Chronic diseases are major killers in the modern era. Physical inactivity is a primary cause of most chronic diseases. The initial third of the article considers: activity and prevention definitions; historical evidence showing physical inactivity is detrimental to health and normal organ functional capacities; cause versus treatment; physical activity and inactivity mechanisms differ; gene-environment interaction (including aerobic training adaptations, personalized medicine, and co-twin physical activity); and specificity of adaptations to type of training. Next, physical activity/exercise is examined as primary prevention against 35 chronic conditions [accelerated biological aging/premature death, low cardiorespiratory fitness (VO2max), sarcopenia, metabolic syndrome, obesity, insulin resistance, prediabetes, type 2 diabetes, nonalcoholic fatty liver disease, coronary heart disease, peripheral artery disease, hypertension, stroke, congestive heart failure, endothelial dysfunction, arterial dyslipidemia, hemostasis, deep vein thrombosis, cognitive dysfunction, depression and anxiety, osteoporosis, osteoarthritis, balance, bone fracture/falls, rheumatoid arthritis, colon cancer, breast cancer, endometrial cancer, gestational diabetes, pre-eclampsia, polycystic ovary syndrome, erectile dysfunction, pain, diverticulitis, constipation, and gallbladder diseases]. The article ends with consideration of deterioration of risk factors in longer-term sedentary groups; clinical consequences of inactive childhood/adolescence; and public policy. In summary, the body rapidly maladapt to insufficient physical activity, and if continued, results in substantial decreases in both total and quality years of life. Taken together, conclusive evidence exists that physical inactivity is one important cause of most chronic diseases. In addition, physical activity primarily prevents, or delays, chronic diseases, implying that chronic disease need not be an inevitable outcome during life.