Substantial advance has been achieved in our knowledge of nasopharyngeal carcinoma within the past two decades. Elsewhere in this issue Moloy and co-workers have presented a paper on the subject. I will present a review of the recent achievements and suggest goals for future research.

Pathology

There is no longer any disagreement that the predominant malignant tumor arising in the nasopharynx of people of all races is a carcinoma of the squamous cell type, although squamous differentiation may not be evident under light microscopy in a proportion of cases if only small biopsy specimens are available for examination. Under electron microscopy, however, features of squamous differentiation can be regularly detected even in such specimens. The nasopharynx is a part of the Waldeyer’s lymphoid ring. Consequently, the presence of lymphocytes in the stroma of the primary tumor or its metastasis in lymph nodes is to be expected. In its metastasis in nonlymphoid tissue such as the liver, however, lymphocytes are either absent or scanty although features of the so-called lymphoepithelioma are present in the primary tumor and metastatic lesions of cervical lymph nodes.1,2 Therefore, the degree of lymphocytic infiltration in biopsy specimens taken from the primary tumor or metastatic nodes cannot be taken to be a guide to prognosis. A nasopharyngeal or even a nodal biopsy specimen is only a tiny fraction of the whole disease, in which islands of keratinization may be found among sheets of anaplastic undifferentiated carcinoma cells, and approximately one quarter of classical squamous cell carcinomas show areas of undifferentiated structure.3 It is, therefore, not unexpected that in careful studies of large series of cases neither the degree of lymphocytic infiltration nor the dominant histologic pattern has been found to be useful in indicating prognosis or in planning treatment.

Etiology

From current epidemiologic and experimental data the most tenable etiologic hypothesis is one that postulates the involvement of three major risk factors: (1) a genetically determined susceptibility that allows an Epstein-Barr virus (EBV) infection in early life of the type that permits (2) the integration of the genomes of the virus into the chromosomes of some nasopharyngeal epithelial cells, priming them for (3) neoplastic transformation by some environmental nasopharyngotropic carcinogen or carcinogens that have gained entry into the infected cells. Alternatively, the environmental agents may trigger the viral genome in the cells to oncogenic activity.4 It must be said, however, that the only evidence suggesting that EBV may be a cofactor in the genesis of nasopharyngeal carcinoma is the regular finding of the DNA of the virus in undifferentiated and poorly differentiated nasopharyngeal cancer cells. Whether it plays a causal role or exists in the cells as a passenger is not known. The virus is ubiquitous, yet a high frequency of nasopharyngeal carcinoma is found only in certain ethnic groups. This suggests that whatever its role in the cause, it can only be a cofactor.

The etiology of nasopharyngeal carcinoma is very likely multifactorial; hence, as long as an environmental factor is an essential cofactor, prevention is possible. Epidemiologic data have favored ingestants rather than inhalants as likely risk factors in southern Chinese. Among ingestants salted fish (prepared by salting and drying) is most suspected to be a major risk factor.5 It was until two to three decades ago traditionally fed to southern Chinese in Hong Kong from early childhood for economic reasons and taste. The suspicion of its causal role was first raised in 19716 and has received strong support from the findings of two recent case-control epidemiologic studies. In one study, 100 Chinese patients with nasopharyngeal carcinoma and 100 neighborhood controls in Malaysia were studied.7 Analysis of the data showed that daily consumption of salted fish in childhood carried a relative risk of 17.4 (95% confidence interval = 2.7, 111.1) compared with nonconsumption. The other study involved 250 incident cases of patients younger than 35 years and an equal number of friend controls in Hong Kong. The data showed that the relative risk for consuming the food at least once a week compared with less than once a month at age 10 years was 37.7 (95% confidence interval = 14.1, 100.4) (M. C. Yu, J. H. C. Ho, S.H. Lai, et al, unpublished data*). Because the subjects were young, many had mothers who could be

*The survey itself was completed in November 1983. A preliminary report will appear in a National Cancer Institute monograph on the proceedings of the Fourth Symposium on Epidemiology and Cancer Registries in the Pacific Basin held in Kona, Hawaii, January 16-20, 1984 (in press). The title of the paper is “The Epidemiology of Nasopharyngeal Carcinoma in Malaysia and Hong Kong” and the authors are M. C. Yu, J. H. C. Ho, B. E. Henderson and R. W. Armstrong.

(Ho JHC: Nasopharyngeal carcinoma [Editorial Comment]. West J Med 1985 Jul; 143:70-73)

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NASOPHARYNGEAL CARCINOMA

Abbreviations Used in Text
AJC = American Joint Committee for Cancer Staging and End-Results Reporting
CT = computed tomography/ic
EBNA = nuclear antigen of the Epstein-Barr virus
EBV = Epstein-Barr virus
UICC = Union Internationale Contre le Cancer
VCA = viral capsid antigen

separately interviewed to check on the data obtained from their children. It is estimated from the latter study that more than 90% of cases of nasopharyngeal carcinoma in young Hong Kong Chinese could be attributed to consuming salted fish during childhood. In both studies the cases and controls were sex and age matched to within five years. As other more nutritious foods have become readily available and salted fish has become more expensive than chicken, the traditional habit of Hong Kong Chinese feeding their children salted fish is fast disappearing. It is tempting to suggest that the sharp progressive drop in their annual age-adjusted incidence rates during 1978 to 1981 from 41.5 per 100,000 to 25.8 for men and from 16.9 to 11.4 for women reported by the Hong Kong Cancer Registry might be related to this change of habit.

Judging from their age-specific incidence curves, the Swedes and American whites and blacks appear to have a different origin for nasopharyngeal carcinoma from that of Hong Kong or Singapore Chinese or Chinese Americans. The curves for the three groups of Chinese have a similar pattern, differing only in height. In Chinese the curves rise sharply after the third decade, whereas those for the non-Chinese groups show a rise after the fourth or fifth decade. If we consider the latency period—that is, the period between carcinogenic initiation and clinical manifestation—in nasopharyngeal carcinoma to be about 20 to 30 years, we should look for environmental initiators operating during early childhood in the case of Chinese and in the non-Chinese groups during their late teens and early adulthood. The Alaskan native population has a curve pattern resembling that for Chinese, but Tunisians have a bimodal curve, with the early peak at the second decade.

The rapid advance in cytogentic and recombinant DNA technology has afforded us an opportunity to look for onco genes in nasopharyngeal cancer cells. Their identification may help us to understand how normal nasopharyngeal epithelial cells may be transformed into carcinoma cells. It may also open new frontiers in the diagnosis and management of cases of nasopharyngeal carcinoma.

Diagnosis
The symptoms of nasopharyngeal carcinoma are well known. It is the unawareness of the disease in low-incidence areas that causes undue delay in its diagnosis. Moloy and colleagues remind us that serious otitis media may be a presenting manifestation of nasopharyngeal carcinoma. In places where both pulmonary tuberculosis and nasopharyngeal cancer are prevalent, blood-stained morning sputum due to coughed-up postnasal drip is often a cause of delay in diagnosis. Patients are usually investigated first for pulmonary tuberculosis and may be treated for it when they have shadows on their chest radiographs because of past infection. A delay of three to six months is not unusual in such cases. Nasopha ryngeal cancer is not thought of until other symptoms and signs of it appear. Cervical lymph nodal enlargement is the most frequent first symptom. Because the cancer is painless, except in the presence of concurrent infection, it is often not noticed by a patient, especially if he or she has a fat neck, until there is a large tumor. Sometimes the primary tumor in such a case may not be found even by computed tomographic (CT) scan if it is small or flat. In the presence of a hypersensitive gag reflex, the nasopharynx may be examined by fiberoptic nasopharyngoscopy or inspected by the use of a Yankauer speculum if the tumor is suspected to be in the fossa of Rosenmüller. The speculum allows biopsy of the fossa under direct vision after topical anesthesia has been applied. If results of the nasopharyngeal biopsies are negative, any enlarged node should be removed and imprint smears made from it for staining for the nuclear antigen of Epstein-Barr virus (EBNA) in the tumor cells before submitting the specimen for histopathology. If the EBNA test is positive, the primary tumor is most likely nasopharyngeal carcinoma, especially if the enlarged node is in the spinal accessory chain. The close association between nasopharyngeal carcinoma and Epstein-Barr virus allows EBV serology to be used in screening for the cancer among high-risk persons, such as first-degree relatives, especially siblings, of patients in high incidence areas. An elevated serum titer of IgA to the viral capsid antigen (VCA) of 1:10 or greater may be the first indication of subclinical nasopharyngeal carcinoma. For such a case, multiple nasopharyngeal biopsy specimens are warranted even in the absence of symptoms or a demonstrable tumor, especially if the titers of other EBV-specific antibodies are also elevated. After specific treatment, EBV serology does not seem to reflect the state of the tumor burden to the same acceptable degree of reliability as before treatment. Hence it is of only limited help in following progress in individual patients. Actually, the production of antibodies to the various EBV-specific antigens is influenced by many factors other than the availability of EBV-specific antigens. In pretreatment cases of stage I nasopharyngeal carcinoma, the false-negative rate may be as high as 12% when the diagnostic titer of IgA anti-VCA is set at greater than 1:5. The false-positive rate is about 10%, which reflects the presence of other tumors.

The value of CT scan is in showing involvement of the soft tissue in the parapharyngeal retrostyloid and prestyloid spaces, the retropharyngeal space and the neck. Primary tumor extensions through the fissures and foramina at the base of the skull to the cranial cavity, the paranasal sinuses and the orbits are clearly shown by CT. However, for showing a small tumor in the nasopharynx, CT is clearly useless as are plain radiography and conventional tomography. In differentiating between cranial nerve involvement by recurrent tumor and irradiation neuropathy, and between temporal lobe irradiation encephalopathy and other nonneoplastic neurologic disorders and meningeal metastasis, CT scan is invaluable. Incidentally, genuine blood-borne metastasis has not been encountered in the brain, although it is not immune to invasion by adjacent meningeal metastasis or cranial extension of the primary tumor. For finding soft tissue involvement or an abnormality in the brain, magnetic resonance imaging is superior to CT. However, magnetic resonance imaging does not show up bones but only the marrow within them.
Staging

We have at present no universally accepted stage classification for nasopharyngeal carcinoma. This is hampering clinical research on the cancer, because no meaningful intercenter or even intracenter comparison of treatment results is possible. A good stage classification is one that gives an accurate indication of the prognosis and the extent of the disease to guide treatment planning. It must provide clear and practical definitions of the anatomic limits and criteria for the various stages. Without such a classification, no meaningful clinical trial can be mounted. Of the number of stage classifications that we have at present, the one formulated by the International Union Against Cancer (Union Internationale Contre le Cancer, UICC), and that by the American Joint Committee for Cancer Staging and End-Results Reporting (AJC) are more widely used than the others, but neither is satisfactory. In the AJC classification, the inferior limit of the nasopharynx is defined as level with the plane of the hard palate. This plane can only be observed in a lateral radiograph of the nasopharynx, however. It cuts across the lower part of the torus tubarius and the fossa of Rosenmuller to reach the posterior wall of the nasopharynx above the tubercle of the anterior arch of the atlas vertebra. To most clinicians the nasopharynx is that part of the pharynx situated above the posterior margin of the soft palate in its resting position and hidden from view through the opened mouth. This definition is much more practical and is adopted by the Ho classification. In the UICC classification, the posterosuperior wall is defined as extending from the level of the junction of the hard and soft palates to the base of the skull. This definition of the lower limit of the posterior wall is vague and presumably it corresponds to the level of the lower margin of the basiocciput and the anterior margin of the foramen magnum. If so, it is about the same level as the lower limit defined in the AJC classification. In both classifications, T1 is defined as tumor confined to one site or region, presumably one wall, and T2 to two sites or regions. The limits of the primary tumor within the nasopharynx are not easy to ascertain, even for an expert. Furthermore, a carcinoma may occur submucosally and not be readily visible. The diagnosis in such a case is established by biopsy. Submucosal infiltration may occur at some distance from the macroscopic tumor. The fossa of Rosenmüller is in fact astride both the lateral and posterior walls and it is a common site of origin of the primary tumor. Consequently, a small tumor there may be reckoned to have involved two sites. It is therefore suggested that T1 and T2 should be combined as T1, as in the Ho classification. From the point of view of correlating with the prognosis, the T3 in both the UICC and AJC classifications could well be downgraded to T2; T4 with tumor involvement of bones below the actual base of the skull downgraded to T3 and the rest, such as involvement of the actual base of the skull and cranial nerves at or above it, to remain as T4. In this respect involvement of cranial nerves at the retrostyloid space should be considered T4 involvement because the upper limit of the space is the jugular foramen at the base of the skull. Involvement of the hypopharynx should also be staged T3 because it carries a very poor prognosis. The nodal staging in the UICC classification is designed primarily as a guide for surgical treatment by block dissection, whereas radiation therapy is the primary treatment of choice not only for the primary tumor in cases of nasopharyngeal carcinoma but also cervical nodal metastases. They are staged by UICC according to the laterality of the involvement and mobility of the involved nodes. Because the nasopharynx is a midline organ with bilateral lymphatic drainage, the cervical nodes should always be treated on both sides and according to the level of involvement, which corresponds better with the prognosis than laterality or mobility of the nodal involvement.

The AJC classification included a measurement of the diameter of the involved nodes, with a diameter of between 2.9 and 3.0 cm as the cut-off point between N1 and N2 and between 5.9 and 6.0 cm as that between N2 and N3. Measurements of the diameters of cervical nodes, especially the deep-seated ones, are most of the time estimated subjectively. They are hence very inaccurate. It is easier to see and feel whether the lower poles of the enlarged nodes have extended below the neck crease at or just below the thyroid notch. The crease is taken arbitrarily to be the boundary between N1 and N2 regions in the Ho classification.

Treatment

The treatment results should be better now that we have the CT scanner to help us detect previously undetected soft tissue involvement to reduce geographic miss. With the availability of the computerized radiotherapy planner, a better dose distribution in the target volume is expected with reduction of dose to normal vital organs such as the brain stem and spinal cord and important organs such as the eyes. Radiosensitizers and radioprotectors are still in the development stage, and hyperbaric oxygen is a disappointment. Prophylactic irradiation of apparently uninvolved cervical lymph nodes has been shown to be unnecessary if a patient can attend regularly for follow-up. Chemotherapy has only limited success in treating visceral metastasis, with a response rate of about 30% with the various agents that have been tried. Primary tumor and bone metastases appear to be almost unresponsive. Although distant metastasis presents a problem, the predominant site of metastasis is in bone where it is most resistant to chemotherapeutic agents. The control of the primary tumor is not just a matter of increasing the irradiation dose. There is a limit, around a time and dose fractionation factor of 108—that is, around 6,600 cGy (centiGray) over six weeks—beyond which the tumor control curve tends to level off and the morbidity curve rises sharply. As the superior margin of the treatment field is above the sella turcica and covers the sphenoid sinus, a potential site of tumor spread, part of both temporal lobes and the pituitary-hypothalamus axis would be within the target volume. In long-term survivors we are seeing complications arising from the heavy irradiation of these parts. Irradiation myelopathy is now rarely encountered because of good shielding of the spinal cord by using an anterior cervical field with a median spinal cord shield and accuracy of beam direction by the use of a transparent Perspex shell specially made for patients to wear to facilitate setting up.

Control of the primary tumor needs further research. Even in stage I cases there is a five-year cumulative primary tumor recurrence rate of 21%. The overall five-year actuarial survival rate for stages I through IV cases is about 45%, and the relapse-free survival rate after initial treatment is 33%. In stage I cases, the corresponding rates are 80% and 63%.

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Patients with primary tumor recurrence often benefit from a second course of radiotherapy, but the rate of late complications such as temporal lobe, brain-stem and cranial nerve (most commonly the 12th, 5th and 6th) irradiation neuropathy, temporomandibular joint capsular fibrosis and perceptive deafness would be higher. By proper shielding of a large part of the oral tongue and minor salivary glands, dryness of the mouth can be minimized. By attention to oral hygiene and the use of fluoride gel, less irradiation dental caries is expected. Prevention is better than cure and for nasopharyngeal carcinoma, prevention is probably not a too-distant possibility.

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