onset diabetics in whom they are effective is undisputed. In contrast, the manner in which phenformin lowers blood glucose in human diabetics, or in animals with alloxan diabetes, remains an enigma, but the fragmentary data available are not reassuring. An effect on insulin secretion has been excluded, although some residual endogenous insulin secretion is necessary for phenformin to be effective in lowering blood glucose. Kruger et al. have reported that phenformin impairs intestinal glucose absorption in man;[29] this compound also increases peripheral glucose utilization, albeit with an increased rate of lactate production.[30] The applicability of data derived from other species must be questioned because of the marked species variation in susceptibility to the hypoglycemic effects of phenformin. Thus, Kreisberg and associates dispute any effect of phenformin on decreasing hepatic glucose production or release in man.[30] However, at high concentrations phenformin does inhibit gluconeogenesis in isolated perfused rat liver.[30] In none of the isolated tissues in which the effects of phenformin have been examined is there clear evidence that phenformin restores a pattern of metabolism resembling that observed in the animal with a normal insulin secretory mechanism.

More to the point, biguanides are ineffective in the prevention of keto-acidosis, and there is no evidence that they have the assured efficacy of insulin in the management of acute symptomatic hyperglycemia. It is obviously not a suitable agent to use in those patients in whom a serious effort to achieve a normal range of blood glucose fluctuation is undertaken with the aim of correcting the underlying derangements in tissue metabolism that may contribute to the pathogenesis of the late complications. In patients in whom efforts at weight reduction have failed to remove the threat of symptomatic hyperglycemia, biguanides have no obvious advantage over insulin or the sulfonylureas (unless one wishes to view its effects on glucose absorption as an advantage). There is thus no obvious requirement for biguanides in the treatment of adult-onset diabetes, unless one will accept its use as an adjuvant to ineffective treatment with sulfonylureas. Since suitable alternatives are available, the justification for the additional risk entailed in this practice escapes us. The UDPG study reported a significant excess cardiovascular mortality in the groups treated with phenformin, but again the causal nature of this relationship is difficult to establish. However, there remains the distinct possibility that phenformin may represent a pharmacologic hazard in a group of patients who tend to develop general or local circulatory insufficiency. We believe this may contribute to the association between phenformin administration and the development of clinical lactic acidosis.[31]

Lactic Acidosis

The pathogenesis of lactic acidosis in those instances in which there is no obvious evidence of local tissue hypoxia is poorly understood. However, it is clear that in many tissues the rate of lactate production under normal conditions is in