centration of drug compatible with the clinical setting.[9] In addition, a portion of the effects of sulfonylureas may relate to inhibition of cyclic AMP phosphodiesterase, with a consequent net increase in cyclic AMP.[10]

One must also keep in mind the significant, and sometimes serious, hypoglycemia induced by sulfonylurea drugs. None of those currently available is an exception. Some of these enhanced hypoglycemic effects of the sulfonylureas have been related to the coincident use of other drugs such as salicylates, monamine oxidase inhibitors, phenylbutazone, sulfonamides, sulfisoxazole, sulfaphenazole, coumarin anticoagulants, and phenyramidol.

Occasional patients on sulfonylurea drugs are suspected of having a rapid loss of endogenous insulin function because it appeared necessary after a short period of treatment to give insulin to control the diabetes. Such observations obviously have suggested that the sulfonylurea might have accelerated the depletion of pancreatic insulin. However, studies in animals chronically treated with sulfonylureas have not supported this concept. Rather, there has been consistent histologic evidence of an increase in the number of beta cell mitoses, hypertrophy of the islets, and an increase in mass of islet tissue.[6, 9]

No data have been presented to suggest that biguanides "wear out" the insulin mechanism. The means by which biguanides lower blood glucose levels in diabetics, but not in normal humans, remains uncertain. By whatever means they act, these substances lower blood glucose levels in diabetic individuals having some available endogenous or exogenous insulin, albeit more gradually than is noted in responsive diabetic individuals following sulfonylureas. Available endogenous or administered insulin simply appears to be more effective when phenformin or other biguanides are administered. In the absence of any demonstrable effect of these compounds upon the pancreatic islet cell, it is not surprising there is no evidence thus far that diabetes is worsened metabolically by their administration.

A number of studies have suggested that sulfonylureas or biguanides may ameliorate "chemical" or "latent" diabetes[6] (as defined by the American Diabetes Association[11]). Although inconclusive, observations of no adverse effects have now accumulated for a sufficient number of years to allow one to assume that at least no worsening of the diabetes is likely to be produced.

Infection

At one time the increased susceptibility of the diabetic to invasive local and systemic infection accounted for an important portion of the morbidity and mortality among diabetics. With improved control of diabetes following the availability of insulin and the proper use of antibiotic treatment, infections in the diabetic now pose much less of a problem.

Recent studies have helped to clarify the issue as to whether the diabetic is indeed more susceptible to infection. Defects in host defense can be related to the degrees of hyperglycemia and/or ketoacidosis.[12, 13] Uncontrolled diabetes of short duration may not be associated with a great likelihood of infection, but when present over a period of weeks and months the patient becomes more susceptible. Thus far no studies have clearly defined the critical degree or duration