a range that represents only a small fraction of the tissues' total capacity. In many tissues the rates of conversion of glucose to pyruvate and lactate are kept at a small fraction of total capacity by chemical signals generated as a consequence of the operation of the Krebs cycle and the electron transport system in which oxygen is the final acceptor. The effect of anoxia on the rate of lactate production in a tissue such as muscle results from a decrease in the signals which are usually generated as a consequence of respiration and an increase in glycolysis. Under these conditions the end product of glycolysis appears primarily as lactate, since a secondary consequence of impaired respiration is an increase in the cytoplasmic free NADH/NAD ratio, which is one of the factors determining the ratio of lactate/pyruvate in the cytoplasm. There is no doubt that in lactic acidosis, as in diabetic ketoacidosis, the rate of production of a normal product can be increased to levels that threaten the organism's existence. Lactate released into the circulation by other tissus is removed in large part by the liver, where it is utilized to a considerable degree for the resynthesis of glucose. The only value of this simplistic outline is to stress the point that factors that permit the expression of the tremendous latent capacity for lactate production in many tissues, or which impair the capacity of the liver to dispose of lactate, may eventuate in lactic acidosis. It is well established in adult-onset diabetics that chronic phenformin administration results in significant elevation of blood lactate concentrations. While in most patients the levels observed give little cause for concern, the effect does appear to be dose related.[32] There is, therefore, the possibility that at sufficiently high concentrations phenformin might induce lactic acidosis in humans either by increasing peripheral lactate production or by decreasing hepatic utilization, or both. This would appear to be the case since there are well documented instances in which phenformin was taken for suicidal purposes, with the subsequent development of lactic acidosis.[33]

The biguanides are unlikely to be the sole cause of the increased frequency of lactic acidosis in diabetics, since this syndrome has been observed in patients who are not receiving these drugs. Adult-onset diabetics are, as a group, individuals at increased risk to the development of a number of acute conditions which may produce local circulatory changes conducive to the development of either increased lactate production or impaired disposition. It seems difficult to exclude the possibility that, under these circumstances, the presence of biguanides may potentiate the development of lactic acidosis. The efforts to exclude this possibility are not totally convincing; thus, the failure of biguanides to potentiate markedly the rise in blood lactate in rats exposed to low oxygen tensions ignores the relative insensitivity of this animal to the effects of these compounds. We find ourselves in agreement with Oliva, who concluded: "It remains possible that the association of phenformin and lactic acidosis is coincidental since lactic acidosis may occur in diabetic subjects not taking phenformin, as well as in non-diabetic subjects. The weight of the indirect evidence, however, strongly suggests that phenformin plays a causal or contributory role in the production of lactic acidosis."[31] It is interesting that the only death specifically ascribed to lactic acidosis in the UDPG study occurred in a patient in the group receiving phenformin.[2] In sum, since phenformin fills no unique requirement in the treatment of adult-onset diabetes, since its mode of action is uncertain but unlikely