Non-Laryngeal Cancer and Voice

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Contents

Preface

Voice, a reflection of well-being, is often neglected in patients with non-laryngeal cancer who suffer a myriad of physical and emotional disturbances. A change in voice quality is rarely given deference in the context of what many physicians perceive as more disabling cancer-induced morbidities. However, dysphonia can be disabling in many patients who are professional voice users including not only singers, but also teachers, physicians, lawyers, and others. The quality-of-life impact of dysphonia is often substantial. The review presented in this book underscores the importance of identifying voice symptoms and signs in patients with cancer. These are very often masked by the overwhelming complaints of affected patients, impairments in other body systems caused by their disease, and the adverse effects of treatment. Dysphonia as a symptom amid the wide spectrum of cancer-related symptoms warrants special attention, particularly in professional voice users who rely on their voice to make a living. Meeting the vocal needs of cancer patients with dysphonia falls within the scope of caring for the whole cancer patient, and not only for the cancer.

This book reviews the literature on voice in cancer patients, with emphasis on both disease-induced and treatment-induced dysphonia. A better understanding of the link between cancer and voice can assist physicians in detecting phonatory disorders early in cancer patients. Proper and timely referral to laryngologists and voice specialists for comprehensive voice evaluation is crucial for adequate diagnosis and treatment. Cancer patients deserve equal attention to their vocal apparatus, similar to that directed to any other systems impacted by their primary disease.

The order of chapters of this book has been chosen in alignment with the frequency of cancers based on the estimated annual incidence listed in the Worldwide Cancer Data[4] and by the American Cancer Society.[14] Lung and breast cancers are considered the most common, followed by colorectal and prostate cancers. Cancers with a low incidence are not discussed in this book.

Cancer of the larynx or other areas of the vocal tract has effects on the voice that are intuitively obvious. However, the impact on voice of non-laryngeal cancers is less apparent. This book is intended as a resource for not only laryngologists, speech-language pathologists, and singing voice specialists, but also oncologists, surgeons, and others who treat patients who depend on their voices, especially professional voice users. The book also is designed to serve as a resource for voice professionals who develop common cancers outside the larynx and want a convenient overview of the disease and the voice-related consequences of the cancer and its treatment.

For non-laryngologists, the first 3 chapters cover basic information about the voice. Chapter 1 reviews clinical anatomy and physiology, Chapter 2 discusses the information obtained from the specialized histories for voice professionals, and Chapter 3

covers the state-of-the-art in physical examination of voice patients.

There are 2.1 million new cases of lung cancer diagnosed annually,[1] and the incidence has increased over the years in both genders. As discussed in Chapter 4, lung cancer and its treatment can affect the voice directly by impairing pulmonary function and thereby decreasing the voice power source (support), paralyzing the vocal folds, metastasizing (including to the larynx), and other mechanisms. Surgery routinely alters voice function, especially if part or all of a lung is resected. Of course, any surgery can alter voice if there are complications with intubation. Chemotherapy and radiation for lung cancer also can cause voice problems. Radiation not only alters laryngeal tissues directly if the larynx is included in the radiation field, but it also can cause recurrent laryngeal nerve paresis or paralysis.

Chapter 5 discusses breast cancer, the second most common cancer in the world and the most common malignancy in women.[2] In 2018, there were more than 2 million new cases.[1] Breast cancer can be particularly disturbing for some women, and the emotional reaction often is reflected in the voice. Breast cancer can metastasize to the vocal tract, and pulmonary metastases can cause recurrent laryngeal nerve paralysis. Vocal fold paralysis in breast cancer patients also can be caused by metastases to the skull base. Anxiety and depression are common in patients with breast cancer, and the consequences of anxiety and depression on voice are well known.[3] Generalized fatigue, pain, and sleep deprivation are common with breast cancer and commonly are associated with dysphonia. Radiation, chemotherapy, and particularly endocrine therapy for breast cancer frequently cause dysphonia. Surgical treatment also can affect the voice, especially if abdominal muscles are used for breast reconstruction, potentially affecting the efficiency of abdominal support.

Colorectal cancer is the third most common cancer in the world, with about 1.8 million new cases in 2018,[1] as reviewed in Chapter 6. In 2018, there were about 161 000 deaths from colon cancer.[4] Colorectal cancer is associated with severe reduction in quality of life. Abdominal discomfort that impairs support, and metastatic disease that can involve the vocal tract and causes vocal fold paralysis can cause dysphonia. Metastases can involve the larynx or structures close to the larynx, including the thyroid gland. Metastases to the neck and chest can cause vocal fold paralysis by compression or invasion. Colorectal cancer is treated by surgical resection with or without chemotherapy. The surgery may affect abdominal support muscle function, and chemotherapy can cause short-term and long-term side effects that result in dysphonia.

Prostate cancer, discussed in Chapter 7, is the second most common cancer in men, with approximately 174 615 new cases in the United States in 2019.[5] The disease usually affects men in their seventh decade, and less than 10% of those affected are below the age of 45 years.[6] Approximately 10% to 15% of patients with prostate cancer have metastasis at the time of diagnosis. Although metastatic disease to the larynx is uncommon, it can occur; and metastasis to the lungs can result in vagus nerve injury and consequent vocal fold paralysis. Metastasis to the thyroid gland also occurs. Like breast cancer, prostate cancer adversely affects mental well-being. Depression and anxiety are common.[7] Treatment for prostate cancer also can cause voice changes, particularly orchiectomy and hormone therapy. Surgery for prostate cancer has various potential adverse effects that can have psychological impact that may be reflected in the voice, including impotence. In 2019, Jarzemski

et al studied the mental well-being of 100 patients with prostate cancer and found an association between physical symptoms and deferred memory, depression, and anxiety.[8] Some chemotherapy used for prostate cancer causes diarrhea, nausea, and vomiting, which can affect the voice in the short term. More research is needed to evaluate the long-term voice consequences of chemotherapy for prostate cancer.

Problems associated with thyroid disease in general, and thyroid cancer specifically, are covered in Chapter 8, and elsewhere.[9] It has been known for decades that even mild hypothyroidism can cause dysphonia, described typically as a sensation of a "veil over the voice." Thyroid cancer and its treatment routinely result in dysphonia. Voice changes may be caused by hypothyroidism, hyperthyroidism, recurrent or superior laryngeal nerve injury, surgical scar adherence to the trachea impairing laryngotracheal vertical motion, and other causes. When thyroid cancer presents with vocal fold paresis, treatment rarely results in restoration of normal neuromuscular function.[10,11]

Chapter 9 reviews non-Hodgkin lymphoma, which accounts for 4.2% of all cancers diagnosed in the United States, with approximately 74 200 new diagnoses in 2019.[12] It accounts for 90% of all lymphomas,[13] and it is more common in patients older than 65 years, affecting men more frequently than women.[14] Hodgkin lymphoma affects primarily the lymph nodes. Non-Hodgkin lymphoma affects lymph nodes, but it also has extranodal manifestations in 30% of patients,[15] most commonly affecting the Waldeyer ring, nasopharynx, oral cavity, salivary glands, thyroid, and paranasal sinuses.[16,17] Weight loss, fever, and night sweats are common, and these impairments of general health affect the voice adversely in the short term. Although uncommon, the larynx can be the target organ for non-Hodgkin lymphoma.[18] Hematopoietic laryngeal neoplasms account for less than 1% of all laryngeal cancers.[19] Non-Hodgkin lymphoma is classified into several subtypes that are not reviewed in detail in this book, but some can involve the larynx. These include diffuse large B-cell lymphoma (DLBCL), mucosa-associated lymphoid tissue (MALT) lymphoma, natural killer (NK) T-cell lymphoma, and T-cell lymphoma. In addition to involving the larynx directly, non-Hodgkin lymphoma can cause vocal fold paralysis by invasion or compression. Non-Hodgkin lymphoma also can cause paralysis through neurolymphomatosis or neoplastic meningitis. Chemotherapy is the primary treatment for non-Hodgkin lymphoma and may be combined with immunotherapy or radiation. Chemotherapy may have direct and indirect effects on the voice. Short-term effects are routine, and long-term effects may occur.[20] Vincristine, a chemotherapy agent used commonly for hematologic malignancies, can be complicated by neurotoxicity with axonal degeneration that can affect neural conduction in multiple cranial nerves, including the vagus nerve.[21,22] Radiation also is used commonly for lymphoma patients and can cause tissue toxicity and neurotoxicity.

In the United States in 2019, there were approximately 74 000 new cases of renal cell carcinoma,[23] discussed in Chapter 10. The incidence has risen over the last 2 decades, particularly in people between 70 and 79 years of age.[24] Renal cell carcinoma commonly has no symptoms until the disease is advanced, and incidental diagnosis is made in 50% of cases, with a minority of patients presenting with the classic triad of flank pain, mass, and hematuria.[25,26] Renal cell carcinoma is likely to metastasize, with metastatic disease identified at the time of diagnosis in 23% to 40% of patients; multiple metastases are common, particularly

in younger patients.[27–30] Metastases to lungs and bones are most common,[31,32] but renal cell carcinoma metastasizes to the head and neck in about 15% of cases.[33,34] Laryngeal metastases have been reported. In addition to direct metastasis affecting the voice, metastasis to the lungs and to the structures in the neck can cause laryngeal nerve paralysis. Esophageal metastasis may result in similar problems, as well as weight loss and deterioration in general health that can cause dysphonia. Nearly half of patients with renal cell carcinoma have depression, and many have comorbid posttraumatic stress syndrome associated with excessive fatigue and sleep disturbance.[35] All of these problems can cause adverse voice changes. Various chemotherapy regimens used for renal cell carcinoma cause dysphonia, and dysphonia has been reported in up to 30% of patients treated with antiangiogenic therapy.[36] Fatigue is common in nearly all patients receiving chemotherapy and commonly is accompanied by dysphonia.

As reviewed in Chapter 11, gastric carcinoma is the fifth most common cancer in the world,[37] with approximately 27 500 cases worldwide diagnosed in 2019.[38] It is most common in people aged 70 years and older, and it occurs in men more than in women. It also is more common in overpopulated countries with low socioeconomic demographics.[39–41] Gastric cancer is notorious for causing weight loss and fatigue that can impair phonation. Like other cancers, depression and anxiety are common, and these also can have adverse effects on voice. Surgery is a mainstay of treatment. In addition to potentially impairing the support system, surgery for gastric cancer commonly causes reflux, sometimes severe reflux, that can damage the larynx. Gastric cancers commonly metastasize, and metastasis may involve the lungs and neck, causing compression or invasion of the vagus nerve resulting in vocal fold paralysis. Chemotherapy for gastric cancer causes problems as previously discussed with other cancers. However, antiangiogenic medications are increasingly and commonly used for gastric cancers, and they can cause severe ischemic vocal fold pathology.[42–45]

Chapter 12 provides an overview of liver cancer. The American Cancer Society estimated that there were 42 030 new cases of liver and intrahepatic bile duct cancer in the United States in 2019.[46] The prevalence of liver cancer increased by 75% worldwide between 1990 and 2015; in the United States, the number of cases more than tripled since 1980. Liver cancer is associated with alcohol, drug use, and fatty foods that can damage the liver. Cirrhosis, chronic infection with hepatitis B or C, and diabetes also increase the risk of liver cancer, as do obesity and unprotected sex. The liver performs more than 500 essential functions including clearing toxins; assisting digestion; storing vitamins and minerals from food; metabolizing carbohydrates, fats, and proteins; and filtering blood. The systemic effects of liver cancer can be profound. Typically, liver cancer presents with loss of appetite and weight, abdominal pain, nausea and vomiting, and jaundice. Hepatocellular carcinoma accounts for approximately 75% of all liver cancers, but other types include fibrolamellar, cholangiocarcinoma (bile duct cancer), angiosarcoma, and secondary liver cancer caused by metastasis from a cancer elsewhere. Although liver transplant is the ideal treatment, only a few patients with liver cancer are appropriate candidates. For most, immunotherapy, partial resection of the liver, chemotherapy, targeted therapy, and interventional radiology are used. Overall, the 5-year survival rate for liver cancer is 18%, although survival is better if the cancer is diagnosed at an early stage. Liver cancer and its treatment

are almost always debilitating. In addition to weight loss, muscle wasting, fatigue, and psychological response to the disease may cause voice dysfunction for reasons discussed earlier in relation to other cancers.

Cancer almost always affects voice. In some cases, the cancer impairs the voice directly. In others, the cancer or its treatment causes debilitation, weight loss, depression, anxiety, and other reactions that interfere with optimal phonation. Dysphonia in cancer patients has a devastating impact on the physical and emotional aspects of their lives. Cancer patients need to be heard, and their voices warrant an attentive medical audience when affected. The authors hope that this book will not only provide useful information for our readers, but also highlight knowledge gaps and inspire further research.

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SECTION I

Basic Science





1

Anatomy and Physiology of the Voice

Robert Thayer Sataloff

To treat voice patients knowledgeably and responsibly, health care professionals must understand the medical aspects of voice disorders and their treatment. This requires core knowledge of the anatomy and physiology of phonation. The human voice consists of much more than simply the vocal folds, popularly known as the vocal cords. State-of-the-art voice diagnosis, nonsurgical therapy, and voice surgery depend on understanding the complex workings of the vocal tract. Psychotherapists specializing in the care of voice patients, especially voice professionals, should be familiar with at least the basics of the latest concepts in voice function. The physiology of phonation is much more complex than this brief chapter might suggest, and readers interested in acquiring more than a clinically essential introduction are encouraged to consult other literature.[1] This chapter is written to be accessible to patients as well as health care providers.

Anatomy

The larynx is essential to normal voice production, but the anatomy of the voice is not limited to the larynx. The vocal mechanism includes the abdominal and back musculature, rib cage, lungs, pharynx, oral cavity, and nose, among other structures. Each component performs an important function in voice production, although it is possible to produce voice even without a larynx, for example, in patients who have undergone laryngectomy. In addition, virtually all parts of the body play some role in voice production and may be responsible for voice dysfunction. Even something as remote as a sprained ankle may alter posture, thereby impairing abdominal, back, and thoracic muscle function, resulting in vocal inefficiency, weakness, and hoarseness.

The larynx is composed of four basic anatomical units: skeleton, intrinsic muscles, extrinsic muscles, and mucosa. The most important components of the laryngeal skeleton are the thyroid cartilage, cricoid cartilage, and two arytenoid cartilages (Figure 1–1). Intrinsic muscles of the larynx are connected to these cartilages (Figure 1–2). One of the intrinsic muscles, the *thyroarytenoid muscle* (its medial belly is also known as the vocalis muscle), extends on each side from the vocal process of the arytenoid cartilage to the inside of the thyroid

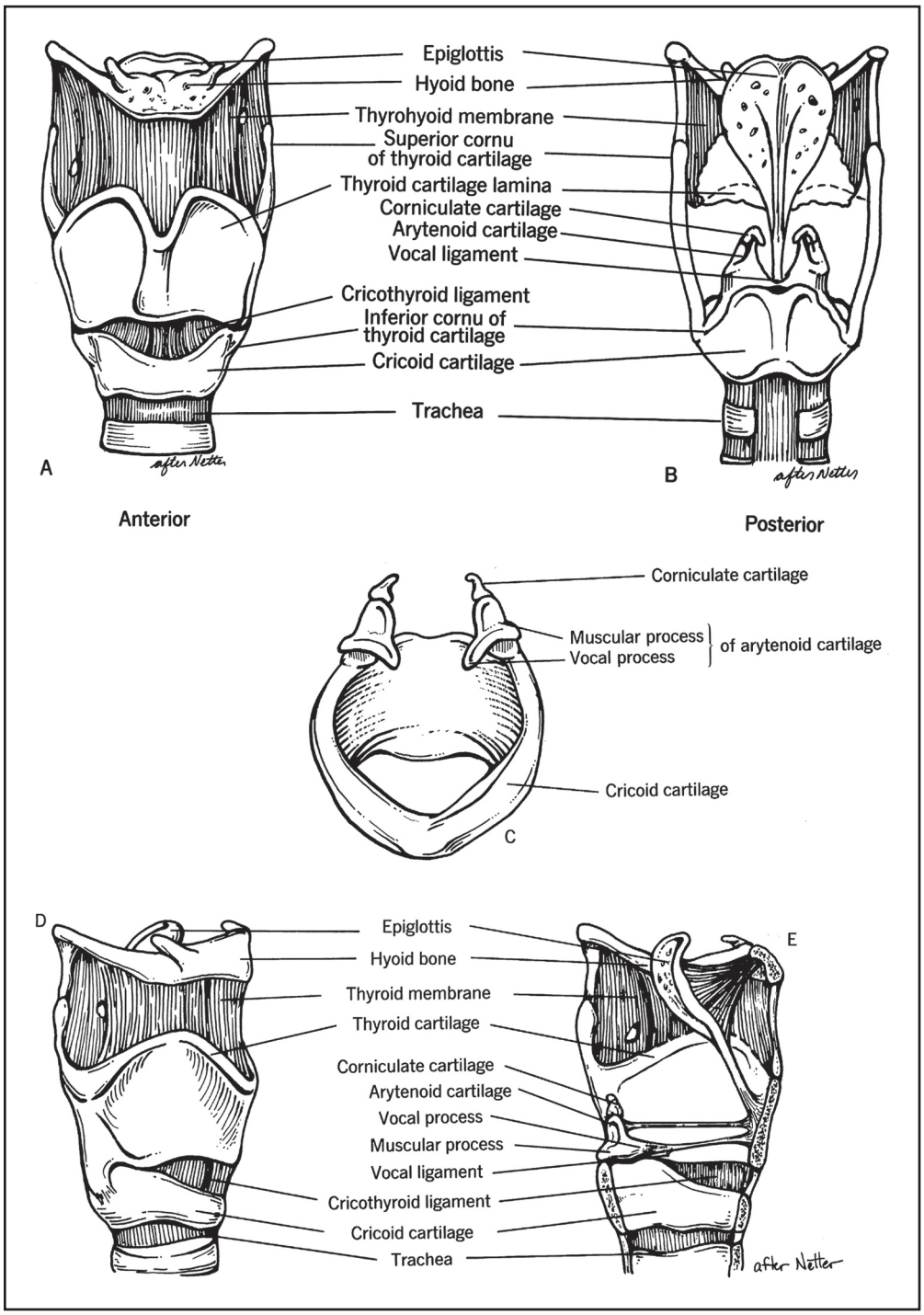

Figure 1–1. Cartilages of the larynx.

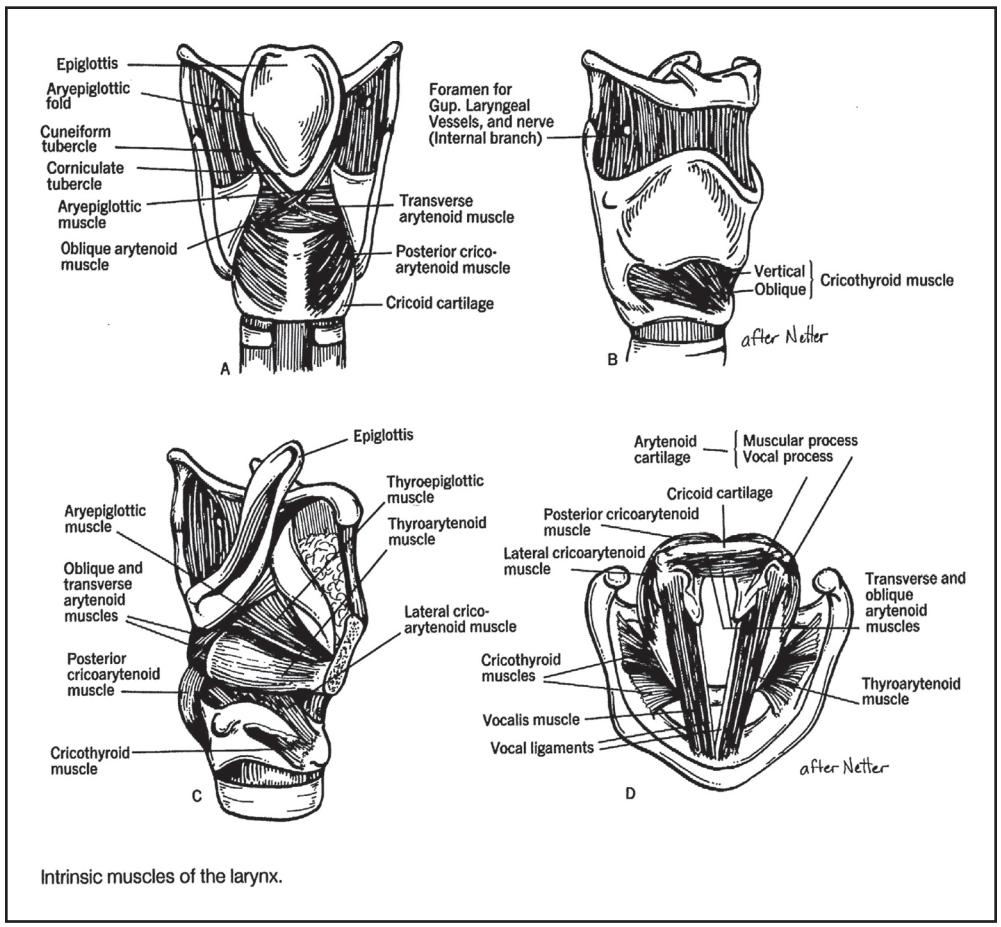

Figure 1–2. Intrinsic muscles of the larynx.

cartilage just below and behind the thyroid prominence ("Adam's apple"), forming the body of the vocal folds. The vocal folds act as the *oscillator* or *voice source* of the vocal tract. The space between the vocal folds is called the *glottis* and is used as an anatomical reference point. The intrinsic muscles alter the position, shape, and tension of the vocal folds, bringing them together (adduction), moving them apart (abduction), or stretching them by increasing longitudinal tension (Figure 1–3). They are able to do so because the laryngeal cartilages are connected by soft attachments that allow changes in their relative angles and distances, thereby permitting alteration in the shape and tension of the tissues suspended between them. The arytenoid cartilages on their elliptic cricoarytenoid joints are capable of motion in multiple planes, permitting complex vocal fold motion and alteration in the shape of the vocal fold edge associated with intrinsic muscle action (Figure 1–4). All but one of the muscles on each side of the larynx are innervated by one of the two *recurrent laryngeal nerves*. Because this nerve runs in a long course (especially on the left) from the neck down into the chest and then back up to the larynx (hence, the name *recurrent*), it is injured easily by

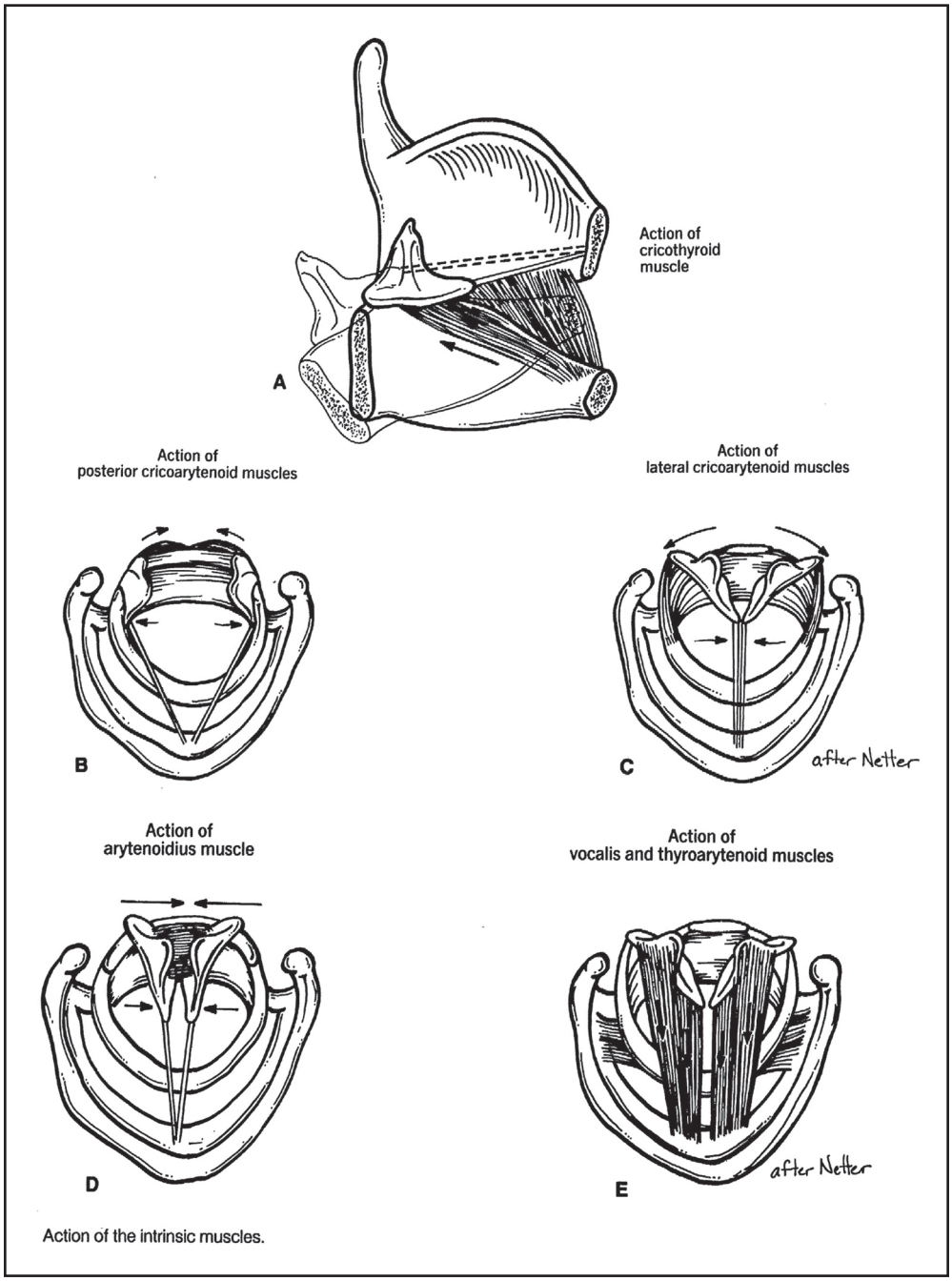

Figure 1–3. Action of the intrinsic muscles.

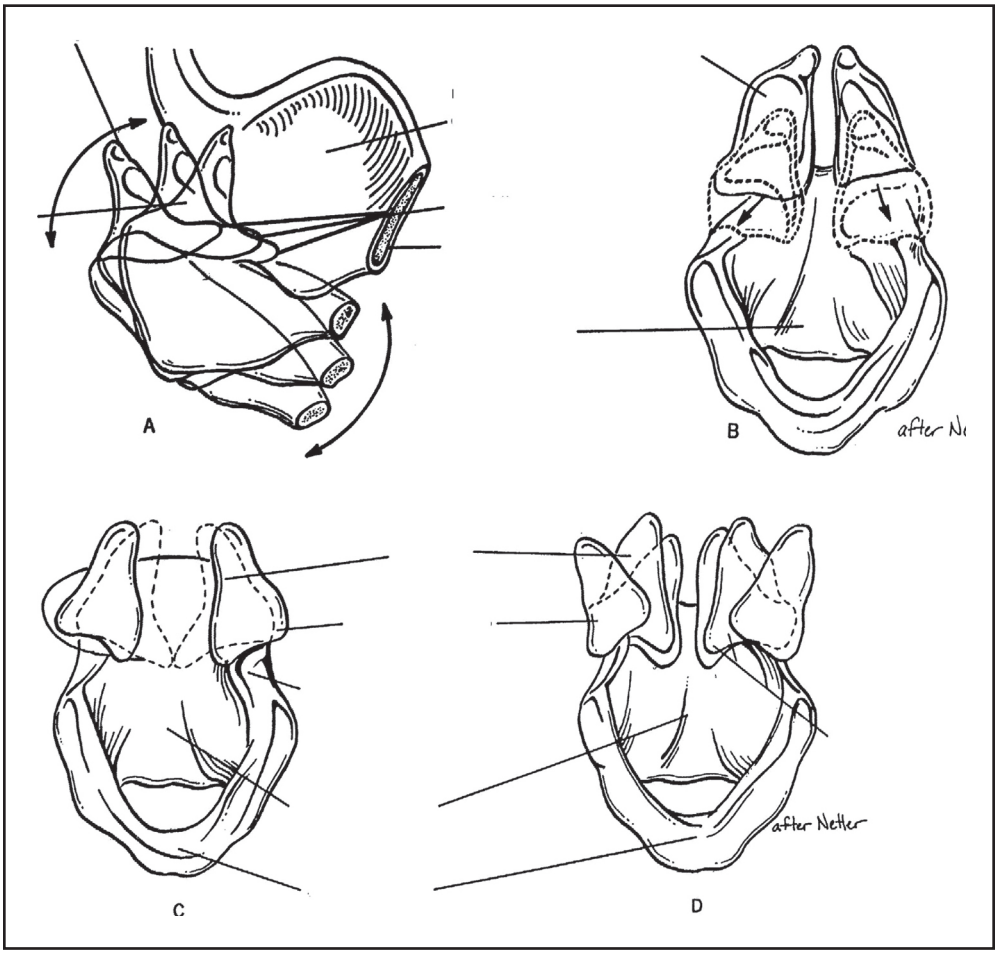

Figure 1–4. Complex arytenoid motion.

trauma, neck surgery, and chest surgery. Injury may result in vocal fold paresis or paralysis. The remaining muscle (*cricothyroid muscle*) is innervated by the superior laryngeal nerve on each side, which is especially susceptible to viral and traumatic injury. It causes changes in longitudinal tension that are important in voice projection and pitch control. The "false vocal folds" are located above the vocal folds, and unlike the true vocal folds, usually do not make contact during normal speaking or singing.[1] The neuroanatomy and neurophysiology of phonation are extremely complicated and only partially understood. As the new field of neurolaryngology advances, a more thorough understanding of the subject is becoming increasingly important to medical and psychological clinicians. Readers interested in acquiring a deeper, scientific understanding of neurolaryngology are encouraged to consult other literature[2] and the publications cited therein.

Because the attachments of the laryngeal cartilages are flexible, the positions of the cartilages with respect to each other change when the laryngeal skeleton is elevated or lowered. Such changes in vertical height are