The following reactions are *difficult to elicit* in test animals used in toxicity tests:

- Immunological reactions, including anaphylaxis and eczema
- Arteriosclerosis. Mild atherosclerotic lesions can be induced by excessively high lipid diets

Furthermore, idiosyncratic drug reactions in humans are likewise generally unpredictable by toxicological investigations. Such reactions are rare and often based on a particular sensitivity of the affected individual, such as in the case of a rare metabolic peculiarity.

Lesions associated with impaired or changed organ function can also affect other organs resulting in "syndromes" such as the hepato–renal syndrome (132), thyroid changes associated with liver hypertrophy (133–137), changes in bones (138) and parathyroids (139) associated with renal disease or the association of hypoxemic lung pathology with adrenal medullary proliferations related to stress (140). Some of these syndromes will be explained in more detail below (Sec. 5.2).

5. TYPICAL NEOPLASTIC CHANGES SEEN IN LIFE-TIME BIOASSAYS

5.1. Introduction

The most important lesions in life-time rodent bioassays are tissue proliferations: hyperplasia, benign tumors, and malignant tumors. The *biological behavior* of these lesions is often not well understood, as—in contrast to human pathology—no biopsies and follow-ups are available. This also renders the establishment of the cause of death difficult (76,141). Histopathological diagnosis of proliferative lesions in rodents is partly based on assumptions and agreement among pathologists, including size criteria to label a tumor as benign or malignant (12). Therefore, standardization of diagnostic criteria is particularly important and the method should be referenced in the report (63,64,78). Deviation from standardized diagnostic criteria is permissible, but must be justified and defined.

Analysis and interpretation of life-time rodent bioassays is among the most *demanding* tasks a pathologist must face (142,143). The development of a compound can be jeopardized by adverse pathological findings just before introduction to the market. On one hand, it is good to remember that there are many more animal carcinogens than human carcinogens (144,145). On the other hand, toxicologists and toxicologic pathologists have the responsibility to make sure that humans and the environment are not exposed to real carcinogens. The diagnostic quality depends on the qualifications and ability of the pathologist, which necessitates many years of postgraduate training in pathology (146). Board certification (US, EU,