PHARMACOLOGY OF THE CORONARY CIRCULATION

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I. INTRODUCTION

The coronary blood flow is the blood which enters the coronary ostia, irrigates the myocardium and drains into the right auricle and ventricle and to a small extent into the left ventricle. The determinants of the amount of coronary blood flow are the head of pressure, *i.e.*, the aortic pressure at the coronary ostia, and the resistance of the coronary bed. If the viscosity of the blood is constant, there are two components to the resistance of the coronary bed: (1) the intrinsic component which is the state of constriction or dilatation of the coronary vessels and (2) the extrinsic component which is the magnitude of the "extravascular support", *i.e.*, the effect that the myocardium exerts on the coronary bed during each systole by compressing the coronary bed from the outside and possibly also during diastole by the effect of its tonus. The part played in determining the resistance of the coronary bed by the pressure existing at the opening of the coronary vessels in the cardiac chambers into which they drain remains to be determined. A discussion of the physiological influences that control the aortic pressure and the magnitude of the extravascular support does not belong in this review and such influences will be mentioned when necessary during the presentation of the effect of drugs on the coronary circulation. The degree of constriction or dilatation of the coronary bed seems to be under nervous control but the metabolites locally produced probably also play a very important rôle in modifying the caliber of the coronary vessels. Probably all and certainly most of the drugs that modify the coronary circulation also affect the dynamics of the general circulation through the action they have on the myocardium and/or on the peripheral vessels. Therefore the knowledge of the effect of a drug on the coronary circulation must of necessity include not only the influence of such a drug on the volume of coronary blood flow and its mechanism or mechanisms of action, but also the effect of that drug on the work and metabolism of the heart.* Indeed what really matters is not the absolute amount of coronary blood flow, but the ratio between cardiac work and coronary blood flow; it is probable that certain drugs which, as will be seen later, increase the coronary flow dramatically, increase the work of the heart relatively more than the coronary flow. It is not known whether there ever are conditions or drugs that increase the work of the heart to such an extent that, even when they increase the coronary flow *pari passu*, the metabolic processes attending myocardial contraction cannot

* Metabolism of the heart is used to embrace the nature and amount of the substances used by the mycardium as a source of energy and the nature and amount of the metabolites produced.

keep up with the increase in the cardiac work. Such a drug, of course, although increasing the coronary flow and keeping the ratio $\frac{\text{cardiac work}}{\text{coronary flow}}$ constant, would be detrimental to the heart. Finally, it should be added that the knowledge of the effect of a drug on the coronary circulation, to be complete, must include, besides its effect on the volume of coronary flow, on the ratio $\frac{\text{cardiac work}}{\text{coronary flow}}$ and on the metabolism of the heart, its effect on the efficiency of the heart. Indeed if a drug increases the efficiency of the heart, *i.e.*, increases the ratio $\frac{\text{mechanical work of the heart}}{\text{total energy liberated by the heart}}$, the heart when under the effect of such a drug will be able to perform more work with the same supply of blood and whatever the blood brings to the myocardium. The effect of such a drug will be tantamount to an increase in the amount of coronary blood flow. In short, a complete knowledge of the effect of a drug on the coronary circulation must include (a) the effect of that drug on the amount of coronary blood flow, (b) its mechanism or mechanisms of action, (c) its effect on the work of the heart and on the ratio $\frac{\text{cardiac work}}{\text{coronary flow}}$ as well as its effect on the metabolism of the heart, and (d) its effect on the efficiency of the heart. It will soon become obvious that our knowledge is far from complete.

II. METHODS

Although the ultimate goal of the physiologist and pharmacologist is to know the effect of an agent or drug on the coronary circulation of the intact unanesthetized animal and eventually of man, it is necessary to resort to more simple preparations than the whole animal in order to analyze the mechanisms of action of physiological or pharmacological agents. It seems, therefore, appropriate at this time to review critically the main preparations and methods that have been used to study the physiology and pharmacology of the coronary circulation.

Meyer (130) is the first one to have studied the reaction to drugs of rings of coronary arteries bathed in oxygenated carbonate or borate Ringer, Locke or Tyrode solutions and defibrinated blood. Even if it is assumed that such rings of coronary arteries separated from their nervous connections and under very artificial conditions react to drugs the same way as they would in the whole animal, such experiments give no information about the effect of the drug on the smaller coronary vessels which are the main component of the coronary bed. Of course such experiments also give no information on the effect of the drug on the other determinants of the coronary flow, *i.e.*, the head of pressure and the extravascular support. In short, it is obvious that little or no information can be obtained from such a preparation as to the effect of a drug in the whole animal and the information obtained with this method is to be interpreted with great caution and concerns only a factor of small importance in the regulation of the coronary flow.

The perfusion of the coronary bed of a heart in ventricular stand-still or ventricular fibrillation is another technic that has been widely used. The consensus is that the best method of perfusing the coronary bed is that in which the coronary arteries are cannulated, although other methods described and analyzed below have been used (117, 139). Wiggers (185) has brought hearts of cats, dogs and rabbits to a standstill by perfusing the coronary bed with non-oxygenated sodium chloride solution, the cannulas being inserted into the mouth of one or both coronary arteries, and he has measured the coronary flow by measuring the overflow from the right auricle and ventricle. Hammouda and Kinosita (92) have used essentially the same technic in the arrested rabbit heart, as well as in the normally beating heart, the artificially driven heart and the heart in ventricular fibrillation. More recently, Katz, Jochim and Weinstein (105) have perfused under constant pressure the cannulated coronary arteries of the isolated dog heart in ventricular fibrillation with defibrinated and heparinized oxygenated dog blood and estimated the coronary blood flow by measuring the outflow of blood from the coronary sinus, the pulmonary artery and the aorta. The purpose of using such preparations as the arrested or fibrillating ventricles is of course to study the effect of a drug on the coronary bed itself without the interference of possible changes in the other determinants of the coronary flow brought about by the drug, such as changes in the extravascular support. It must be kept in mind, however, that in such preparations the reactivity of the nerves controlling the coronary circulation may deteriorate unless the cerebral circulation is maintained. Also it does not necessarily follow that, because the ventricles are at a standstill or fibrillating, the extravascular support of the coronary bed is constant, although it is said to have remained constant or nearly so in a series of experiments by Katz and Lindner (106) on the effect of an excess of sodium, potassium and calcium ions on the coronary circulation. In short, it seems logical to conclude that the data obtained by perfusing the coronary bed of hearts in ventricular standstill or fibrillation may give information about the possible mechanisms of action of a drug but give no information about its effect on the coronary circulation of the whole animal.

The third type of preparation used is the perfusion of the coronary bed in the isolated beating heart via a cannula inserted into the aorta. This technic was originated by Porter (139) and Langendorff (117). Porter (139), using this technic, has perfused the beating heart of cats with defibrinated blood under constant pressure and measured the outflow of blood from the venae cavae. Although the head of pressure is assumed to be constant in such a preparation, there is little doubt that the heart beat influences somewhat the perfusion pressure and that, if the drug under study affects the strength of the heart beat, the head of pressure may not remain constant. Furthermore the magnitude of the extravascular support may also change if the drug under study modifies the strength of the ventricular contraction. The second pitfall of the technic is that the aortic valves are not competent in every preparation and some of the perfusion fluid leaks back into the left ventricle (185), which may result in

changes of the left intraventricular pressure and changes in the magnitude of the extravascular support. It need hardly be mentioned that in such a preparation that portion of the coronary flow which drains into the left ventricle cannot be measured. Criticizing this technic, Wiggers (185) also points out a third pitfall, namely, that the perfusion fluid may accumulate at times in the cavities of the right heart and not escape completely to the outside; thus a falsely low estimate of the coronary flow is obtained. Against the first pitfall of the method, Wiggers (185) recommends the use of the arrested heart and not the beating heart, but as pointed out above this is not completely satisfactory. To obviate the errors due to the leakage of fluid back into the left ventricle and the accumulation of fluid in the right cavities of the heart and in the left ventricle, Wiggers (185) suggests to drain the left ventricle or to cannulate the coronary arteries instead of perfusing them via an aortic cannula, and to drain widely the right cardiac chambers. As mentioned above, Hammouda and Kinosita (92) have also used the perfusion of the beating rabbit heart with oxygenated carbonate-buffered Ringer fluid and oxygenated borate-buffered Ringer fluid.

In the preparations mentioned above, the amount of coronary flow has been estimated by collecting and measuring the outflow from the right cardiac chambers, attention being paid to draining the right chambers freely. Brodie and Cullis (21) have used an ingenious plethysmographic method to record continuously the coronary outflow. Sassa (146) has used Atzler and Frank's method (14) to measure the coronary inflow; the method consists essentially in counting the number of air bubbles entering the constant pressure bottle which contains the perfusion fluid. Whatever the method of recording and/or measuring the amount of coronary flow may be, it seems that the perfusion of the coronary bed in the isolated beating heart as a method of approach to the study of the coronary circulation has very marked limitations for most purposes. Its greatest usefulness probably lies in the study of the intimate mechanism by which changes in heart rate and strength of the ventricular contraction may affect the coronary flow. The perfusion of the isolated heart in ventricular standstill or fibrillation probably abrogates to a great extent the interference of changes in the extravascular support and gives information about the effect of the agent under study on the coronary bed itself but it fails to give much information about the effect of an agent or drug on the coronary circulation of the whole animal.

A great step forward was made when the heart-lung preparation became reliable (101, 113). It has proven very useful in the study of the different factors that affect the coronary circulation because in the heart-lung preparation the heart beats in a fairly natural manner and one determinant of the coronary flow can be changed while all the others can be kept constant. A great deal of information about the physiology and pharmacology of the coronary circulation has been gathered with the heart-lung preparation which is more physiological than the preparations previously described and gives more and better information. However, it must be kept in mind that such a preparation is still very different physiologically from the whole animal. Therefore, the informa-

tion gathered with this technic must be critically appraised when an attempt is made to integrate it into the physiology and pharmacology of the coronary circulation of the whole animal. For example, in the heart-lung preparation, although stimulation of the vagi and sympathetic nerves is still effective, the reflex nervous control of the coronary circulation is abolished since there is no cerebral circulation in the ordinary heart-lung preparation. It must also be remembered that those features of the heart-lung preparation that constitute its advantages are also its drawbacks. It is, of course, of great interest in the study of the effect of a physiological or pharmacological agent to be able, as in the heart-lung preparation, to keep blood pressure, heart rate and cardiac output and work constant and to conclude that the increase or decrease in coronary flow observed is due to a decrease or an increase, respectively, in the resistance of the coronary bed. Although observations made with the heart-lung preparation tell what an agent can do to the coronary flow and the coronary bed, they do not reveal what it actually does to the coronary flow or the coronary bed in the whole animal. It may well be that an agent or drug, when acting in the whole animal, has a direct effect on the coronary bed and flow which is neutralized or even offset by the indirect effect of the drug's action on the blood pressure, heart rate, cardiac output and cardiac work. In other words, to fulfill the four desiderata mentioned at the end of the introduction, experimentation on the whole animal is necessary to establish the effect of the drug on the coronary circulation, and the work, the metabolism and the efficiency of the heart, but experimentation on simpler preparations, such as the isolated heart and the heart-lung preparation, is necessary to establish the intimate mechanisms of action of the drug. Of these simpler preparations, the heart-lung seems to be the best and the most widely useful. As has been mentioned above, one objection to the heart-lung preparation is that in such a preparation there is no cerebral circulation which makes it impossible to study the central and reflex regulation of the coronary circulation. To obviate this objection, Anrep and Segall (12, 13) have designed the innervated heart-lung preparation which is an ordinary heart-lung preparation in which the heart and brain are supplied with blood from separate sources that can be controlled independently. The coronary blood supply comes from the aorta of the heart-lung preparation or from a perfusion flask whereas the cerebral blood supply comes from another heart-lung preparation, a pump or the circulation of another animal. In this manner the heart retains its connection with a living central nervous system. This preparation has all the advantages of the ordinary or denervated heart-lung preparation and also affords the opportunity to study the effect of central and reflex nervous factors on the coronary circulation.

The whole anesthetized animal has been used by numerous investigators (1, 2, 78, 79, 140, 171, 184). There is no doubt that the study of a physiological or pharmacological agent in the whole anesthetized animal is more likely than the previously described technics to reveal the effect of that agent in the unanesthetized animal or man, but it often reveals little as to the mechanism of action of the agent studied. Because of technical difficulties, in most experi-

ments on the whole anesthetized animal the only available information, besides the amount of coronary flow, is the arterial blood pressure and the heart rate. From coronary flow, arterial blood pressure and heart rate it is difficult to infer much about the mechanism of action of the agent studied. During the period of action of a drug, for example, it is only when coronary flow and blood pressure vary in opposite direction or when either varies alone that something is learned about the mechanism of action of that drug. If a drug increases both coronary flow and arterial blood pressure, it is impossible to know whether the increase in flow is due to the increase in the head of pressure alone or whether the drug may also have decreased directly or indirectly the resistance of the coronary bed. When a drug lowers both flow and pressure, it is impossible to know whether the decrease in flow is accounted for by the decrease in the head of pressure alone or whether the drug has also increased the resistance of the coronary bed. However, if a drug decreases the blood pressure and the flow remains the same or rises, then the drug has decreased the resistance of the coronary bed. If a drug lowers the flow whereas the blood pressure remains the same or rises, there is no doubt that the drug has increased the resistance of the coronary bed. It must be added that, although in such favorable examples as just mentioned above, a conclusion can be reached as to what the effect of a drug is on the coronary flow and on the resistance of the coronary bed, this insight into the mechanism of action of the drug remains frustrating. Indeed, if under favorable circumstances the conclusion has been reached that a drug has increased the coronary flow by decreasing the resistance of the coronary bed, it still is impossible to know whether that decrease in the resistance is due to a decrease in the magnitude of the extravascular support or to a dilatation of the coronary bed. *A fortiori* is it impossible to determine whether the dilatation of the coronary bed, if dilatation there has been, is due to the effect of the drug directly on the blood vessel wall itself or indirectly on the blood vessels via nervous influences, either local or reflex in origin. It is even impossible to know whether such a dilatation may not be due to a relative ischemia of the myocardium (73), the drug increasing the cardiac work more than the coronary flow and the metabolites which accumulate locally being ultimately responsible for at least part of the dilatation of the coronary bed.

To measure the coronary flow in the preparations that have just been reviewed, numerous methods have been used. Some of the simpler and older ones have already been described. Great progress was made in the study of the coronary circulation when Morawitz and Zahn (132) designed a special cannula which, when inserted into the coronary sinus via the right atrium, drains the coronary sinus outflow. Numerous studies (5, 49, 125) seem to indicate that the volume of coronary sinus outflow amounts to about 60 per cent of the total coronary flow and bears a constant relationship to the total coronary flow under wide variations of cardiac output, aortic blood pressure and heart rate. If such is the case, the measure of the coronary sinus outflow is a very good approach to the study of the coronary circulation, the only objection being that the pressure at the end of the Morawitz-Zahn cannula is not the same as the pressure

at the ostium of the coronary sinus; this may affect the amount of coronary sinus outflow. Although Anrep, Blalock and Hammouda (5) report that in most of their measurements the coronary sinus outflow represents between 60 and 67 per cent of the total coronary flow, they have found that in a few measurements the sinus outflow may vary from 48 to 71 per cent of the total coronary flow. Other investigators (104, 105, 109, 131, 166) have also been led to conclude that the ratio between coronary sinus outflow and total coronary flow is highly variable and therefore the sinus outflow is not a reliable index of the total coronary flow. Recently Gregg and Shipley (87), using better methods of measuring coronary inflow and coronary sinus outflow in the whole animal, have been able to show that under a wide variety of experimental conditions in which reasonably normal hemodynamic conditions prevail the relationship between coronary flow in the left coronary artery and coronary sinus outflow remains constant in the same animal. They have concluded that in any one experiment, when reasonably normal hemodynamic conditions prevail, changes in coronary sinus outflow can probably serve as a directional indicator of left coronary inflow and presumably also of total coronary inflow, although the actual volume of total coronary flow cannot be accurately predicted from the coronary sinus outflow since the relationship of coronary sinus flow to left coronary artery flow varies in different experiments. This very important question has obviously not been definitely settled and it would be most useful to have it settled before further work is done with technics based on the assumption that the sinus outflow bears a constant relationship to the total coronary flow. In 1925, Anrep and Downing (7) designed their anemometer to record the rate of coronary inflow when a cannulated coronary artery is perfused under constant pressure from a flask containing blood. The volume of blood flowing out of the flask causes the displacement of an equal amount of air through the upper part of the flask which contains a hot platinum wire. The air displacement cools the wire and the changes brought about in the electrical resistance of the wire by the cooling are recorded by a sensitive galvanometer. This instrument has given a great deal of information but can only be used when the coronary arteries are perfused from a constant pressure bottle. Furthermore, it has a considerable time lag and cannot record accurately rapid flow changes. Stehle (157), using a Langendorff preparation, has measured the coronary inflow by photographing the movement of a globule of toluene, colored deep red with iodine, placed in the inflow tube. Anrep, Davis and Volhard (6) have photographed the movement of a droplet of mercury placed in the blood stream. Both technics have a considerable lag but are of value when no accurate picture of the phasic changes of the coronary flow is desired. Wiggers and Cotton (187) have devised a technic consisting in the perfusion of a coronary artery with oxygenated Locke solution from a small reservoir connected to a chamber filled with air. Prior to each determination of flow, the air pressure is raised well above systolic aortic pressure and thus the perfusion fluid is driven into the coronary bed under a slowly declining pressure for a few beats. The flow is measured by recording the pressure changes that occur as the Locke solution

enters the coronary artery, the slope of the curve giving the rate of coronary inflow. Although this technic has enlarged our knowledge of the dynamics of the coronary circulation, it has now been discarded for several reasons: the effect of the perfusion with Locke solution, even oxygenated, on the heart muscle; the constant changes of the perfusion pressure; the impossibility of having a continuous record; the necessity of using a perfusion pressure different from the natural one, quantitatively as well as qualitatively. In 1934, Soskin, Priest and Schultz (155) designed the first bubble flowmeter which has been recently used in the study of the coronary circulation by Eckenhoff, Hafkenschiel and Landmesser (36). This flowmeter is used to measure the mean blood flow by timing the speed of an air bubble of proper size injected into the blood stream when it passes through a glass tube of known volume inserted in the vascular bed under study. The air bubble serves to mark off the forward movement of the blood. This technic can only measure mean blood flow, it overestimates the flow if the bubble is too large or too small (22) and it cannot measure blood flow continuously.

In 1928, Rein (141) constructed the first thermostromuhr, which was later modified by Baldes and Herrick (15). It consists of a small diathermy unit, supplying a small and constant amount of heat, and two thermocouples. When the different parts, mounted into a compact unit, are snugly applied to an unopened blood vessel, part of the heat supplied by the diathermy unit is carried away by the stream of blood and the difference between the temperature of the two thermocouples, a function of the rate of the blood flow, is recorded by a sensitive galvanometer. Although the thermostromuhr only measures the mean blood flow, its advantages are great. The blood flow is measured in an unopened vessel. If it is desired, blood flow studies can be conducted on the unanesthetized animal since, after the thermostromuhr unit has been placed around the artery under anesthesia, the animal can be allowed to recover and used for several weeks thereafter. A few years ago, Gregg and his associates (78, 79, 83, 149) pointed out several sources of error in the thermostromuhr technic. It seems fair to state, however, that although the absolute values for blood flow obtained with the thermostromuhr must undoubtedly be interpreted with caution, the instrument can give a great deal of information within a wide range of physiological conditions. This is attested by the fact that none of the results or conclusions obtained with the thermostromuhr by the Mayo group has been disproven.

Green, Gregg and Wiggers (72) and Gregg, Green and Wiggers (82) have taken advantage of the fact that the rate of flow in a coronary artery at any instant is a function of the difference between the pressure in the central end of that coronary artery and the pressure in its peripheral end. Since the central coronary pressure is essentially similar to the aortic pressure (186), these authors record the aortic pressure near the coronary ostia as the central coronary pressure. The peripheral coronary pressure is recorded from a side branch of one of the main coronary arteries. The curve obtained by subtracting the corrected peripheral pressure curve from the aortic pressure curve represents, at any

instant, the instantaneous rate of flow and the area beneath the curve obtained during a cardiac cycle gives an index of the volume of coronary flow. The assumptions upon which this "differential pressure method" is based have not proven to be entirely valid and it seems that the method under certain circumstances may neither indicate the directional shifts of flow nor represent the magnitude of the changes in flow. While such a procedure has added to our knowledge, it must be discarded as a method of quantitating the coronary flow (79). In 1940, Gregg and Green (81) described a recording orifice meter. It is based on the fact that if the lateral pressure is recorded above and below a point of constant constriction in a flowing stream, the difference in the pressures which can be directly recorded with a differential manometer is a function of the rate of flow. This technic permits a continuous recording of the phasic changes of coronary flow. However, when the value of the mean coronary flow is desired, the differential pressure curve must be redrawn on a linear ordinate scale before it can be integrated, which involves a great deal of tedious work. Nevertheless this technic has added a very great deal to our knowledge of the coronary circulation.

The rotameter, first used in 1942 to measure blood flow (88), consists essentially in a vertical tube with tapered bore in which there is a small, freely movable float the height of which varies with the rate of flow. It has been modified by Shipley and Crittenden (26, 147) to permit continuous recording of the flow. It measures only mean blood flow but it is accurate, easy to use and is probably one of the best methods to record mean blood flow.

Recently the nitrous oxide method, first used to measure cerebral blood flow (110), has been used to measure the coronary blood flow through the left ventricle (35). It is based on the Fick principle, *i.e.*, the flow of blood through an organ per unit of time is equal to the amount of a substance taken up from the blood by that organ per unit of time divided by the difference between the concentration of that substance in the arterial blood and its concentration in the total venous blood drained from that organ during that time. In the nitrous oxide method as applied to the measurement of the coronary blood flow, the arterial nitrous oxide concentration is determined on blood drawn from any available artery and the venous nitrous oxide concentration is determined on blood drawn from the coronary sinus without contamination. The amount of coronary blood flow through those parts of the heart whose venous drainage occurs via the coronary sinus is equal to the nitrous oxide uptake of the heart divided by the arterio-venous nitrous oxide difference. The numerator of this fraction is assumed to be equal to the concentration of nitrous oxide in the venous blood after equilibrium between blood and heart tissue has been established multiplied by a partition coefficient for nitrous oxide between blood and heart tissue. The denominator is obtained by computing the integrated difference between the concentrations of nitrous oxide in arterial and venous blood during the period of equilibration, during which the animal inhales a mixture of nitrogen and oxygen containing 15 per cent of nitrous oxide. From the formula it is easy to obtain the amount of coronary blood flow per minute per 100 grams

of that part of the myocardium whose venous drainage occurs via the coronary sinus, *i.e.*, per 100 grams of left ventricle. The method can be used in lightly anesthetized or even unanesthetized animals which are in conditions closer to normal than in any other method except the thermostromuhr method. The agreement between figures for coronary flow obtained by the nitrous oxide method and by the bubble flowmeter is good (35); but Green, Gregg and Czerwonka (75) have been unable to obtain agreement in experiments in which they have measured the coronary flow simultaneously with a rotameter and the nitrous oxide method. A disadvantage of the nitrous oxide method is that it can be used only if the conditions under which the flow is measured remain constant for at least the ten minutes required for the procedure. This precludes its use under circumstances in which rapid fluctuations of flow occur. The pitfalls of contamination of the coronary sinus blood by atrial blood, of occluding the venous drainage and of trauma to the coronary system cannot be disregarded. Finally, the effect of nitrous oxide itself on the coronary flow has not been determined.

Because relatively little information is obtained when only arterial blood pressure, heart rate and coronary flow are measured, several authors have recently tried to measure not only coronary flow, arterial blood pressure and heart rate but also cardiac output in the whole anesthetized animal. Eckenhoff, Hafkenschiel and Landmesser (36) have measured arterial blood pressure, heart rate, cardiac output and coronary flow, the latter two by the Fick method and the bubble flowmeter, respectively. Eckenhoff, Hafkenschiel, Landmesser and Harmel (37) have simultaneously determined coronary flow, arterial blood pressure, heart rate, cardiac output, cardiac work and cardiac efficiency. Very recently, Wégria, Frank, Misrahy, Sioussat, Sommer and McCormack (176–178) have designed a technic by which the output of the left ventricle, the coronary blood flow, the mean arterial blood pressure and the heart rate can be simultaneously and continuously recorded in the whole anesthetized animal, the flows being recorded by the simultaneous use of two rotameters, one for the coronary flow and one for the cardiac output. In addition the cardiac work can be calculated from the data obtained. Although such technics should prove valuable, it must be kept in mind that the anesthetized animal, especially with open chest, under artificial respiration and having undergone varied operative procedures, may well be different in its reactions from the unanesthetized animal and human being, quantitatively and possibly even qualitatively. Unpublished data (172) seem to indicate, for example, that vasodilator drugs lower the arterial blood pressure more markedly in the anesthetized than in the unanesthetized dog. It has also been our observation that the type of anesthetic used may make a difference in the type of reaction observed (172). For example, in a dog under chloralose anesthesia, a dose of nitroglycerin may lower the arterial blood pressure very markedly and still increase the coronary flow, whereas a smaller dose of nitroglycerin given to a dog under morphine-barbital anesthesia may lower the blood pressure less markedly and yet the coronary flow will be markedly decreased. These quanti-

tative and sometimes qualitative differences between the effects of physiological and pharmacological agents on the coronary circulation, depending upon the type of anesthetic used, are not surprising since most anesthetics are known to influence markedly the cardiovascular system and its regulatory mechanisms. For example, sodium pentobarbital has been shown to have a marked effect on the coronary circulation (47). However, it is comforting that, in a study of the effect of a large number of drugs on the coronary circulation in a series of dogs anesthetized with chloralose (175) and in a series of unanesthetized dogs (47), no qualitative difference has been observed between the two groups. To obviate the objection of anesthesia and operative procedures, some work has been done on the unanesthetized animal with the thermostromuhr (47). The part of the thermostromuhr which has to be placed around the coronary artery, *i.e.*, the thermocouple unit, is applied under general anesthesia and the insulated wires connecting the thermocouple unit with the recording part of the thermostromuhr are brought through the skin. The dog is allowed to recover and can be used for a certain number of days or even weeks. Recently the nitrous oxide method has been used in unanesthetized human beings to study coronary circulation (16).

It is obvious from what has been said that it is difficult to study experimentally the effect of a physiological or pharmacological agent on the different functions that must be taken into consideration when a complete knowledge of the effect of that agent on the coronary circulation is to be gained. Even when this is achieved on the unanesthetized animal, there always remains the possibility that the reactions observed in the coronary circulation of the animal may be different from those in the coronary circulation in man. For these reasons, there have been many attempts to design methods to evaluate indirectly the effect of physiological or pharmacological agents on the human coronary circulation. The most widely used approach to the problem has been to study the effect of the agent, generally a drug, on anginal pain (143). Since anginal pain is probably due to anoxia of the myocardium caused by an absolute or relative ischemia of the myocardium, it is assumed that if a drug prevents or relieves angina it does so by preventing or relieving the ischemia. Although such an approach when judiciously used can give a great deal of practical information, it reveals little about the mode of action of the drug and from such data it is impossible to know whether the drug is effective by increasing the coronary flow, by decreasing the work of the heart, by increasing the efficiency of the heart or by a combined action. Neither can it be determined whether an increase of coronary flow, if such occurs, is only relative to an increase in the work of the heart or whether the drug acts only by increasing coronary flow without modifying the work of the heart (181). Another objection to this method is that it offers more technical difficulties than would appear. The validity of the results obtained depends upon the study of the patient during a long control and experimental period. It must be remembered that the nature of coronary sclerosis, the main cause of relative coronary insufficiency, is often such that, as collateral circulation takes over the rôle of the narrowed vessel, the frequency

of the anginal attacks decreases spontaneously and the pain may even disappear. The same may be true after the offending vessel has become completely occluded. Also there is a stage during the evolution of the disease at which the severity of the coronary insufficiency is such that even drugs of proven value do not affect the frequency or the intensity of the attacks. On the other hand, there are patients whose coronary insufficiency is so slight that the psychic effect of taking a placebo seems sufficient to decrease the frequency of the attacks. In short, if the effect of a drug on the anginal attacks in patients with coronary sclerosis is to be tested, the method is not as easy as it first appears and even if it gives practical information about the usefulness of a drug, it reveals nothing about its mode of action. However, such clinical tests must ultimately be done on drugs which pharmacological studies indicate to be promising. In recent years, clinical tests have been used to reveal a latent coronary insufficiency. These tests consist essentially in exerting the patient by different types of exercise (127) or subjecting the patient to a certain degree of anoxic anoxia by making him breathe a mixture of nitrogen and oxygen containing approximately 10 per cent oxygen (138). In these tests, the appearance of anginal pain and/or characteristic electrocardiographic changes during the period of exertion or anoxia is an index of latent coronary insufficiency. Drugs have been studied for their ability to prevent or delay the appearance of pain and/or electrocardiographic changes in these tests (120, 144, 189). Although exercise and anoxemia tests have the advantages of avoiding long periods of observation and of giving information of direct clinical applicability, they reveal nothing about the mechanisms of action of the drug. Recently, Wégria, Segers, Keating and Ward (182) have determined the minimal restriction of coronary flow which induces electrocardiographic changes in the ischemic area of the myocardium. Whether such a preparation may lend itself to the study of drugs remains to be determined but it is conceivable that a drug might abolish the electrocardiographic changes due to the ischemia by modifying the metabolism of the ischemic area and/or by dilating the coronary bed distal to the constriction; this technic may prove to be a valuable approach.

To conclude this review of the methods used to study coronary circulation, it should again be stated that to obtain exact knowledge of the effect of a drug on the coronary circulation as defined above, it is necessary to use a gamut of methods of approach, extending from a study of the effect of a drug on the coronary circulation of simple preparations, such as the isolated heart in ventricular fibrillation or standstill, to a study of its effect on angina in human beings; each of the technics constitutes a necessary step toward the ultimate goal.

III. PHYSIOLOGY

It seems indispensable to consider briefly the physiology of the coronary circulation before discussing its pharmacology. In this section will be discussed the determinants of the coronary flow, their respective rôles and how they are modified by cardiac or extracardiac influences. It will thereafter be much easier to approach rationally the pharmacology of the coronary circulation.

A great deal of information is obtained from an inspection of tracings representing phasic changes of coronary flow during a cardiac cycle, as recorded by an adequate flowmeter such as the orifice meter (73, 81). Although such flow tracings vary under different hemodynamic conditions and although there are differences between the patterns of flow in the left and right coronary arteries, the coronary flow tracings present certain constant essential features. At the onset of the isometric contraction of the ventricles, there is an abrupt decrease of the coronary flow and during this phase there may even be a flow of blood backward from the coronary arteries into the aorta. This decrease of flow which occasionally culminates in a temporary backflow is undoubtedly due to the compression exerted on the coronary bed by the contracting myocardium. As the aortic valves open and the pressure rises in the aorta, the forward flow of blood is resumed if a backflow has occurred during the isometric contraction, or the coronary flow suddenly increases if the flow has only decreased during the isometric contraction. When the pressure in the aorta decreases after having reached a peak, the coronary flow decreases. The changes that occur in the aortic pressure during systole explain adequately the fluctuations of the coronary flow at this stage. From protodiastole on, the ventricular myocardium relaxes, the compression of the coronary bed by the myocardium decreases, the intensity of the extravascular support of the coronary bed reaches its minimum and, as a result, the coronary flow increases markedly and abruptly. Although the pressure in the aorta decreases steadily due to the run off of blood towards the periphery, the coronary flow remains high but slowly declines, however, as is to be expected from the decrease in the head of aortic pressure. At the onset of the isometric contraction of the ventricles, the sudden decrease of flow occurs as mentioned above. This flow pattern has been well established and all investigators agree that it is characteristic of the flow of blood at least in the large coronary arteries. From this pattern it is relatively simple to appraise, at least qualitatively, the influence of factors such as heart rate and aortic blood pressure on the coronary flow. To do this, as well as to determine the effect of a drug on the coronary flow, two types of experiments are necessary. The first type of experiment is performed on simple preparations such as the isolated heart, and conditions are set so that there is only one variable, *i.e.*, the variable whose influence on the coronary flow is being studied. This type of experiment can reveal what a change in heart rate does to the coronary flow, but it does not reveal what a change in heart rate does to the coronary flow in the whole animal. Therefore the effect of changes in heart rate on the coronary flow must also be studied on the whole animal or on equivalent preparations.

Heart rate. Under essentially normal cardiovascular conditions, more coronary flow occurs during diastole than during systole. Therefore it is to be expected that within limits an increase in heart rate *per se* will decrease the amount of coronary flow per minute and a decrease in heart rate will increase it, which is what Anrep and Häusler (9) have found on the isolated heart perfused under constant pressure. However, if the rate of the heart is such that each beat becomes very weak, the decrease in coronary flow due to the shortening of diastole may be offset by the decrease in the restriction of flow due to systole;

instead of decreasing as the heart rate increases, the coronary flow may then remain unchanged or even increase. In experiments by Anrep and King on the denervated heart-lung preparation (11) and by Anrep and Segall on the innervated heart-lung preparation (13), changes in heart rate within wide limits have been found to have no effect on the coronary flow, whereas Hausner, Essex, Herrick and Baldes (94) have described an increase in coronary flow with an increase in heart rate in the denervated heart-lung preparation. Recently Wégria and Keating (18) have reported that an increase in heart rate in the anesthetized dog produces a temporary decrease in the coronary flow, followed by a rise in the coronary flow above control level, within wide limits of tachycardia. If the rate of the tachycardia is very high, the coronary flow decreases and then only comes back to the control level, and sometimes remains below it. In short, most investigators are agreed that a rise in heart rate *per se* tends to reduce the coronary flow since it increases the period of lower coronary flow (systole) and decreases the period of higher coronary flow (diastole). However, there are some experimental data which do not substantiate this view. Most investigators hold that changes of heart rate *per se*, over a wide range of rates, do not influence the coronary flow; at least, they agree that, in the whole animal, the effect which a change in heart rate must have on the coronary flow is compensated for or offset by the other cardiovascular effects of the drug or the agent responsible for the change in heart rate.

Aortic blood pressure. Although it has been shown that a rise in the aortic pressure, by increasing the strength of the ventricular contraction, tends to decrease the coronary flow by increasing the restriction of flow during systole (2), *a priori* considerations about the pattern of the coronary flow throughout the whole cardiac cycle, as well as all the available experimental data, confirm that a rise in the aortic blood pressure *per se* results in an increase of coronary blood flow and that a decrease of aortic pressure leads to a decrease in the coronary flow (2, 94, 125). Smith, Miller and Graber (153) believe that the diastolic pressure is the most important but Anrep and King (11) point out that diastolic pressure must be understood as mean diastolic pressure if the view of Smith, Miller and Graber is to be accepted. The effect of an increase of aortic pressure on coronary flow via its effect on cardiac work is discussed below.

Cardiac output and work. Markwalder and Starling (125) were the first investigators to show that changes in the output of the heart in a denervated heart-lung preparation do not modify the coronary sinus outflow as long as the mean arterial blood pressure remains constant. The problem has been reinvestigated by Anrep and Segall (13) in the denervated and the innervated heart-lung preparation. They have concluded that in the denervated heart-lung preparation the arterial blood pressure is the only mechanical factor which determines the coronary flow and that neither a change in heart rate nor a change in systolic output nor a change in minute output have any influence *per se* on the coronary flow. In the innervated heart-lung preparation, on the contrary, the cardiac output is an important determinant of the coronary flow, an increase in output producing a rise in the coronary flow. This influence is thought to be of reflex

origin since it is abolished by section of the vagi (13). Recently Gregg, Pritchard, Shipley and Wearn (84) have showed that a rise in the right ventricular pressure produced by pulmonary constriction, which results in an increase in the work and the metabolism of the heart, increases the blood flow in the right and the left coronary arteries. Gregg and Shipley (36) have also observed that a rise in the left ventricular pressure caused by a constriction of the aorta central to the coronary ostia, which increases the work and the metabolism of the heart, increases the blood flow in the left coronary artery. The same effects are also observed after section of the vagi and of the cardiac nerves from the sympathetic chain. The increase in flow is accompanied by a more complete oxygen desaturation of the coronary venous blood. It is thought by these investigators that the increase in coronary flow due to the increase in cardiac work is the result of an increased local production of metabolites and/or the appearance of a local relative anoxia. These experiments have also confirmed the conclusions of Anrep and Häusler (8) that, although a rise in the aortic pressure tends to decrease the coronary flow by increasing the magnitude of the extravascular support during systole, this effect is offset by the other mechanisms producing an increase in the coronary flow, the net result being an increase in the coronary flow. The coronary flow is also increased when the increase in the work of the heart is due only to an increase in the cardiac output. This was first demonstrated by Anrep and Segall (13) on the innervated heart-lung preparation. In conclusion, it seems that all investigators are generally agreed that an increase in the work of the heart *per se* does not modify the coronary flow in the denervated heart-lung preparation if the mean arterial blood pressure remains unchanged. In the innervated heart-lung preparation and in the whole animal, an increase in the work of the heart increases the coronary flow.

Nervous influences. The coronary blood vessels are richly supplied with nerves (190). Degeneration experiments have showed that the larger arterial branches are innervated by vagal and sympathetic fibers but mostly by sympathetic nerves whereas the smaller branches receive fibers mostly of vagal origin. No nerve supply to the capillaries has been demonstrated. It is very difficult to assess the rôle of nervous influences on the coronary circulation because the usual technics used to study nervous influences, such as stimulation and section of the nerves under study, besides exerting their effect on the coronary bed itself, also have numerous cardiodynamic effects such as changes in heart rate, blood pressure and cardiac output. Even when this obstacle is overcome, the effect proven by stimulation or section of a nerve only reveals what such a nerve can do but not what the rôle of that nerve actually is. In attempting to study the effect of sympathetic and parasympathetic nerves on the coronary bed, it is also difficult to gain information by the use of the corresponding chemical mediators, epinephrine, sympathin or acetylcholine, for the same reasons.

From their experiments on the innervated heart-lung preparation, Anrep and Segall (13) have concluded that the vagi exert a tonic constrictive influence on the coronary vessels, since section of the vagi in the cervical region increases the coronary flow even when heart rate, cardiac output and aortic blood pres-

sure are kept constant. These vasomotor coronary fibers are much less sensitive to atropine than are the cardioinhibitory fibers. Stimulation of the peripheral end of the vagi furthermore decreases the coronary flow and this seems to be due to coronary constriction (13). The same authors have also proved that stimulation of the carotid sinus by a rise in the cephalic pressure lowers the coronary flow by producing constriction of the coronary bed; this has been confirmed by Stella (158). That the vagi play an important rôle in the regulation of the coronary circulation seems to be shown by the fact that an increase of the cardiac output *per se* increases the coronary flow in the innervated heart-lung preparation only if the vagi are intact (13). Similar results confirming the rôle of the vagi have been reported by Rein (142) using his thermostromuhr on the whole animal. In experiments on the innervated heart-lung preparation, Anrep and Segall (13) have showed that the sympathetic nerves contain fibers which, when stimulated electrically or reflexly, produce a dilatation of the coronary bed. It must be added, however, that the conclusions reached by Anrep and Segall (13) as to the influence of the vagi and sympathetic nerves on the coronary circulation are valid only if no change in the extravascular support occurred during their experiments. It is true that in the experiments of these authors the aortic blood pressure and the cardiac output did not change but the volume of the heart may have changed during nerve stimulation or after nerve section, thereby possibly changing the magnitude of the extravascular support, in which case the effects ascribed to coronary constriction or dilatation may well have been due to increase or decrease of the extravascular support. This however, appears improbable, and it seems most likely that the conclusions reached by Anrep and Segall (13) in their classic studies are correct. Gregg and Shipley (85) using the orifice-meter and the rotameter in the anesthetized dog have found that electrical stimulation of the stellate ganglia and/or the cardiac nerves therefrom increases the coronary flow without necessarily changing aortic blood pressure or heart rate, from which they conclude that the sympathetic nerves when stimulated produce coronary vasodilatation. However, it must be pointed out that changes in the extravascular support have not been ruled out. Moreover, since these authors did not measure the changes in cardiac output that may have occurred during sympathetic stimulation, it may well be that the probable vasodilatation observed during stimulation of the sympathetic nerves is due to an increase in the output and the work of the heart. In a second paper on the same subject, Shipley and Gregg (148) have indeed found that in such experiments cardiac output, work and metabolism are increased. They have finally concluded that simulation of the sympathetic nerves to the heart produces dilatation of the coronary bed but have been unable to prove that such stimulation produces coronary dilatation directly, because it also increases cardiac output, work and metabolism; these changes afford an adequate explanation for the coronary dilatation. The experiments of Anrep and Segall (13), however, seem to indicate clearly, with the qualification mentioned above about changes in the extravascular support, that the vagi have a tonic vasoconstrictive influence on the coronary bed and that the sympathetic

nerves contain vasodilating fibers to the coronary bed. It must be added that Katz and Jochim (103), using the perfused isolated heart in ventricular fibrillation with normal cerebral circulation, have found that in the dog the vagi carry only tonically active cholinergic coronary vasodilator fibers; the cardiac sympathetic nerves carry adrenergic coronary dilator and adrenergic coronary constrictor fibers, both of which are tonically active, the tonic action being predominantly vasoconstrictor.

It is probable that part of the regulation of the coronary circulation is reflex in origin. The effect of an increase in the cerebral pressure (13) and in the pressure within the carotid sinus (158) has already been mentioned. For a number of years, it has been postulated by clinicians, probably from analogy with the peripheral circulation, that ligation or occlusion of one coronary branch can produce reflex constriction in other coronary branches (118, 124, 128). Although such reflex constriction has never been adequately proven (36, 79, 136), its existence has not been excluded. The effect of electrical stimulation of various afferent nerves upon the coronary circulation has been studied by several investigators but the significance of such studies remains to be determined. Greene (76), for example, has followed the changes in coronary flow produced by stimulation of the central end of cut sciatic, splanchnic and phrenic nerves and found an increase in coronary flow with weak stimuli but frequently a decrease with stronger stimuli. Electrical stimulation of afferent nerves may result in a diphasic effect on the coronary flow, first an increase then a decrease. Whether such changes are due to coronary dilatation and constriction remains to be proven. Distention of the stomach, the gallbladder and the esophagus has been claimed to increase the coronary flow while the arterial blood pressure rises above, remains at or falls below control level (100). On the other hand, Eckenhoff, Hafkenschiel and Landmesser (36) in a recent investigation of the effect of distention of the gallbaldder on coronary flow have found that the changes are variable and always in the same direction as the changes in blood pressure, the most common response being a decrease in coronary flow and blood pressure with an increase in heart rate. Gilbert, LeRoy and Fenn (58) have observed that distention of the stomach or peritoneal cavity in the anesthetized dog often causes a decrease in coronary flow while the blood pressure rises or remains unchanged. It has also been shown (57) that in the decerebrate dog stimulation of the nasal mucous membrane with ice water decreases coronary flow. Pulmonary embolus has been postulated to produce a reflex coronary vasoconstriction (29) but this has not been proven.

Asphyxia, anoxia, hypercapnia and myocardial ischemia. Certain chemical changes in the blood have been shown to affect the coronary circulation very markedly. Asphyxia (73) produced by shutting off the artificial respiration in the open chest dog increases the coronary flow within a few seconds in the absence of any changes in blood pressure or heart rate. Therefore this increase in coronary flow must be due to a decrease in the resistance of the coronary bed, brought about by dilatation of the coronary bed and possibly also by a decrease in the magnitude of the extravascular support (73). Of course if asphyxia lasts

long enough, the arterial blood pressure rises and this rise affects the coronary circulation. Asphyxia has been shown to have a similar effect on the coronary circulation in the dog heart-lung preparation (125). Anoxia (36, 73, 99) and cyanides (73, 99) have essentially the same effect as asphyxia on the coronary circulation. There is less agreement about the effect of hypercapnia on the coronary circulation. Markwalder and Starling (125) have found that the inhalation of a mixture of air and about 12 per cent CO_2 increases the coronary flow in the dog heart-lung preparation by decreasing the resistance of the coronary bed. The effect of CO_2 is less marked than that of asphyxia. Hilton and Eichholtz (99) have obtained the same results as Markwalder and Starling (125) with the inhalation of air containing around 7 per cent CO_2 and with the addition of lactic acid to the blood of the heart-lung preparation. Whether in the latter experiments the increase in flow was due to changes in blood pH or to specific effects of lactate ions is not known. Experimenting on the whole animal, Green and Wégria (73) as well as Eckenhoff, Hafkenschiel and Landmesser (36) have been unable to confirm the previous work on the effect of CO_2 on the coronary circulation. In these experiments, the inhalation of air containing 5 to 8 per cent CO_2 never produced any increase in coronary flow and the only change in flow was a slight decrease when the arterial blood pressure began to fall. It must be added that in unpublished experiments the author has observed a marked increase in coronary flow and arterial blood pressure during the inhalation of similar mixtures of air and CO_2. In these experiments the dogs had been anesthetized with chloralose (173) and not with morphine-sodium barbital (73), morphine-pentobarbital or morphine-chloralose (36). A marked decrease in pH (36) has been shown to lower the mean arterial blood pressure and to decrease the cardiac output whereas the coronary flow remains essentially unchanged, indicating that the change in pH must have directly or/and indirectly decreased the resistance of the coronary bed. Elek and Katz (39) have also reported that a decrease, as well as an increase, in the pH of the blood used to perfuse the coronary bed of the dog heart in ventricular fibrillation increases the coronary flow.

Complete ischemia of a portion of the myocardium produced by temporarily preventing blood from entering an area irrigated via a coronary branch, such as the ramus descendens anterior, induces a marked increase in the coronary flow to that area (36, 73, 107), even if the ischemia lasts only a few seconds. This increase in flow is due exclusively to a decrease in the resistance of the coronary bed. The same effect has been found to occur when the ischemia is only partial (182).

In summary, it seems that the effect of hypercapnia on the coronary circulation is disputed by different groups of investigators. In the experiments in which an excess of CO_2 increases the coronary flow, the increase is slight compared to that caused by anoxia. On the other hand, asphyxia, systemic anoxia produced by the inhalation of gas mixtures low in oxygen, local anoxia due to the intracoronary administration of cyanide and partial or total ischemia of the myocardium all increase the coronary flow markedly before or without inducing

any change in blood pressure or heart rate. This increase in flow must, therefore, be due to a decrease in the resistance of the coronary bed. It seems probable that the decrease in the resistance of the coronary bed is due to dilatation of the vascular bed but it remains possible that a decrease in the extravascular support contributes to the decrease in the coronary resistance (73). The intimate mechanisms by which the resistance of the coronary bed is decreased are far from certain but several possibilities have been suggested: anoxia in the whole animal and in the innervated heart-lung preparation increases cardiac work (13, 84, 86) which through reflex influences and/or chemical influences locally in the myocardium, as mentioned above, leads to increased coronary flow; myocardial anoxia and ischemia cause the local production and accumulation of vasodilator metabolites such as adenosine and adenylic acid (169), local changes in pH (36) and local production of histamine (4).

Coronary venous pressure. A priori, it might be anticipated that, when the pressure increases on the venous side of the coronary bed, the flow of blood in the coronary arteries would decrease if no compensatory mechanism sets in. Experiments on the isolated dog heart (164) have indeed established that a decrease in the pressure gradient between coronary arteries and veins reduces the coronary flow. It is a difficult problem to study in the whole animal because, if the pressure on the venous side of the coronary bed is raised by increasing the pressure in the right chambers of the heart either by increasing the venous return of blood or by constricting the pulmonary artery, important cardiodynamic changes and compensatory mechanisms are evoked. These compensatory mechanisms may mask the intrinsic effect of the increase in the coronary venous pressure and make difficult the interpretation of the results observed, as will be remembered from what was said above about the effect of an increase in cardiac output and work on the coronary circulation. Furthermore, unless all the coronary artery blood flow and all the coronary venous outflow are measured in experiments on the whole animal, the conclusions drawn from the results obtained are hazardous because of the possibility of shunts opening between the different coronary arteries and between the different venous channels. For these reasons little is known about the effect of changes, especially moderate changes, in the coronary venous pressure on the coronary circulation in the whole animal. Acute occlusion of the coronary sinus, although causing a considerable rise of pressure in the coronary sinus (80), reduces the blood flow in the left coronary artery only very slightly, an average of 8 per cent (87). When the anterior cardiac veins are acutely occluded, the right coronary flow decreases 0 to 63 per cent, an average of 21 per cent. These experiments must not necessarily be interpreted as meaning that an increase in the pressure on the venous side of the coronary bed may have little effect on the coronary arterial inflow. They more probably mean that there exist many collateral communications between the different venous draining channels. In short, the effect of changes in the coronary venous pressure on the coronary artery inflow remains to be defined.

Digestion and exercise. Essex, Herrick, Baldes and Mann (41) have shown

that digestion increases the coronary flow in the unanesthetized dog. The same authors have also studied the effect of exercise on coronary blood flow, mean arterial blood pressure and heart rate in the unanesthetized dog (43, 44) and observed that exercise increases coronary flow, blood pressure and heart rate but that the change in coronary blood flow follows that in heart rate much more closely than that in blood pressure. Bilateral cardiac sympathetic ganglionectomy from the eighth intercostal space anteriorly and including the stellate ganglion does not significantly alter the reactions of coronary flow, blood pressure and heart rate to exercise. After bilateral cervical vagotomy, exercise increases the coronary flow in those animals in which the exercise raises the blood pressure; in those dogs in which exercise does not increase the blood pressure, the coronary flow remains essentially unchanged. After bilateral vagotomy, exercise produces only a slight acceleration of the heart.

Temperature. Mart and Miller (126) raised the temperature of the right ventricle about 6°F. by applying diathermy over the heart and could not show any significant change in coronary flow. On the other hand, Cruickshank and Subba Rau (27) have found that isolated coronary arteries of ox, dog and man relax on cooling and contract on warming when the temperature varies between 27 and 38°C., a finding which has been confirmed by Kountz (114). As pointed out before, however, the results of such experiments are difficult to evaluate in terms of coronary circulation. Anrep and Häusler (9) have reinvestigated this problem on the heart-lung preparation by perfusing a coronary artery under constant pressure with blood at different temperatures. They have showed that cooling and warming the blood perfusing a coronary artery increases and decreases, respectively, the blood flow through this artery, the coronary vessels dilating on cooling and contracting on warming. However, if the temperature of the heart muscle itself decreases, the coronary flow tends to decrease, whereas an increase of the heart muscle temperature tends to increase the coronary flow. These latter changes are due to the fact that cooling of the heart muscle produces a more forceful and more prolonged heart beat which increases the systolic restriction of flow in the preparation used by Anrep and Häusler (9). These authors conclude that the direct effect of lowering the temperature on the coronary vessels, which tends to increase the coronary flow, is more pronounced than the indirect effect which tends to decrease the coronary flow by increasing the strength of the myocardial contraction. This conclusion has been confirmed by Nakagawa (133) who, measuring the coronary sinus outflow in the heart-lung preparation, has shown that cooling the blood from 38–40° to 28–30°C. increases the coronary flow. Further cooling seems to decrease the coronary flow.

Valvular lesions. As previously mentioned in the section on the effect of changes in cardiac output and work on the coronary circulation, acute pulmonary and aortic stenosis (84, 86) in the whole dog increases the coronary flow in the right and left coronary arteries, provided the aortic pressure remains fairly constant. Either lesion increases the work and the metabolism of the corresponding ventricle. No experimental data are available about the effect of mitral lesions

on the coronary circulation. The effect of aortic insufficiency has not been adequately studied but it seems that aortic insufficiency increases the coronary flow during systole and lowers it during diastole. When aortic insufficiency is marked enough to lower the diastolic pressure markedly, the increase in coronary flow during systole does not compensate for the decrease in flow during diastole and the mean coronary flow decreases (71). In one patient with aortic insufficiency, the output and the work of the left ventricle have been found to be increased, as also were the oxygen consumption per 100 grams of left ventricle and the coronary flow per 100 grams of left ventricle (16).

Shock. With the demonstration that there can be an element of myocardial depression (179) in shock, it became imperative to find whether the myocardial depression of shock might not possibly be due to the probable decrease in coronary flow brought about by the decrease in blood pressure. Opdyke and Foreman (135) have shown that in hemorrhagic hypotension and shock the coronary flow decreases as the blood pressure falls but that the resistance to flow in the coronary bed is greatly reduced; this decrease in the resistance of the coronary bed has been interpreted as being due mainly to vasodilatation of the coronary bed. Following reinfusion of all withdrawn blood and restoration of mean aortic pressure to control level, the coronary flow increases markedly above its control value. This increase in coronary flow has also been interpreted as being due to coronary dilatation. Obviously concomitant determinations of coronary flow, cardiac work and metabolism throughout the period of hypotension and shock are necessary for a complete understanding of the mechanisms through which myocardial depression develops in shock.

Cardiac metabolism and efficiency. The state of nutrition of the myocardium depends not only upon the ratio between the volume of coronary blood flow and the amount of work performed by the heart, but also upon the metabolism and the efficiency of the heart. Although the effect of an increase in cardiac work on the coronary flow has been discussed previously, no systematic discussion has been presented of how a change in the amount of cardiac work affects the metabolism of the heart and whether physiological agents may affect the efficiency of the myocardium.

Evans and Matsuoka (48) have showed that in the heart-lung preparation an increase in the work of the heart produced by an increase in the arterial pressure or an increase of cardiac output leads to an increase in the oxygen consumption of the heart and an increase in its efficiency up to a certain level of work, beyond which the efficiency of the heart decreases. An increase in work due to an increase in output is performed by the heart more economically than an increase in work due to a rise in arterial blood pressure; therefore the heart is able to work better over wider ranges of output than of arterial pressure. Starling and Visscher (156) have demonstrated in the heart-lung preparation that the oxygen consumption of the heart, maintained under constant chemical and temperature conditions, is determined by its diastolic volume and, therefore, by the initial length of its muscular fibres and that during the whole of an experiment the oxygen consumption at a given diastolic volume is always the same,

whatever the work the heart is performing at this volume. Since, in a heart in good condition, every increase or decrease in work is accompanied by a proportional increase or decrease in diastolic size, it follows that an increase in work demanded of the heart is met by a corresponding increase in the oxygen consumption of the heart, consequent on the increased initial length of its muscle fibres. As the heart tires, although the total energy as measured by oxygen consumption liberated at any given initial length of fibre remains unchanged, the amount of useful work performed decreases. In other words, to do the same amount of work the heart has to dilate continuously and the work is maintained constant at an ever-increasing cost in total energy.

These conclusions have been essentially confirmed by several investigators (66, 90, 96, 111). Starling and Visscher (156) have demonstrated that at the same diastolic length of fibre the heart uses more oxygen per beat when contracting at a low rate than at a high rate. However, slowing of the heart enables it to do a given amount of work per unit of time more economically; this has been corroborated by Cohn and Steele (24). These latter workers have also found that the oxygen consumption per gram of heart decreases with age (25). Gollwitzer-Meier and Krüger (69) have showed on the innervated heart-lung preparation that electrical or reflex stimulation of the vagi decreases the oxygen consumption of the heart and increases its efficiency whereas stimulation of the stellate ganglion increases the oxygen consumption of the heart and decreases its efficiency.

A number of studies has been done on the whole animal. Harrison, Friedman and Resnik (93) have confirmed that an increase in cardiac work brought about by increasing the cardiac output or raising the arterial blood pressure increases the coronary flow, the oxygen consumption of the heart and its mechanical efficiency. Gregg and Shipley (86) and Shipley and Gregg (148) have observed that an increase in cardiac work produced by artificially raising the pulmonary or the aortic pressure or by stimulating the stellate ganglia increases the oxygen consumption of the heart. Eckenhoff, Hafkenschiel, Foltz and Driver (34) have observed that, after the subdural injection of procaine hydrochloride or the intravenous injection of tetraethylammonium chloride, the fall in arterial blood pressure is associated with a diminished cardiac output and coronary flow; cardiac work, oxygen consumption and efficiency are reduced. Eckenhoff, Hafkenschiel, Landmesser and Harmel (37) have found that when a primary increase in mean arterial blood pressure is induced by a compression of the aorta severe enough to decrease the cardiac output, the cardiac work decreases, the coronary flow increases, the oxygen consumption of the heart rises and the cardiac efficiency decreases. When a primary increase in cardiac output is induced by the infusion of blood and/or isotonic gelatin in saline, blood pressure, coronary flow, cardiac work, oxygen consumption and efficiency rise. In anoxic anoxia, the cardiac output and work decrease, the coronary flow increases, the blood pressure and cardiac oxygen consumption remain constant and the cardiac efficiency falls. These authors have interpreted their findings as meaning that cardiac efficiency tends to vary directly with cardiac output and inversely with arterial blood pressure.

IV. PHARMACOLOGY

After a review of the methods used to study the coronary circulation and a review of the physiology of the coronary circulation, it will now be much easier to discuss the pharmacology of the coronary circulation. As a general pattern, it is planned first to present the available information on the effect of each drug on the whole animal; then, through an analysis of work done on more artificial preparations, an attempt will be made to elucidate the mechanisms of action of each drug by discussing its effect on the different determinants of the coronary flow. In the case of many drugs, such a program cannot be fulfilled because of lack of data. For convenience, the different drugs have been divided into three groups: (1) the drugs which are known for their vasopressor property; (2) the drugs known for their vasodepressor property; and (3) a group of miscellaneous drugs that are not especially known for their pressor or depressor effects after usual doses, although some of them exhibit pressor or depressor effects after higher doses.

Vasopressor drugs

Except under unusual circumstances of dosage and route of administration, in which case the vasopressor drugs may increase the coronary flow without modifying the mean arterial blood pressure, all the drugs discussed in this section increase both blood pressure and coronary flow. The mechanism of the increase in coronary flow is not entirely clear. Undoubtedly, the mechanical effect of an increase in the arterial blood pressure is responsible for at least part of the increase in flow. When the blood pressure rises, it is probable that the work of the heart increases and even when the dose of the drug is such that the arterial blood pressure does not rise it is probable that the work of the heart increases because of the increase in cardiac output (54). In either case, the increase in cardiac work is probably responsible for part of the increase in coronary flow (13, 84, 86). Whether all or some of the drugs presented in this section also have a direct effect on the coronary bed, independently of the increase in cardiac work, will be discussed when data are available, as will also be the effect of such drugs on the ratio $\frac{\text{cardiac work}}{\text{coronary flow}}$ and on the mechanical efficiency of the heart.

Epinephrine. In all the recent work, several groups of workers have shown that in the whole dog, anesthetized or unanesthetized, epinephrine always increases the coronary flow. Essex, Wégria, Herrick and Mann (47) have found that in the unanesthetized dog, doses of 0.002 to 0.1 mgm. of epinephrine given intravenously to dogs weighing from 12 to 20 kg. increase the blood flow in the left and in the right coronary arteries. The effect lasts from 1 to 4 minutes and only occasionally longer. In anesthetized dogs, weighing from 15 to 35 kg., Wégria, Essex, Herrick and Mann (175) have observed that doses of 0.025 to 0.050 mgm. of epinephrine injected intravenously markedly increase the coronary flow in both the right and the left coronary arteries and raise the mean arterial blood pressure. The heart rate is decreased during the early stage of the action of the drug. Blood pressure, heart rate and coronary flow return to control levels simultaneously, generally in 2 to 3 minutes, although the effect

of the drug occasionally lasts longer. After reaching the control level, coronary flow and blood pressure occasionally fall and remain below the control level. Sometimes the blood pressure returns to, or falls below, the control value, while the blood flow in both coronary arteries is still increased. Green, Wégria and Boyer (74), using an orifice-meter in anesthetized dogs, have studied the effect of intravenous and intracoronary administration of commercial epinephrine solutions and of solutions of the pure drug. They have shown that the two types of preparation have essentially the same effect. The minimal intracoronary effective dose is 0.001 mgm. of epinephrine. Doses of epinephrine of 0.10 mgm. or less in dogs weighing an average of 15 kg. always increase coronary flow. The increase in coronary flow occurs simultaneously with the rise in blood pressure or a few seconds after signs of myocardial stimulation are present; with small doses of epinephrine given by the intracoronary route, there may be no increase in blood pressure but only an increase in the vigor of the myocardial contraction. Eckenhoff, Hafkenschiel and Landmesser (36), using the bubble flowmeter in anesthetized dogs weighing an average of 13 kg., have observed that the intracoronary injection of 0.00002 to 0.002 mgm. of commercial epinephrine increases the coronary flow. With the smaller doses, a definite increase in coronary flow occurs without any significant change in blood pressure or heart rate whereas higher doses increase both blood pressure and coronary flow. Doses of 0.050 to 0.5 mgm. of epinephrine given intravenously have an effect similar to that reported above (74, 175) and increase both blood pressure and coronary flow. The observations of Shipley and Kohlstaedt (150) have essentially confirmed the work previously mentioned. However, in their experiments, when small doses of epinephrine (0.0002 to 0.00002 mgm.) are injected into a coronary artery, first a definite increase in coronary flow occurs without any change in blood pressure or heart rate, and then the blood pressure rises and the coronary flow increases further.

It seems that there is little doubt that the effect of epinephrine in minimally effective as well as in larger doses is to increase the coronary flow in the whole dog, anesthetized and unanesthetized. When epinephrine raises the arterial blood pressure, the increase in arterial blood pressure undoubtedly accounts for at least some of the increase in coronary flow. It is also probable that the doses of epinephrine studied in the papers mentioned above increase cardiac output and work, as has been observed recently by Frank, Misrahy, Sioussat, Sommer, McCormack and Wégria (54), which would be another cause of the increase in coronary flow. Whether or not epinephrine, besides increasing coronary flow by increasing blood pressure, cardiac output and cardiac work, also induces a dilatation of the coronary bed by direct action has been a moot question for many years. In the experiments mentioned above, Wégria, Essex, Herrick and Mann (175) have calculated the changes in the resistance of the coronary bed produced by epinephrine from the formula, resistance $= \frac{\text{pressure}}{\text{flow}}$ and found that epinephrine decreases the resistance of the coronary bed. Whether such a simple approach to a complex problem is valid remains to be established.

However, Green, Wégria and Boyer (74) have arrived at the same conclusion by a more reliable approach. They have determined the ratio of the instantaneous rate of flow to the aortic pressure at the very end of diastole, a time of the cardiac cycle at which the extravascular support is more likely to be minimal and to remain constant under different hemodynamic conditions. This ratio, which they have called conductance, is markedly increased by the administration of epinephrine, especially when the drug is injected directly into a coronary artery. They have also shown that, during the rise of aortic blood pressure due to epinephrine, the ratio $\frac{\text{mean coronary flow}}{\text{mean aortic pressure}}$ is increased, the coronary flow increasing relatively more than the blood pressure, whereas an equal increase in aortic pressure produced by compression of the aorta decreases the ratio $\frac{\text{mean coronary flow}}{\text{mean aortic pressure}}$, the coronary flow rising relatively less than the aortic pressure. The rise in the ratio $\frac{\text{mean coronary flow}}{\text{mean aortic pressure}}$ is especially marked when epinephrine is injected directly into a coronary artery. Green, Wégria and Boyer (74) have concluded that epinephrine increases the coronary flow by increasing the blood pressure and possibly the cardiac output, but also that epinephrine decreases the resistance of the coronary bed. Because epinephrine increases the ratio $\frac{\text{flow}}{\text{pressure}}$ at the end of diastole, Green, Wégria and Boyer (74) have thought it legitimate to conclude that the decrease in the resistance of the coronary bed is due to dilatation of the coronary bed and not to a decrease in the magnitude of the extravascular support; this conclusion, it must be said, is probably correct but far from definitely proven. Eckenhoff, Hafkenschiel and Landmesser (36) have also reached the conclusion that epinephrine dilates the coronary bed since small intracoronary doses increase the coronary flow without affecting heart rate or arterial blood pressure. In their experiments, however, they did not rule out the possibility of changes in the magnitude of the extravascular support as a cause of the decrease in the resistance of the coronary bed; this possibility, it is granted, is unlikely. Shipley and Kohlstaedt (150) have confirmed the findings of Eckenhoff, Hafkenschiel and Landmesser (36).

As can be seen, the several groups of workers who have been interested in the effect of epinephrine on the coronary circulation are agreed that part of the effect of epinephrine on the coronary circulation is to decrease the resistance of the coronary bed, probably by producing dilatation of the coronary bed. The mechanism of this vasodilatation is more difficult to determine. It is agreed that when epinephrine is given in doses that increase the cardiac work by raising the blood pressure and/or increasing the cardiac output, coronary vasodilatation is probably due at least in part to the increase in cardiac load and metabolism, as has been discussed previously. However, since small doses of epinephrine injected directly into the coronary artery increase the coronary flow without modifying the blood pressure (36, 150), it seems possible that epinephrine pro-

duces vasodilatation by acting directly on adrenergic receptors of smooth muscle cells in the wall of the coronary vessels. Green, Wégria and Boyer (74), however, never observed an increase in the coronary flow after the intracoronary administration of epinephrine which occurred before the rise in blood pressure or the increase in vigor of the ventricular contraction. On the contrary, the increase in flow begins several seconds after the first manifestations of myocardial stimulation, and since the above authors were recording phasic changes in coronary flow they were in a better position than the other groups (36, 150) to detect early manifestations of cardiac stimulation. Therefore it is felt that, if epinephrine dilates the coronary bed by a direct action on the coronary vessels, it has not been demonstrated in the work that has just been reviewed.

The amount of research on the effect of epinephrine on the coronary circulation is tremendous and reference will be made only to those investigations which add something new to what has already been said about epinephrine from experiments performed on the whole animal with modern technics. Space does not permit mention of those studies performed with old technics or in highly artificial preparations, except those that throw some additional light on the mechanism of action of the drug.* An elegant attempt to determine whether epinephrine has a direct vasodilating effect on the coronary bed has been made by Katz, Lindner, Weinstein, Abramson and Jochim (108) who have studied the effect of epinephrine in cats and dogs by perfusing the coronary bed of the isolated heart in ventricular fibrillation under constant pressure with defibrinated blood. This preparation has been discussed in the section on methods. In the cat heart, epinephrine decreased the coronary flow in four experiments and increased it in eight experiments. In the dog heart, epinephrine either increased the coronary flow or increased it after having decreased it momentarily. No correlation was found between dose or concentration of the drug on the one hand and the nature and magnitude of the response on the other hand. This work is of great interest because it brings out the fact that different species may possibly react differently to the same drug. Other workers (92, 125) have concluded from their experiments that epinephrine dilates the coronary bed, probably by a direct action on the blood vessels.

In short, epinephrine increases the coronary flow in the whole animal. This increase in flow is due to an increase in cardiac load produced by an increase in cardiac output and/or a rise in blood pressure, which leads to a decrease in the resistance of the coronary bed, probably due to coronary vasodilatation. Epinephrine also seems to dilate the coronary vessels by acting directly on the coronary wall, although in certain species epinephrine may produce constriction of the coronary bed. There is little information available on the effect of epinephrine on the ratio $\frac{\text{coronary flow}}{\text{cardiac work}}$ and on the efficiency of the heart. In the denervated heart-lung preparation, epinephrine increases coronary flow and oxygen consumption of the heart but decreases efficiency of the heart. There is a short initial period during which the work of the heart is increased and the

* For supplementary bibliography, see references 70, 74, 102, 108, 140, 151 and 175.

oxygen consumption is unchanged, which indicates an increase in the efficiency of the heart (67). In the innervated heart-lung preparation and in the whole animal (68), the reflex effects of epinephrine may counterbalance or even offset the direct effects of epinephrine on the myocardium and the coronary circulation.

It is pertinent to mention that Levine, Ernstene and Jacobson (119) have been able to induce anginal pain in patients with coronary sclerosis by the subcutaneous injection of epinephrine. Unless it is postulated that epinephrine induces a constriction of the coronary artery, it must be accepted that at least in persons with coronary sclerosis the drug decreases the efficiency of the heart and/or increases the work and the metabolism of the heart more than the coronary flow. If this view is correct, it does not follow that epinephrine has the same effect in normal individuals in whom the coronary vessels may be able to accommodate an amount of coronary flow commensurate with the increase in cardiac work and metabolism.

Nor-epinephrine. Recently, Wégria, Ward, Frank, Dreyfuss, Brown and Hutchinson (183) have studied the effect of *l*-nor-epinephrine on arterial blood pressure and coronary blood flow in the anesthetized dog and found that nor-epinephrine is essentially similar in its action to epinephrine, although no systematic comparative study was carried out. Given intravenously in doses of 0.002 mgm. to 0.030 mgm. per kg., it increases coronary flow and arterial blood pressure. Its effect lasts from 2 to 6 minutes. No attempt was made to calculate the changes in the resistance of the coronary bed during the period of action of the drug and it is not known whether the increase in coronary flow is entirely due to the increase in the aortic pressure or whether the drug also modifies the resistance of the coronary bed. During that part of the period of action of the drug when either blood pressure or coronary flow has returned to the control level, no consistent effect on the coronary resistance is observed. The effect of the drug is the same in dogs in good condition and in dogs whose circulatory condition has deteriorated, as judged by the level of their blood pressure.

Ephedrine. Stoland and Ginsberg (159) have observed that the intravenous injection of 2.5 to 10 mgm. of ephedrine in dogs weighing between 8 and 13 kg. increases the arterial blood pressure and the coronary sinus outflow. The maximal increase in coronary flow occurs after the blood pressure has returned to control level. Some increase in flow sometimes persists for 30 to 90 minutes or longer. Obviously the increase in the coronary flow cannot all be explained by an increase in the aortic pressure, since in the experiments described above there is a time when the coronary flow is still increased but the blood pressure has returned to or even fallen below the control level. It cannot be stated whether this obvious decrease in the resistance of the coronary bed is due to a direct effect of the drug on coronary vessels, to an increase in the work of the heart, the cardiac output being still increased when the blood pressure is back to the control level, or to the lasting effect of a relative myocardial ischemia that develops during the hypertensive stage of the action of the drug. Leyko (121) has reported that ephedrine and ephetonine increase the coronary sinus outflow

in the dog heart-lung preparation in which arterial blood pressure and cardiac output are constant. Since in Leyko's experiments the volume of the heart decreased with ephedrine and ephetonine, it would seem that these drugs increase the coronary flow not by decreasing the extravascular support but by dilating the coronary bed by acting directly on the blood vessel walls. Narayana (134) has essentially confirmed Leyko's findings.

Paredrine. Paredrine hydrobromide and paredrinol sulfate have been studied by Elek and Katz (39) and found to have the same action. Using the perfusion of the dog heart in ventricular fibrillation under constant pressure as previously described (108), Elek and Katz have observed that doses of 0.5 to 1.5 mgm. of paredrine have no effect but that doses of 2 mgm. of paredrine cause a prompt and marked increase of the coronary flow lasting from one-half to one hour. The increase in coronary flow was interpreted as due to coronary dilatation. It is probable that the effect of this drug on the coronary flow of the whole animal is qualitatively similar to that of epinephrine and ephedrine, although to our knowledge the effect of this drug on the coronary flow of the whole animal has not been investigated.

Nicotine. Kountz (114) has studied the effect of nicotine on the coronary flow of the revived human heart, perfused under constant pressure according to the Langendorff method, and found that nicotine decreases the coronary flow and increases the rate and the amplitude of contraction of the ventricles. It also either constricts rings of human coronary arteries or has no effect on them (114). However, in the whole animal nicotine increases blood pressure and coronary flow, its effect being very similar to that of epinephrine (174).

To summarize our knowledge of the vasopressor drugs, it can be said that a great deal is known about epinephrine, much less about nor-epinephrine, ephedrine, paredrine and nicotine. About other similar drugs, nothing at all is known as to their effects on the coronary circulation. Studies of their effect simultaneously on blood pressure, coronary flow and cardiac output, work, metabolism and efficiency are needed. From what is known, it seems that all the drugs considered above have qualitatively a similar type of effect.

Vasodepressor drugs

In this section will be reviewed those drugs that are conspicuous for being vasodilator and, if given in sufficient dose, hypotensive. A few preliminary considerations that apply to the group as a whole will ultimately save time and space.

All these drugs have in common the capacity to increase the coronary flow even when a dose large enough to decrease the blood pressure, within reason, has been given. The "within reason" cannot be expressed precisely, may vary with different drugs and seems to depend on factors such as the type of anesthesia, as has been pointed out previously, and the condition of the animal. These drugs differ in intensity and duration of action and it is always hazardous to make any statement about the former when the animals on which the drugs are tested have been subjected to anesthetics and extensive operative procedures.

These drugs may also differ in the mechanisms by which they produce systemic vasodilatation and in the fact that some have a direct effect on the myocardium and others do not. As has been said, all these drugs increase the coronary flow in the whole animal unless the decrease of blood pressure is too marked. The increase in the coronary flow is due to a decrease in the resistance of the coronary bed. With the data available, it is often difficult to ascertain whether the decrease in the resistance of the coronary bed is due to vasodilatation or to a decrease in the magnitude of the extravascular support. It is equally difficult to determine whether the dilatation of the coronary bed, if such is proven, is due to a direct effect of the drug on the coronary vessel wall or whether it is caused by an indirect effect of the drug on the coronary bed via an effect of the drug on cardiac output, work and metabolism; in turn this effect on cardiac output, work and metabolism may be the result of a direct action on the myocardium or an indirect result of the hypotensive action (23, 181). It must also be remembered that hypotension *per se* reflexly affects the coronary circulation (13, 158) by way of the carotid sinus. Thus it is obvious that the simultaneous effects of each of these drugs on blood pressure, coronary flow, and cardiac output, work, metabolism and efficiency should be studied.

Papaverine. Papaverine increases the coronary flow of the unanesthetized (47) and anesthetized (175) dog. Doses of 15–20 mgm. given intravenously to dogs weighing from 12 to 15 kg. decrease blood pressure and increase heart rate and coronary flow. These observations have been confirmed by Eckenhoff and Hafkenschiel (33). The increase in coronary flow is marked and lasts from 2 to 5 minutes. Lindner and Katz (122) have observed an increase in the coronary flow following papaverine in the perfused dog heart in ventricular fibrillation. It remains for future investigation to determine how much of the increase in the coronary flow in the whole animal is due to the direct effect of papaverine on the coronary bed and how much is due to other factors, especially a possible increase in the work and the metabolism of the heart. It is of interest that Russek, Smith, Baum, Naegele and Regan (145) have reported that, in a patient with coronary sclerosis, papaverine given intravenously or orally can prevent to a great extent the anginal pain and the electrocardiographic changes pathognomonic of myocardial anoxia induced by a standard exercise tolerance test.

Nitrites. In the unanesthetized dog amyl nitrite and nitroglycerin increase the coronary flow (41, 47). The intravenous administration of 0.22 mgm. to 1.3 mgm. of nitroglycerin to dogs weighing around 15 kg. or the inhalation of amyl nitrite increases the coronary flow for 1 to 3 minutes. When similar doses of nitroglycerin are given by mouth, the increase in flow persists for longer than 16 minutes (47). In the anesthetized dog, Boyer and Green (20) have showed with the orifice-meter that the intracoronary or intravenous injection of nitroglycerin or sodium nitrite lowers blood pressure and increases coronary flow and heart rate; they conclude that nitroglycerin and sodium nitrite decrease the resistance of the coronary bed by inducing directly a dilatation of the coronary vessels. Whether changes in cardiac work also play a rôle cannot be

determined in their experiments. In the anesthetized dog, Wégria, Essex, Herrick and Mann (175) have observed that amyl nitrite by inhalation increases the coronary flow in both right and circumflex coronary arteries, increases the heart rate and lowers the mean arterial blood pressure; the increase in flow lasts 1 to 6 minutes. The intravenous injection of nitroglycerin has essentially the same effects. Eckenhoff and Hafkenschiel (33), using a bubble flowmeter in anesthetized dogs, have showed that the smallest effective dose of nitroglycerin (0.002 to 0.02 mgm.) given by intracoronary injection increases the coronary flow as long as the mean arterial blood pressure does not fall too much. A larger dose, 0.2 mgm., increases the coronary flow until the drug reaches the systemic circulation at which time, if the arterial blood pressure falls markedly, the coronary flow decreases. Essentially similar effects result from the intramuscular, intravenous, subcutaneous and sublingual administration of the drug. Amyl nitrite (33) also lowers arterial blood pressure and increases heart rate and coronary flow. Katz, Lindner, Weinstein, Abramson and Jochim (108) have shown that sodium nitrite and nitroglycerin dilate the coronary vessels of the perfused isolated dog heart in ventricular fibrillation. Bodo (18) has observed in the dog heart-lung preparation that both amyl nitrite and sodium nitrite increase coronary flow while arterial blood pressure and cardiac output remain constant; but, whereas amyl nitrite does not modify the size of the heart, sodium nitrite, at least in large doses, causes the heart to dilate. Bodo's experiments show, of course, that the nitrites can decrease the resistance of the coronary bed by dilating the coronary vessels directly, but it is difficult in experiments in which the heart size is altered to draw any definite conclusion as to the rôle played by the probable changes in the magnitude of the extravascular support. It is of interest that Levy, Bruenn and Williams (120) have showed that, in patients with coronary sclerosis, nitroglycerin delays the appearance of the anginal pain and diminishes the intensity of the electrocardiographic signs pathognomonic of the cardiac anoxia induced by an anoxemia test. This has been confirmed in one patient by Russek, Smith, Baum, Naegele and Regan (145) by the use of a standard exercise tolerance test.

Nucleic acid derivatives. Drury and Szent-Györgyi (32) have shown that the coronary sinus outflow in a dog heart-lung preparation is increased by adenosine and adenylic acid, a finding which has been confirmed by Wedd (167) on the perfused rabbit heart. Wedd and Drury (169), measuring the coronary sinus outflow with a Morawitz-Zahn cannula in the anesthetized dog, have shown that adenosine, muscle and yeast adenylic acid and yeast cytidylic acid given intravenously increase the coronary flow while the arterial blood pressure is unchanged or lowered; the increase in flow lasts about 3 minutes. Essex, Wégria, Herrick and Mann (47) have observed an increase in the coronary flow of the unanesthetized dog given muscle adenosine phosphoric acid. Recently Eckstein, Chambliss, Demming and Wells (38) have reported that a product liberated in the mechanical destruction of red cells, probably ADP or ATP, is a potent coronary dilator.

Histamine. Doses of 0.1 to 0.5 mgm. histamine acid phosphate given intra-

venously to unanesthetized dogs weighing around 20 kg. increase the coronary flow (47) for 2 to 3 minutes. In the anesthetized dog (175), the same effect is observed. The curves of the effects of histamine on blood pressure, heart rate and coronary flow are essentially the same as those of papaverine and nitroglycerin. Katz, Lindner, Weinstein, Abramson and Jochim (108) have shown that histamine dilates the coronary vessels of the perfused fibrillating dog ventricles. The effect of histamine on other preparations is generally to increase the coronary flow but it is sometimes difficult from these preparations to derive any new information as to the mechanisms of action of the drug in the whole animal. For example, histamine increases the coronary flow in the revived beating human heart probably by dilating the coronary bed; but, in the revived human heart arrested by perfusion with solutions of high pH, histamine has a variable effect, and when the heart has been arrested by perfusion with solutions of low pH histamine has no effect or increases the coronary flow slightly (116). Narayana (134) has shown conclusively that histamine increases the coronary flow in the dog heart-lung preparation. As suggested by Gunn (91), there may be a species difference in the response of the coronary vessels to histamine as he has observed that histamine increases the coronary outflow of the perfused cat heart but decreases it in the rabbit heart, the effect on flow in either case being probably due mainly to a direct effect of the drug on the coronary bed.

Procaine. Wégria, Ward, Frank, Dreyfuss, Brown and Hutchinson (183) have recently shown that the intravenous administration of 1 to 10 mgm. of procaine hydrochloride per kg. to anesthetized dogs has essentially the effect of the hypotensive drugs; it produces an immediate and temporary decrease in blood pressure and coronary flow, after which both increase. The coronary flow comes back to the control level and in most cases rises above it, at which time the blood pressure is still below or at the control level. The transient decrease in coronary flow and blood pressure may be absent. During most of its period of action, procaine obviously decreases the resistance of the coronary bed. The effect of the drug lasts from 2 or 3 minutes to more than 23 minutes. Eckenhoff, Hafkenschiel, Foltz and Driver (34) have observed that in the anesthetized dog the subdural administration of a dose of procaine sufficient to lower the arterial blood pressure and reduce the cardiac output and work, decreases the coronary flow, the cardiac oxygen consumption and the efficiency of the heart.

Khellin. The effect of khellin on the coronary circulation has recently aroused a great deal of interest. Anrep, Barsoum, Kenawy and Misrahy (3) were the first to study the effect of khellin on the coronary circulation experimentally and clinically. They have shown that in the dog heart-lung preparation 10 mgm. of khellin increases the coronary sinus outflow very markedly and this increase remains maximal for over 3 hours. Concentrations of khellin as low as 1:2,000,000 are effective. Since the size of the heart does not change, it seems likely that khellin increases the coronary flow in the denervated heart-lung preparation by dilating the coronary vessels. In the anesthetized dog, rapid intra-

venous injections of 20 to 30 mgm. of khellin lower the heart rate and the blood pressure for 1 or 2 minutes, but slow intravenous injections of khellin at the rate of 2 mgm. per 30 seconds can be continued for a long time without such effects. In the whole anesthetized dog, 1 mgm. per kg. of khellin does not lower the blood pressure but increases the coronary flow markedly for more than one hour. It is probable that in the whole animal, other mechanisms than the direct effect of the drug on the coronary vessels play a rôle. Such mechanisms have been mentioned in the introduction to the discussion of the vasodepressor drugs. Killam and Fellows (112), Fellows, Killam, Toner, Dailey and Macko (50) and Wégria, Ward, Dreyfuss, Brown and Hutchinson (183) have essentially confirmed these observations on the anesthetized dog. Khellin has also been reported to prevent and to relieve the anginal pain and to prevent the appearance of pain and electrocardiographic changes induced by exercise in a standard exercise tolerance test (3, 10, 30, 143). Recently much less favorable results have been reported by one group of investigators (89).

Tetraethylammonium. In the anesthetized dog, it has been shown with the rotameter that 0.125 to 2.0 mgm. doses of tetraethylammonium chloride per kg. given intravenously decrease blood pressure, coronary flow and heart rate (183). During the period of recovery, a decrease in the resistance of the coronary bed is seen in some experiments and an increase in others. Eckenhoff, Hafkenschiel, Foltz and Driver (34) have observed that the intravenous injection of 2 or 4 mgm. of tetraethylammonium chloride per kg. in dogs lowers arterial blood pressure and decreases coronary flow as well as cardiac output, work, oxygen consumption and efficiency.

Xanthines. Essex, Wégria, Herrick and Mann (47), using the thermostromuhr in the unanesthetized dog, have shown that the intravenous administration of 120 to 480 mgm. of theophylline ethylenediamine (aminophylline) to dogs weighing from 7.5 to 20 kg. increases the coronary flow for 2 to 24 minutes or longer. Wégria, Essex, Herrick and Mann (175) have observed that doses of 240 to 480 mgm. of aminophylline given intravenously to dogs weighing 18 to 35 kg. and anesthetized with chloralosane increase the heart rate, lower the blood pressure and increase the coronary flow in both right and circumflex coronary arteries. In some cases, the flow is still increased after 28 minutes. In short, the effect of these doses of aminophylline on heart rate, coronary flow and arterial blood pressure is essentially similar to that of other vasodepressor drugs. The effect of aminophylline generally lasts longer than that of the other vasodepressor drugs discussed above, except khellin. Since in these experiments the coronary flow is increased while the arterial blood pressure is lowered or unchanged, aminophylline increases the coronary flow by decreasing the resistance of the coronary bed. Green (70) and Boyer and Green (20), studying the effect of the intracoronary and intravenous administration of theophylline, theobromine, aminophylline and theophylline monoethanolamine (theamine), have confirmed that the xanthines increase the coronary flow by decreasing the resistance of the coronary bed, this decrease probably being brought about by dilatation of the coronary bed. However, Boyer and Green (20) mention

that the tracing of the coronary flow recorded with an orifice-meter affords evidence of a stimulating effect of the xanthines on the myocardium; whether the dilatation of the coronary bed is due to the effect of changes in the work of the heart on the coronary bed or to a direct effect of the drug on the coronary vessels or both remains to be determined. Eckenhoff and Hafkenschiel (33) have observed with the bubble flowmeter that in the anesthetized dog the intracoronary injection of 1 mgm. of aminophylline increases the coronary flow and raises the arterial blood pressure slightly. The intravenous administration of 60 to 120 mgm. of aminophylline has the same effect as that reported above (175); it lowers the arterial blood pressure and increases coronary flow and heart rate. Essentially similar results have been observed by Stoland, Ginsberg, Loy and Hiebert (161) who measured the effect of aminophylline on the coronary sinus outflow in the dog denervated heart-lung preparation and in the anesthetized dog. Gilbert and Fenn (55), measuring the coronary sinus outflow with a Morawitz-Zahn cannula, have confirmed that the xanthines, given intravenously in doses similar to those used in humans, increase the coronary flow. Recently Foltz, Rubin, Steiger and Gazes (52) have studied the effect of the intravenous administration of 4 mgm. of aminophylline per kg. on the coronary circulation of anesthetized dogs. Since the method used to determine the coronary flow was the nitrous oxide method, a period of 30 minutes has to be allowed between the control determinations and the measurements after administration of the drug. This period of 30 minutes allows the animal to eliminate the nitrous oxide inhaled during the first determination. The second set of determinations is obtained after the blood pressure has stabilized following the injection of aminophylline. Because control experiments of similar duration, during which no aminophylline is injected, show a great deal of spontaneous variation in the different cardiac functions measured, it is difficult to assess the effect of aminophylline from this work, as the authors themselves point out. It seems, however, that under the experimental conditions mentioned, aminophylline increased the heart rate, the cardiac output and the work of the heart; the arterial blood pressure was unchanged or lowered at the time of the measurement; the changes in coronary flow and cardiac oxygen consumption were of no statistical significance; the coronary oxygen arteriovenous difference was increased in two experiments and essentially unchanged in the other two. Realizing the shortcomings of this work, Foltz, Rubin, Steiger and Gazes (52) have followed the effect of the doses of aminophylline used in the work mentioned above, on the coronary oxygen arteriovenous difference in experiments of shorter duration without measuring the coronary flow. They have demonstrated that aminophylline consistently decreases the oxygen content of the coronary sinus venous blood and increases the coronary oxygen arteriovenous difference at the peak of the effect of the drug, which is of interest but difficult to interpret decisively without concomitant measurement of the coronary flow. These latter results also cast doubt on the validity of the first part of the work in which two out of four experiments failed to show this increase in the coronary oxygen arteriovenous difference.

Numerous papers deal with the effect of the xanthines on the perfused isolated heart of different species and all authors are agreed that the xanthines increase the coronary flow in such preparations. However, in general, little decisive information about the mechanism of action of the xanthines is gained from such experiments. Heathcote (95) has found that caffeine, theophylline and theobromine, in order of increasing potency, all augment the coronary flow in the perfused rabbit heart. Smith, Miller and Graber (152) have shown in the perfused rabbit heart that caffeine-sodium benzoate and theobromine sodium salicylate in 1:25,000 concentration have little or no effect on the coronary flow, whereas theophylline and aminophylline in similar concentration increase the coronary flow probably by dilating the coronary bed. Kountz (114) has observed that caffeine-sodium benzoate increases the rate and the strength of the ventricular contraction as well as the coronary flow in revived human hearts perfused by the Langendorff method. Kountz and Smith (115) have also found that the xanthines increase the coronary flow in the revived human heart, dilated as well as not dilated, in which the coronary bed is perfused under constant pressure. Lindner and Katz (122), using the perfused dog heart in ventricular fibrillation, have shown that aminophylline and caffeine-sodium benzoate dilate the coronary vessels, caffeine being less effective than aminophylline with respect to duration and intensity of effect. The concensus therefore seems to be that the xanthines increase the coronary flow in the whole animal by dilating the coronary bed through a direct action on the coronary vessels but other mechanisms mentioned in the discussion of the vasodepressor drugs also play a part. A study of the effect of the xanthines simultaneously on coronary flow and cardiac output, work and efficiency is highly desirable.

Gold, Kwit and Otto (63) have concluded from careful clinical observations that theobromine and aminophylline, given orally for one to 25 weeks, influence neither the capacity for work nor the frequency or the severity of attacks of angina. This has been confirmed by Boyer (19) who, in a review of the subject, concludes that clinical evaluation of the usefulness of the xanthines in the treatment of coronary artery disease is far from satisfactory and that it seems wise to place the burden of proof on those who claim therapeutic efficacy for the xanthines in anginal pain due to coronary sclerosis. Fowler, Hurevitz and Smith (53) have reported that aminophylline promotes the development of the collateral circulation in experimentally induced cardiac infarction in the dog. Unfortunately neither Wiggers and Green (188) nor Gold, Travell and Modell (65) have been able to confirm these findings. It must be remembered, however, that Levy, Bruenn and Williams (120) have reported that, in patients suffering from angina due to coronary sclerosis, aminophylline in doses of 0.48 gram given intravenously causes a prolongation of 63 per cent in the time of appearance of pain and decreases the electrocardiographic manifestations of cardiac anoxia in anoxemia tests. Aminophylline taken orally has the same effect but it is less marked. It may well be that in attempts to evaluate the clinical usefulness of the xanthines the importance of the level of the drug in the blood has been neglected (165).

Acetylcholine, acetyl-beta-methylcholine (methacholine), carbamylcholine (carbachol). Essex, Wégria, Herrick and Mann (47), using the thermostromuhr on the unanesthetized dog, have observed that 0.2 mgm. of methacholine given intravenously to a 13 kg. dog increased the coronary flow for 3 minutes. In the anesthetized dog (175) similar doses first increase and then decrease the flow in both the circumflex and the right coronary arteries, but after about 30 seconds the flow increases and remains elevated for 4 minutes or longer. The heart rate is increased throughout the period of action and the blood pressure falls very markedly, reaching a minimum within one minute after the injection; it then rises progressively toward the control level. Eckenhoff, Hafkenschiel and Landmesser (36), using the bubble-flowmeter in the anesthetized dog, have reported that 0.02 to 2.0 micrograms injected into a coronary artery produce an immediate and marked acceleration of flow lasting 1 to 3 minutes, without necessarily inducing any change in blood pressure or heart rate. Larger doses usually elicit a considerable increase in flow followed by a transitory asystole and decrease in flow. After atropine, acetylcholine is without effect. When given intravenously into the systemic circulation, acetylcholine always produces hypotension and a decrease in coronary flow. Anrep (2) reports that acetylcholine in small and large doses always increases the coronary flow in the dog heart-lung preparation as well as in the whole animal, and the effect is not abolished by atropine. Narayana (134) has confirmed that acetylcholine in doses of 6 mgm. increases the coronary flow in the dog heart-lung preparation. Katz, Lindner, Weinstein, Abramson and Jochim (108) have studied the effect of acetylcholine and methacholine on the coronary flow of the perfused isolated dog and cat heart in ventricular fibrillation. In the cat, concentrations of acetylcholine stronger than 1:820,000 cause vasoconstriction only, but with weaker concentrations vasoconstriction or vasodilatation or a diphasic reaction results. Methacholine to be effective has to reach a concentration stronger than 1:250,000 and then produces constriction. In the dog, acetylcholine and methacholine produce coronary dilatation only. Whatever the effect of the two drugs, it lasts from 2 to 4 minutes. Atropine abolishes or diminishes the effect of both drugs in the cat and the dog. Wedd (168) has studied the effect of acetylcholine, methacholine and carbachol on the coronary sinus outflow in the perfused beating heart of cats and rabbits as well as in the whole anesthetized dog, measured with a Morawitz-Zahn cannula. The results observed seem to be qualitatively the same with the three drugs but are quite variable in different experiments, even in the same species. However, the first intravenous injection of any one of the three drugs in the dog induces an increase in the coronary sinus outflow despite a decrease in arterial blood pressure, which confirms most of the previous work.

It is obvious that the effect of the choline derivatives on the coronary circulation deserves further study. At the present time it seems to be the consensus that during most of their period of action the choline derivatives increase the coronary flow in the whole dog unless the arterial blood pressure decreases too markedly. It seems that, at least in the dog, part of this increase in coronary

flow may be due to a direct effect of the drugs on the coronary vessels. The rôle played in increasing the coronary flow by the effect of the drugs on cardiac output and work (170) remains to be determined.

MISCELLANEOUS DRUGS

In this section will be presented the drugs which do not conspicuously raise or lower the arterial blood pressure. Some of these drugs, however, have a definite effect on the blood pressure, but they are classified as miscellaneous drugs and not as vasodepressor or vasodepressor agents because of other pharmacological actions which set them aside from the drugs previously discussed.

Thyroxin. Essex, Herrick, Baldes and Mann (41) using the thermostromuhr have shown that 1 mgm. of thyroxin per kg. given intravenously increases the coronary flow of the unanesthetized dog within 48 hours. A maximal increase is reached within 48 to 96 hours, then the coronary flow decreases progressivelye Bing and his coworkers (16) have studied one patient with hyperthyroidism. and slight anemia and found that cardiac output, work of the left ventricle and coronary flow per 100 grams of left ventricle were definitely higher than in a group of normal human beings.

Angiotonin and renin. Hill and Andrus (98) have shown that renin does not alter the coronary flow but that angiotonin decreases it in the isolated cat heart perfused with Ringer-Locke solution by the Langendorff method. The decrease caused by angiotonin is frequently followed by a slight rise. The decrease in flow is probably not due to a change in amplitude of ventricular contraction since the decrease in flow is also observed when the ventricles are kept fibrillating. Lorber (123) has observed in the isolated cat and dog heart that angiotonin produces a decrease in coronary flow accompanied by a decrease in diastolic size of the heart and an increase in oxygen consumption, work and efficiency of the heart. Because of the decrease in diastolic size of the heart, it is impossible to be certain that the decrease in coronary flow might not have been caused at least partly by an increase in extravascular support. Elek and Katz (39) have observed that renin and angiotonin have variable effects on the coronary flow of the perfused dog heart in ventricular fibrillation; both renin and angiotonin decrease coronary flow in some preparations, increase it in others and sometimes are without effect, although both more often increase coronary flow.

Pentobarbital. Using the thermostromuhr, Essex, Wégria, Herrick and Mann (47) have shown in one experiment that the intravenous administration of 300 mgm. of pentobarbital sodium to a 19.5 kg. unanesthetized dog increased the coronary flow markedly. The flow was still definitely above the control value 82 minutes after administration of the drug.

Glucose. Ginsberg, Stoland and Loy (60) studied the effect of dextrose, given as a 50 per cent solution, on the coronary circulation. Using a modified Morawitz-Zahn cannula to measure coronary sinus outflow in the whole dog, they found that 5 grams of glucose injected in 2 minutes increased the coronary flow; the maximal increase occurred within 2 to 41 minutes and some increase persisted for 40 minutes or longer; the arterial blood pressure rose slightly but occasionally it decreased. When a second injection was given, it produced as great an increase

in coronary flow or a greater increase than the first injection. The injection of 10 grams produced a greater increase than 5 grams. Similar amounts of glucose had no effect, slightly increased or slightly decreased the coronary flow of the denervated and innervated dog heart-lung preparation in which cardiac output and arterial pressure were presumably kept constant. The slight and very transitory decrease in the viscosity of the blood produced by the injection of the solution of glucose in the whole animal does not account for the marked and prolonged increase in coronary flow. It seems probable that the increase in output, work and metabolism of the heart due to the increase in the blood volume of the whole animal is responsible for the increased coronary flow. However, it must be added that in the whole animal a hypertonic solution of glucose increases the coronary flow more than does an equally hypertonic solution of sodium chloride. Ginsberg, Stoland and Loy (60) conclude that dextrose has no direct effect on the coronary circulation and that the main factor responsible for the increase of the coronary flow in the whole animal is an increase in blood volume and cardiac output, work and metabolism. Lindner and Katz (122) have shown in the perfused dog heart in ventricular fibrillation that dextrose in concentrations of 2 to 27 per cent dilates the coronary vessels although perfusion with large volumes of more concentrated solutions can stop the coronary flow.

Insulin. Smith has reviewed the effect of insulin and hypoglycemia on the heart (151). From a study of the effect of hypoglycemia and hyperinsulinemia upon the electrocardiogram of dogs, Soskin, Katz and Frisch (154) believe that insulin has a dual deleterious effect on the heart, one induced by hypoglycemia and another not antidoted by correcting or preventing the hypoglycemia. In an attempt to find out if insulin might possibly have a direct effect on the coronary vessels, Elek and Katz (39) have studied its effect on the coronary bed of the perfused dog heart in ventricular fibrillation and observed that it produces a marked coronary dilatation. They concluded that the deleterious effect of insulin must be due to its direct action on the myocardium. It must be added that besides the likely direct effect of insulin on the myocardium, insulin also increases the work of the heart when it induces hypoglycemia (40). Bodo (18), on the other hand, has observed that in the dog denervated heart-lung preparation insulin in small doses (5 units) has little or no effect on the coronary flow and in doses of 10 units always decreases coronary flow, the blood pressure, cardiac output and work remaining constant. However, since the volume of the heart decreases, it may well be that the decrease in flow is due to an increase in magnitude of extravascular support.

Camphor. Bodo (18), measuring coronary sinus outflow in the dog heart-lung preparation, has reported that camphor increases coronary flow slightly; since the heart increases in size, although the cardiac work remains constant, it may well be that this increase in coronary flow is not due to coronary dilatation but to a decrease in extravascular support. Kountz (114) has confirmed Bodo's findings on the effect of the drug on coronary flow in the revived human heart perfused by the Langendorff technic.

Pentamethylenetetrazol (pentylenetetrazol, metrazol). Stoland and Ginsberg (160),

measuring the sinus outflow with a Morawitz-Zahn cannula in the dog denervated heart-lung preparation and in the anesthetized dog, have found that in the heart-lung preparation 90 to 180 mgm. of metrazol increase the coronary flow but a rise in blood pressure which sometimes occurs may be responsible. However, in some experiments, the coronary flow rises whereas the blood pressure falls. It seems, therefore, that metrazol increases the coronary flow at least partly by decreasing the resistance of the coronary bed. In the whole animal, doses of 20 to 90 mgm. have practically no effect on either blood pressure or coronary flow. In contrast to Stoland and Ginsberg's results, Leyko (121) has reported that metrazol does not affect the coronary circulation in the dog heart-lung preparation over a wide range of doses. Lindner and Katz (122) have shown that doses of 100 mgm. of metrazol increase coronary flow in the perfused dog heart in ventricular fibrillation. The increase in flow is slight and lasts about 2 minutes.

N–N-Diethyl-3-pyridinecarboxamide (*coramine, nikethamide*). Stoland and Ginsberg (160) have observed that in the dog denervated heart-lung preparation 250 mgm. of nikethamide produce a marked increase in coronary flow even when a temporary fall in blood pressure occurs; doses of 50 mgm. produce a slight and temporary increase in flow. Since no mention is made of changes in the size of the heart, even if an unchanged cardiac output is presumed it is impossible to rule out changes in the extravascular support as a possible cause of the increase in coronary flow. The same authors have found that in the whole anesthetized dog 250 mgm. is the smallest dose that will change coronary sinus outflow. In dogs weighing between 8 and 15 kg., 250 to 500 mgm. of nikethamide given intravenously increase coronary flow markedly even when the fall in arterial blood pressure is not artificially compensated. Wégria, Essex, Herrick and Mann (175) have observed that intravenous administration of 250 to 500 mgm. of nikethamide to anesthetized dogs weighing around 20 kg. increases blood pressure and coronary flow after an initial and very brief decrease in blood pressure and coronary flow. The increase in coronary flow generally lasts longer than the rise in blood pressure. In some experiments, the coronary flow increases while the blood pressure remains unchanged. The increase in flow lasts from 2 to 14 minutes. Greene (77) has reported that 625 mgm. of nikethamide given intravenously to a dog weighing 11 kg. increased the coronary flow very markedly although the arterial blood pressure decreased. Similar effects of nikethamide on coronary flow have been observed in the unanesthetized dog (47). Eckenhoff and Hafkenschiel (33) have recently studied the effect of nikethamide on the coronary circulation of the anesthetized dog with the bubble flowmeter. They have observed that 5 mgm. injected into a coronary artery increased the coronary flow; the arterial blood pressure remained unchanged and the heart rate was increased. The intravenous administration of 125 to 750 mgm. of the drug did not produce any consistent change in coronary flow or any great change in heart rate or arterial blood pressure. It seems, however, from the average of the data of all the experiments, that the coronary flow generally increases slightly, the arterial blood pressure decreases slightly and

the heart rate remains unchanged. In four experiments in which the same authors gave 70 mgm. of nikethamide per kg. intravenously to anesthetized dogs, it was observed that such a dose of coramine increases coronary flow, heart rate and cardiac output and work as well as oxygen consumption of the left ventricle; the arterial blood pressure was lowered and the mechanical efficiency of the left ventricle decreased. Leyko (121) has observed that concentrations of the drug up to 1:50,000 do not affect the heart in the dog heart-lung preparation. With concentrations of 1:10,000 to 1:25,000, the size of the ventricles and the coronary flow increase. Obviously the mechanism responsible for the increase in coronary flow cannot be decided since it is not known whether the increase in coronary flow is due to coronary dilatation or to a decrease in extravascular support. Finally, it must be added that Elek and Katz (39) have observed that nikethamide increases coronary flow of the perfused isolated dog heart in ventricular fibrillation presumably by dilating the coronary bed.

Heparin and dicumarol. Recently Gilbert and Nalefski (59), measuring the coronary sinus outflow of the anesthetized dog with a Morawitz-Zahn cannula, have shown that the sodium salt of heparin increases coronary flow slightly without altering blood pressure or heart rate; the barium salt of heparin has no effect on coronary flow. It is the opinion of Gilbert and Nalefski that soluble barium salts constrict coronary vessels and these authors, therefore, believe it reasonable to assume that the barium salt of heparin has no effect on the coronary circulation because the effect of the barium ion neutralizes the effect of heparin. The disodium salt of dicumarol increases coronary flow markedly and lowers blood pressure slightly. The increase in flow is prolonged and may last longer than that produced by the xanthines. Dicumarol also increases the coronary flow of the beating isolated dog heart whose coronary arteries are perfused under constant pressure. In this preparation, dicumarol also increases the amplitude of ventricular contraction, which effect appears after the increase in coronary flow has begun.

*Digitalis, digitalis bodies and digitalis-like drugs.** Essex, Herrick, Baldes and Mann (42), using a thermostromuhr in unanesthetized dogs, have studied the effect of successive doses of digitalis (digiglusin, Lilly) administered intramuscularly on coronary blood flow and blood pressure. One cat unit of digiglusin was given intramuscularly to a 16 kg. dog twice the first day, once the second day, twice the fourth and once the fifth day of the period of observation. Such doses of digitalis do not alter either coronary blood flow, arterial blood pressure or heart rate. Essex, Herrick and Visscher (46) have studied the effect of intravenous administration of digilanids A, B and C and K-strophanthin on coronary flow and blood pressure in the unanesthetized dog and have concluded that doses just subliminal for nausea and vomiting do not affect either coronary flow or blood pressure. Dearing, Essex, Herrick and Barnes (28) have observed the effect of intravenous administration of digifoline, digalen, digitoxin and lanatoside A on the coronary blood flow and blood pressure of unanesthetized dogs. They have studied the effect of calculated "therapeutic doses" of the prepara-

* For additional bibliography, see reference 28.

tions mentioned above, which they have considered equal to 30 per cent of the minimal lethal doses, and of "toxic doses," *i.e.*, doses equal to about 60 per cent of the minimal lethal doses. Therapeutic doses of digalen and digitoxin, for example, do not alter the coronary flow, but toxic doses of digitoxin, for example, decrease flow 4 to 6 hours after administration of the drug and the decrease persists for two or more days. The changes in coronary flow cannot be correlated consistently with changes in heart rate or blood pressure. Nausea and vomiting, when they occur after the injection of one of the digitalis bodies, increase the coronary flow.

When experiments on the effect of digitalis and digitalis-like drugs on coronary flow are conducted on anesthetized animals in which coronary sinus outflow is measured, the results are not as clear cut as in the experiments reported above on the unanesthetized animal. This should be no surprise since most of these drugs require some time to achieve their full effect and the circulatory status of an anesthetized dog with chest open and under artificial respiration can hardly be said to remain constant. Gilbert and Fenn (56) measuring the sinus outflow in anesthetized dogs have studied the effect of several preparations of digitalis leaf, ouabain and digitoxin (American and German) on heart rate, blood pressure and coronary flow. The results obtained in different dogs were somewhat variable and one digitalis leaf preparation gave results somewhat different from the results observed with two other digitalis leaf preparations. It seems, however, that 20 to 30 per cent of the lethal dose of most preparations tested produce some decrease in coronary flow that must have been due to an increase in resistance of the coronary bed. These authors think that the increase in resistance of the coronary bed is due to constriction of the coronary vessels. Ginsberg, Stoland and Siler (61) have investigated the effect of fresh digitalis tinctures, digiglusin (Lilly), digalen, digifoline, strophanthin and scillaren on the coronary sinus outflow in the dog denervated heart-lung preparation and in the anesthetized dog. The results were quite variable in different dogs and with different digitalis preparations. However, it seems that in the heart-lung preparation the most consistent effect is a decrease of coronary flow for about 10 minutes, after which the coronary flow generally increases. In the whole animal, similar effects occur but they are still less definite. The authors point out that often the coronary flow of the whole dog is not affected. It seems from the data presented that the decrease in flow, when it occurs, must be due to an increase in resistance of the coronary bed. Page, Wendel, Sheldon and Foltz (137) have recently investigated the effect of ouabain in the anesthetized dog. They determined coronary flow with the nitrous oxide method and also followed arterial blood pressure, heart rate, cardiac output, work, efficiency and oxygen consumption, systemic total peripheral resistance and resistance of the coronary bed. Comparing the data of control experiments and the data collected in experiments in which ouabain was given, these authors conclude that doses of 0.026 mgm. of ouabain per kg. modify significantly only one function studied, cardiac output, which increases. Doses of 0.037 mgm. per kg. raise arterial blood pressure slightly, lower heart rate, increase systemic total peripheral resistance and do

not significantly alter other functions. The shortcomings of such a method have been mentioned in the discussion of the xanthines. Recently Bing, Maraist, Damman, Draper, Heimbecker, Daley, Gerard and Calazel (17) have investigated the effect of intraarterial injection of strophanthus preparations on the coronary circulation of unanesthetized normal human beings and of patients with cardiac failure. The coronary flow was estimated with the nitrous oxide method and the cardiac output by the direct Fick method. These authors have found that in normal persons, strophanthus decreases the output, work and efficiency of the left ventricle whereas coronary blood flow, mean arterial blood pressure, coronary oxygen arterio-venous difference and cardiac oxygen consumption are unchanged. In cardiac failure, strophanthus increases the output, work and efficiency of the left ventricle whereas coronary flow and oxygen arterio-venous difference are unchanged. Bodo (18) has shown in the dog heart-lung preparation that 0.0025 mgm. of g-strophanthin per 100 cc. of blood, as well as digitalis tincture and digitalis infusion in equivalent doses, reduces the size of the heart; arterial pressure and cardiac output and work remain constant and coronary flow is slightly increased. The increase in coronary flow as well as the decrease in the size of the ventricles does not appear immediately. The increase in coronary flow while the blood pressure remains unchanged must be due to a decrease in resistance of the coronary bed. Since the size of the ventricles decreases, it seems probable that the decrease in the resistance of the coronary bed is due to coronary dilatation. Lindner and Katz (122), investigating the effect of k-strophanthin, digifolin and ouabain on the coronary circulation of the perfused dog heart in ventricular fibrillation, have reported sometimes an increase in coronary flow, presumably due to dilatation of the coronary bed, and sometimes a decrease in flow, presumably due to constriction. From their clinical observations, Fenn and Gilbert (51) believe that digitalis in therapeutic doses can induce anginal pain in human beings by constricting the coronary arteries. On the other hand, Gold (62, 64) is of a different opinion because, in a large series of patients suffering from effort angina due to coronary sclerosis without cardiac failure, digitalization did not seem to influence either the frequency of pain or the capacity for work.

In conclusion, it seems that in the unanesthetized dog therapeutic doses of digitalis, digitalis bodies and digitalis-like drugs do not modify the coronary flow very much, if at all. Large doses may decrease the coronary flow. The studies made in acute experiments on anesthetized animals which have undergone rather extensive operative procedures have yielded conflicting data, as have studies made on the heart-lung preparation or similar preparations.

Quinidine. Bodo (18) has shown in the dog heart-lung preparation that 0.0066 to 0.01 gram quinidine sulfate increases the diastolic size of the heart but, everything else remaining constant, it does not alter the coronary circulation. In very large doses, however, the drug causes an increase, then a decrease in coronary flow, interpreted by Bodo as due to dilatation followed by constriction of the coronary vessels. Kountz (114) as well as Elek and Katz (39) have observed that quinidine does not affect the coronary flow either in the revived human heart

perfused by the Langendorff method (114) or in the perfused dog heart in ventricular fibrillation (39). Massive doses, however, produce coronary dilatation (39).

Morphine. Kountz (114) has observed that morphine increases the coronary flow of the revived human heart perfused by the Langendorff method, but since the doses used depressed the amplitude of ventricular contraction this increase in flow may well have been due to a decrease in extravascular support. Elek and Katz (39) have reported that 0.8 to 1.6 mgm. of morphine sulfate increase the coronary flow in the perfused fibrillating dog ventricles, presumably by dilating the coronary bed. Van Egmond (163) using the Langendorff perfusion technic in cats reported that morphine does not modify coronary flow. In the whole anesthetized dog Wégria, Ward, Frank, Dreyfuss, Brown and Hutchinson (183) have found that 5 to 10 mgm. of morphine sulfate given intravenously to dogs weighing between 11 and 27 kg. either do not affect blood pressure and coronary flow or more often produce a fall in blood pressure and coronary flow. During the recovery from the effect of the drug in those experiments in which morphine has lowered blood pressure and coronary flow, evidence of an increase in resistance of the coronary bed is observed more often than a decrease.

Sodium chloride, calcium chloride, calcium gluconate, potassium chloride, magnesium sulfate. Katz and Lindner (106) have studied the effect of an excess of Na, K and Ca ions on the coronary flow of perfused fibrillating dog ventricles. When the concentration of sodium in the defibrinated blood used for the perfusion is increased to 1.2 to 2.75 times the normal concentration by the addition of sodium chloride, a definite coronary dilatation results; it is of short duration, lasting 1 to 4 minutes. Concentrations of calcium 1.3 to 24 times the control concentration, produced by the addition of calcium chloride, cause a more marked coronary dilatation than an increase in the sodium concentration, the dilatation generally lasting 3 to 15 minutes. Calcium gluconate, however, has no effect or induces only a very slight dilatation of the coronary bed (122). When the concentration of potassium reaches a level of 1.04 to 1.5 times its normal concentration in defibrinated blood after addition of potassium chloride, coronary dilatation results. Concentrations of potassium between 1.55 and 1.66 times the normal concentration cause either coronary dilatation or constriction. With concentrations of 1.66 to 2.5 times the normal concentration, marked coronary constriction is observed. Katz and Lindner (106) point out that even a marked change in the character of the ventricular fibrillation induced by an excess of calcium or potassium does not seem to affect coronary flow in their preparation in which the cavities of the heart are open to atmospheric pressure. Magnesium sulfate always causes a marked coronary dilatation as shown by Elek and Katz (39) on the same type of preparation.

Atropine. Essex, Wégria, Herrick and Mann (47), using the thermostromuhr, have shown that atropine administered intravenously markedly increases heart rate and coronary flow in the unanesthetized dog for 45 minutes or longer. Wégria, Essex, Herrick and Mann (175) have observed that atropine increases the coronary flow of both left and right coronary arteries of the anesthetized

dog. The heart rate increases; the blood pressure is not affected or is very slightly increased. The coronary flow reaches its peak within a few minutes and remains maximally increased for as long as one hour. The increase in flow is due mostly, and in most experiments exclusively, to a decrease in resistance of the coronary bed. It is probable that the effect of atropine is similar to cutting both vagi, which procedure has been shown to increase coronary flow in the innervated dog heart-lung preparation (13) in the absence of any changes in heart rate, blood pressure or cardiac output. Whether in the whole animal other changes, such as an increase in cardiac output and work, occur after administration of atropine is not known. Essex, Herrick, Mann and Baldes (45) have shown that atropine increases heart rate and coronary flow in the unanesthetized dog and in the unanesthetized dog with a bilateral sympathetic ganglionectomy from T8 or T9 upward to include the stellate ganglia. Atropine, however, is without effect on heart rate, blood pressure and coronary flow after bilateral cervical vagotomy. Kountz (114) has observed that atropine increases heart rate and diminishes coronary flow in the revived beating human heart perfused by the Langendorff method; atropine also decreases coronary flow in the human heart in standstill.

Neostigmine. Mendez and Ravin (129) have shown in the dog heart-lung preparation that neostigmine decreases slightly the coronary sinus outflow measured with a Morawitz-Zahn cannula.

Pilocarpine. Pilocarpine is said to increase coronary flow of the revived beating human heart perfused by the Langendorff technic as well as the human heart in standstill (114).

Ethyl alcohol. Although alcohol has been recommended by numerous authors for the therapy of angina pectoris, there are few critical experimental or clinical data on the effect of alcohol on the coronary circulation. Dixon (31) reports that concentrations of alcohol of 0.1 to 0.2 per cent dilate the coronary vessels, whereas stronger concentrations (1 to 2 per cent) first constrict and then dilate the coronary vessels of the cat heart in a Langendorff preparation. Sulzer (162), measuring coronary sinus outflow in the dog heart-lung preparation, has observed that concentrations of 0.1 to 0.2 per cent of alcohol in the blood always decrease the coronary flow and increase the diastolic size of the heart, everything else remaining constant. Whether the decrease in coronary flow is due to coronary constriction remains to be established. Recently, Russek, Naegele and Regan (144), studying the effect of alcohol given orally in patients with angina pectoris due to coronary sclerosis, have made the observation that alcohol, although as effective as nitroglycerin in preventing the anginal pain induced by a standard exercise test, fails to prevent the electrocardiographic changes observed during control exercise tests; nitroglycerin does prevent such changes. These authors conclude that alcohol acts mainly by raising the threshold for pain.

Pitressin. There is no disagreement about the effect of pitressin on the coronary circulation. In the anesthetized (175) and the unanesthetized (47) dog, it has been shown with the thermostromuhr that 0.5 to 4 pressor units of pitressin given intravenously decrease the coronary flow very markedly for as long as 45 minutes whereas the blood pressure sometimes decreases, sometimes increases

and sometimes first increases and then decreases. The heart rate is always decreased. There is no doubt that pitressin decreases coronary flow by increasing resistance of the coronary bed. Green, Wégria and Boyer (74) have observed the same results with the orifice meter in the anesthetized dog and they have concluded that pitressin is a powerful constrictor of the coronary bed. Bodo (18) has shown in the dog heart-lung preparation that pituitrin decreases coronary flow and produces dilatation of the heart, everything else remaining unchanged. The effect of pituitrin on the coronary flow in the dog heart-lung preparation has been confirmed by Narayana (134). Katz, Lindner, Weinstein, Abramson and Jochim (108) have demonstrated that pitressin produces a marked constriction of the coronary bed in the perfused dog heart in ventricular fibrillation. In the revived human heart perfused by the Langendorff method and in the arrested human heart, pituitrin generally decreases the coronary flow although it sometimes increases it at the end of an experiment and in dilated hearts; the difference in the effect observed is probably due to a difference in the effect of the drug on the myocardium (114, 115, 116). It has indeed been observed that, at the beginning of an experiment, pituitrin modifies amplitude of ventricular contraction very little and decreases heart rate, whereas it increases amplitude of ventricular contraction and heart rate in those preparations in which it increases coronary flow (114–116). Although it seems certain that pitressin decreases coronary flow by constricting the coronary bed, a study of the effect of the drug simultaneously on blood pressure, coronary flow and cardiac output, work and metabolism is still to be done.

V. CONCLUDING REMARKS

After a résumé of the technics generally used for the study of the coronary circulation and a short discussion of the main features of the physiology of the coronary circulation, the effect of drugs on the coronary circulation has been reviewed. With apology for his errors of omission and commission, the reviewer hopes to have pointed out that to gain complete knowledge, as previously defined, of the effect of a drug on the coronary circulation it is mandatory to investigate the effect of that drug not only on simple, very artificial preparations but also on more complicated preparations including ultimately unanesthetized healthy and sick human beings. It hardly needs to be said that a great deal remains to be done.

REFERENCES

1. ANREP, G. V.: The regulation of the coronary circulation. Physiol. Rev., 6: 596–629, 1926.
2. ANREP, G. V.: Lane Medical Lectures. Studies in cardiovascular regulation. Stanford University Publications. Medical Sciences, 3: 245–288, 1936.
3. ANREP, G. V., BARSOUM, G. S., KENAWY, M. R. AND MISRAHY, G.: Ammi Visnaga in the treatment of the anginal syndrome. Brit. Heart J., 8: 171–177, 1946.
4. ANREP, G. V., BARSOUM, G. S. AND TALAAT, M.: Liberation of histamine by the heart muscle. J. Physiol., 86: 431–451, 1936.
5. ANREP, G. V., BLALOCK, A. AND HAMMOUDA, M.: The distribution of the blood in the coronary blood vessels. J. Physiol., 67: 87–96, 1929.
6. ANREP, G. V., DAVIS, J. C. AND VOLHARD, E.: The effect of pulse pressure upon the coronary blood flow. J. Physiol., 73: 405–426, 1931.
7. ANREP, G. V. AND DOWNING, A. C.: A method for the quantitative measurement of quick changes in the outflow of liquids. J. Scient. Instruments, 3: 221–224, 1925–26.

8. ANREP, G. V. AND HÄUSLER, H.: The coronary circulation. I. The effect of changes of the blood pressure and of the output of the heart. J. Physiol., 65: 357-373, 1928.
9. ANREP, G. V. AND HÄUSLER, H.: The coronary circulation. II. The effect of changes of temperature and heart rate. J. Physiol., 67: 299-314, 1929.
10. ANREP, G. V., KENAWY, M. R. AND BARSOUM, G. S.: The coronary vasodilator action of khellin. Am. Heart J., 37: 531-542, 1949.
11. ANREP, G. V. AND KING, B.: The significance of the diastolic and systolic blood pressures for the maintenance of the coronary circulation. J. Physiol., 64: 341-349, 1927-28.
12. ANREP, G. V. AND SEGALL, H. N.: The central and reflex regulation of the heart rate. J. Physiol., 61: 215-231, 1926.
13. ANREP, G. V. AND SEGALL, H. N.: The regulation of the coronary circulation. Heart, 13: 239-260, 1926.
14. ATZLER, E. AND FRANK, L.: Beitrage zur Methodik der Froschgefässdurchspülung. Arch. f. d. ges. Physiol., 181: 141-148, 1920.
15. BALDES, E. J. AND HERRICK, J. F.: A thermostromuhr with direct current heater. Proc. Soc. Exper. Biol. & Med., 37: 432-435, 1937.
16. BING, R. J., HAMMOND, M. M., HANDELSMAN, J. C., POWERS, S. R., SPENCER, F. C., ECKENHOFF, J. E., GOODALE, W. T., HAFKENSCHIEL, J. H. AND KETY, S. S.: The measurement of coronary blood flow, oxygen consumption and efficiency of the left ventricle in man. Am. Heart J., 38: 1-24, 1949.
17. BING, R. J., MARAIST, F. M., DAMMANN, J. F., JR., DRAPER, A., JR., HEIMBECKER, R., DALEY, R., GERARD, R. AND CALAZEL, P.: Effect of strophantus on coronary blood flow and cardiac oxygen consumption of normal and failing human hearts. Circulation, 2: 513-516, 1950.
18. BODO, R.: The effect of the "heart tonics" and other drugs upon the heart-tone and coronary circulation. J. Physiol., 64: 365-387, 1927-28.
19. BOYER, N. H.: Aminophylline and related xanthine derivatives. Present status of therapeutic claims. J. Am. M. A., 122: 306-309, 1943.
20. BOYER, N. H. AND GREEN, H. D.: The effects of nitrites and xanthines on coronary inflow and blood pressure in anesthetized dogs. Am. Heart J., 21: 199-214, 1941.
21. BRODIE, T. G. AND COLLIS, W. C.: The innervation of the coronary vessels. J. Physiol., 43: 313-214, 1911.
22. BRUNER, H. D.: Bubble flow meter. Methods in medical research. (POTTER, V. R., editor.) The Year Book Publishers, Chicago, 1948.
23. CHARLIER, R.: Le rôle des régions sinusales et cardioaortique dans la régulation réflexe du débit cardiaque. Acta cardiologica, 3: 1-47, 1948.
24. COHN, A. E. AND STEELE, J. M.: The influence of frequency of contraction of the isolated mammalian heart upon the consumption of oxygen. Am. J. Physiol., 113: 654-658, 1935.
25. COHN, A. E. AND STEELE, J. M.: The metabolism of the isolated heart of dogs related to age. J. Clin. Investigation, 14: 915-922, 1935.
26. CRITTENDEN, E. C., JR. AND SHIPLEY, R. E.: An electronic recording flowmeter. Rev. Scient. Instruments, 15: 343-346, 1944.
27. CRUICKSHANK, E. W. H. AND SUBBA RAU, A.: Reactions of isolated systemic and coronary arteries. J. Physiol., 64: 65-77, 1927-28.
28. DEARING, W. H., ESSEX, H. E., HERRICK, J. F. AND BARNES, A. R.: Experiments with calculated therapeutic and toxic doses of digitalis. Am. Heart J., 25: 719-733, 1943.
29. DE TAKATS, G., BECK, W. C. AND FENN, G. K.: Pulmonary embolism. Surgery, 6: 339-367, 1939.
30. DEWAR, H. A. AND GRIMSON, T. A.: Khellin in the treatment of angina of effort. Brit. Heart J., 12: 54-60, 1950.
31. DIXON, W. E.: The action of alcohol on the circulation. J. Physiol., 35: 346-366, 1906-07.
32. DRURY, A. N. AND SZENT-GYÖRGYI, A.: The physiological activity of adenine compounds with especial reference to their action upon the mammalian heart. J. Physiol., 68: 213-237, 1929-30.
33. ECKENHOFF, J. E. AND HAFKENSCHIEL, J. H.: The effect of nikethamide on coronary blood flow and cardiac oxygen metabolism. J. Pharmacol. & Exper. Therap., 91: 362-369, 1947.
34. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., FOLTZ, E. L. AND DRIVER, R. I.: Influence of hypotension on coronary blood flow, cardiac work and cardiac efficiency. Am. J. Physiol., 152: 455-553, 1948.
35. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., HARMEL, M. H., GOODALE, W. T., LUBIN, M., BING, R. J. AND KETY, S. S.: Measurement of coronary blood flow by the nitrous oxide method. Am. J. Physiol., 152: 356-364, 1948.
36. ECKENHOFF, J. E., HAFKENSCHIEL, J. H. AND LANDMESSER, C. M.: The coronary circulation in the dog. Am. J. Physiol., 148: 582-596, 1947.
37. ECKENHOFF, J. E., HAFKENSCHIEL, J. H., LANDMESSER, C. M. AND HARMEL, M.: Cardiac oxygen metabolism and control of the coronary circulation. Am. J. Physiol., 149: 634-649, 1947.
38. ECKSTEIN, R. W., CHAMBLISS, J., DEMMING, J. AND WELLS, K.: Coronary vasodilatation following intracoronary injections. Federation Proc., 9: 36, 1950.
39. ELEK, S. R. AND KATZ, L. N.: Further observations on the action of drugs on coronary vessel caliber. Paredrine, angiotonin, renin, quinidine, insulin, coramine, magnesium sulphate, morphine, acid and alkali. J. Pharmaco. & Exper. Therap., 75: 178-182, 1942.
40. ERNSTENE, A. C. AND ALTSCHULE, M. D.: The effect of insulin hypoglycemia on the circulation. J. Clin. Investigation, 10: 521-528, 1931.
41. ESSEX, H. E., HERRICK, J. F., BALDES, E. J. AND MANN, F. C.: Blood flow in the circumflex branch of the left coronary artery of the intact dog. Am. J. Physiol., 117: 271-279, 1936.
42. ESSEX, H. E., HERRICK, J. F., BALDES, E. J. AND MANN, F. C.: Digitalis and coronary blood flow. Proc. Soc. Exper. Biol. & Med., 38: 325-328, 1938.

43. Essex, H. E., Herrick, J. F., Baldes, E. J. and Mann, F. C.: Influence of exercise on blood pressure, pulse rate and coronary blood flow of the dog. Am. J. Physiol., **125**: 614–623, 1939.
44. Essex, H. E., Herrick, J. F., Baldes, E. J. and Mann, F. C.: Effects of exercise on the coronary blood flow, heart rate and blood pressure of trained dogs with denervated and partially denervated hearts. Am. J. Physiol., **138**: 687–697, 1943.
45. Essex, H. E., Herrick, J. F., Mann, F. C. and Baldes, E. J.: The effect of atropine on the coronary blood flow of trained dogs with denervated and partially denervated hearts. Am. J. Physiol., **138**: 683–686, 1943.
46. Essex, H. E., Herrick, J. F. and Visscher, M. B.: Influence of certain glucosides of digitalis lanata on the coronary blood flow and blood pressure in the trained dog. Am. Heart J., **16**: 143–148, 1938.
47. Essex, H. E., Wégria, R., Herrick, J. F. and Mann, F. C.: The effect of certain drugs on the coronary blood flow of the trained dog. Am. Heart J., **19**: 554–565, 1940.
48. Evans, C. L. and Matsuoka, Y.: The effect of various mechanical conditions on the gaseous metabolism and efficiency of the mammalian heart. J. Physiol., **49**: 378–405, 1915.
49. Evans, C. L. and Starling, E. H.: The part played by the lungs in the oxidative processes of the body. J. Physiol., **46**: 413–434, 1913.
50. Fellows, E. J., Killam, K. F., Toner, J. J., Dailey, R. A. and Macko, E.: Comparative pharmacology of khellin, visnagin and khellol glucoside. Federation Proc., **9**: 271, 1950.
51. Fenn, G. K. and Gilbert, N. C.: Anginal pain as a result of digitalis administration. J. Am. M. A., **98**: 99–104, 1932.
52. Foltz, E. L., Rubin, A., Steiger, W. A. and Gazes, P. C.: The effects of intravenous aminophylline upon the coronary blood-oxygen exchange. Circulation, **2**: 215–224, 1950.
53. Fowler, W. M., Hurevitz, H. M. and Smith, F. M.: Effect of theophylline ethylenediamine on experimentally induced cardiac infarction in the dog. Arch. Int. Med., **56**: 1242–1249, 1935.
54. Frank, C. W., Misrahy, G. A., Sioussat, R. S., Sommer, L. M., McCormack, G. H., Jr. and Wégria, R.: The effect of l-nor-epinephrine and l-epinephrine on cardiac output and arterial blood pressure in the anesthetized dog. To be published.
55. Gilbert, N. C. and Fenn, G. K.: The effect of the purine base diuretics on the coronary flow. Arch. Int. Med., **44**: 118–127, 1929.
56. Gilbert, N. C. and Fenn, G. K.: Effect of digitalis on the coronary flow. Arch. Int. Med., **50**: 668–683, 1932.
57. Gilbert, N. C., Fenn, G. K., LeRoy, G. V. and Hobbs, T. G.: The rôle of sympathetic inhibition in the production of attacks of angina pectoris. Tr. A. Am. Physicians, **56**: 279–290, 1941.
58. Gilbert, N. C., LeRoy, G. V. and Fenn, G. K.: The effect of distention of abdominal viscera on the blood flow in the circumflex branch of the left coronary artery of the dog. Am. Heart J., **20**: 519–524, 1940.
59. Gilbert, N. C. and Nalefski, L. A.: The effect of heparin and dicumarol in increasing the coronary flow volume. J. Lab. & Clin. Med., **34**: 797–805, 1949.
60. Ginsberg, A. M., Stoland, O. O. and Loy, D. T.: Studies on the coronary circulation. III. Effect of intravenous injections of dextrose on the coronary circulation. Arch. Int. Med., **55**: 42–51, 1935.
61. Ginsberg, A. M., Stoland, O. O. and Siler, K. A.: Studies on coronary circulation. VI. The effect of some members of the digitalis group on the coronary circulation. Am. Heart J., **16**: 663–674, 1938.
62. Gold, H.: Drug therapy in coronary disease. J. Am. M. A., **112**: 1–6, 1939.
63. Gold, H., Kwit, N. T. and Otto, H.: The xanthines (theobromine and aminophylline) in the treatment of cardiac pain. J. Am. M. A., **108**: 2173–2179, 1937.
64. Gold, H., Otto, H., Kwit, N. T. and Satchwell, H.: Does digitalis influence the course of cardiac pain? A study of 120 selected cases of angina pectoris. J. Am. M. A., **110**: 859–863, 1938.
65. Gold, H., Travell, J. and Modell, W.: The effect of theophylline with ethylenediamine (aminophylline) on the course of cardiac infarction following experimental coronary occlusion. Am. Heart J., **14**: 284–296, 1937.
66. Gollwitzer-Meier, K., Kramer, K. and Krüger, E.: Der Gaswechsel des suffizienten und insuffizienten Warmblüterherzens. Arch. f. d. ges. Physiol., **237**: 68–92, 1936.
67. Gollwitzer-Meier, K., Kramer, K. and Krüger, E.: Die Wirkung des Adrenalins auf die Energetik des Herzens. Arch. f. d. ges. Physiol., **237**: 639–650, 1936.
68. Gollwitzer-Meier, K. and Kroetz, C.: Sauerstoffverbrauch und Kranzgefässdurchblutung des innervierten Saugetierherzens unter Adrenalinwirkung. Arch. f. d. ges. Physiol., **241**: 248–262, 1938–39.
69. Gollwitzer-Meier, K. and Krüger, E.: Einfluss der Herznerven auf den Gaswechsel des Warmblüterherzens. Arch. f. d. ges Physiol., **240**: 89–110, 1938.
70. Green, H. D.: Effect of pitressin, the nitrites, epinephrine and the xanthines on coronary flow in mammalian hearts. Blood, Heart and Circulation, A. A. A. Sc. Publication No. 13, 1940.
71. Green, H. D. and Gregg, D. E.: Changes in the coronary circulation following increased aortic pressure, augmented cardiac output, ischemia and valve lesions. Am. J. Physiol., **130**: 126–129, 1940.
72. Green, H. D., Gregg, D. E. and Wiggers, C. J.: The phasic changes in coronary flow established by differential pressure curves. Am. J. Physiol., **112**: 627–639, 1935.
73. Green, H. D., and Wégria, R.: Effects of asphyxia, anoxia and myocardial ischemia on the coronary blood flow. Am. J. Physiol., **135**: 271–280, 1942.
74. Green, H. D., Wégria, R. and Boyer, N. H.: Effects of epinephrine and pitressin on the coronary artery inflow in anesthetized dogs. J. Pharmacol. & Exper. Therap., **76**: 378–391, 1942.
75. Green, P. A., Gregg, D. E. and Czerwonka, L. J.: To be published. Quoted in Coronary Circulation by Gregg, D. E. Lea and Febiger, Philadelphia, 1950.
76. Greene, C. W.: Control of the coronary blood flow by reflexes arising in widely distributed regions of the body. Am. J. Physiol., **113**: 399–415, 1935.

77. GREENE, C. W.: Dilation of the coronary vessels by certain organic extracts and drugs. J. Pharmacol. & Exper. Therap., 57: 98–112, 1936.
78. GREGG, D. E.: The coronary circulation. Physiol. Rev., 26: 28–46, 1936.
79. GREGG, D. E.: Coronary circulation. Lea and Febiger, Philadelphia, 1950.
80. GREGG, D. E. AND DEWALD, D.: The immediate effects of the occlusion of the coronary veins on the dynamics of the coronary circulation. Am. J. Physiol., 124: 444–456, 1938.
81. GREGG, D. E. AND GREEN, H. D.: Registration and interpretation of normal phasic inflow into a left coronary artery by an improved differential manometric method. Am. J. Physiol., 130: 114–125, 1940.
82. GREGG, D. E., GREEN, H. D. AND WIGGERS, C. J.: Phasic variations in peripheral coronary resistance and their determinants. Am. J. Physiol., 112: 362–373, 1935.
83. GREGG, D. E., PRITCHARD, W. H., ECKSTEIN, R. W., SHIPLEY, R. E., ROTTA, A., DINGLE, J., STEEGE, T. W. AND WEARN, J. T.: Observations on the accuracy of the thermostromuhr. Am. J. Physiol., 136: 250–262, 1942.
84. GREGG, D. E., PRITCHARD, W. H., SHIPLEY, R. E. AND WEARN, J. T.: Augmentation of blood flow in the coronary arteries with elevation of right ventricular pressure. Am. J. Physiol., 139: 726–731, 1943.
85. GREGG, D. E. AND SHIPLEY, R. E.: Changes in right and left coronary artery inflow with cardiac nerve stimulation. Am. J. Physiol., 141: 382–388, 1944.
86. GREGG, D. E. AND SHIPLEY, R. E.: Augmentation of the left coronary inflow with elevation of left ventricular pressure and observations on the mechanism for increased coronary inflow with increased cardiac load. Am. J. Physiol., 142: 44–51, 1944.
87. GREGG, D. E. AND SHIPLEY, R. E.: Studies of the venous drainage of the heart. Am. J. Physiol., 151: 13–25, 1947.
88. GREGG, D. E., SHIPLEY, R. E., ECKSTEIN, R. W., ROTTA, A. AND WEARN, J. T.: Measurement of mean blood flow in arteries and veins by means of the rotameter. Proc. Soc. Exper. Biol. & Med., 49: 267–272, 1942.
89. GREINER, T., GOLD, H., CATTELL, MCKEEN, TRAVELL, J., BABST, H., RINZLER, S. H., BENJAMIN, Z. H., WARSHAW, L. J., BOBB, A. L., KWIT, N. T., MODELL, W., ROTHENDLER, H. H., MESSELOFF, C. R. AND KRAMER, M. L.: A method for the evaluation of the effects of drugs on cardiac pain in patients with angina of effort. A study of khellin (Visammin). Am. J. Med., 9: 143–155, 1950.
90. GREMELS, H.: Zur Physiologie und Pharmakologie der Energetik des Saugetierherzens. Arch. f. exper. Path. u. Pharmakol., 169: 689–723, 1932–33.
91. GUNN, J. A.: The action of histamine on the heart and coronary vessels. J. Pharmacol. & Therap., 29: 325–337, 1926.
92. HAMMOUDA, M. AND KINOSITA, R.: The coronary circulation in the isolated heart. J. Physiol., 61: 615–628, 1926.
93. HARRISON, T. R., FRIEDMAN, B. AND RESNIK, H.: Mechanism of acute experimental heart failure. Arch. Int. Med., 57: 927–948, 1936.
94. HAUSNER, E., ESSEX, H. E., HERRICK, J. F. AND BALDES, E. J : Control of coronary blood flow in the heart-lung preparation. Am. J. Physiol., 131: 43–53, 1940–41.
95. HEATHCOTE, R. ST. A.: The action of caffeine, theobromine and theophylline on the mammalian and batrachian heart. J. Pharmacol. & Exper. Therap., 16: 327–344, 1920–21.
96. HEMINGWAY, A. AND FEE, A. R.: The relationship between the volume of the heart and its oxygen usage. J. Physiol., 63: 299–303, 1927.
97. HERRICK, J. F , ESSEX, H. E., MANN, F. C. AND BALDES, E. J.: The effect of feeding desiccated thyroid gland on the flow of blood in the femoral artery of the dog. Am. J. Physiol., 105: 434–435, 1933.
98. HILL, W. H. P. AND ANDRUS, E. C.: The cardiac factor in the "pressor" effects of renin and angiotonin. J. Exper. Med., 74: 91–103, 1941.
99. HILTON, R. AND EICHHOLTZ, F.: The influence of chemical factors on the coronary circulation. J. Physiol., 59: 413–425, 1924–25.
100. HINRICHSEN, J. AND IVY, A. C.: Effect of stimulation of visceral nerves on coronary flow in dogs. Arch. Int. Med., 51: 932–937, 1933.
101. JERUSALEM, E. AND STARLING, E. H.: On the significance of carbon dioxide for the heart beat. J. Physiol., 40: 279–294, 1910.
102. JOCHIM, K.: Vascular and extravascular factors influencing coronary blood flow. Blood, Heart and Circulation, A. A. A. Sc. Publication No. 13, 1940.
103. KATZ, L. N. AND JOCHIM, K.: Observations on the innervation of the coronary vessels of the dog. Am. J. Physiol., 126: 395–401, 1939.
104. KATZ, L. N., JOCHIM, K. AND BOHNING, A.: The effect of the extravascular support of the ventricles on the flow in the coronary vessels. Am. J. Physiol., 122: 236–251, 1938.
105. KATZ, L. N., JOCHIM, K. AND WEINSTEIN, W.: The distribution of the coronary blood flow. Am. J. Physiol., 122: 252–261, 1938.
106. KATZ, L. N. AND LINDNER, E.: The action of excess Na, Ca and K on the coronary vessels. Am. J. Physiol., 124: 155–160, 1938.
107. KATZ, L. N. AND LINDNER, E.: Quantitative relation between reactive hyperemia and the myocardial ischemia which it follows. Am J. Physiol., 126: 283–288, 1939.
108. KATZ, L. N., LINDNER, E., WEINSTEIN, W., ABRAMSON, D. I. AND JOCHIM, K.: Effects of various drugs on the coronary circulation of the denervated isolated heart of the dog and cat. Arch. internat. de pharmacodyn. et de thérap., 59: 399–415, 1938.
109. KATZ, L. N., WEINSTEIN, W. AND JOCHIM, K.: The variability in the distribution of the outflow from each of the three major coronary arteries. Am. J. Physiol., 113: 76, 1935.
110. KETY, S. S. AND SCHMIDT, C. F.: The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. Am. J. Physiol., 143: 53–66, 1945.

111. KIESE, M. AND GARAN, R. S.: Mechanische Leistung, Grösse und Sauerstoffverbrauch des Warmblütenherzens. Arch. f. exper. Path. u. Pharmakol., **188:** 226–246, 1937–38.
112. KILLAM, K. F. AND FELLOWS, E. J.: Pharmacology of khellin. Federation Proceedings, **9:** 291, 1950.
113. KNOWLTON, F. P. AND STARLING, E. H.: The influence of variations in temperature and blood pressure on the performance of the isolated mammalian heart. J. Physiol., **44:** 206–219, 1912.
114. KOUNTZ, W. B.: Studies on the coronary arteries of the human heart. J. Pharmacol. & Exper. Therap., **45:** 65–76, 1932.
115. KOUNTZ, W. B. AND SMITH, J. R.: The flow of blood in the coronary arteries in pathological hearts. J. Clin. Investigation, **17:** 147–152, 1938.
116. KOUNTZ, W. B., PEARSON, E. F. AND KOENIG, K. F.: Observations on the effect of vagus and sympathetic stimulation of the coronary flow of the revived human heart. J. Clin. Investigation, **13:** 1065–1078, 1934.
117. LANGENDORFF, O.: Untersuchungen am überlebenden Säugetierherzen. Arch. f. d. ges. Physiol., **61:** 291–332, 1895.
118. LEROY, G. V., FENN, G. K. AND GILBERT, N. C.: The influence of xanthine drugs and atropine on the mortality rate after experimental occlusion of a coronary artery. Am. Heart J., **23:** 637–643, 1942.
119. LEVINE, S. A., ERNSTENE, A. C. AND JACOBSON, B. M.: The use of epinephrine as a diagnostic test for angina pectoris. Arch. Int. Med., **45:** 191–200, 1930.
120. LEVY, R. L., BRUENN, H. G. AND WILLIAMS, N. E.: The modifying action of certain drugs (aminophyllin, nitrites, digitalis) upon the effects of induced anoxemia in patients with coronary insufficiency. Am. Heart J., **19:** 639–654, 1940.
121. LEYKO, E.: The action of some heart tonics. J. Pharmacol. & Exper. Therap., **38:** 31–49, 1930.
122. LINDNER, E. AND KATZ, L. N.: Further observations on the action of drugs on the caliber of coronary vessels. Papaverine hydrochloride, digitalis derivatives, aminophyllin, caffein, glucose, calcium gluconate and metrazol. J. Pharmacol. & Exper. Therapy., **72:** 306–310, 1941.
123. LORBER, V.: The action of angiotonin on the completely isolated mammalian heart. Am. Heart J. **23:** 37–42, 1942.
124. MANNING, G. W., MCEACHERN, C. G. AND HALL, G. E.: Reflex coronary artery spasm following sudden occlusion of other coronary branches. Arch. Int. Med., **64:** 661–674, 1939.
125. MARKWALDER, J. AND STARLING, E. H.: A note on some factors which determine the blood flow through the coronary circulation. J. Physiol., **47:** 275–285, 1913–14.
126. MART, J. A. AND MILLER, J. R.: The effect of diathermy on coronary flow. Am. Heart J., **29:** 390–395, 1945.
127. MASTER, A. M., FRIEDMAN, R AND DACK, S.: The electrocardiogram after standard exercise as a functional test of the heart. Am. Heart J., **24:** 777–793, 1942.
128. MCEACHERN, C. G., MANNING, G. W. AND HALL, G. E.: Sudden occlusion of coronary arteries following removal of cardiosensory pathways. Arch. Int. Med., **65:** 661–670, 1940.
129. MENDEZ, R. AND RAVIN, A.: On the action of prostigmine on the circulatory system. J. Pharmacol. & Exper. Therap., **72:** 80–89, 1941.
130. MEYER, O. B.: Über einige Eigenschaften der Gefässmuskulatur mit besonderer Berücksichtigung der Adrenalinqirkung. Ztschr. f. Biol., **48:** 352–397, 1906.
131. MOE, G. K. AND VISSCHER, M. B.: The distribution of coronary blood flow. Blood, Heart and Circulation. A. A. A. Sc. Publication No. 13, 100–104, 1940.
132. MORAWITZ, P. AND ZAHN, A.: Uber den Koronarkreislauf am Herzen in situ. Zentralbl. f. Physiol., **26:** 465–470, 1912.
133. NAKAGAWA, T.: On the coronary circulation in the heart-lung preparation. J. Physiol., **56:** 340–347, 1922.
134. NARAYANA, B.: Vasoconstricteurs et vasodilatateurs coronaires. Compt. rend. Soc. de biol., **114:** 550–552, 1933.
135. OPDYKE, D. F. AND FOREMAN, R. C.: A study of coronary flow under conditions of hemorrhagic hypotension and shock. Am. J. Physiol., **148:** 726–739, 1947.
136 OPDYKE, D. F. AND SELKURT, E. E.: A study of alleged intercoronary reflexes following coronary occlusion. Am. Heart J., **36:** 73–88, 1948.
137. PAGE, R. G., WENDELL, H , SHELDON, W B, AND FOLTZ, E. L.: Effects of ouabain on the coronary circulation and cardiac energetics. Federation Proc., **9:** 306, 1950.
138. PATTERSON, J. E., CLARK, T. W. AND LEVY, R. L.: A comparison of electrocardiographic changes observed during the anoxemia test on normal persons and on patients with coronary sclerosis. Am. Heart J., **23:** 837–846, 1942.
139. PORTER, W. T.: The influence of the heart beat on the flow of blood through the walls of the heart. Am. J. Physiol., **1:** 145–163, 1898.
140. RATNOFF, O. D. AND PLOTZ, M.: The coronary circulation. Medicine, **25:** 285–342, 1946.
141. REIN, H.: Die Thermo-Stromuhr. Ein Verfahren zur fortlaufenden Messung der mittleren absoluten Durchflussmengen in uneröffneten Gefässen in situ. Ztschr. f. Biol., **87:** 394–418, 1927–28.
142. REIN, H.: Die Physiologie der Herz-Kranz-Gefässe. I. Mitteilung. Ztschr. f. Biol., **92:** 101–114, 1931–32; II. Mitteilung. Ibid., **92:** 115–127, 1931–32.
143. ROSENMAN, R. H., FISHMAN, A. P., KAPLAN, S. R., LEVIN, H. G. AND KATZ, L. N.: Observations on the clinical use of visammin (khellin) J. Am. M. A., **143:** 160–165, 1950.
144. RUSSEK, H. I., NAEGELE, C. F. AND REGAN, F. D.: Alcohol in the treatment of angina pectoris. J. Am. M. A., **143:** 355–357, 1950.
145. RUSSEK, H. I., SMITH, R. H., BAUM, W. S., NAEGELE, C. F. AND REGAN, F. D.: Influence of saline, papaverine, nitroglycerine and ethyl alcohol on electrocardiographic response to standard exercise in coronary disease. Circulation, **1:** 700–705, 1950.
146. SASSA, K.: Untersuchungen über den Coronarkreislauf des überlebenden Säugetierherzenes. Arch. f. d. ges Physiol., **198:** 543–563, 1923.

147. SHIPLEY, R. E. AND CRITTENDEN, E. C., JR.: An optical recording rotameter for measuring blood flow. Proc. Soc. Exper. Biol. Med., **56**: 103-105, 1944.
148. SHIPLEY, R. E. AND GREGG, D. E.: The cardiac response to stimulation of the stellate ganglia and cardiac nerves. Am. J. Physiol., **143**: 396-401, 1945.
149. SHIPLEY, R. E., GREGG, D. E. AND WEARN, J. T.: Operative mechanism of some errors in the application of the thermostromuhr method to the measurement of blood flow. Am. J. Physiol., **136**: 263-274, 1942.
150. SHIPLEY, R. E. AND KOHLSTAEDT, K. G.: Unpublished experiments. Quoted in GREGG, D. E. Coronary Circulation. Lea and Febiger, Philadelphia, 1950.
151. SMITH, F. M.: The pharmacology of the coronary circulation in Diseases of the coronary arteries and cardiac pain, R. L. LEVY, editor. The Macmillan Company, New York, 1936.
152. SMITH, F. M., MILLER, G. H. AND GRABER, V. C.: The effect of caffein sodio-benzoate, theobromin sodio-salicylate, theophyllin and euphyllin on the coronary flow and cardiac action of the rabbit. J. Clin. Investigation, **2**: 157-166, 1925-26.
153. SMITH, F. M., MILLER, G. H. AND GRABER, V. C.: The relative importance of the systolic and the diastolic blood pressure in maintaining the coronary circulation. Arch. Int. Med., **38**: 109-115, 1926.
154 SOSKIN, S , KATZ, L. N. AND FRISCH, R.: The dual nature of the action of insulin upon the heart. Ann. Int. Med., **8**: 900-906, 1934-35.
155. SOSKIN, S., PRIEST, W. S. AND SCHULTZ, W. J.: The influence of epinephrin upon the exchange of sugar between blood and muscle. Am. J. Physiol., **108**: 107-117, 1934.
156. STARLING, E. H. AND VISSCHER, M. B.: The regulation of the energy output of the heart. J. Physiol., **62**: 243-261, 1926-27.
157. STEHLE, R. L,: A method for studying variations in coronary inflow during a series of cardiac cycles or for determining inflow rates generally. J. Pharmacol. & Exper. Therap., **46**: 471-476, 1932.
158. STELLA, G.: Some observations on the effect of pressure in the carotid sinus upon the arterial pressure and upon the coronary circulation. J. Physiol., **73**: 45-53, 1931.
159. STOLAND, O. O. AND GINSBERG, A. M.: Studies on coronary circulation. II. The effect of ephedrine on the coronary circulation. J. Pharmacol. & Exper. Therap., **49**: 345-351, 1933.
160. STOLAND, O. O. AND GINSBERG, A. M.: Studies on coronary circulation. V. The effect of pyridine-Beta carboxylic acid diethylamide (coramine) and pentamethylenetetrazol (metrazol) on the coronary circulation. J. Pharmacol. & Exper. Therap., **60**: 396-406, 1937.
161. STOLAND, O. O., GINSBERG, A. M., LOY, D. L. AND HIEBERT, P. E.: Studies on coronary circulation. IV. A. The duration of the coronary dilator action of theophylline ethylenediamine. B. The effect of insulin-free pancreatic extract on the coronary circulation. J. Pharmacol. & Exper. Therap., **51**: 387-397, 1934.
162. SULZER, R.: The influence of alcohol on the isolated mammalian heart. Heart, **11**: 141-150, 1924.
163. VAN EGMOND, A. A. J.: Über die Wirkung des Morphins auf das Herz. Arch. f. exper. Path. u. Pharmakol., **65**: 197-213, 1911.
164. VISSCHER, M. B.: The restriction of the coronary flow as a general factor in heart failure. J. Am. M. A., **113**: 987-990, 1939.
165. WAXLER, S. H. AND SCHACK, J. A.: Administration of aminophylline (theophylline ethylenediamine). J. Am. M. A., **143**: 736-739, 1950.
166. WEARN, J. T.: The rôle of the Thebesian vessels in the circulation of the heart. J. Exper. Med., **47**: 293-316, 1928.
167. WEDD, A. M.: The action of adenosine and certain related compounds on the coronary flow of the perfused heart of the rabbit. J. Pharmacol. & Exper. Therap., **41**: 355-366, 1931.
168. WEDD, A. M.: The action of certain choline derivatives on the coronary flow. J. Pharmacol. & Exper. Therap., **57**: 179-192, 1936.
169. WEDD, A. M. AND DRURY, A. N.: The action of certain nucleic acid derivatives on the coronary flow in the dog. J. Pharmacol. & Exper. Therap., **50**: 157-164, 1934.
170. WÉGRIA, R.: Action de quelques médicaments (icoral, cardiazol, coramine, doryl) sur le débit cardiaque. Arch. internat. de pharmacodyn. et thérap., **55**: 156-174, 1937.
171. WÉGRIA, R.: Circulation coronaire. Rapport sur la physiologie, la physiopathologie et la thérapeutique coronariennes. Bull. Soc. belge cardiol., No. 3, 193-202, 1939.
172. WÉGRIA, R.: Unpublished data.
173. WÉGRIA, R.: Unpublished data.
174. WÉGRIA, R.: Unpublished data.
175. WÉGRIA, R., ESSEX, H. E., HERRICK, J. F. AND MANN, F. C.: The simultaneous action of certain drugs on the blood pressure and on the flow in the right and left coronary arteries. Am. Heart J., **20**: 557-572, 1940.
176. WÉGRIA, R., FRANK, C. W., MISRAHY, G. A., SIOUSSAT, R. S., MCCORMACK, H. G., JR. AND SOMMER, L. S.: A new technique for the continuous recording of the cardiac output. Proc. Soc. Exper. Biol. & Med., **74**: 551-552, 1950.
177. WÉGRIA, R., FRANK, C. W., MISRAHY, G. A., SIOUSSAT, R. S., SOMMER, L. S. AND MCCORMACK, G. H., JR. The effect of auricular fibrillation on cardiac output, coronary blood flow and mean arterial blood pressure. Am. J. Physiol., **163**: 135-140, 1950.
178. WÉGRIA, R., FRANK, C. W., MISRAHY, G. A., SIOUSSAT, R. S., SOMMER, L. S. AND MCCORMACK, G. H., JR.: Effect of auricular fibrillation on cardiac output, coronary flow and arterial blood pressure. Federation Proc., **9**: 133-134, 1950.
179. WÉGRIA, R., GUEVARA, R. A. AND WIGGERS, C. J.: A study of spontaneous fulminant shock in a heart-long-dog preparation. Am. J. Physiol., **138**: 212-229, 1942-43.
180. WÉGRIA, R. AND KEATING, R. P.: Coronary flow in auricular and ventricular tachycardia. Am. Heart J. **37**: 685, 1949.

181. WÉGRIA, R., NICKERSON, J. L., CASE, R. B. AND HOLLAND, J. F.: The effect of nitroglycerine on the cardiovascular system of normal persons. Am. J. Med. **10**: 414, 1951.
182. WÉGRIA, R., SEGERS, M., KEATING, R. P. AND WARD, H. P.: Relationship between the reduction in coronary flow and the appearance of electrocardiographic changes. Am. Heart J., **38**: 90–96, 1949.
183. WÉGRIA, R., WARD, H. P., FRANK, C. W., DREYFUSS, F., BROWN, E. M. AND HUTCHINSON, D. L.: The effect of nor-adrenalin, morphine, procaine, tetraethyl-ammonium and khellin on the coronary blood flow. To be published.
184. WIGGERS, C. J.: The physiology of the coronary circulation. Diseases of the coronary arteries and cardiac pain. (R. L. LEVY, editor.) The Macmillan Company, New York, 1936.
185. WIGGERS, C. J.: The innervation of the coronary vessels. Am. J. Physiol., **24**: 391–405, 1909.
186. WIGGERS, C. J. AND COTTON, F. S.: Studies on the coronary circulation. I. The coronary pressure pulses and their interpretation. Am. J. Physiol., **106**: 9–15, 1933.
187. WIGGERS, C. J. AND COTTON, F. S.: Studies on the coronary circulation. II. The systolic and diastolic flow through the coronary vessels. Am. J. Physiol., **106**: 597–610, 1933.
188. WIGGERS, C. J. AND GREEN, H. D.: The ineffectiveness of drugs upon collateral flow after experimental coronary occlusion in dogs. Am. Heart J., **11**: 527–541, 1936.
189. WILLIAMS, N. E., CARR, H. A., BRUENN, H. G. AND LEVY, R. L.: Further observations on the effects of certain xanthine compounds in cases of coronary insufficiency as indicated by the response to induced anoxemia. Am. Heart J., **22**: 252–266, 1941.
190. WOOLLARD, H. H.: The innervation of the heart. J. Anat., **60**: 345–373, 1925–26.