5.

A NEW METHOD OF STUDYING THE MAMMALIAN HEART.

By H. NEWELL MARTIN, M. A., D. Sc. M. D. With Plate IX.

IN the course of some experiments made by me in conjunction with Dr. W. T. Sedgwick, on blood pressure in the coronary arteries of the heart, the fact was impressed upon me that the mammalian heart is no such fragile organ as one is usually inclined to assume, but possesses a very considerable power of bearing manipulation. On the other hand, I knew of various unsuccessful attempts to isolate the mammalian heart and study its physiology apart from the influence of extrinsic nerve centres, in a manner more or less similar to the methods so frequently used for physiological investigations on the heart of a cold-blooded animal; the mammalian heart, however, always died before any observations could be made on it. Thinking over the apparent contradiction, it occurred to me that the essential difference probably lay in the coronary circulation; in the frog, as is well known, there are no coronary arteries or veins, the thin auricles and spongy ventricle being nourished by the blood flowing through the cardiac chambers, but in the mammal the thick-walled heart has a special circulatory system of its own and needs a steady flow through its vessels, and cannot be nourished (as appears to have been forgotten) by merely keeping up a stream through auricles and ventricles. The greater respiratory needs of the heart of the warm-blooded animal also needed consideration; the lungs ought either to be left connected with it, or replaced by some other efficient aërating apparatus; if entirely separated from the central nervous system there seemed no need to replace the natural lung by an artificial one, and, though I hope ultimately to do this, my work hitherto has been confined to the study of heart and lungs living together, when all the rest of the body of the animal was dead. Under such circumstances, with uniform artificial respiration, the lungs may be regarded as purely physical organs adapted for gaseous diffusion; and probably better for this purpose than any substitute which could be constructed.

My first experiments were made with cats. The animal was narcotised with morphia, tracheotomised, and a cannula put in the

[Johns Hopkins Univ., Stud. biol. lab. 1881-2, ii] rotid. Then the thorax was opened, (artificial respiration g started), the innominate artery tied beyond the origin of the left carotid but proximal to the point where the right subclavian and right carotid separate; the left subclavian was ligatured near its origin; and the aortic arch tied immediately beyond the organ of the left subclavian. Finally, the superior and inferior cavæ and the root of one lung were tied; the cannula in the left carotid was connected with the manometer of the kymographion, and tracings taken in the usual manner. Under these circumstances the course of the blood was—left auricle, left ventricle, aortic arch and the ligatured arterial stumps connected with it, the coronary vessels, the right auricle, the right ventricle, the pulmonary circulation through one lung, and back to the left auricle. All circulation was cut off from every organ in the body except heart and lungs; the brain and spinal cord soon died, the muscles became rigid, and kidneys and liver had no longer any physiological connection, either through the nervous system or the blood, with the heart; which, though still in the body, was physiologically isolated from everything but the lungs; yet as my preliminary experiments shewed (Johns Hopkins University Circular, No. 10, p. 127, April, 1881,) the heart went on beating with considerable force and regularity for more than an hour.

The method, however, still left much to be desired; I wanted the heart alive much longer; a means of keeping it at a uniform temperature; a method of renewing the blood which, either because clogged with waste products usually removed by the kidneys or other organs, or because certain nutritive materials in it were used up, ceased to be efficient in keeping the heart alive after a certain time; and opportunity to run blood, to which various substances had been added, through the heart from time to time in order to study their action upon it.

After several attempts the apparatus represented in Plate IX was devised, and has been found to answer admirably; with it I have kept a heart, isolated physiologically from everything but the lungs, beating with beautiful regularity for more than five hours, and have no doubt I could keep it considerably longer were that necessary.

In the plate the heart is represented very diagrammatically and of hugely disproportionate size; the pulmonary vessels also are entirely omitted, as they are not interfered with in the experiment.

At first I thought the immense disproportion in capacity between the complete pulmonary system of vessels and the systemic circulation reduced to only its coronary portion would injure the working of the heart, and I tied up, as above stated, the root of one lung and sometimes one or two lobes of the other; but I have since found that this is quite unnecessary; the left auricle takes only what it wants, no matter how much blood is accumulated in the lungs, and the circulation is thus confined to the quantity of blood which under a given aortic pressure is sent through the coronary system in a given time.

The course of an experiment is as follows: Tracheotomy having been performed, each pneumogastric nerve is divided in the neck; this is, I find, of importance as saving the heart from the effects of powerful dyspnœic inhibition when subsequently all the cerebral circulation is cut off. A cannula, *p*, is then placed in the left carotid, *o*; and another, *s*, in the right carotid, *r*; the purpose of these will be mentioned presently. Next the first pair of costal cartilages and the piece of sternum between them are resected, artificial respiration started, and the internal mammary arteries found and ligatured where they pass forwards between the apices of the lungs. The sternum and the sternal ends of the ribs are then cut away down to the diaphragm, and if the day is cold a cloth soaked in moderately hot water laid over the posterior half of the chest so as to keep lungs and heart warm, care being taken that it does not touch the pericardium; this hot damp cloth is renewed from time to time as necessary; on a warm day it may be omitted.

Next the superior cava is pushed aside and the right subclavian artery, *w*, clamped and opened. The bulb of a slender thermometer, *a*, is then placed in the vessel and, the clamp being removed, is pushed down into the innominate trunk and tied so as to keep it there. This gives the temperature of the blood flowing through the heart, which cannot be deduced accurately from the temperature of the chamber in which the apparatus is placed; partly because the blood warms and cools more slowly than the air in the box, and partly because in its circuit through the lungs it is cooled. A very small twig given off from the innominate trunk to the anterior mediastinum is also tied. Next the left subclavian, *m*, is isolated and a cannula, *x*, placed in it; and the aortic arch, *l*, tied just beyond the origin of the left subclavian. When the subclavians and aorta are tied (the carotid flow being already stopped) anæmic or dyspnœic convulsions occur, and arterial pressure rises very high, as evidenced by the great size to which the stumps connected with the aortic arch become distended; to obviate this strain on the heart, the aortic arch is tied as quickly as possible after putting the cannula in the left subclavian, and before the dyspnœa is extreme a large quantity of blood drawn off through the cannula, *s*, in the right carotid; when what appears sufficient is drawn the screw-clamp *u* is tightened up again. Finally the inferior cava, *e*, is ligatured, and the azygos vein, *f*; and a cannula, *h*, put in the superior cava, *g*. This finishes the operative procedure.

To get rid of the blood now present in the heart and lungs, which would be apt to clot in the cannula during a subsequent prolonged observation, and to replace it by defibrinated blood, of which about two litres are obtained from other dogs before the experiment, is the next step. The cannula *h* is filled with whipped blood and connected with a funnel containing the same warmed to 35° C.; the clamp *t* on the right carotid is then again opened and from 300 to 400 c. c. of defibrinated blood run through the heart and lungs—in by the superior cava and out by the carotid—washing out and replacing the blood previously present; the blood drawn is whipped and strained and added to the stock on hand. The supply should be slow and sent in under a pressure equal to that exerted by a column of blood about 20 centimetres in height. The carotid is then again clamped and the vena cava a second or two later, after the heart and lungs have filled up with blood. The funnel is now removed and the heart, still lying in the chest, is ready for transference to the chamber in which it is to be kept warm and moist and fed with fresh defibrinated blood.

This chamber consists of a box five feet long, three high, and two and a half wide. It has no floor; has one wooden end, I; a wooden back; a glass front; a glass roof, K; and a glass end, L. The front can be entirely removed and has also a door in it through which matters can from time to time be arranged inside and temperatures read off without removing the whole front. The chamber rests on a galvanized iron trough, *DD*, which contains about an inch and a half of water. In it is a Bunsen's regulator connected with the burners *CC*, and serving to maintain a uniform temperature in the interior. In the chamber about an hour before the experiment are placed the glass cylinders 27 and 28, each containing about 800 c. c. of fresh whipped and strained dog's blood, which has thus time to attain the temperature of the interior of the box.

All being ready the front of the chamber is removed and the dog stretcher *GG*, having on it the dead body of the dog with the living heart and and lungs, is put in. The heart alone is indicated in the diagram to make description of its connections easier. The cylinders 27 and 28 are elevated on a block at the anterior end of the stretcher, so that their lower ends are ten or twelve centimetres above the auricular end of the heart. These cylinders are Marriott's flasks. Each is closed air-tight at the top by a cork through which four tubes pass; one tube in each case (9 and 12 respectively) allows air to enter from the interior of the chamber and reaches to near the bottom; another (5, 6) dips a little deeper into the blood and acts as a syphon to draw it off. The remaining tubes (7 and 10, 8 and 11, respectively,) only reach a short way through the cork. Each has on its upper end a bit of rubber tubing which can be closed air-tight by a clamp, and is so when the cylinder is in use. These short tubes are for filling the reservoirs; when one cylinder is nearly empty, as for instance 27 in the diagram, the clamp, 2, on the tube leading from it to the heart is screwed up, and the communication between the heart and the other reservoir opened; while this second one is feeding the heart the first is refilled by opening the clamps 18 and 17, putting the funnel 19 on the rubber tubing of 11, and refilling the reservoir through it; as the blood enters the air escapes through 10; when the cylinder is filled the clamps 17 and 18 are again screwed tight and the cylinder is again ready for use long before its fellow has emptied.

The syphons leading from each Marriott's flask meet in the Y-piece *z* from which passes the rubber tubing *i*. As soon as the animal is placed in the chamber this bit of tubing is filled with blood by opening its connection with one of the reservoirs and is immediately slipped over the end of the cannula, *h*, in the superior cava, from which the clamp is removed: the heart is thus steadily supplied with blood from each reservoir in turn. The outflow tube, *q*, passes from the left carotid, *o*, which is not used for the preliminary bleeding and washing out which, with the object of avoiding any clotting in the left, are done through the right carotid as above described; now that there is only defibrinated blood to deal with there is no longer any danger of such clotting. Over the cannula, *p*, is slipped one end of the rubber tube, *q*, which leads to the glass tube 21, which passes through the wooden end of the box and has on it a stopcock, 22, beyond which the tube curves round and reënters the box. By means of the stopcock the rate of irrigation can be regulated without opening the chamber; the blood which flows through is received in the vessel 24, which is set aside within the box and replaced by another from time to time as necessary, until one of the Marriott's flasks needs refilling. In this way the blood being nearly always inside the chamber does not get a chance to cool more than a degree or two, and so has ample time to heat up again to the proper point while the other Marriott's flask is emptying. The rate of flow permitted is usually a pretty rapid dropping; but if a low arterial pressure is desired the stop-cock, 22, is opened wider; if a higher it is more closed. Even a slow dropping keeps the heart well alive for a long time; if signs of feebleness come on, all that is needed is to open the stop-cock wide for a few seconds and thoroughly renew the blood in the heart.

Arterial pressure and the pulse curves are obtained from the mercurial manometer 26. This, by means of connecting tubes, filled with sodic carbonate solution in the usual manner, is attached to the cannula *x* in the left subclavian.

All the connections having been made the front is replaced on the chamber and henceforth the heart beats on in it without disturbance, except as from time to time a small door is opened to change the receptacle 24, or take out blood to refill one of the Marriott's flasks and change the one connected with the heart by opening or closing the clamps 1 or 2, or note the temperature of the thermometer *a*.

The description of the various connections to be made after the animal is placed in the chamber takes some time, but the whole thing is done in two or three minutes. While the front of the chamber is out the air in it cools considerably, but the blood of course much less on account of its high specific heat, and in a very few minutes, while one waits for the heart to get uniform and to be sure that brain and spinal cord are dead, all inside is again at a uniform temperature and a series of observations can be commenced. Before commencing these I always wait until all signs of reflex excitability are lost and the muscles begin to exhibit rigor; this occurs at latest in half an hour after ligaturing the various arteries. Sometimes Traube's curves are seen for a few minutes after the animal is placed in position, shewing that the medulla is not quite dead; but they very soon pass off never to return, though when the heart begins to die something simulating them (to which I will return later) usually occurs..

It is, I think, clear that by this plan of work the study of the physiology of the mammalian heart is made possible to an extent never before attainable; I have now made a considerable number of observations which shew that for at least four hours and often for considerably longer, great regularity and power in the heart's beat can be maintained. I give below in tabular form the successive observations as to pressure in the subclavian and pulse rate made in two experiments, which shew the perfect availability of the method. To investigate the direct action of any drug on the heart one would have only to inject it by a hypodermic syringe into the cardiac end of the tube *i*, as in the usual manner of injecting curari into a vein. By altering the temperature of the chamber one can readily study the effect of various temperatures on the pulse rate, arterial pressure being kept at a given level while the tracings (at intervals of five or ten minutes) are being taken, by altering the outflow through the stopcock, if necessary; between the readings a uniform flow is kept up irrespective of arterial pressure. By keeping the temperature constant and altering the stopcock the direct influence of various arterial pressures on the pulse rate can be readily studied. On these two latter points I have already made a number of interesting observations, which are not, however, yet quite ready for publication. The chemical products of muscular work apart from those eliminated by the lungs must also accumulate in the blood which has flowed round and round the beating heart for hours, and probably can there be examined better than in any other organ at present at our disposal. It seems also to me practicable to unite a given organ, say kidney or liver, with the heart and keep it alive for study, but this I have not yet tried. At any rate it is clear that a large field for investigation of various points of great interest is made available for study under much more favorable circumstances than hitherto.

When the heart begins to die the first symptom is an irregular rhythm which cannot be removed by free irrigation with the blood in the reservoirs. Whether this is immediately due to changes in the heart itself, or to the consumption of food materials in the stock of blood, or to the accumulation in it of wastes usually removed by the kidneys or other organs I cannot at present state. Whether it be due to the first of the above causes could readily be decided by taking an entirely fresh stock of defibrinated blood. The irregularity manifests itself by a large beat followed by three or four smaller ones, and so on for more than an hour. Then the small beats become feebler and feebler, and, arterial pressure being consequently very low, the pulse due to the more powerful beat very conspicuous. Finally the large beats alone remain, and they gradually become less and less until they disappear. In its earlier stages the phenomenon has an interesting resemblance to the secondary rhythm observed in the frog's heart under certain circumstances; it is what I referred to above in stating that late in the experiment something simulating Traube's curves is often seen.

For the guidance of those who may repeat the experiment, I may add that the thing most to be avoided is sending blood into the superior cava too fast or under too high a pressure; this is far more fatal than considerable cooling or delay.

The following tables give the results of two experiments. In each case the number indicated in the column headed "pressure" is the pressure in millimetres of mercury indicated by the manometer connected with the left subclavian artery. The numbers in the column headed "pulse" give the number of heart beats per minute. Temperatures, when given, (Table II.) are not accurately those of the heart or blood, but those of the chamber in which the heart lay. The introduction of a thermometer into the innominate trunk is one which I have only used in later experiments on the influence of temperature changes on the pulse rate, when an accurate knowledge of temperature was essential; in the experiments given here the point I had in view was merely to determine whether an isolated heart could be kept alive long enongh for study; and accuracy as regards temperature readings within a degree or two was not essential.

Table I records the first experiment, which showed me that the end I had in view was really attainable, and is given partly, perhaps, because I have a special interest in it on that account, but chiefly because it illustrates how well the heart will live under very rough experimental conditions. At the time when it was made I had not arranged any warm chamber, and the heart was simply warmed in the roughest manner by inverting a tin pan over the body of the dog and putting a Bunsen's burner under this; with some wet cloths to keep the atmosphere moist. From time to time, the gas was turned down or up as I thought the temperature round the heart was too high or too low, but no thermometer readings were taken, and the temperature no doubt varied very much in the course of the experiment. At this time also the use of the Marriott's flasks had not been thought of: from time to time, as the heart seemed weakening, fifty cubic centimetres of whipped blood were run in by the vena cava and an approximately equal bulk removed through the carotid. The numbers given therefore as to pulse rate and arterial pressure have little or no value; and the whole experiment simply serves to show with what rude appliances the isolated heart can be kept at work for a long time when the coronary circulation is maintained.

Table I.

EXPERIMENT OF APRIL 1, 1881.

Time. P. M.	Pressure.	Pulse.	Remarks.
1 h. 35′.			Finished tying up all the vessels but those of the pulmonary and coronary circuits.
1 h. 40′.	68	96	
2 h. 20′.	74	87	
2 h. 22′.			Fresh blood run in.
2 h. 23′.	96	104	
2 h. 30′.	93	102	
2 h. 37′.	118	96	
2 h. 40′.	80	93	
2 h. 50′.	96	100	
3 h. 04′.	60	100	Fresh blood run in at 3 h. 3′.
3 h. 21′.	86	96	
3 h. 28′.	104	42	Cold blood run in at 3 h. 27′.
3 h. 50′.	32	96	
3 h. 51′.			Fresh warm blood run through.
3 h. 52′.	92	112	
4 h. 06′.	41	88	
4 h. 13′.	25	80	
4 h. 15′.			Fresh warm blood run through.
4 h. 16′.	92	86	

Table I.—*Continued.*

Time. P. M.	Pressure.	Pulse.	Remarks.
4 h. 29′.			Fresh warm blood run through.
4 h. 30′.	92	79	
4 h. 39′.			Fresh warm blood run through.
4 h. 40′.	90	88	
4 h. 47′.	56	88	
4 h. 59′.			Fresh warm blood run through.
5 h. 00′.	76	86	
5 h. 09′.	43	96	
5 h. 10′.			Fresh blood taken from another dog and not used before in the course of this experiment, run through.
5 h. 18′.	140	88	
5 h. 23′.	58	72	
5 h. 26′.			Fresh blood.
5 h. 29′.	116	83	
5 h. 33′.	52	76	
5 h. 35′.			Fresh blood.
5 h. 40′.	60	82	
5 h. 44′.			Fresh blood.
5 h. 45′.	102		Chronograph pen out of order, so the pulse rate cannot be given.
5 h. 48′.	76		
5 h. 53′.			Fresh blood.
5 h. 55′.	92	92	
6 h. 00′.	37	88	
6 h. 02′.			Fresh blood.
6 h. 03′.	61	98	
6 h. 11′.			Fresh blood.
6 h. 14′.	88	92	
6 h. 20′.	42	88	
6 h. 22′.			Fresh blood run in; none drawn off.
6 h. 24′.	118	98	
6 h. 30′.	32	97	
6 h. 35′.	24	96	
6 h. 36′.			Fresh blood run in; none drawn off.
6 h. 38′.	118	100	
6 h. 41′.	28	84	
			The beat immediately afterwards became very irregular, and ceased finally at 7 h. 10′.

The above experiment, as already stated, justifies no conclusions except that an isolated mammalian heart can be kept beating for several hours. It, however, suggests (and subsequent experiments, which I hope shortly to publish, confirm) that the pulse rate of the isolated heart is very independent of arterial pressure, though, as no accurate temperature observations were made in this case, the experiment by itself is not worth much in that respect.

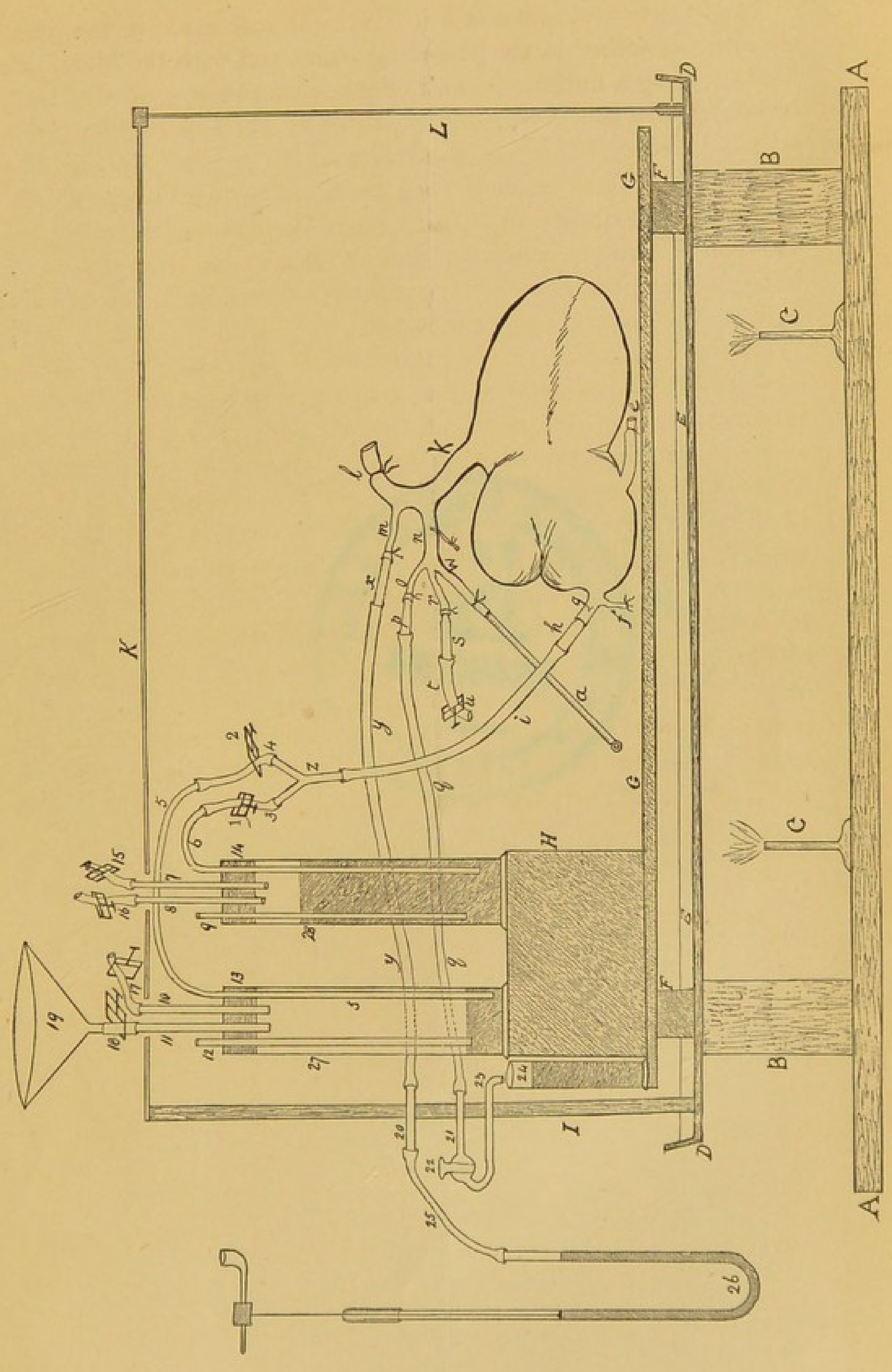
Table II.

Experiment of May 26, 1881.

Time. P. M.	Temp. in degrees C°	Pres-sure.	Pulse.	Notes.
1 h. 50′.				All vessels tied but those of the coronary and pulmonary circuits. Then 150 c. c. of warm whipped blood sent through the heart in order to wash out the blood already in it and in the lungs.
2 h. 05′.				Animal removed to warm chamber and the irrigation started from the Marriott's flasks and maintained thenceforth.
2 h. 15′.		72		Pulse rate not known, as the chronograph was not working.
2 h. 45′.	95°	72	92	
3 h. 00′.	99°	86	118	
3 h. 15′.	98°	87	118	
3 h. 55′.	99°	90	120	
4 h. 15′.	99°	91	120	
4 h. 35′.	100°	87	118	
4 h. 50′.	100°	86	120	
5 h. 10′.	100°	68	117	
5 h. 45′.	100°	64	117	
6 h. 00′.	100°	60	118	
6 h. 15′.	99°	56	117	Arterial pressure now began to fall markedly, and while a fresh supply of blood was being obtained from another dog (that in use having already circulated round the heart many times, and being presumably full of wastes) the organ ceased to beat at 6 h. 45′.

The experiment described in Table II was made in the warm chamber described in the preceding pages and with the Marriott's flasks, giving a uniform instead of the intermittent supply of fresh blood used in the experiment of Table I. It is one of a number which all shew the great regularity which can be obtained for some hours in the heart's work under such circumstances; and hence the possibility of readily observing the influence on its activity of various conditions and of drugs: in other words, it indicates that the separated organ is in a fit condition for physiological or therapeutical experiment.

During the earlier part of the above experiment (from 2.15 to 3.00 P. M.) the chamber and its contents were considerably cooled in consequence of one of the Marriott's flasks being out of order and necessitating the keeping open of the doors, for its repair. When this was accomplished, we find for the subsequent two hours (3 h. 00′ to 4 h. 50′) a very remarkable uniformity in the heart's work. Arterial pressure only varies between 86 and 91 mm. of mercury, and the pulse rate between 118 and 120 per minute. Probably under no conditions would a heart still connected physiologically with the rest of the body display so great a uniformity in its activity for so long a time. The pulse, it will be seen, still remained very regular to the end of the experiment, although arterial pressure fell; this again illustrates the slight influence exerted by aortic pressure upon the rhythm of the isolated heart.



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