Development of Urinary Bladder Cancer in the Rat *

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I. General Introduction .................................................. 146
II. The Normal Mucosa of the Urinary Bladder ...................... 147
  1. Histology ......................................................... 147
  2. Enzyme Histochemistry ........................................... 149
  3. Regeneration ..................................................... 153
III. Carcinogenesis in the Bladder Mucosa ............................ 155
  1. Enzyme-Histochemical Investigations ............................ 155
     a) Introduction .................................................. 155
     b) Material and Methods ........................................ 155
     c) Results ....................................................... 157
     d) Discussion ................................................... 167
     e) Summary ...................................................... 170
  2. Combined Enzyme-Histochemical and Autoradiographic Investigations ........................................ 170
     a) Introduction .................................................. 170
     b) Material and Methods ........................................ 170
     c) Results ....................................................... 172
     d) Discussion ................................................... 177
     e) Summary ...................................................... 179
  3. Stages of Transformation in Papillomas .......................... 180
     a) Introduction .................................................. 180
     b) Material and Methods ........................................ 180
     c) Results ....................................................... 181
     d) Discussion ................................................... 192
     e) Summary ...................................................... 194
  4. Proliferation Kinetics of Transformation Stages within Papillomas ........................................ 195
     a) Introduction .................................................. 195
     b) Material and Methods ........................................ 195
     c) Results ....................................................... 197
     d) Discussion ................................................... 199
     e) Summary ...................................................... 202
  5. Morphology, Classification and Histogenesis of Carcinomas ........................................ 203
     a) Introduction .................................................. 203
     b) Material and Methods ........................................ 203
     c) Results ....................................................... 203

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I. General Introduction

As early as 1895 — long before any clues to the etiology of tumors in other organs were apparent — Rehn reported his observations of the increased occurrence of tumors of the urinary bladder in laborers who had daily contact with basic fuchsin over a long period. He suspected a causal connection between aniline, nitrobenzol, toluidine, and basic fuchsin and the development of the observed tumors. The years immediately following this report did not see confirmation of the suspected carcinogenicity of these substances (for a review of the literature see Temkin, 1963; Sarma, 1969; Price, 1971). Nevertheless, Rehn’s observations did initiate an early intensive search for substances that could induce tumors in the human bladder.

At present four chemical substances are known with certainty to cause tumors in the human bladder (Temkin, 1963; Sarma, 1969; Price, 1971). These are β-naphthylamine, benzidine, 4-aminodiphenyl, and chlornaphazine, a substance closely related to β-naphthylamine which has been used to treat polycythemia vera (Thiede and Christensen, 1969). All these substances, with the exception of chlornaphazine, have proved to be carcinogenic in animal experiments as well, particularly in dogs (Temkin, 1963; Price, 1971).

In time, other chemical compounds became known that could induce bladder tumors in experimental animals, such as o-aminoazotolual, 3,2-dimethyl-4-aminodiphenyl, 2-methoxy-3-aminodibenzfurene, and N-2-fluorenlyacetamide (for review of the literature see Temkin, 1963; and Price, 1971). Our knowledge regarding experimental carcinogenesis in the bladder has nevertheless remained quite limited, simply because a carcinogenic substance was not available which induced bladder tumors in a sufficiently high yield in small experimental animals such as rats or mice; therefore it was not possible to draw any conclusions on the basis of a sizable number of animals.

This handicap, however, was overcome with the synthesis of di-N-butylnitrosamine and N-butyl-N-(4-hydroxybutyl)-nitrosamine (Druckrey et al., 1962, 1964) and the discovery of the carcinogenic properties of 4-ethyilsulphonylnaphthalene-1-sulphonamide (Bonser and Clayson, 1964) and of N-[4-(5-nitro-2-furyl)-2-thiazolyl] formamide (Ertürk et al., 1967), which opened up new opportunities for the study of carcinogenesis in larger experimental series.

Di-N-ButylNitrosamine (DBN)

\[
\begin{align*}
\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3 \\
\text{O} = \text{N-N} \\
\text{CH}_2\text{-CH}_2\text{-CH}_2\text{-CH}_3
\end{align*}
\]