SUMMARY. Understanding and controlling the consequences of myocardial ischemia requires us to acknowledge that we are dealing with a complex, dynamic, and highly variable process. The severity and progression of ischemic injury is not solely determined by the extent of oxygen deprivation, but by many other factors, including the accumulation of toxic metabolites. It may not be justified to assume that injury to the myocyte necessarily determines the survival of the organ; other components, such as the endothelium and the conducting system, may play a crucial role. Many factors can influence the severity and evolution of ischemic injury, perhaps the most important being the extent of residual (or collateral) flow to the affected tissue. If the ischemia is relatively mild, then the myocardium may survive for some time, and drugs and other interventions may be used to further extend this period. However, reperfusion and the establishment of an adequate level of coronary flow is an absolute prerequisite for sustained tissue survival. The more severe the ischemia, the earlier must be the reperfusion. However, reperfusion of previously ischemic tissue is not without hazard, and it may precipitate potentially lethal events such as arrhythmias. Reperfusion may possibly result in the death of cells that were potentially viable in the moments before reflow was established, and there is good evidence that manipulation of reperfusion conditions may accelerate and possibly enhance recovery from ischemia. Much remains to be learned about myocardial ischemia and reperfusion, and in doing this we should perhaps put some of the older, yet well established, concepts behind us.

KEY WORDS. ischemia, myocardial metabolism, oxygen imbalance, reperfusion

The Imbalance of Supply And Demand: A Variable and Dynamic Condition

Through their choice of the title: "Modern concepts in the Treatment of Ischemic Heart Disease," the editors of this symposium have, perhaps by intention, cast a shadow of doubt over the validity of some established concepts relating to myocardial ischemia and its management. Have our concepts changed, should they change, or could it be that we are rediscovering old problems, but this time giving them glamorous and credible names? The "stunned cardiologist" [1] of the 1980s has suffered from a barrage of terminology (silent ischemia, stuttering ischemia, stunned myocardium, jeopardized myocardium, blighted myocardium, hibernating myocardium, condemned myocardium, infarct size limitation, and reperfusion-induced injury, to mention a few) and might be forgiven for seeking reassurance and/or clarification.

Fortunately, the cornerstone of our understanding of ischemia remains more or less intact [2, 3]. Thus, ischemia involves an imbalance between the needs of the tissue for life-sustaining blood and the ability of the vasculature to respond adequately to this requirement. In recent years, however, our understanding of the origins of this condition has become considerably more sophisticated. It is now acknowledged that it is not invariably a simple thrombotic occlusion that generates a zone of potentially lethal ischemia, but other factors, such as progressive atherosclerosis, plaque rupture, coronary spasm, and adverse drug-induced effects may also initiate the event. From this broader view of ischemia and its origins, has come the important recognition that the phenomenon is by no means static, but is highly dynamic (such that the affected tissue may experience waves of ischemia of varying severity and duration) and involves other important factors in addition to supply and demand. As will be discussed later, the impairment of washout may be of equal or even greater importance than deficient supply.

Since traditional definitions of ischemia can be flawed on at least two counts, (1) they fail to take account of the dynamic state of the cell and the ischemic process and (2) they fail to take account of problems of washout as well as supply, it may be appropriate to define ischemia as it will be used in the context of this article. Ischemia arises when coronary blood flow is inadequate to maintain steady state metabolism. This will result in the development of an anaerobic metabolism and an intensifying metabolic imbalance, a condition that will be expressed in a number of ways, e.g., the

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net degradation of the adenine nucleotide pool, which occurs as a consequence of an inadequate ability to support a sufficient rate of ATP turnover. Unless halted, this deterioration of metabolic imbalance will culminate in cell death, a process that may be hastened by failure of washout as well as supply.

Ischemia and the Extent of Flow Reduction

Although ischemia is often studied in its most severe form (sustained zero coronary flow), it is important to appreciate that total cessation or even marked deficiency of blood flow is not a prerequisite for myocardial ischemia. Tissue can suffer significant ischemic injury when blood flow is still substantial. It can even be argued that tissue with a relatively normal blood flow at rest may become ischemic under conditions of increased demand for energy because of the failure of its vasculature to respond sufficiently to the requirement of an increased cardiac output.

The Crucial Role of the Collateral Circulation

Besides our appreciation that the occlusion of a coronary artery need not be total for ischemia to ensue (such that myocardial infarction might well occur in the absence of occlusion [4]), we have also realized that even in the presence of complete obstruction, coronary flow may not fall to zero. Collateral flow [5-9] from cardiac and extracardiac sources can provide a lifeline to tissue that has been deprived of its more usual source of blood [6, 10]. Thus in dogs [6] and many patients with coronary artery disease, extensive artery-to-artery anastomoses are found between adjoining coronary perfusion beds. These collateral connections may supply the equivalent of a third or more of the normal blood flow and may explain why, despite transmural zones of ischemia, only a subendocardial infarct may develop. Thus, residual or collateral flow to an ischemic zone may well result in the salvage of a significant amount of tissue. Younger patients, and species such as the pig [6] and baboon, are normally devoid of collateral vessels, and in them coronary occlusion results in the rapid development of a fully transmural infarct. The guinea pig [6] is blessed with a totally collateralized coronary anatomy and as such is naturally resistant to ischemia and infarction.

The Severity of Ischemia

Although the extent of residual or collateral flow to an area of regional ischemia is the single most important determinant of the severity of that ischemia, and hence the fate of the tissue, other factors such as heart rate, inotropic state, myocardial oxygen consumption (MVO₂), and coexisting diseases such as diabetes mellitus, hypertension, and thyroid disorders all act to reduce or intensify the severity (and hence affect the outcome) of an ischemic episode [10, 11]. Unfortunately some of these factors, particularly coexisting disease, are difficult to reproduce in the laboratory, a consideration that has significantly limited our understanding of human myocardial ischemia.

Surprisingly, the crucial relationships between the extent and duration of ischemia and its outcome are rather poorly defined. We know, for example, that myocytes can survive very severe ischemia (zero flow) only for short times (perhaps 30 to 40 minutes) but may survive moderate deprivation of flow lasting several hours. In this connection, we [12, 13] have suggested that ischemia be designated tolerable, critical, or lethal. In a dog study [13], we observed that reductions of coronary flow up to approximately 50% had relatively little effect upon the tissue content of high-energy phosphates, even if the reduction in flow was maintained for as long as 2 hours. In this state of tolerable ischemia, tissue energy balance is probably maintained by a combination of increased oxygen consumption per unit flow, reduced contractile performance, and more efficient utilization of substrate (for example, switching from fatty acid to glucose utilization). Thus, although contractility may be reduced, tissue in this state should remain free of major metabolic or morphological injury for long or indefinite periods. It should not become infarcted (unless excessively stimulated) and thus represents a tolerably but chronically ischemic tissue mass, which may respond well to metabolic or pharmacological interventions designed to make the most of the energy supply/energy demand status. Drugs such as coronary vasodilators might afford real protection to such tissue with a sustained improvement in, or even a normalization of, contractile performance.

In our second proposed state of ischemic injury, reductions in flow of about 60%-80% in the dog heart caused the tissue energy levels to decline. The greater the reduction in flow, or the greater the duration of ischemia, the greater was the energy imbalance. In this phase, designated as critical ischemia [12], small changes in flow or in duration of ischemia could result in large changes in tissue energy status. It is possible that tissue in this state could be appropriately iden-