clearly that the first preparatory cellular response to the contact with carcinogenic agents occurs in the epithelial lining of the bladder. These epithelial changes, occasionally, may advance even as far as an early infiltrative malignant lesion before any appreciable reaction of the surrounding vasculoconnective tissue is noticeable. It is this type of lesion which may escape cystoscopic discovery as it may not produce mucosal thickening or be associated with papillary projections or vascular reactions which would attract attention and provide visible evidence.

Chronic inflammatory, obliterative and ectatic vascular and fibrotic changes are apparently secondary and nonspecific. They are present in only part of the lesions and are often accompanied by atrophic epithelial alterations. The frequent formation of endothelial granulomas and the subsequent vascular obliteration may be attributed to three possible causes: 1) As they are found most often in polyps, it appears likely that the topographical distortion connected with the formation of the polyps may exert a twisting or stretching effect on the vessels and thereby elicit endothelial damage and proliferation. 2) Endothelial injury and regenerative proliferation also may result from the resorption of toxic products through the mucosa into the intraepithelial capillaries and thus angiectases may be caused. 3) There exists, moreover, the possibility that chemospecific allergic reactions are involved in the formation of endothelial granulomas, especially as many of the early lesions show intravascular and extravascular eosinophilia and marked interstitial edema (Hueper, 1936; Pagel; Reuterwall).

The frequency of vascular hyperemia and proliferation, which are observed in the great majority of precancerous reactions, suggests that an increase in the blood supply is an essential preparatory feature of neoplastic cell growth (Paschkis and Bruegel). This conception receives support from various sources. Ewing stated that increased vascularity has been demonstrated in the beginning of many carcinomas and has been assumed to account for the awakening of many cell rests. Thiessen found in his studies of the relative vascularity of benign and malignant gastric lesions that in an entirely unexpected and, as he felt, paradoxic way, the vascularity increased progressively from the simple ulcer to the ulcer with cytoplasia to the ulcer with early malignancy and decreased as the carcinoma became well established. Kreyberg concluded from his experimental investigations of the precancerous changes in the skin of tarred mice that marked local vascular hyperemia accompanies epithelial hyperplasia and, in association with other factors, may exert a stimulating effect on cellular proliferation. This conception is, moreover, in full agreement with well established experiences in regard to the nutritive influences controlling sustained cell growth (Hueper, 1933; Hueper and others, 1933). The observations made during the study of the early lesions of the bladder do not support, on the other hand, the belief that permanent vascular and circulatory insufficiency and fibrosis are the primary responses and that the neoplastic