms and assists in other parts of the technique.

Solutions:

(1) 70 per cent aqueous solution of diodrast.*
(2) 0.9 per cent solution of sodium chloride.
(3) 2 per cent solution of procaine hydrochloride.
(4) 1–1000 solution of epinephrine hydrochloride.
(5) 2 per cent aqueous solution of sodium cyanide.
(6) Ether U. S. P.

Apparatus (see Fig. 1):

(1) Needles:

1 needle-stopcock unit:† a modified 12-gauge Lindemann transfusion needle connected to a two-way Luer-Lok stopcock having an inside

* Made by the Winthrop Chemical Co., Inc. In the beginning this solution was prepared by concentration of the commercial 35 per cent preparation to 70 per cent by evaporation in a distillation flask. Recently the sterile 70 per cent solution having a pH of approximately 7.4 has been prepared by the manufacturer and provided for this study.

† Made by Becton, Dickinson and Co.

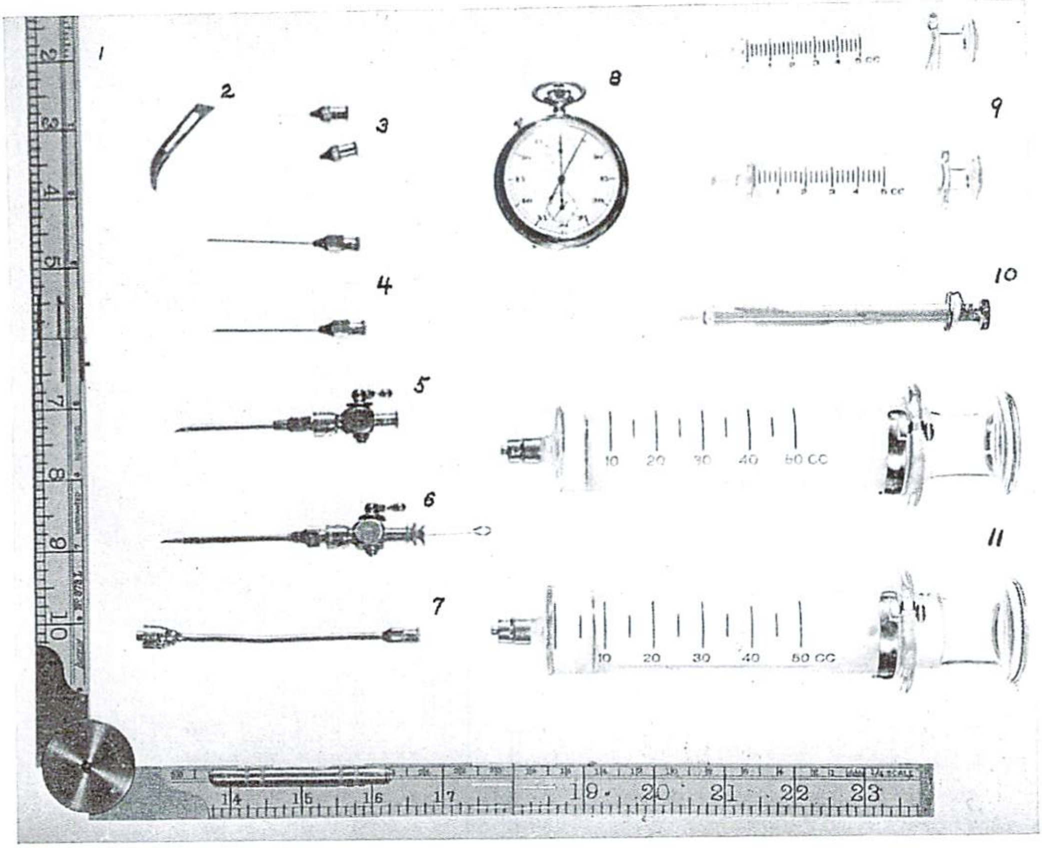

Fig. 1. Apparatus: *1*, protractor rule; *5*, 12-gauge bevelled point transfusion needle and two-way Luer-Lok stopcock unit (used originally and in majority of injections; replaced recently by No. 6); *6*, 12-gauge modified Lindemann needle-stopcock unit; *7*, flexible metal adapter; *11*, 50 cc. Luer-Lok syringe with 12-gauge tip.

diameter of 0.083 inches (12-gauge) instead of the standard 0.054 inches.* The outer cannula is 1½ inches long and remains attached to the stopcock. The inner cannula and needle, which are fused together, extend through both stopcock and outer cannula.

2 18-gauge needles, 2 inches long—for the transfer of diodrast and other solutions.

2 26-gauge hypodermic needles, ½ inch long.

(2) Syringes:

2 50 cc. Luer-Lok syringes with 12-gauge tip instead of the standard bore of 0.073 inches.†

2 5 cc. syringes.

1 1 cc. syringe graduated in hundreths of a cubic centimeter.

(3) Bard-Parker knife blade.

(4) Stopwatch.

(5) Roentgenographic equipment:

(a) A power unit having a capacity of at least 300 ma. and 75–100 kv. (peak), and an exposure time of 1/20 second or less at a distance of 72 inches.

(b) A casette shifter requiring 2 seconds or less to shift films.

The following exposure factors can be used but give poorer results: 50 ma., 75 kv. (peak), exposure time 1/5 second, and distance 60 inches.

(6) Lead screen or apron.

(7) Angle meter.‡

(8) Tourniquet, adhesive tape, alcohol, sterilizer, and sterile gauze squares.

Technique. Roentgenoscopic examination of the chest usually precedes visualization of the heart and aorta in order to find the optimal position of the thorax for the right and left anterior oblique views. The degree of rotation for each position is measured by means of an angle meter or a revolving stool designed for

* This greater bore increases the cross-sectional area by more than 100 per cent and doubles the speed of injection.

‡ The 2-foot protractor rule made by the Lufkin Rule Co. is satisfactory.

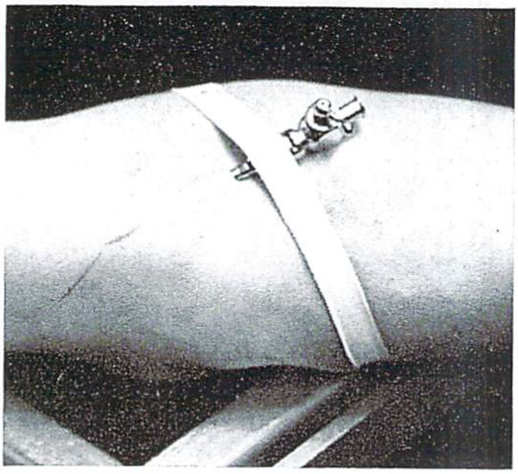

Fig. 2. Arm resting on table during first stage. Needle-stopcock unit in median basilic vein and held in position by adhesive tape. Note alignment of needle and vein. Mark on arm indicates course of vein.

this purpose.* To test the correctness of the position and the roentgenographic technique, a control roentgenogram is made and developed at once. Blood pressure and heart rate are recorded. Epinephrine, 0.3 to 0.5 cc., should be given if allergic tendency, drug sensitivity, or arterial hypotension is present. The apparatus used for injection is sterilized and the sterile solutions of diodrast and sodium chloride are warmed to, and maintained at, body temperature. Hypodermics of procaine and epinephrine are prepared, and a 50 cc. syringe is filled with sodium chloride solution.

The patient now is seated with one arm resting upon a table. Selection of the arm for injection is governed by the position to be used and will be discussed later. A tourniquet is applied to the arm tightly enough to cause intense engorgement of the veins, and the principal vein, preferably one having a diameter of 6 mm. or more, is selected. After anesthetization with 0.2 to 0.3 cc. of procaine solution, the skin at the site of proposed puncture is nicked with the knife blade. The stopcock with the needle attached is grasped in the right hand between the index and middle fingers in front and the thumb behind. The outer end of the stopcock against which the thumb presses is protected by a sterile gauze square. The needle thus held is inserted into the vein and advanced 2 to 3 cm. within the lumen. When venipuncture is successful the gauze square becomes stained with blood. The tourniquet is then released; the combined inner cannula and needle is removed quickly, and the stopcock is closed. The cannula with stopcock is aligned with the vein and fixed in this position by a band of adhesive tape (Fig. 2). To test the adequacy of location of the needle, the 50 cc. syringe containing the sodium chloride solution is attached to the stopcock and the liquid is injected rapidly. Thereafter, needle and vein are flushed with salt solution every three to four minutes to prevent clotting. It is essential that the stopcock should remain closed except when connected to a syringe, and that the arm used for injection should be extended while the needle is in place; if necessary, extension can be maintained by use of a posterior splint or adhesive strap.

The ether arm to pulmonary capillary[20] and the cyanide arm to carotid[43,44] circulation times, when indicated, are determined at this point by adaptation of the original techniques. One-half cubic centimeter of ether is added to 20 cc. of salt solution in a 50 cc. syringe and dissolved by shaking. The arm is elevated and the ether and saline solution is injected rapidly. The interval between the beginning of the injection and the detection of ether on the patient's breath is recorded by stopwatch. The cyanide circulation time method is modified in a similar manner; an effective dose of sodium cyanide, usually 0.3 to 0.4 cc. of the 2 per cent solution, is dissolved in saline solution and injected into the elevated arm. The interval between the start of injection and the onset of hypernea is measured.

The patient then takes his seat before the casette in the desired position, and is held there by a chest band. The sensations to be experienced are described to him by the injector, and the respiratory movements used in the procedure are practiced. The arm for injection is raised to the horizontal and the 50 cc. syringe containing the diodrast is attached securely to the stopcock. To prevent change in position of the needle during withdrawal of blood and injection, the patient's elbow is grasped by the injector's left hand; the fingers support the patient's arm while the thumb anchors the stopcock and needle by pressing them against the arm. Venous stasis is induced again and approximately 20 cc. of blood is drawn into the syringe slowly, to prevent diffusion. Being lighter, the blood rises to the top and later, when the arm is raised, it forms a column above the diodrast. The syringe, still connected to the stopcock, is

* Designed by Dr. I. Seth Hirsch, Department of Radiology, New York University College of Medicine.

held by the injector's right hand; the index and middle fingers straddle the upper end of the barrel, and the thumb presses against the side of the plunger close to the barrel to prevent movement of the plunger until the time for injection. The arm is raised to an angle of approximately 45 degrees above the horizontal and the tourniquet is released (see Figs. 3 and 4).

The patient is now ready for the injection. At the direction, "Breathe OUT," he exhales forcibly until stopped by the command, "Breathe IN." He then inspires quickly, and at the same instant the stopwatch is started by the technician and the injection is begun. The contents of the syringe is injected in two seconds or less. The inspiration usually is completed in two to three seconds but should be finished in one second if the vena cava or right auricle is to be visualized. The inspiratory position is held until the opaque material has arrived in the pulmonary arterial tree and the roentgenogram has been made. Then, at the order, "Relax," the patient exhales passively. The inspiratory position is assumed again shortly before the time of opacification of the left chambers of the heart and the aorta, and is held until the instruction, "Breathe naturally," is given after the last exposure has been made. When the longest interval between injection and exposure is less than 8 seconds, the first inspiratory position should be maintained throughout the procedure. Roentgenograms are made after predetermined intervals. The injector, who stands at the patient's side during the exposures, is protected from radiation by the lead screen or apron.

Fig. 3. Right anterior oblique position, immediately before injection (viewed from the side). Syringe containing diodrast attached to needle-stopcock unit. Note column of blood above diodrast and position of injector's hands.

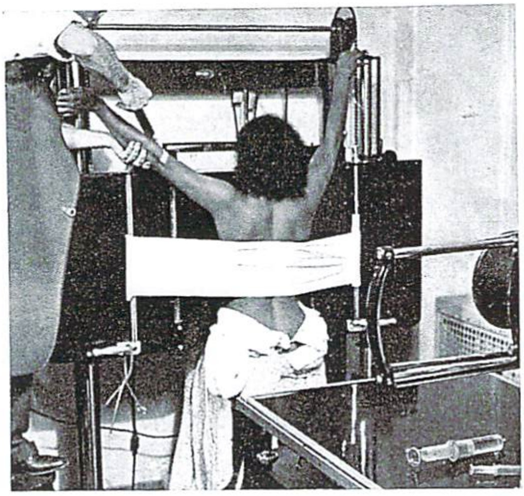

Fig. 4. Posteroanterior position. Note elevation of arms. Injector protected by lead apron stands at side of casette shifter.

After the last exposure, the syringe is disconnected, the chest band is released, and the needle and vein are flushed with sodium chloride solution. The patient is seated again at the table, and the blood pressure and the heart rate are determined while the needle is being removed. Bleeding from the puncture wound is prevented by elevation of the arm and pressure. A sterile dressing is applied and the patient is permitted to leave unless a pyelogram is desired.

Dosage. The dosage varies roughly with the body weight and the region to be visualized. In the average person 35 cc. of the 70 per cent solution containing 24.5 grams of diodrast is sufficient for opacification of the left chambers of the heart and the thoracic aorta; 25 to 30 cc., or 17.5 to 21 grams, suffices for visualization of the pulmonary blood vessels. Larger quantities are necessary in patients having thick chests, cardiac enlargement, or pulmonary engorgement. The dosage has ranged from 25 to 45 cc., or 17.5 to 31.5 grams.

Rate of Injection. The duration of injection is two seconds or less. This rate of injection offers no difficulty in the average person. In the emphysematous patient, however, in whom the aspiratory action of the thorax is diminished, this rate can be attained only by delaying the injection for one-half to one second after the beginning of inspiration.

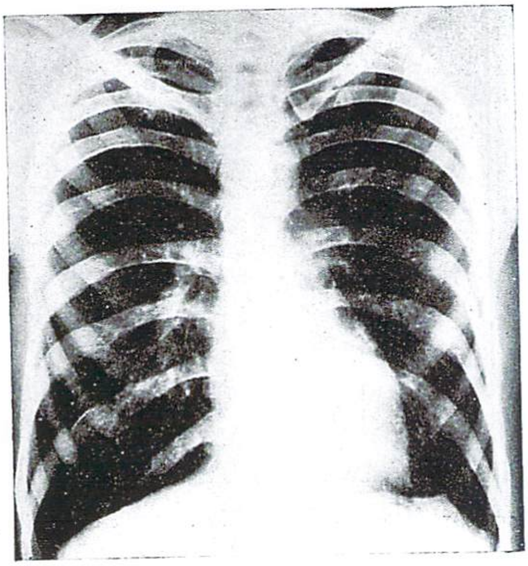

FIG. 5. Normal control.

Position during Roentgenography. The posteroanterior position is used routinely for visualization of the superior vena cava, the lung roots, and the pulmonary circulation. The oblique positions are necessary for study of the heart and the thoracic aorta. The left anterior oblique position is used routinely; the right oblique view also is employed when a side view of the heart is desired. The value of each position will be discussed later.

It is necessary to modify the conventional posteroanterior and oblique positions to allow elevation of the arm during injection. In the posteroanterior position both arms are extended upward and outward, thus tending to obscure the apices. Either arm may be used for the injection. When better definition of the apices is necessary, the conventional position in which the shoulders are in contact with the casette can be used, although the technique is more difficult and the injection is slower. In this case the syringe tip is connected to the stopcock by means of a flexible adapter* which is attached to the stopcock and bent upward at a right angle after the patient is in position for the test. Before the syringe is attached, air should be expelled from the adapter by filling it with blood from the vein. In the left anterior oblique position used in this study, the left arm encircles the head in the usual way, but the right arm which is used for injection is extended upward and laterally instead of being flexed with the hand on the hip. In the right anterior oblique position, this procedure is reversed.

Time for Exposure. For visualization of the superior vena cava and the right auricle, the time for exposure regularly is one and a half seconds after the beginning of injection. For the right ventricle and the pulmonary arterial tree, the interval is usually three seconds, but may be six seconds or longer if there is pulmonary emphysema or other cause for slow venous inflow. In such patients the appropriate interval should be learned before injection by determining the arm to lung circulation time and subtracting one to two seconds.† The time

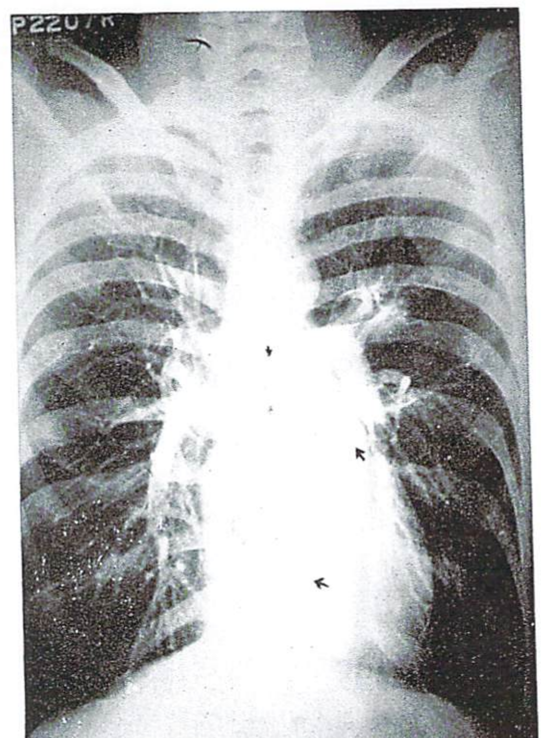

FIG. 6. Contrast roentgenogram. Three seconds after the beginning of injection. Normal, aged twenty. The right chambers of the heart, the pulmonic conus, and the entire pulmonary arterial tree are filled with diodrast. The interventricular septum is indicated by the lower arrow, and the left cusp of the pulmonic valve by the upper arrow. The right branch of the pulmonary artery is bracketed by darts.

* Made by Becton, Dickinson and Co.

† Since this paper was written, experience has shown the advisibility of determining the arm to pulmonary capillary circulation time at least once in every patient in whom the right side of the heart and the pulmonary circulation are to be visualized.

for exposure of the left ventricle generally varies between six and nine seconds with an average of eight, but it may exceed twenty seconds. Because of this variability, it should be determined routinely for each patient before injection. The cyanide circulation time indicates the optimal time for the thoracic aorta, and the left ventricular time is obtained from it by deducting one to two seconds.

Roentgenographic Technique. Overexposure is necessary, as in bronchography, to obtain good contrast and definition. An increase of 8 to 12 kv. (peak) in the voltage needed for the conventional film usually suffices. For example, the control roentgenogram (Fig. 5) is that of a patient weighing 112 pounds and having a posteroanterior diameter of the chest of $8\frac{3}{4}$ inches. The exposure factors were: 300 ma.; distance, 6 feet; duration of exposure, 1/20 second, and kv. (peak) 62. In the contrast film (Fig. 6), the kv. (peak) was increased to 70 while the other factors were unchanged. In other respects the roentgenographic technique is identical with that in general use. If stereoscopic films are desired, the interval between exposures must be short, approximately two seconds. More often, the second roentgenogram is used for the visualization of another part of the cardiovascular structure; this is illustrated by Figure 8 which was made five seconds after Figure 6.

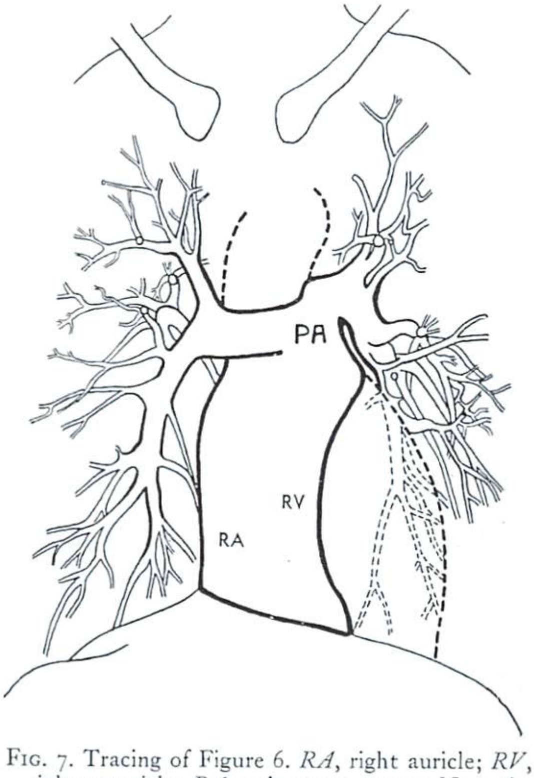

FIG. 7. Tracing of Figure 6. *RA*, right auricle; *RV*, right ventricle; *PA*, pulmonary artery. Note the right and left branches of the pulmonary artery and their numerous subdivisions.

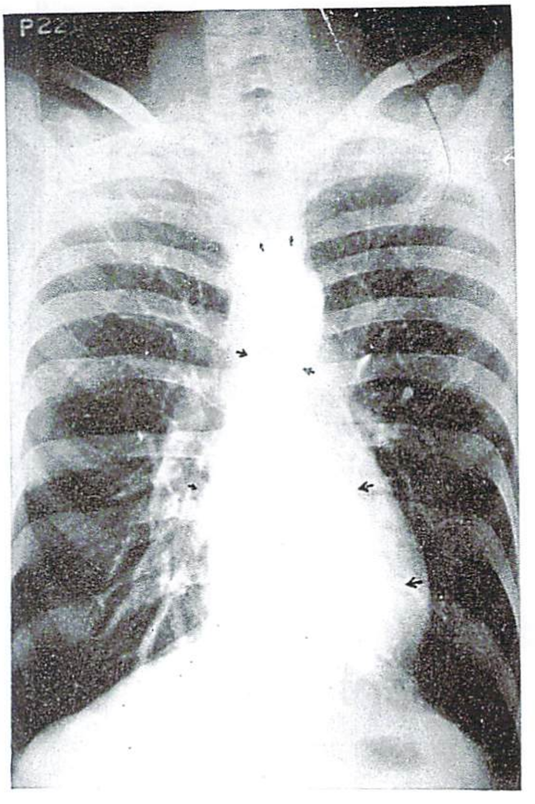

FIG. 8. Same patient as in Figures 6 and 7. Contrast roentgenogram. Eight seconds after injection. The left auricle and the left ventricle are indicated by the middle and lowest arrows on the left side; a pulmonary vein by the lower right dart. The ascending aorta is enclosed by small arrows. Note the two branches from the aortic arch and the left axillary artery.

Precautions.

(1) Accepted contraindications to the use of diodrast are severe liver disorders, nephritis and hyperthyroidism.[32] Contrary to general belief,[32] this drug caused no ill effect when given to patients with active tuberculosis. The test should be used cautiously in patients with heart disease and circulatory failure. It should not be used in patients who are critically ill.

(2) Premedication with a barbiturate compound is advisable for extreme nervousness.

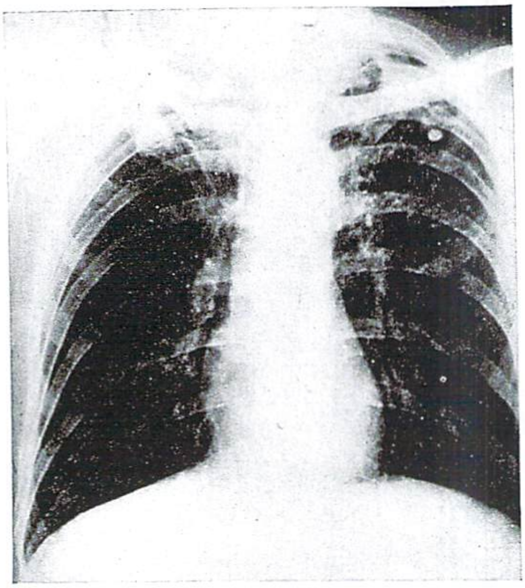

FIG. 9. Control. Productive tuberculosis upper lung fields. Pulmonary blood vessels indistinct.

Epinephrine should be given when there is an allergic tendency or low blood pressure.

(3) A hypodermic of epinephrine should be ready for administration in case of severe reaction.

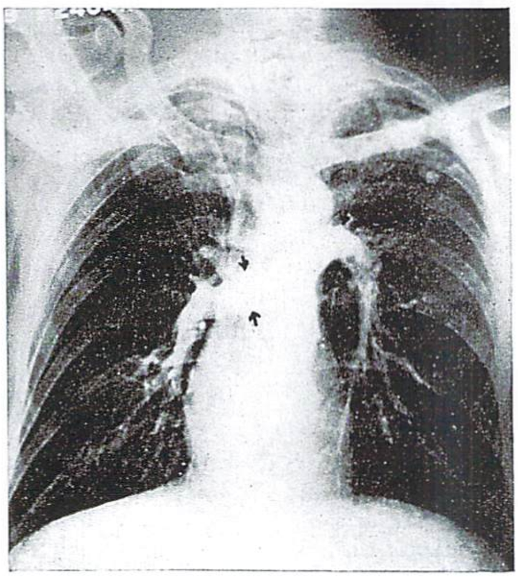

FIG. 10. Contrast film at three seconds. The left branch of the pulmonary artery is pulled up by the tuberculous process. Note the decreased vascularity to the upper lobes.

(4) The stomach should be empty or nearly so to prevent nausea and vomiting.

(5) The sensations to be experienced should be described to the patient to allay apprehension before injection and to prevent excitement during the immediate reaction.

(6) The point and cutting edges of the needle should be sharp, and the vein large and distended until taut, to facilitate venipuncture.

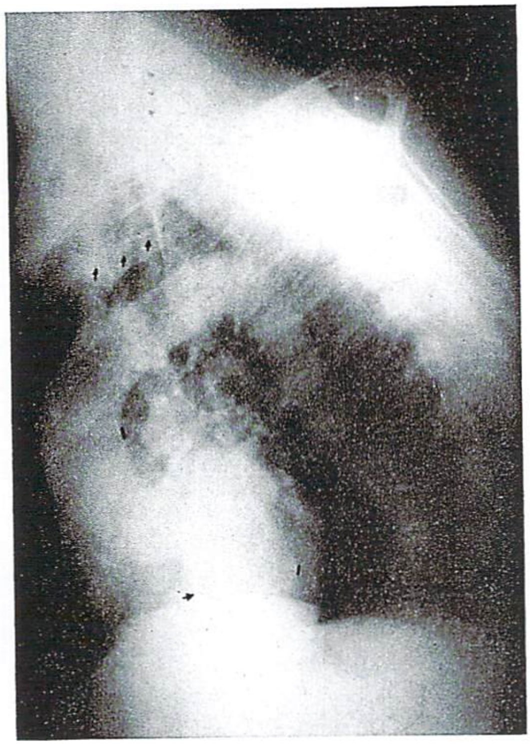

FIG. 11. Contrast roentgenogram. Left anterior oblique position (extreme). Eleven seconds after beginning of injection. Patient, aged thirty-seven, with hypertensive heart disease. Note enlargement of left ventricular cavity and wall (1.7 cm.) and the dilatation and "uncoiling" of the aorta. The lower dart denotes the interventricular septum; the upper three darts indicate the innominate, the left common carotid, and the left subclavian arteries.

(7) The radiopaque solution must be clear and warmed to 37.5° C. If a precipitate is present, the solution should be heated in a water bath until it has dissolved.

(8) Injection must be made only when there is free communication between the needle and the vein. When there is doubt, another vein should be tried or the test postponed.

(9) Vein and needle must be watched during injection to prevent change in position of the needle or overdistention of the vein, and to stop the injection if perivascular infiltration starts.

(10) In case of infiltration, normal sodium chloride solution should be injected immediately through the needle, while it is still in place, to dilute the diodrast and thus lessen irritation.

(11) The precautions ordinarily used to prevent infection from intravenous injection should be observed. The syringes must be scrupulously clean to prevent sticking of the plungers during rapid injection.

RESULTS

These results comprise the entire experience with this method including the early trials in which the technique was crude and only one roentgenogram per injection was made. A total of 238 injections was made in 127 patients of whom 42 were normal, 47 had pulmonary disease and 38 cardiac disease. Their ages varied between sixteen and seventy-four. Males predominated, 122 to 5. The number of injections per patient ranged from one to twelve; 20 received three injections or more. Subsequent injections usually were made after an interval of at least twenty-four hours. Forty-eight injections were for pharmacologic study and 190 for visualization.

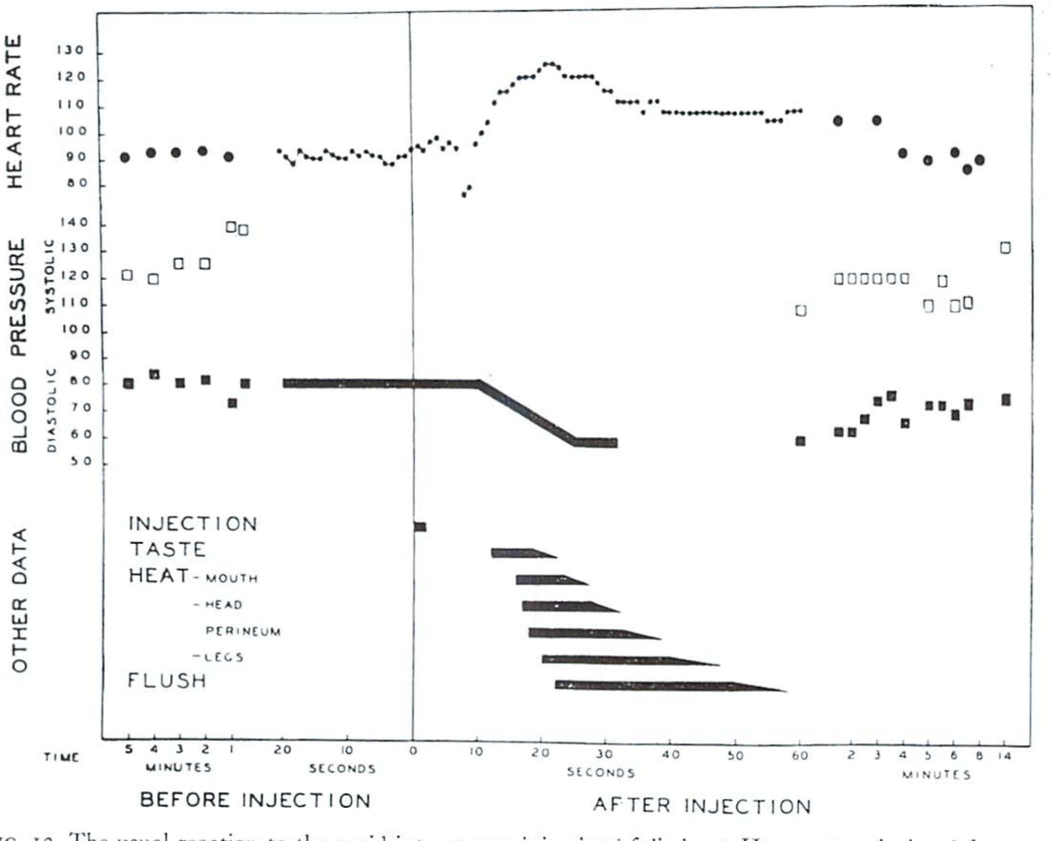

FIG. 12. The usual reaction to the rapid intravenous injection of diodrast. Heart rate calculated from continuous electrocardiogram. Blood pressure determined by the auscultatory method. Observe the interval between injection and reaction, the initial bradycardia followed by tachycardia and fall in blood pressure, and the progressive spread of "heat" through the body. Note the mild and transient nature of the reaction.

Eight injections were primarily for visualization of the superior vena cava, three for the collateral circulation from the arm, and one for the renal blood vessels. All were successful. The pulmonary circulation was outlined 75 times in the 79 injections made for this purpose. The following structures also were seen: innominate and peripheral veins, 54 times; superior vena cava, 56; right auricle, 65; right ventricle, 67; interventricular septum, 61; pulmonary conus, 63; and pulmonary artery, 62. One or both chambers of the right and the left sides of the heart were visualized 68 times in the 76 injections for cardiac study. The following major divisions were identified: superior vena cava 56 times; right auricle, 57; right ventricle, 64; pulmonary artery, 56; left auricle, 30; left ventricle, 41; and thoracic aorta, 44. Other structures visualized were: peripheral veins, 58 times; auriculo-ventricular groove, 9; tricuspid valve, 1; pulmonic valve cusps, 23; aortic cusps, 12; right ventricular wall, 34; left ventricular wall, 29; interventricular septum, 50; pulmonic sinuses, 35; aortic sinuses, 22; left coronary artery (probably), 1; innominate, left common carotid, and left subclavian arteries, 20; axillary and brachial arteries, 3, and renal vessels twice. The thoracic aorta was visualized 21 times in the twenty-three injections for this purpose. With the present technique it was possible with one injection to visualize the right auricle and ventricle and the pulmonary arterial tree in nearly every case, and the left auricle or ventricle and the thoracic aorta in 80 per cent of the attempts; many of their component parts could also be seen. Less uniform success was obtained in patients with great cardiac enlargement, pulmonary engorgement, mitral stenosis, interventricular septal defect, and auricular fibrillation.

The anatomy of the heart, of the pulmonary circulation, and of the great vessels was demonstrated in normal persons,[40] and abnormalities were observed in heart[41] and lung[47] disease. In 3 patients with stenosis or occlusion of the innominate vein from mediastinal tumor, the site of the lesion and the collateral circulation were demonstrated. The superior vena cava was displaced or distorted by mediastinal neoplasm in 2 patients, by tuberculous adenitis in another, and by a dilated pulmonary artery in a third patient with mitral stenosis. In 2 patients with displacement of the heart due to funnel chest and pulmonary fibrosis respectively, the superior vena cava, the chambers of the heart and the aorta were identified, whereas the heart was completely obscured in the conventional roentgenogram.[48] The normal pulmonary circulation and heart are illustrated in Figures 5 to 8. Figure 5 is the conventional postero-anterior roentgenogram; Figures 6 and 8 are contrast films showing the pulmonary arterial tree and the right chambers in the first one, and the pulmonary veins, the left chambers and the thoracic aorta in the other. The round opacities near each hilum are arteries seen on end and not calcifications. The changes occurring in productive tuberculosis are shown in Figure 10 in which the left branch of the pulmonary artery is elevated and the vascularity of the upper lobes is decreased. Similar changes were observed in the pulmonary fibrosis associated with bronchiectasis and carcinoma of the bronchus, and in hilar adenitis. The pulmonary artery and its branches were differentiated from neoplasm, cysts, calcified nodes, parenchymal calcification and aortic aneurysm at the hilum.

Enlargement of the right ventricle and the pulmonary artery was observed in 3 patients with mitral stenosis, in 4 patients with cor pulmonale, and in 1 patient with interventricular septal defect. The left auricle was enlarged in the first condition but it was normal in size in the other two. Dilatation of the pulmonary veins also was noted in mitral stenosis. The left ventricular cavity was enlarged and the wall thickened in the presence of mitral insufficiency, aortic insufficiency, and arterial hypertension. The changes occurring in severe hypertension are shown in Figure 11 in which the left ventricular wall measured 1.7 cm. Aneurysm of the aorta was demonstrated in 3 patients with syphilis, one of whom had aneurysms of both ascending and descending portions. Diffuse dilatation of this vessel was observed in 6 patients with syphilis, and in 5 others who had both syphilis and hypertension. In one instance, a large aneurysm, previously diagnosed as aortic, was found to involve the pulmonary artery. The dilatation and elongation of the aorta and the striking widening and angulation of the aortic arch found in severe arterial hypertension are shown in Figure 11.

DISCUSSION

Important practical features of this method are the 70 per cent solution of diodrast, adequate dosage, rapid intravenous injection, accurate determination of the time for exposure, and proper positioning during roentgenography.

The radiopaque substance, diodrast,[32] was used because of the mildness of its pharmacological action observed in animals[6,14,23,38] and man.[42] Skiodan[32] and hippuran[32] were tried, but were found to cause undesirable reactions when injected in effective concentration and amount. Neo-iopax[32] was not used because of its reported tendency to cause pain in the arm and shoulder during injection. The 70 per cent solution of diodrast proved the most satisfactory for visualization of the left chambers of the heart and the aorta; lower concentrations, even 40 per cent, were sufficient for outlining the superior vena cava, the right side of the heart, and the pulmonary blood vessels.

Diodrast is the organic iodide compound, 3,5-diiodo-4-pyridone-N-acetic acid and diethanolamine, containing 49.8 per cent iodine. It is not radioactive. Although relatively inert, it causes a prompt fall in blood pressure, tachycardia, respiratory stimulation, an increase in the volume of various organs, and an increase in intestinal tone when injected intravenously in animals.[6,14,23,38] The changes in blood pressure and organs are due to the generalized dilatation of the arterioles and capillaries caused by direct action of the drug. The increase in respiration and intestinal tone were ascribed to direct stimulation of the respiratory center and the intestinal musculature.[14] The mechanism of the tachycardia is not known; in the isolated heart perfusion with diodrast caused an increase in coronary blood flow and amplitude of cardiac contraction, but no change in heart rate.[14] In man, the slow intravenous injection of the drug for urography frequently causes flushing of the face and a sense of warmth; occasionally it is followed by transient nausea and vomiting, erythematous eruptions, respiratory distress and cyanosis—effects which also are produced by similar iodine compounds.[32] A moderate fall in blood pressure results when the substance enters the blood stream more rapidly, as in vasography.[8] The commercial 35 per cent solution causes no detectable injury to the blood vessels or other structures of man[31] or animal[6,14,23,38] when administered in the customary dosage and manner,[32] or even when injected rapidly into artery[6] or vein.[8] There is little or no diffusion of the compound into the erythrocytes or other tissue,[24,46] and it is excreted promptly by the kidney without change.

The *immediate reaction* to diodrast, as it is given in this method, appears ten to twenty seconds after the injection. It consists of a metallic taste, and a wave of intense heat which starts in the mouth and spreads through the body reaching the lower extremities last. Concurrently there is a fall in arterial blood pressure which rarely exceeds 30 mm. Hg, a rise in heart rate of approximately 30 beats per minute, and flushing of the face and the shoulders. Dizziness, weakness, and nausea are observed occasionally. Severe vomiting, sweating, pallor and hypotension occurred in 13 instances, but were relieved promptly by recumbency except in 3 patients who were given epinephrine as well. The reaction is usually over in two to three minutes, although in 5 cases it lasted one-half hour. Transient pain and venospasm at the site of injection occurred in a few instances; but cardiac pain was never produced, not even in the 2 patients who suffered from angina pectoris. Palpitation was experienced rarely; respiratory distress, cyanosis, and syncope did not occur. The usual reaction to diodrast is shown in Figure 12.

The occurrence of severe reactions led to investigation of diodrast's effect in man, and to search for a suitable antagonist.[42] Continuous electrocardiographic tracings, arterial blood pressure determinations, and clinical observations were made in 23 persons before, during, and after injection; and were repeated in many of this group after therapeutic doses of one or more of the following drugs: sodium amytal, evipal, morphine sulphate, atropine sulphate, ergotamine tartrate, pitressin, and prostigmin. In one case the reaction was studied in both sitting and supine positions. In 4 patients observations were made before and after block of both carotid sinuses to learn the rôle played by the carotid sinus[16,49] in the fall of blood pressure and the cardiac acceleration which occurred regularly, and in the respiratory stimulation and momentary bradycardia observed occasionally. Diodrast (35 per cent solution) was injected into the common carotid artery in 2 instances to investigate its action upon the carotid sinus, the diencephalic centers[7,36] and the cerebral cortex.[22] Intradermal injection of diodrast was made in 25 patients to determine if sensitivity could be detected. To find out if the rapid injection of 60 cc. of liquid would overload the vena cava or the heart,[2] the venous pressure was measured continuously in 3 patients, one of whom had serious heart disease.

These observations in man, although incomplete, indicate that the fall of blood pressure results from the direct dilating effect of diodrast on the small blood vessels, and that the tachycardia may be due to one or more mechanisms: direct stimulation of the sino-auricular node or cardio-accelerator center by the drug; or indirect stimulation of these structures by reflexes initiated in the brain or periphery, or through epinephrine secretion. The carotid sinus is not a factor in the causation of the hypotension and plays little or no part in the tachycardia; it is responsible, however, for the transient bradycardia and the respiratory stimulation. There is no evidence to suggest that the cardiovascular response is caused by direct stimulation of the diencephalic centers or the cerebral cortex, or that the tachycardia results from distention of the right chambers of the heart. The absence of significant change in the electrocardiogram excludes noteworthy effect upon the myocardium, and the normal venous pressure throughout rules out spasm of the vena cava and heart failure from the injection. Posture had no effect upon the reaction in the one patient in whom this problem was studied carefully. Recent observations[30] suggest that the sensation of heat is due to stimulation of nerve endings in the vicinity of the capillary bed by diodrast which has diffused through the capillary wall. Sensitivity to the drug could not be detected by skin test, even in 5 patients who subsequently had severe reactions. No drug completely counteracted the untoward effect of diodrast: amytal, evipal, ergotamine tartrate, pitressin and prostigmin lessened but did not abolish its vasomotor and cardiac effects; morphine and atropine were ineffective, and epinephrine and ephedrine controlled the fall in blood pressure but increased the tachycardia.

Delayed reactions occurred infrequently. Urticaria appeared promptly in 15 patients and angioneurotic edema in 2 others; epinephrine gave prompt relief. Dermatitis medicamentosa occurred only once; iodism was never observed. A slight elevation of temperature was observed 9 times; in 2 other patients, a chill and high fever followed injection. Mild thrombophlebitis developed at the site of injection 33 times but was unimportant since it involved only a small segment and caused neither discomfort nor embolism. In 3 of the 5 cases examined several months afterward the vein was patent; and even when the obstruction persisted, the vein above and below it remained open and could be used for injection. In the 5 instances of perivascular infiltration the inflammatory reaction was mild, thrombophlebitis developed only once, and ulceration did not occur.

No *toxic effect* upon the heart, the lungs, the kidneys, the liver and the blood was discovered although searched for. Clinical and roentgenographic examinations of the heart and the lungs were made repeatedly in more than half of the patients and many were followed in ward or clinic for months. No activation or aggravation of pulmonary disease was detected. Electrocardiograms made in 28 patients showed significant change but once: a man, aged seventy-one, who had had a coronary occlusion previously, developed another thirty hours after injection. Urinalysis in 34 patients, and the dilution and concentration and phenolsulphonphthalein tests in 5 patients disclosed no renal impairment. The bromsulphalein test and the concentration of serum bilirubin and urinary urobilinogen in another 5 patients gave no indication of hepatic disease. The immediate effect upon the blood was investigated carefully in 5 patients and no significant change was detected. In a larger series, comparison of the routine blood examinations made before and for weeks after injection revealed no evidence of injury to the hemopoietic system.

In summary, diodrast, is a suitable radiopaque medium since it is freely miscible with the blood, rapidly eliminated, relatively nontoxic and inert, and nonirritating except at the site of injection in a few patients.

Visualization of the cardiovascular structures in the thorax requires adequate dosage and rapidity of injection of the contrast substance. The dose must be sufficient to make opaque enough blood to fill the right chambers of the heart and the pulmonary circulation at the same time and, later on, the left chambers of the heart and the thoracic aorta. The delivery of diodrast into the vena cava must be fast enough to produce a high degree of radiopacity in the blood entering the heart so that there may be an effective concentration after passage through the heart and the lungs. The minimal effective concentration of diodrast, calculated from the work of Lopo de Carvalho and Egas Moniz[26] would be approximately 3.4 per cent which would permit a twentyfold dilution of the injected solution. Rapidity of injection is achieved by the use of large bore apparatus, Luer-Lok connections, large vein, elevation of the arm, and simultaneous inspiration. Prompt arrival in the vena cava is insured by the forcible flushing of the peripheral veins with the blood which overlies the diodrast in the syringe. Delay in passage through the pulmonary circulation due to the involuntary increase of intrathoracic pressure, which tends to occur during maintenance of the inspiratory position, is prevented by the passive exhalation which follows injection.

The roentgenograms must be made at the proper moment and in the best position for each structure. Since the intervals between injection and opacification of the right side of the heart and the pulmonary circulation are short and nearly uniform, standard intervals can be used successfully in the average patient.* In the exceptional case, the interval can be learned before injection from the ether circulation time to the lungs. In 7 patients the ether circulation time averaged five seconds, whereas the time required for the opaque medium to reach the pulmonary arterial tree was 3.3 seconds. The cyanide method was used to determine the circulation time to the thoracic aorta, although other methods[12,13,51] would probably be satisfactory. To insure accuracy, enough cyanide must be given to produce a conspicuous stimulation of respiration having an abrupt onset, for the onset indicates the time of arrival in the carotid sinus and also in the descending aorta. Frequently both the left chambers and the thoracic aorta are made opaque at this time due to the stringing out of diodrast in its passage through the heart and the lungs. Maximal opacification of the left side of the heart, however, is attained a second or two earlier.

The sitting position was used routinely.

* See footnote page 6.

Neither prone nor supine position was suitable, as the need for elevation of the arm excluded the first one, and poor roentgenographic results the other. The posteroanterior position of the chest provides an excellent view of the superior vena cava, the lung roots, and the pulmonary blood vessels, but it gives an unsatisfactory picture of the heart and the aorta because they lie obliquely in the thorax and thus are seen from an angle. For accurate study, the heart must be looked at directly from its apex or side.[35,45] The apical view is obtained by use of the left anterior oblique position in which the apex is pointed toward the film, the two ventricles lie side by side, and the aorta crosses in lateral view. This position is suitable for study of the cavities and walls of both ventricles, the interventricular septum, the left branch of the pulmonary artery, the pulmonic and aortic valves and the entire thoracic aorta. The right anterior oblique position gives a lateral view of the heart in which the ventricles lie anteriorly with the auricles behind, the pulmonary artery is more in profile than in the left position, and the aortic arch appears on edge. The auricles, the auriculo-ventricular groove, the inflow and outflow portions of the right ventricle, the tricuspid and mitral valves, and the right branch of the pulmonary artery were viewed best in this position. The superior vena cava can be outlined in posteroanterior, lateral and oblique positions.

Experience has shown that this method is safe. Although it is generally true that rapid intravenous injection is dangerous,[19] clinical trial showed that the 70 per cent solution of diodrast could be given in this way without serious ill effect. The immediate reaction usually was mild, and severe reactions, when they occurred, were transient. Delayed effects were unimportant. Pulmonary embolism from blood clot formed in the apparatus was not observed, probably because the frequent flushing with normal salt solution prevents clotting in the needle and the stopcock, and the diodrast prevents it in the syringe. In 2 instances blood from the syringe failed to clot after fifteen minutes and two hours, respectively, although the bleeding and clotting times were unaffected in the 5 patients in whom blood studies were made before and after injection. The absence of fatality and noteworthy injury is final proof that the method is harmless.

The procedure is no more difficult to perform than many diagnostic tests, and it can be carried out in both ambulatory and bed patients. No aftertreatment is required. The usual roentgenographic and laboratory apparatus is used with little or no modification. The technique of injection is relatively simple requiring, however, more skill than is ordinarily needed for venipuncture and injection. The discomfort experienced by the patient is usually moderate, comparable to that caused by gastric lavage, bronchography and spinal puncture. Two patients actually liked the test: one, a man aged seventy-four, with syphilitic aortitis, found the reaction "pleasantly warm"; the other, a boy of nineteen, described it as "an exquisite sensation." The reaction to diodrast, whether mild or severe, does not interfere with visualization since it invariably occurs after the roentgenograms have been made.

Certain obvious technical improvements can be made. Synchronization of heart beat and exposure[18] would permit the roentgenograms to be made during the diastolic pause or at other points in the cardiac cycle, and thereby make possible accurate observation and mensuration. By using cineroentgenography[48] or rapid, serial roentgenography, it should be possible with one injection to visualize all the important divisions of the heart and of the thoracic blood vessels to be seen in the position used. By making serial roentgenograms simultaneously[34] in the frontal and lateral positions or in the two oblique positions, each region could be visualized in two planes and from this three-dimensional study volumetric determinations[21] could be made. Of practical importance, a complete study of the heart could then be made with one injection. Roentgen kymography[17] during opacification should give a graphic record of the movement of both surfaces of the cardiac and the vascular walls, information not obtainable by ordinary visualization or roentgen kymography. Simplification of the technique of injection by dispensing with the respiratory maneuvers and the flushing in of diodrast with blood may be feasible. Finally it is possible that the undesirable side-effects can be eliminated by developing a more inert radiopaque compound or by finding a better antagonist. Larger doses then could be given and greater radiopacity produced.

Clinical experience has proved this method to be of value in the diagnosis of heart and lung disease. In both fields it frequently was possible to establish diagnoses which formerly were based upon less direct evidence. At the present time the chief value in pulmonary disease is twofold: the recognition of abnormalities of the mediastinal and the hilar blood vessels whether due to intrinsic disease or to distortion or displacement from without, and the differentiation of these blood vessels from adjacent structures such as mediastinal neoplasm hilar adenitis, pulmonary cyst and calcification. Less striking results are obtained in disease of the pulmonary parenchyma. Decreased vascularity was demonstrated in pulmonary emphysema and the localized fribrosis due to tuberculosis and suppurative disease, but this method gave no assistance in the diagnosis of tuberculous cavitation, lung abscess, and neoplasm. It is possible that characteristic deviations from the normal vascular pattern of the lung can be worked out for pulmonary disease.

In heart disease visualization permits a precision in diagnosis previously impossible. No longer must roentgenographic evidence of disease depend upon change in the silhouette of the entire heart or the distortion of adjacent structures. Instead, each chamber and great vessel can be visualized separately, and the nature and degree of abnormality ascertained. Exact mensuration of the heart thus becomes a possibility. At the same time, the circulation time of the blood to the various parts of the cardiovascular system can be determined objectively. Characteristic changes were observed in congenital, rheumatic, pulmonary, hypertensive, and syphilitic heart disease. Diagnosis was made possible in 3 patients with cor pulmonale and another with syphilitic aneurysm of the pulmonary artery. In a third patient with syphilis, hypertension, and widening of the aortic arch, dilatation of the aorta was excluded. This method promises to be of practical value in the differential diagnosis of heart disease, the recognition of early organic change, and the exclusion of heart disease in the normal.

SUMMARY

Visualization of the heart and the thoracic blood vessels is a practical procedure. The method consists of the rapid injection of 25 to 45 cc. of a 70 per cent solution of diodrast into an arm vein, and the making of roentgenograms when the chambers of the heart and the blood vessels are opaque to the roentgen ray. The interval between injection and exposure depends upon the region to be visualized. Average intervals can be used for the right side of the heart but the circulation time to the left chambers and the aorta should be determined. The frontal position is used for study of the pulmonary circulation, the oblique positions for the heart and the aorta. The organic iodide compound, diodrast, has negligible toxicity and is rapidly excreted by the kidneys. Its pharmacological effects are usually mild, and it is nonirritating except at the site of injection in a small proportion of cases. Two hundred and thirty-eight injections were made without serious ill effect.

This method provides information regarding the anatomy and the physiology of the normal and diseased cardiovascular system heretofore unobtainable. It is possible to determine the site of stenosis or

occlusion of the superior vena cava and its tributaries, and the course and extent of the collateral circulation. The vascular nature of the hilum may be demonstrated and these vessels differentiated from adjacent structures. Accurate study of the arterial and venous patterns of the lung can be made. The internal structure of the living heart has been revealed for the first time and abnormalities due to disease have been observed. The following structures became visible: the superior vena cava and its tributaries, the four chambers of the heart, the ventricular walls and the interventricular septum, the tricuspid, pulmonic and aortic valves, the pulmonic and aortic sinuses, the pulmonary artery, and the entire thoracic aorta including its wall and the branches from the arch.

CONCLUSIONS

(1) Visualization of the chambers of the heart, the pulmonary circulation, and the great vessels in man is safe and practical.

(2) This procedure gives exact information regarding these structures which has heretofore been unobtainable.

(3) It opens up a new field for the study of the anatomy and the physiology of the circulation.

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