of cancer-prone female transgenic HER-2/neu mice.[24] In 2008, we observed a 38% increase in life span delay in female SHR mice treated with metformin starting from the age of 3 months.[25] Then, it was for the first time shown that metformin is less effective as a geroprotector in adult and old females of the same strain.[26] We also observed that the effects of metformin depend on the sex of the animals—it extended the life span in female but reduced it in male 129/Sv mice.[27] At the same time, Smith *et al.*[28] failed to increase life span in male F344 rats by treatment with metformin. Notably, the neonatal treatment of 129/Sv mice with metformin inverted its gender-dependent effect: in males an increase of life span was observed whereas the female longevity was reduced.[29]

17.3 Effect of Antidiabetic Biguanides on Aging and Life Span in Rats

F344 rats of both sexes were used in the National Cancer Institute Bioassay of Phenformin for Possible Carcinogenicity.[30] The matched control groups included 15 animals each and groups exposed to phenformin consisted of 35 animals each. Phenformin was given in doses 400 and 800 ppm in diet for 78 weeks starting at the age of 8 weeks. Measurement of food consumption allowed doses of phenformin to be estimated as 300–625 mg kg^{-1} day^{-1}. The treatment was followed by an observation period of 26 weeks, than all survived animals were sacrificed. The mean body weights were consistently lower as compared with the controls during the treatment period, while the body weights of males were unchanged by the drug. 53% of control male rats survived until the age of 105 weeks, among them 67% high-dose and 91% low-dose treated males. There were no significant differences between the mortality in the different groups of female rats. 83% of the high-dose group, 68% in the low-dose group and 67% in the control group survived to the end of the study. The incidences of tumors of any localization in males as well as of the majority of tumors in female rats were similar in the control and in the phenformin-treated groups. However, the incidence of tumors of reproductive system was statistically less (21% and 17%) than that in the matched controls (47%) ($p = 0.027$).

Buformin was given 5 times a week in a single dose of 5 mg rat^{-1} day^{-1} orally to female Leningrad Institute Oncology (LIO) rats starting from the age of 3.5 month until a natural death.[18,20] The treatment slightly increased mean life span of rats (by 7%; $p > 0.05$). The mean life span of the last 10% survivors increased by 12% ($p < 0.05$), and the maximum life span increased by 2 months (+5.5%) as compared with controls. The body weight of rats treated with buformin was slightly (5.2 to 9.4%) but statistically significantly ($p < 0.05$) decreased in comparison with the control. At the age of 16–18 months, 38% of control rats revealed disturbances in the estrus cycle (persistent estrus, repetitive pseudopregnancies or anestrous), whereas in females treated with buformin these disturbances were observed only in 9% of rats ($p < 0.05$). The