tumors, small foci of irregular and atypical epithelium which were entirely unrelated to the neoplastic formations but which represented minute preneoplastic lesions.

XI. LOCALIZATION AND THE DEVELOPMENTAL MECHANISM

In spite of the fact that carcinogenic aromatic amines or their organic conversion products circulate in the blood, tumors are formed almost exclusively in the bladder, rarely in any other part of the urogenic tract (kidney, renal pelvis, ureter) (Rehn, 1906; Marchand; Sebening; Leuenberger; Oppenheimer, 1926; Mueller, 1936; Gay) and, as far as is known, never in the skin or in the digestive and respiratory organs, which are the sites of the most massive and direct primary contact and the ports of entrance of the aromatic amines to the organism. Theoretically, there are two ways by which the urinary epithelium of the bladder and the other parts of the urinary tract may come in contact with the carcinogenic agent. The carcinogen circulating in the blood may escape from the terminal capillaries into the mucosa and thus enter the epithelial cells—either directly or, after release into the contents of the bladder, by resorption. The second possibility is that the carcinogen, possibly produced from the original substances by metabolic action of the liver or of the kidneys, is excreted with the urine into the bladder and can then act on the mucosa for a prolonged period, until discharged.

The majority of investigators favor the last mentioned conception (Oppenheimer; Engel, 1937; Hueper, 1934; and others). It has been pointed out by them that the urine, containing the suspected carcinogenic substances, passes rather rapidly through the kidney, renal pelvis and ureters and that therefore these organs, as far as time of contact is concerned, are less exposed than the bladder, where the urine collects and remains for some time. In addition to the prolonged exposure of the bladder wall, there is the presence in the bladder of an increased amount of the carcinogenic agent, depending on the quality of urine contained in the lumen. It may be contended that this factor might be of importance by assuming that the concentration of the carcinogenic substances must reach a certain upper limit before a proliferative response is elicited; the same argument has been applied with reference to the concentration of aromatic amines in the blood to explain the absence of aniline tumors in other organs. Oppenheimer suggested that the carcinogenic substances are possibly precipitated from the urine on the wall of the bladder and act thereby directly on the mucosa. This conception may possess a certain merit, as the solubility of the urinary metabolites of the aromatic amines depends on the reaction of the urine, becoming progressively lower with increasing alkalinity of the urine. Precipitates thus formed would settle and collect on the floor of the bladder, i.e., the place in man where the majority of bladder tumors are situated. In this connection it may be mentioned that the reaction of the urine in dogs with experimental bladder tumors (Hueper,