Introduction: The World Health Organization (WHO) “Blue Book” on the Pathology and Genetics of Head and Neck Tumors is the ninth in a series of ten books devoted to the classification of tumors. It was published in 2005 by the IARC Press in Lyon, France and edited by Barnes, Eveson, Reichart and Sidransky with the assistance of a 37 member Advisory Committee.

The book, with contributions from 130 authors from 28 countries, contains 890 colored illustrations, computer tomography –magnetic resonance images, and charts, 2918 references, and 430 pages. It sells for $110.00 (US).

Organization: In the past, the WHO used four different “Blue Books” to cover head and neck neoplasms:
(1) Oral and Oropharyngeal Tumors—published in 1971, 8 contributors, 48 pages and 40 illustrations
(2) Tumors of the Upper Respiratory Tract and Ear—published in 1991, 12 contributors, 201 pages and 200 illustrations
(3) Salivary Gland Tumors—published in 1991, 10 contributors, 113 pages, and 124 illustrations

The current “Blue Book” represents a combination of all four of the above books, and is organized into the following eight chapters: (1) Nasal Cavity and Paranasal Sinuses, (2) Nasopharynx, (3) Hypopharynx, Larynx and Trachea, (4) Oral Cavity and Oropharynx, (5) Salivary Glands, (6) Odontogenic Tumors, (7) Ear, and (8) Paraganglionic System.

In the old “Blue Book” each tumor was accompanied by a definition, a brief histologic description and usually a single illustration. This contrasts with the current “Blue Book” in which many of the tumors are thoroughly discussed and illustrated using the following subtitles: (1) definition, (2) epidemiology, (3) etiology, (4) clinical features, (5) gross and microscopic descriptions, (6) precursor lesions, (7) differential diagnosis, (8) immunohistochemistry, (9) electron microscopy, (10) molecular biology, (11) genetics, and (12) prognosis and predictive factors.
What’s New:

1. Chapter on Nasal Cavity and Paranasal Sinuses

A. Schneiderian Papillomas

The Schneiderian papillomas are classified into three types—exophytic, inverted and oncocytic. The terms “exophytic” and “oncocytic” are now proposed to replace the old respective terms of “fungiform” and “columnar cell.”

B. Adenocarcinomas

Adenocarcinomas, other than salivary-type, are more clearly defined and divided into intestinal and non-intestinal types based on morphology and immunohistochemistry. The intestinal-type are usually CK7+, CK20+, and CDX2+, while the non-intestinal types are CK7+, CK20-, and CDX2-.

C. Glomangiopericytoma

Glomangiopericytoma has emerged as the most preferred or at least an equivalent term for “sinonasal-type hemangiopericytoma.”

D. Nasal Chondromesenchymal Hamartoma (NCMH)

NCMH is a newly recognized tumefactive lesion arising in the sinonasal tract with mixed chondroid, stromal and occasionally osseous components that is somewhat similar to the chest wall hamartoma.

E. Respiratory Epithelial Adenomatoid Hamartoma (REAH)

REAH is a benign non-neoplastic overgrowth of glands lined by ciliated respiratory epithelium that arises most often on the posterior nasal septum and less often in the paranasal sinuses or nasopharynx. The glands are surrounded by a hyalinized basement membrane and are associated with a background of polypoid rhinosinusitis. REAH is typically unilateral, rarely bilateral, and must be distinguished from the inverted papilloma. Conservative excision is curative.
2. Chapter on Nasopharynx

A. Nasopharyngeal Carcinoma

The classification of nasopharyngeal carcinoma is the same as proposed in 1991 with the exception that “basaloid squamous cell carcinoma” has been added.

Classification of Nasopharyngeal Carcinoma

1. Keratinizing squamous cell carcinoma
2. Non-keratinizing carcinoma
   (a) undifferentiated
   (b) differentiated
3. Basaloid squamous cell carcinoma

B. Nasopharyngeal Papillary Adenocarcinoma (NPAC)

NPAC is a rare, recently described, low-grade, exophytic neoplasm comprised of papillary fronds and glands. The tumor may contain PAS-positive, diastase-resistant and mucicarmineophilic intracytoplasmic secretions. EMA and cytokeratin stains are positive. Although psammoma bodies are occasionally seen, there is no reactivity for thyroglobulin and no association with the Epstein-Barr virus. NPAC is only locally invasive with no metastases recorded thus far. Complete excision is usually curative.
3. Chapter on Hypopharynx, Larynx and Trachea

A. Terminology of Premalignant Lesions

The terminology of premalignant mucosal lesions is controversial and not uniformly applied throughout the body. The three most common classifications in the head and neck and equivalent terms for each are given in the following table:

<table>
<thead>
<tr>
<th>2005 WHO Classification</th>
<th>Squamous Intraepithelial Neoplasia (SIN)</th>
<th>Ljubljana Classification Squamous Intraepithelial Lesions (SIL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous cell hyperplasia</td>
<td>Squamous cell (simple) hyperplasia</td>
<td></td>
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<tr>
<td>Mild dysplasia</td>
<td>SIN 1</td>
<td>Basal/parabasal cell hyperplasia*</td>
</tr>
<tr>
<td>Moderate dysplasia</td>
<td>SIN 2</td>
<td>Atypical hyperplasia**</td>
</tr>
<tr>
<td>Severe dysplasia</td>
<td>SIN 3***</td>
<td>Atypical hyperplasia**</td>
</tr>
<tr>
<td>Carcinoma in-situ</td>
<td>SIN 3***</td>
<td>Carcinoma in-situ</td>
</tr>
</tbody>
</table>

* Basal/Parabasal cell hyperplasia may histologically resemble mild dysplasia, but the former is conceptually benign lesion and the latter the lower grade of precursor lesions.

** ’Risky epithelium’. The analogy to moderate and severe dysplasia is approximate.

*** The advocates of SIN combine severe dysplasia and carcinoma in-situ

B. Terminology of Neuroendocrine Tumors

The terminology of neuroendocrine tumors is another controversial issue. For consistency, the classification and terminology as used in the lung are applied to those in the head and neck.

Classification of Neuroendocrine Tumors

1. Typical carcinoid
2. Atypical carcinoid
3. Small cell carcinoma, neuroendocrine type
4. Combined small cell carcinoma, neuroendocrine type
5. Paraganglioma
   a. Benign
   b. Malignant
4. Chapter on Oral Cavity and Oropharynx

A. Follicular Dendritic Cell Sarcoma/Tumor

This tumor is derived from follicular dendritic cells and may arise in nodal or extranodal sites. The oral cavity—oropharynx, especially the tongue and palate, is one of the most frequent extranodal sites of origin. The tumor typically grows beneath an intact mucosa and is comprised of fascicles, whorls, or nodules of spindle to ovoid cells with admixed, small lymphocytes. The cells possess poorly defined cell borders slightly vesicular nuclei and distinct nucleoli and are positive for CD21, CD23, and CD35. Most cases are treated by surgery, with or without adjuvant chemotherapy and radiotherapy. The tumors are regarded as low to intermediate grade with an overall recurrence rate of at least 40% and a metastatic rate of at least 28%.

5. Chapter on Salivary Glands

A. Carcinoma ex Pleomorphic Adenoma

Carcinoma ex pleomorphic adenoma is classified into three types based on the degree of invasion of its capsule:

1. Non-invasive (in-situ carcinoma, intracapsular carcinoma)
2. Minimally invasive (1.5 mm or less of invasion beyond the capsule)
3. Invasive (more than 1.5 mm of invasion beyond the capsule)

B. Low-Grade Cribriform Cystadenocarcinoma (LGCCC)

The WHO has proposed that the tumor originally described as low-grade salivary duct carcinoma be renamed as LGCCC in order to avoid confusion with salivary duct carcinoma, a high-grade, aggressive tumor.

These tumors resemble the spectrum of breast lesions from atypical ductal hyperplasia to micropapillary and cribriform low-grade ductal carcinoma in-situ. A few may be invasive. In contrast to salivary duct carcinoma, LGCCC is strongly positive for S-100 protein and negative for androgen receptor and HER2-neu. Following complete excision, the prognosis is excellent.
6. Chapter on Odontogenic Tumors

A. The lesion traditionally known as odontogenic keratocyst has been renamed as “keratocystic odontogenic tumor” as it more appropriately reflects its potential for local, destructive behavior.

7. Chapter on the Ear

A. Endolymphatic Sac Tumor (ELST)

ELST is a non-metastasizing, slowly-growing adenocarcinoma of endolymphatic sac origin which widely invades the temporal bone, and may have an association with von Hippel-Lindau disease. Although many names have been applied to this tumor, the WHO has endorsed ELST

B. Idiopathic Pseudocystic Chondromalacia (IPC)

IPC is a non-neoplastic painless swelling of the pinna due to a localized accumulation of fluid with the elastic cartilage. It most often occurs in young to middle-aged adults. Minor trauma may be an instigating factor. Microscopically, the lesion is a pseudocyst within the confines of the elastic cartilage. The cavity may be lined by cartilage, granulation and/or fibrous tissue.

8. Chapter on the Paraganglionic System

A. Laryngeal paragangliomas are distinctly unusual tumors, and in the past, have been erroneously assumed to be malignant in 25% of cases. Critical review of the alleged malignant cases has revealed that virtually all are actually unrecognized atypical carcinoid tumors.