REGULATION OF CORONARY BLOOD FLOW*

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SINCE the organizers of this symposium have invited a cardiologist, rather than a physiologist, to discuss the regulation of coronary blood flow, I have assumed that they wish me to stress clinical implications of coronary flow regulation. I hope this is true, because I do not intend to review the evidence that coronary flow is regulated in any detail, nor shall I spend time discussing just *how* it may be regulated.

This has been admirably reviewed elsewhere by Berne (1964). Let me then start by saying that I believe that coronary flow *is* regulated according to the needs of the heart and that there are three principal reasons why I think that this is so.

The first is the fact that blood withdrawn from the coronary sinus both in the unanesthetized dog (Gregg *et al.*, 1965) and in man (Messer, 1962) is extraordinarily constant in oxygen content. Coronary sinus oxygen remains more or less around the value of 30 per cent saturated over a wide range of heart rates and blood pressures, and this means that the changing metabolic demands of the myocardium are reasonably accurately met by adjustments of coronary flow.

It is almost inconceivable that this constancy could be chance: that is, the net effect of factors that might influence coronary flow, such as blood pressure and heart rate. A meaningful adjustment of flow in accordance with metabolic needs seems much more likely.

However coronary flow not only changes with myocardial oxygen consumption. If the latter is held constant, coronary flow can be shown to change also with the oxygen content of the coronary arterial blood. Reduction of arterial oxygen content, whether this is the result of anemia or hypoxemia, will cause coronary flow to increase.

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Systemic hypoxia of itself may result in increased sympathoadrenal stimulation and increased myocardial work. Thus Moret and his colleagues (1963) found that even when coronary arterial blood was kept fully saturated, severe systemic hypoxia caused a considerable increase in coronary flow. But quite apart from this, when such effects are eliminated by avoiding any change in arterial oxygen saturation, coronary flow will increase with reduction in coronary artery oxygen content. Thus Berne (1964) found that when the aortic oxygen and pressure was held constant, isolated reduction of coronary arterial oxygen content from 18.5 to 12.6 vol./100 ml. caused a 61 per cent increase in coronary flow without any change in myocardial oxygen consumption. Likewise Sobol and his colleagues (1962) found that increasing oxygen values above normal caused a reduction of coronary flow.

We have found a reflection of this during some studies of myocardial oxygen tension (Fam and McGregor, 1966). A Clark-type Po_2 electrode needle was inserted into the myocardium while another sensed the Po_2 in blood that was continuously withdrawn from the coronary sinus. When inspired gas was changed from air to oxygen, Po_2 rose transiently in both coronary sinus and myocardium. By 1½ minutes values had returned nearly to control levels. It is hard indeed to explain these changes by any mechanism other than by some form of regulation determined by myocardial oxygen tension or something very closely related to oxygen tension.

Then there is the phenomenon of reactive hyperemia. When flow through a coronary artery is temporarily occluded there is, following release, a transient elevation of flow in excess of the control value. Coffman and Gregg (1965), who made a systematic study of this reaction in the dog found that the increased flow and oxygen consumption during reactive hyperemia varied with the debt incurred during occlusion, although there was generally overpayment of both. They also noted that the coronary sinus oxygen was higher than control for some time following release of the occlusion, which led them to suggest, besides other possibilities, that the increase in coronary sinus oxygen concentration during reactive hyperemia might be secondary to the opening of the arteriovenous shunts.

We have made observations, again using myocardial Po_2 electrodes, that indicate that there is probably a real increase of tissue flow

during reactive hyperemia and that shunts need not be involved. We found (Fam and McGregor, 1966) that clamping a branch of the coronary artery produces a precipitate fall of Po_2 in the areas of muscle distal to the clamp. This is roughly proportional to the length of the occlusion. However, on release of the clamp, reactive hyperemia is associated with an elevation of Po_2 in the myocardium. Values always exceed those recorded before occlusion for some minutes. This suggests that the increase of coronary sinus Po_2 observed by Gregg and by ourselves during reactive hyperemia is not the result of arteriovenous shunts but of increased flow through the capillary bed.

This has some bearing on the way in which the regulating mechanism may work. One current theory is that the vasodilatation that occurs in anoxia, or when arterial pressure declines, is caused by deficiency of oxygen per se in the vascular smooth muscle (Guyton *et al.*, 1964). The fact that increased flow persists for some time in spite of restoration of Po_2 to levels higher than were present before occlusion is more compatible with the concept that some vasodilator metabolite is produced by hypoxic myocardium and that this accumulates in extracellular spaces and causes vasodilatation.

I shall not attempt to review the several possible substances that, it has been suggested, may play such a role (see Berne, 1964). They include adenosine, adenosine monophosphate and diphosphate, histamine, potassium, bradykinin, carbon dioxide, and hydrogen iron. However, I think present evidence points to a mechanism such as this.

According to this hypothesis active muscle cells produce a substance that we will call substance X, which has a direct action on the precapillary vessel in accordance with its concentration (Johnson, 1964). Its production increases with increasing oxygen consumption or with diminishing oxygen supply. Increasing concentration causes vasodilatation which, by restoring local Po_2, diminishes its production. In addition there may be increased rate of removal of the vasodilator substance as a result of the increased flow. It is not impossible that substance X may also be the so-called "pain substance." Apart from its direct effect on smooth muscle, when its concentration passes a threshold level, it may provide the stimulus to nerve endings that causes ischemic pain.

If this mechanism is indeed the means whereby blood flow is adjusted to metabolic needs, the site of flow adjustment must be the

arteriole lying in intimate contact with the myocardial cell, as there is no evidence that neurogenic reflexes take any part in autoregulatory phenomena.

Consider now the possible significance of this hypothesis in the normal and diseased heart. First, I suppose such a mechanism would not only regulate the total coronary flow according to the metabolic needs, but would ensure its even distribution in the myocardium in the face of mechanical factors that must tend to cause inhomogeneous flow distribution. For example, during systole the pressure surrounding subendocardial blood vessels must be greater than that surrounding the subepicardial vessels, and measurements suggest that the deep intramyocardial pressure may considerably exceed arterial systolic pressure (Eckstein *et al.*, 1963, Johnson and Di Palma, 1939). We know, however, that in spite of this a considerable volume of blood continues to flow into the coronary vessels during systole, and Gregg and his colleagues (1965) report that in the dog the flow in systole may rise to 85 per cent of that in diastole.

If deep intramyocardial pressure is indeed higher than aortic systolic pressure, that portion of coronary flow that takes place in systole must be directed into the more superficial layers of myocardium. In spite of this there is good evidence that under reasonably normal circumstances the blood flow per unit mass of tissue does not differ between the deep and superficial layers of muscle (Bloor and Roberts, 1965; Cutarelli and Levy, 1963). Equity must thus be restored during diastole, and it is hard to see how this could be achieved except by vasoregulation of small precapillary vessels.

If metabolically determined regulation of coronary blood is important to the function of the normal myocardium, it must be even more important in the presence of patchy obstructive coronary disease. One must picture the coronary flow as passing through resistances arranged both in series and in parallel (Figure 1).

As blood leaves the aorta it first traverses the large vessels (R_1), which branch and divide, eventually terminating in the precapillary vessels (R_2). Probably in the normal heart the resistance in these conductive channels, "R_1" in Figure 1, is small. Greater resistance is presumably offered by the precapillary vessels (R_2), the site of supposed autoregulation. Should there be narrowing of a conductive vessel with a localized increase of R_1, the lower oxygen tension in

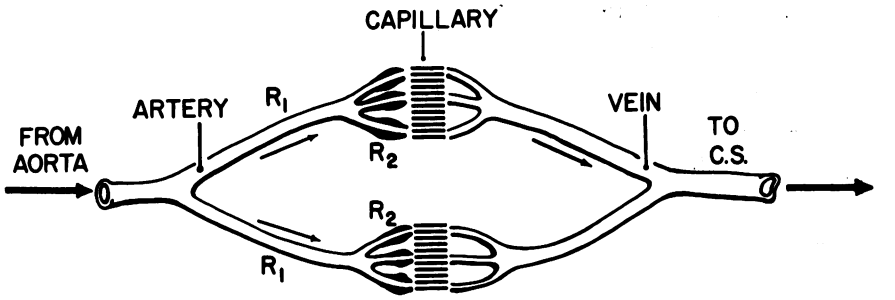

Fig. 1. Resistances in the coronary bed. Precapillary resistance is divided into R1, consisting of all the larger conducting blood vessels, and R2, the small precapillary vessels (see text).

the vascular territory of this vessel would provoke a reduction in R2 and flow distribution would remain normal. This model represents each branch of the coronary system as virtually an end artery. While this is more or less true in health, in the presence of narrowing of a coronary branch there is a tremendous growth of intercoronary collateral vessels.

One may find in the heart of an anginal patient a situation such as that represented in Figure 2, in which one branch is completely occluded but there is no infarction distal to it. The potentially ischemic muscle is supplied by collateral vessels, and flow to the potentially ischemic area (surrounded by a rectangle) is dependent of an adequate pressure at the site of origin of the collateral channels. This pressure may be less than normal as blood flow to both healthy and ischemic areas must pass through the remaining patent conductive branch, and this vessel itself may be the seat of some disease. During angina, R2 in the ischemic area will be low due to maximal vasodilatation. Reduction of R2 in the surrounding nonischemic areas of muscle by drug administration cannot be expected to increase collateral flow and may actually reduce it.

If, with a model such as this in mind, one were trying to find a drug that would bring more blood to the ischemic area of muscle, one would search for a substance that had a selective effect on the large conductive vessels or on the collateral channels, but that left the autoregulatory function of the small resistive vessels intact. Administration of such a drug might well cause a transient rise of coronary flow but, because autoregulation was intact, flow would rapidly return to control levels. The conductive vessels on the surface of the heart following this drug would remain enlarged and their resistance

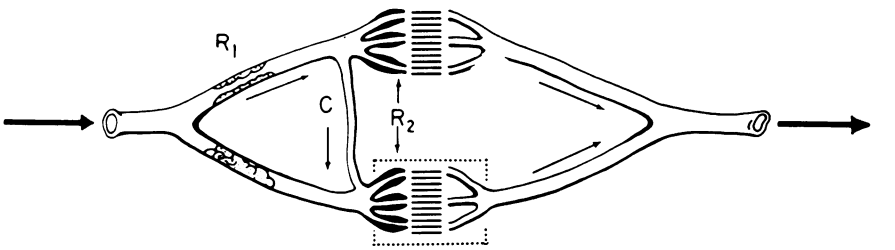

Fig. 2. A model of the coronary vascular circuit in the presence of occlusive vascular disease. In this example the lower conductive vessel is completely occluded, its myocardial territory (rectangle) being supplied by collateral channels (*C*).

reduced. The only drugs that appear to conform to this description are the nitrites.

Furthermore, in any search for antianginal drugs one would surely avoid those that impaired coronary flow regulation, and it is interesting that a generation of pharmacologists has done just the opposite. These investigators have sought the drug that would produce the greatest elevation of coronary flow in the normal heart. This effect could be achieved only by interfering with autoregulatory function. Let us compare the effects of one of the most potent coronary vasodilator drugs, dipyridamole, with nitroglycerin. Following intravenous nitroglycerin there is a transient increase in coronary flow that may last from 30 to 120 seconds. It may last even up to 3 minutes following a sublingual nitroglycerin tablet (Bernstein *et al.*, 1966), but it is unnecessary to remind you that the therapeutic effect lasts for at least 20 minutes, and that there is angiocardiographic evidence in man of a sustained increase in the bore of all the conductive blood vessels (Gensini *et al.*, 1962). Thus from 3 to 20 minutes nitroglycerin appears to vasodilate the large conductive vessels without increasing coronary flow. This suggests that it acts primarily on R_1 (Figure 2), leaving regulatory function at R_2 intact. Dipyridamole, by contrast, over the same time period causes a sustained increase of coronary flow and coronary sinus oxygen content. This is associated with impairment of autoregulatory function. It appears to act primarily on R_2 (Fig. 2).

How far can these statements be justified? We should like, of course, to measure R_1 and R_2 respectively. This we cannot do. However we can examine the gradient down a relatively short segment of one of the conductive vessels. Using the normal dog, we have placed an electromagnetic flow probe on the anterior descending branch of the left coronary artery. At the same time we have cannulated a

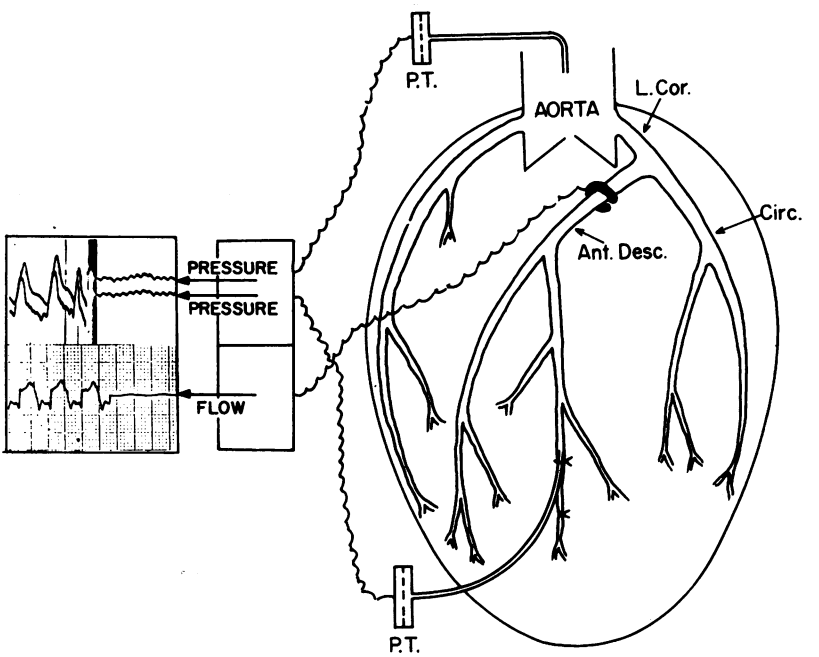

Fig. 3. Experimental preparation for examining changes in a segment of the conductive vessels. Cannulae connect the aorta and a distal branch of the anterior descending coronary artery to pressure transducers (P.T). An electromagnetic flow probe is placed on the anterior descending branch. Changes in resistance of the anterior descending coronary artery from its origin to all points in each branch of equal pressure to that recorded by the cannulas can be estimated by relating the measured flow to the measured pressure difference. Likewise total resistance in the anterior descending branch is the difference between aortic mean pressure and coronary sinus pressure (considered 0) divided by flow.

small distal branch and, by measuring aortic pressure, we could observe the pressure difference from the aorta to this distal site (Figure 3). In this way we could estimate the resistance throughout the arterial system from its origin down to all points at which there is a pressure equivalent to that at the tip of the distal cannula. This measures only a small portion of "R1" but the direction of change in this segment should tell us the direction of change in R1 as a whole. A drug that selectively vasodilates the large conductive vessels should reduce the pressure gradient from aorta to the distal coronary branch without causing any permanent flow change.

In spite of considerable pressure fluctuation with each respiratory cycle apparent in Figure 4, it may be seen that the pressure gradient down the coronary artery has definitely narrowed following nitroglycerin (0.6 mg.) given intravenously over 1 minute. The resistance

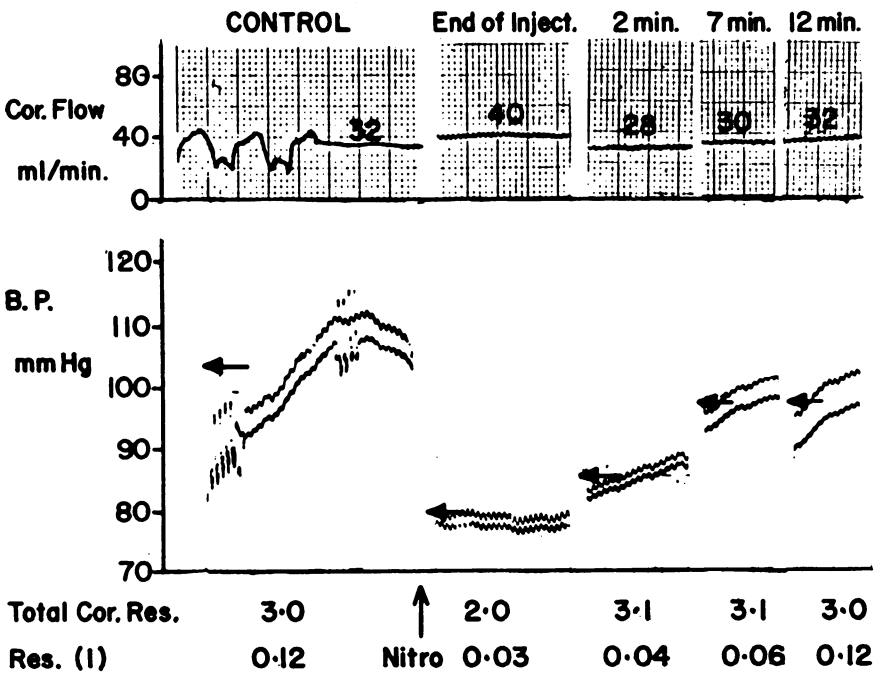

Fig. 4. Anterior descending coronary flow, aortic and distal coronary pressure, total anterior descending coronary resistance, and the resistance in that portion of the coronary artery under study (Res. 1) before and after the intravenous injection of 0.6 mg. nitroglycerin over 1 minute (see Figure 3). Horizontal arrows denote mean aortic pressure over three respiratory cycles.

of this segment of vessels (Res. 1) falls. The total coronary resistance, however, is virtually unchanged from 2 minutes onward.

Following dipyridamole the changes are quite different (Figure 5). There is now a sustained increase in coronary flow and the pressure gradient down the cannulated segment of R1 increases. The resistance of this segment is unchanged and total coronary resistance has fallen. Vasodilatation must have taken place distal to the segment of artery examined.

We have not made a systematic study of autoregulation. We have compared these two drugs, however, as regards their effect on reactive hyperemia in the open-chest, anesthetized, otherwise normal dog (see Figure 6). In the control experiment during occlusion of the circumflex branch for 30 seconds there is an increase of flow in the nonoccluded anterior descending branch and, on release of the clamp, there is typical reactive hyperemia. Four minutes after 0.6 mg. intravenous nitroglycerin, flow values are unchanged and the changes in flow

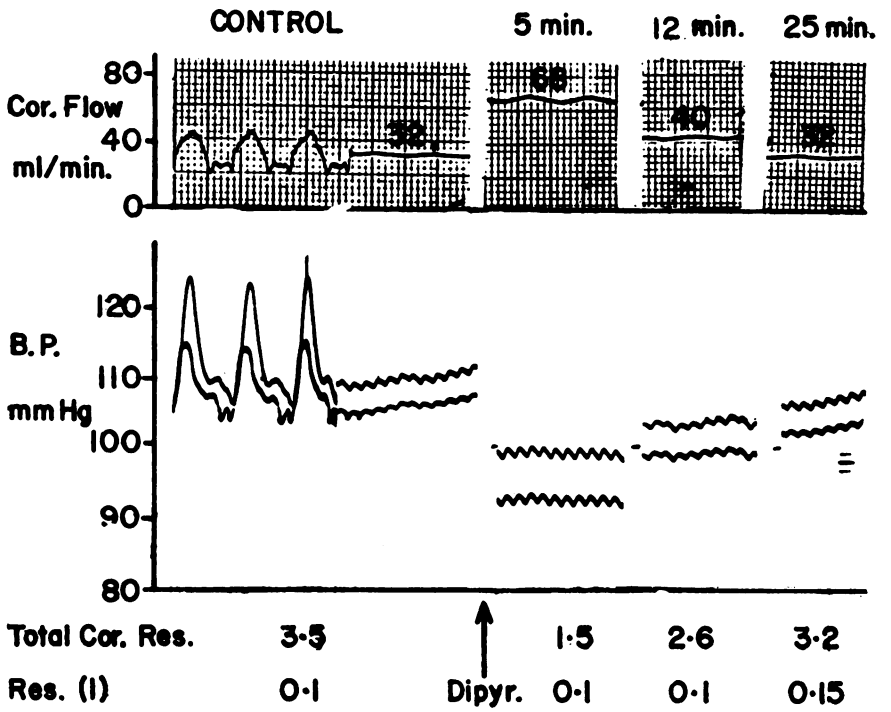

Fig. 5. The same variables as in Figure 4 following the intravenous injection of 5 mg. dipyridamole over 1 minute.

associated with clamping and release are identical. Seven minutes after 5 mg. intravenous dipyridamole, however, flow in both vessels is still greatly elevated, clamping provokes no increase in flow but rather a decrease in the anterior descending artery, and reactive hyperemia in the circumflex branch is virtually abolished. Exactly comparable phenomena are reflected in the changes observed in myocardial and coronary sinus oxygen tension (Fam and McGregor, 1966).

In summary, if nitrites lower the resistance in the conductive vessels without affecting the autoregulatory function of the small vessels they should promote blood flow through collateral channels into the ischemic territory as outlined above. By contrast dipyridamole, by dilating the small resistance vessels that control flow in accordance with demand, should increase blood flow from artery to vein in the area of healthy vessels but might actually reduce the blood available to perfuse the ischemic area via collateral channels.

We have attempted to create a suitable model to test this hypothesis. It is possible, in the dog, to occlude slowly a coronary branch with

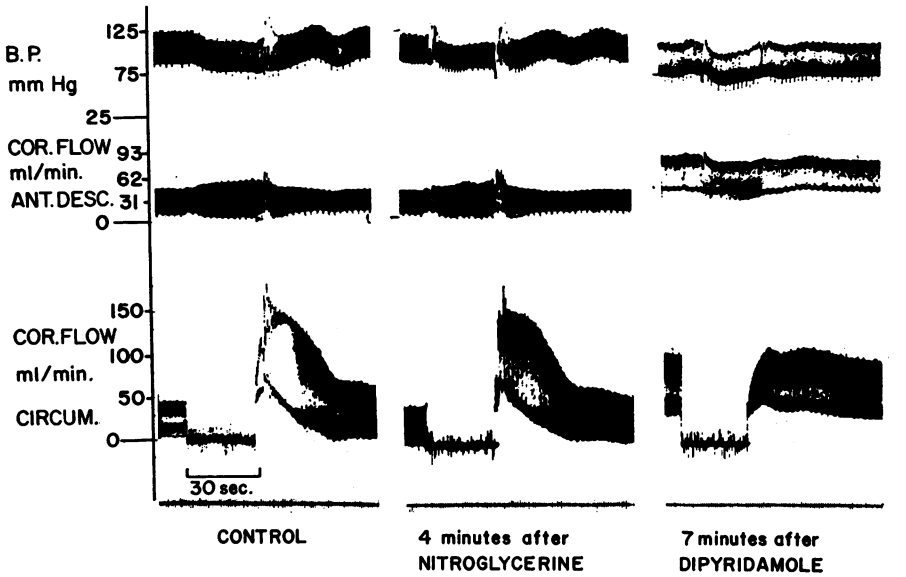

Fig. 6. Aortic pressure, anterior descending coronary flow, and circumflex coronary flow. Increased anterior descending flow during circumflex occlusion, and reactive hyperemia in the circumflex vessel are not modified by nitroglycerin, but are abolished by dipyridamole.

a device called an ameroid constrictor, which produces 90 to 100 per cent of complete occlusion within about 3 weeks (Vineberg *et al.*, 1960). In this time collateral vessels develop to such a degree that they are quite capable of sustaining the function of the myocardium without infarction. If this branch is cannulated just distal to the site of occlusion some months later, the retrograde flow that emerges gives some idea of the extent of intercoronary collateral blood flow. We have found that at any given aortic pressure nitroglycerin increases this flow without increasing total blood flow from aorta to coronary sinus. By contrast, dipyridamole increases total flow but does not increase the retrograde flow (Fam and McGregor, 1964). Furthermore, in similar studies in which we observed the oxygen tension in the ischemic area and in an adjacent healthy area without measuring retrograde flow, we found that nitroglycerin caused an increase in oxygen tension in the ischemic area distal to the site of occlusion without causing any change in the oxygen tension of adjacent healthy areas. By contrast, dipyridamole caused an increase in oxygen tension in healthy areas without increasing oxygen tension in the ischemic area (Fam and McGregor, 1966).

Conclusion

It seems extremely likely that coronary blood flow to each area of the heart is indeed regulated by the concentration of a vasodilator metabolite acting on the precapillary arteriole. The presence of this mechanism is probably essential to the even distribution of blood to heart muscle in health and, particularly, in coronary occlusive disease.

It is most unlikely that drugs that impair this autoregulatory function will increase the blood flow to ischemic areas of myocardium. The very fact that a drug raises flow and coronary sinus oxygen content to higher than normal levels in the healthy heart indicates that it is impairing the mechanism that we suppose regulates flow to demand.

In the search for better coronary vasodilator drugs, we should therefore not look for drugs that increase coronary flow in the normal heart, but should search rather for drugs that confine their vasodilator action to the large conductive blood vessels without impairing regulatory function. It is likely that the effectiveness of nitrate preparations in relieving angina pectoris is largely attributable to this characteristic. Nitrites of course have other actions that may cause reduction of myocardial oxygen consumption; these are considered in detail elsewhere (Hoeschen *et al.*, 1966).

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