then drilled (#62 drill or smaller, depending upon size of needle to be used). All sharp edges around the chamber are removed with a fine file or sandpaper.

The lower figures of the illustration show the lateral and cross-sectional views of splints and chamber in position on the mouse, the graft resting on the panniculus carnosus beneath the transparent chamber.

Operative procedure: Time is saved if anesthesia is induced with ether, immediately supplemented with 0.2 ml (1.2 mg) of a 1:10 dilution of Veterinary Nembutal. Clipping and depilation (with depilatory cream) may then be done without delay. A wooden or lucite block (3″ × 2″) provided with a V-groove is used to hold the mouse in position during passage of sutures, skin dissection, and fixation of the chamber.

The four arteries of the skin of the dorsum being identified by transillumination, they are apposed, and the fold of skin transfixed with a suture at the highest point of the skin fold, or seized with towel forceps, which enclose the wire arch also, at this same point. Fixation sutures are then passed through the periphery of the skin fold, and fastened by twisting with serrafin clamp or by tying. If the very small arterial needles (#16 Diamond drill-eyed sharps) are not available, #9 Milliner's may be used. The base of the traction splint may be given additional anchorage by passing sutures through it and the skin, at its two ends.

Should loss of proper flap tension or loosening of sutures occur, additional or replacement sutures are readily placed where needed, with this type of splint.

The fold of skin being fixed in traction, graft bed and chamber site are prepared as follows: At the center of the proposed chamber site, the skin is carefully nicked with fine scissors and, by blunt dissection, gently raised in radial fashion from the underlying panniculus carnosus. This procedure is facilitated if an initial bleb of skin is raised by injection of a drop of saline with a very fine hypodermic needle. The separation of skin from panniculus completed, the skin is removed so as to leave a circular wound of approximately the same diameter as that of the chamber (*2*). During this procedure damage to the vascular panniculus must be scrupulously avoided. Only one skin layer is treated in this fashion, its panniculus being the bed of the graft. The opposite skin layer and panniculus are preserved intact.

Splint and chamber are then placed over the circular opening, and over the graft (if used). The back splint is then applied, and sutures are passed through both splints and around the wire traction splint, as shown. The three through-and-through sutures of the chamber are then passed and tied after making sure that the chamber is lying upon the panniculus, and within the edge of the skin wound. A seal of fibrin from the exudate soon cements the outer edge of the chamber to the edge of the circular incision.

Materials required are sheet lucite: 0.025″ and 0.008″; lucite cement: 5% lucite in chloroform; copper wire: 18-gauge, bare; solder: resin core.

Tools required are drill press: "Handee," "Casco," etc.; drill: #62 (64); circular saw blade for drill; soldering iron: "pistol type" preferred, with fine tip; pliers: one long-nosed, one side-cutting; bench-vise: small; shears or heavy scissors; wood gouges: ⅜″ and ⅝″; brass tubing: ⅝″ ID; small files; fine sandpaper.

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Manuscript received November 27, 1951.

A Variable Heart Pump Permitting Independent Control of Rate, Output, and Ejection Velocity

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Since the cardiovascular apparatus is an integrated system, it is often difficult to differentiate between purely cardiac and purely vascular responses. One approach to the understanding of the functioning of a complex system is to isolate its various parts. In this way the responses of each segment may be studied under controlled conditions undistorted by the reactions of the other parts. A great advance was made by Starling (*1*) who, utilizing the living heart and lungs, substituted an artificial vascular system which could be altered at will. Starling thus was able to analyze the effects on the heart alone of controlled variations in venous return, temperature, and peripheral resistance. However, the reverse experiment, that of studying the reactions of the isolated vascular system in response to controlled variations in the cardiac pumping mechanism, has not yet been undertaken.

Recent advances, particularly the development of plastics which do not interfere with the coagulability of the blood, have made it possible to construct a workable "artificial heart" (*2, 3*). It seems possible, therefore, to develop a heart pump that can be altered at will over a wide range in regard to rate, output, and ejectile velocity and to substitute this pump for the living heart in the experimental animal. A means would thus be provided for studying the effects of controlled variations in the cardiac pumping mechanism on flow, pressure, etc., in the isolated vascular system. In addition, this technique would be useful in separating vascular from cardiac effects of various drugs and hormones which influence the cardiovascular apparatus. This report describes a pump, which, while being substituted for either chamber of the heart, can be regulated over a wide range in respect to rate, output, and ejectile velocity.

Preliminary studies on dogs are being made with the diaphragm pump shown in Fig. 1. The pump is driven by a variable speed motor contained in an

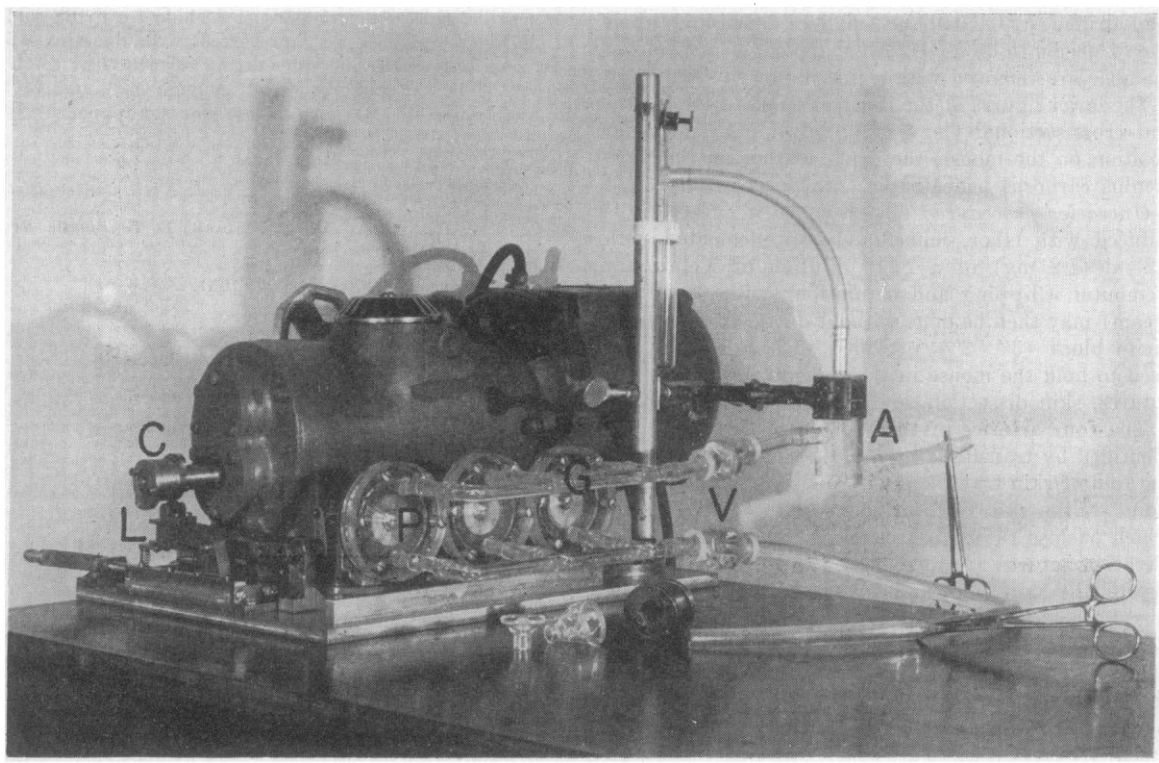

FIG. 1. Variable cardiac pump.

explosion-proof housing, with a range from 44 to 350 rpm. The driving cam, *C*, is so shaped that the discharge characteristics from the pump are similar to those from the heart. A selection of cams is available, so that the ejection time can be varied from one tenth to three quarters of the whole cycle. *L* is a lever with a movable fulcrum so that the output per stroke can be varied at will from zero to the maximum. Pump heads, *P*, are made so that the blood is in contact only with plastic. The heads are made of machined and polished methyl methacrylate, and the diaphragms are covered with thin sheets of polyethylene. Junction of the outputs of the three pumps is made with a glass connector, *G*, covered on the inside with silicone, to reduce the coagulation of blood. The ball check valves, *V*, are machined from solid methyl methacrylate and carefully polished. The ball is made of hollow methyl methacrylate with a specific gravity approximately equal to 1. Hufnagel (*4*) has shown that clotting does not take place in properly constructed valves made of suitable plastic material. Input and output connections are made of Tygon plastic tubing 1 cm in diameter. *A* is an air trap.

It should be emphasized that the present pump is not designed to substitute for the entire heart and lungs; rather, it may be used to replace either the right or the left ventricle, leaving the lungs and the opposite chamber of the heart to function normally. Thus, in the present preliminary experiments the input side of the pump is connected to the left auricle, and the output connects directly to the aorta. The right side of the heart and the pulmonary circulation are left undisturbed. The changes in arterial pressure, flow, and pulse wave contours, as well as venous pressure and venous return in response to controlled variations in the pumping mechanism, are then measured.

Figs. 2, 3, and 4 provide specimen data to illustrate

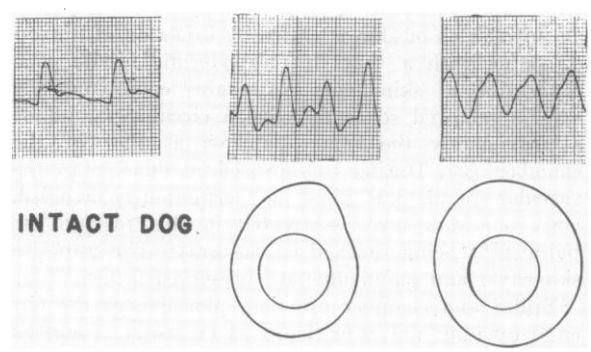

FIG. 2. Cuttings taken from record of femoral arterial pressure pulses (above) and outlines of cam shapes (below). Rotation of cams from right to left. Note alteration of pulse wave form in response to varying the cam shape.

different applications of the pump in physiological studies. Fig. 2 shows the effect of varying cam shapes on the femoral arterial pressure tracing; Fig. 3 illustrates the effect of a sudden increase in stroke output of the pump on systemic arterial pressure, venous pressure, and pulmonary arterial pressure; Fig. 4 shows the difference between the type of arterial pressure response to epinephrine in the intact dog

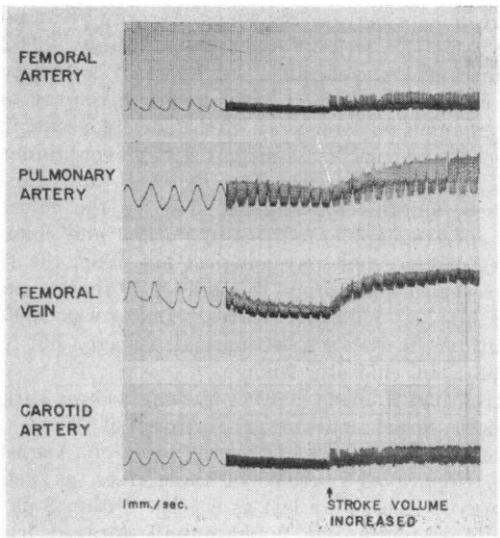

FIG. 3. Cuttings from tracings in femoral, carotid, and pulmonary arterial pressures and systemic venous pressure. Paper speed at 25 mm/sec changed to 1 mm/sec. Stroke volume of pump was suddenly increased at the arrow, resulting in an abrupt elevation of systemic arterial pressure, followed by a more gradual elevation of pulmonary arterial pressure and venous pressure. (The pulsations in the latter probably are transmitted from the aorta, the catheter being introduced into the femoral vein and advanced into the inferior vena cava.)

as compared to same animal when the pump is used to substitute for the left ventricle. This application appears to be a useful method of separating the peripheral from the cardiac actions of agents that affect the cardiovascular system. Detailed physiological data will be reported elsewhere.

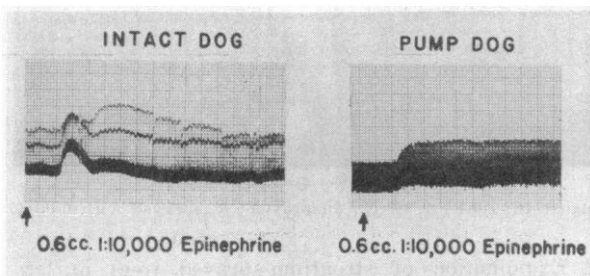

FIG. 4. Cuttings of femoral arterial pressure following the intra-aortic injection of 0.6 mg epinephrine in a dog before and after substituting the pump for the left ventricle. In the intact dog an initial vasoconstrictor response is seen as the epinephrine stimulates the peripheral vessels. Later, as this agent reaches the heart the cardiac effects predominate, with a further rise in systolic and a fall in diastolic pressure. After replacing the left ventricle with the cardiac pump, a similar dose produces only the initial vasoconstrictor response.

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Manuscript received November 28, 1951.

Kallikrein and Shwartzman-Active Substances

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An observation is described concerning a combined action of Kallikrein and certain filtrates from bacterial cultures capable of producing the Shwartzman (*1*) phenomenon. This phenomenon in its basic form is a hemorrhagic reaction in rabbit skin. An intracutaneous injection of the bacterial filtrate, followed 24 hr later by an intravenous injection of the same filtrate, elicits the reaction at the prepared skin site within 4 hr after the intravenous injection. Many variations and modifications of the phenomenon are known, but it has remained unexplained. Kallikrein, the blood pressure lowering factor described by Kraut, Frey, and Werle (*2*), is chiefly found in the pancreas, from which it enters the blood and is kept inactivated, being activated only under certain conditions, such as stasis and changes in the pH. Kallikrein, given intravenously, brings about dilatation of the peripheral vessels, thus lowering the blood pressure. It also enhances the permeability of the dilated vessels. Much intricate detail is known concerning the enzymelike behavior of Kallikrein. The factor has not been isolated chemically.

Two experiments with different ways of combining Shwartzman-active substances and Kallikrein are reported here, but other combinations have been examined with the same result: hemorrhagic reaction.

One hundred sixty units of Kallikrein were dissolved in 0.5 ml of Shwartzman-active meningococcus bacterial filtrate and injected intravenously into the ear of a rabbit. The ear was clamped for 3 min, during which the injection was performed. In less than 4 hr a severe hemorrhagic-edematous reaction was evident in the ear, which was hanging down thick and filled with blood. A slight pull caused the hairs of the ear to come off in tufts, exposing a wet, dark red-blue distended surface.

Control rabbits receiving Kallikrein only, and in a dose of 160 units, showed hyperemia of some duration, but no other reaction.

In the second experiment, when an intracutaneous injection into the skin of the abdomen of the rabbit was made with meningococcus bacterial filtrate, and followed 24 hr later by an intravenous injection of 160 units of Kallikrein, a strong hemorrhagic-edematous reaction resulted at the site of the intracutaneous injection in less than 4 hr after the intravenous injection.

Further work on the subject, together with the interesting theoretical aspects, will be published.

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