

tion to these general and fundamental aspects of experimental tar cancer, its accomplishment supplied, for the first time, definite experimental proof of the occupational origin of cancers observed among several groups of workers exposed to tar, pitch, and related substances. The great, continued interest, which the original investigations of Yamagiwa and Itchikawa have aroused, is reflected in the great number of experimental studies on tar cancer which have followed their work. These investigations have covered numerous aspects important in regard to tar cancer and occupational tumors in general. In view of this fact, and considering that no industrial neoplasm has been studied experimentally as thoroughly as tar cancer, especially in connection with the effect which other exogenous agents may exert upon its genesis and course, a comprehensive presentation of data on experimental tar cancer is essential and pertinent. The information supplied by experimental investigations is of distinct value for confirming, adjudging, and supplementing observations made in man, particularly when the evidence available is controversial or defective.

*Historical Aspects.* Many failures preceded the successful production of tar cancer by Yamagiwa and Itchikawa in 1915. Hanau (1889) and Lubarsch (1890) applied tar to rats for several months without obtaining any neoplastic responses. Negative results were recorded by Cazin in 1894 after painting dogs with tar for a corresponding period of time. Brosch applied this agent to the skin of guinea pigs for 3 to 4 months without eliciting any cutaneous tumors (1900). Stahr painted mice, rats, and rabbits with soot, tar, and xylol-paraffin without success (1907). Ullmann rubbed paraffin oil into the ears of rabbits (1912), and Haga (1913) applied pitch to the scrotum of these animals without obtaining tumors. These failures were due, in part, to the use of species of animals possessing a more or less marked resistance to carcinogenic action of agents employed, but mainly, to an insufficiently long period of application. Therefore, success came when Yamagiwa and Itchikawa repeatedly painted the ears of rabbits with hard coal tar for many months until metastasizing carcinomas appeared at the sites of application. These results were confirmed, subsequently, by numerous investigators using rabbits and other species of animals (Tsutsui (1918); Bloch; Bierich; Itchikawa; Deelman; and Teutschlaender; in mice). The first experimental production of pitch cancer in mice was accomplished by Kennaway who obtained 9 tumors (3 papillomata, 6 epitheliomata) among 27 survivors of 100 mice treated with a suspension of pitch in lanolin. These results were substantiated by Leitch who used a suspension of pitch in sebum, and were elaborated upon by Kennaway and Jordan who, by applying a solution of pitch in benzol to the skin of mice, produced cutaneous malignancies.

*Constitutional Factors* (Differences in the Susceptibility of Various Strains and Species). In numerous attempts made to confirm and extend the original observations of Yamagiwa and Itchikawa, and Tsutsui, marked variations in