In his 1906 treatise, Crile (1) anticipated a favorable outcome for patients with head and neck squamous cell carcinoma (HNSCC). He boldly proposed that HNSCC could be eradicated more readily than tumors at other sites, based on the suppositions that: 1) the upper aerodigestive tract is readily accessible to inspection, 2) early neoplasia of the upper respiratory tract is easily recognized, 3) tumor growth remains relatively confined, and 4) en bloc excision permits complete tumor removal. Even with a substantial improvement in the diagnostic and therapeutic armamentarium, however, the outlook for patients with HNSCC has not changed substantially over the past several decades (2).

The inability to meet Crile’s high expectations has not been explained satisfactorily by traditional histopathologic methods. In fact, histologic findings and clinical outcomes are often widely disparate. Inexplicably, excised tumors recur in the face of microscopically free margins; patients treated effectively for HNSCC at one site develop second tumors at other sites, and premalignant lesions that regress during chemoprevention reappear and progress once therapy is halted. Something is awry with Crile’s initial supposition—something beyond the scope of traditional light microscopy.

Understanding the molecular underpinnings of HNSCC promises to provide a more complete and useful picture of the ways in which tumors arise and advance. True to current models of tumorigenesis, the initiation and progression of HNSCC are driven by the accumulation of specific genetic alterations, including deletions on chromosomal arms 3p, 9p, and 17p (3). Recent observations, however, have challenged the notion that the accumulation of genetic damage is invariably accompanied by predictable morphologic patterns. For example, genetic alterations may be widespread throughout the respiratory tract even in the absence of overt histopathologic changes of malignancy (4–7). Similarly, the epithelium of the upper respiratory tract may harbor numerous genetic alterations, yet it may lack any histopathologic evidence of dysplasia (3,8). In some instances, the detection of critical genetic alterations in histologically normal mucosal biopsy specimens has been useful in uncovering the site of tumor origin in patients with cervical lymph node metastases and clinically occult tumors (Califano J, Westra W, Sidransky D: unpublished observations).

The presence of morphologically intact but genetically damaged cells may account for certain distressing patterns of tumor behavior. We have found, for example, that the presence of genetically damaged cells could account for tumor recurrence following seemingly “complete” surgical resection (9). We noted that specific genetic alterations that were present in a resected HNSCC were also sometimes present at the margins of surgical resection, even when these margins had been declared histologically free of tumor. Importantly, the presence of these genetically damaged cells at the surgical margins was found to be a strong predictor of local tumor recurrence. Extension of genetically damaged cells beyond the clinical and microscopic boundaries of a tumor may also explain why patients with HNSCC are so apt to develop second tumors. When multifocal tumors of the head and neck are compared at the genetic level, they often harbor identical genetic alterations (10–12). Apparently, a single progenitor clone can expand to populate contiguous regions of the respiratory tract via re-epithelialization or intramucosal migration of cells at the submicroscopic level. From these examples, it would seem that total reliance on the visual recognition of tumor is, at best, inadequate. At worst, it is outright misleading.

The article published in this issue by Mao et al. (13) provides yet another disturbing example of the disparity between phenotype and genotype—this time in the arena of chemoprevention. Chemoprevention is a strategy aimed at arresting or reversing disease progression before the development of invasion and metastatic dissemination (14). One of the major obstacles in the field of chemoprevention has been the inability to monitor disease response. Aside from direct measurement of cancer incidence—a costly, protracted, and complicated undertaking—there has been no satisfactory way to measure the ultimate response of a high-risk epithelium to chemopreventive agents. Although measurement of histologic parameters is commonplace, histopathologic assessment is fraught with difficulties: The histopathologic features of premalignant lesions of the respiratory tract are subtle and overlap with non-neoplastic reactive processes; interpretation of these features is subjective, and there is considerable variation among pathologists in the recognition and grading of premalignant lesions; and the validity of histopathologic assessment as a marker of disease regression is not well established. This last point is underscored by the observation that premalignant lesions that fully regress during the course of chemoprevention may reappear and progress once therapy is halted (15).

Mao et al. (13) report on the poor relationship between the phenotypic and genotypic appearances of advanced premalignant lesions following chemoprevention therapy. Among the nine patients with premalignant lesions showing loss of heterozygosity (LOH) at 9p21 prior to chemoprevention, eight had persistent LOH following treatment. Importantly, the genetic alterations persisted even in those lesions that completely resolved both clinically and histologically. These observations fur-
ther erode confidence in clinical and histologic parameters as valid markers of disease response.

While exposing the inadequacies of histopathologic assessment, the study by Mao et al. falls short of establishing specific genetic alterations as valid biomarkers. Whether the presence and persistence of certain genetic alterations will ultimately predict clinical outcomes is a critical question that awaits a larger sample size and more extended follow-up of patients. Nonetheless, monitoring disease evolution at the genetic level is a concept worth pursuing. First, carcinogenesis—at its most fundamental level—is a chronic disease process representing the culmination of specific genetic alterations (16). Direct monitoring of genetic damage, therefore, has a strong mechanistic basis. Second, certain genetic loci meet many of the established criteria as useful biomarkers (17): They are altered in such a way that they can be measured objectively; these alterations can be detected even in small tissue specimens; they are altered in high-risk tissues but not in normal tissues; and they are altered in the early stages of cancer development.

There is an old Malayan proverb that goes: “Don’t think there are no crocodiles just because the waters are calm.” When it comes to patients at high risk for HNSCC, the sense of assurance afforded by clinical and histologic appearances is often false and short-lived. Crile and others saw only the untroubled surface and predicted the best of outcomes for patients with HNSCC. They were disappointed. Today, molecular genetic analysis now allows us to probe beneath the surface for trouble lurking much deeper. The ability to do so should facilitate more rational strategies for the prevention, management, and surveillance of HNSCC.

REFERENCES

(1) Crile G. Excision of cancer of the head and neck with special reference to the plan of dissection based upon 132 operations. JAMA 1906;47:1780–6.