treated with metformin. This project is based on data showing increased life span of mice and rats supplemented with metformin and on results of clinical observations that demonstrated decrease of mortality in diabetic patients treated with metformin.[4–7] Moreover, a 15% increase was reported in survival of type 2 diabetic patients primarily treated with metformin as compared with healthy people without diabetes.[8] These findings and the planning of the TAME clinical trial[2] raise the question of the safety of long-term administration of metformin in non-diabetic people. In this chapter, we mainly evaluate the available results of preclinical studies on the geroprotective effects of metformin (*N*,*N*-dimethylbiguanide) and other antidiabetic biguanides, phenformin (1-phenylethylbiguanide), and buformin (1-butylbiguanide hydrochloride), and give perspectives on their wide introduction in clinical practice. We focus mainly on end-point results of studies to get answers to two critical questions: (1) could biguanides promote life span extension in non-diabetic individuals? and (2) are they safe for long-term treatment? The mechanisms of the geroprotective, anti-carcinogenic and antitumor effects of biguanides are being intensively studied at present. The findings of these investigations are reported in a lot of comprehensive reviews.[9–12]

17.2 Milestones in Research on Biguanides as Drugs for Aging Prevention in Rodents

In the early 1900s, guanidine was identified as an active compound of the botanic medicine plant *Galega officinalis* (French Lilac), which was commonly used in medieval Europe for the treatment of polyurea in diabetic patients.[13] However, due to the discovery of insulin in 1921, only 30 years later the first biguanides (phenformin, buformin and metformin) were synthesized. The drugs were approved in the middle of the last century in the USA and Europe for the treatment of type 2 diabetes mellitus.

In 1971, Dilman[14] proposed that antidiabetic biguanides may be promising as potent anti-aging and anti-cancer drugs. In the middle of the 1970s, he initiated a series of experiments in mice and rats in the N.N. Petrov Research Institute of Oncology to prove this suggestion. In 1974, it was shown for the first time that phenformin inhibits 7,12-dimethylbenz(*a*)anthracene (DMBA)-induced mammary carcinogenesis in female rats.[15] Five years later, the first article on the inhibitory effect of phenformin on spontaneous mammary carcinogenesis and life span extension in female C3H/Sn mice was published.[16,17] At the same time, we reported the results of studies of the impact of buformin and phenformin on the aging of the reproductive system, life span and incidence of spontaneous tumors in female rats.[18–20] In the same period, a lot of research studies showed the capacity of biguanides to prevent chemically- and irradiation-induced carcinogenesis in rodents. Data on the cancer preventive and anti-tumor effects of biguanides have been analyzed in some recent papers.[21–23] In 2005, it was shown that metformin prolongs the life span and inhibits the development of mammary adenocarcinomas