Diagnosis and Treatment of Voice Disorders

Fourth Edition

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Preface

It has been almost 10 years since publication of the third edition of *Diagnosis and Treatment of Voice Disorders*. This past decade has heralded in a new digital age, the likely eponym for the subsequent half century. There has been a veritable explosion of advances based on the associated sharing of information, and these advances have informed practically every aspect of voice care, from the bench to the operating table.

Wilbur James Gould, mentor and dear friend of each of the editors, foresaw the benefits of information sharing, its implicit role in scientific advancements to voice care, and the crucial role of such a multidisciplinary approach to patient welfare. We once again dedicate this fourth edition to Dr Gould and rededicate ourselves to his vision.

The fourth edition now has 58 chapters (compared with 48 in the third edition). It is subdivided into units: Basic Science (Chapters 1–12), Clinical Assessment (Chapters 13–23), and Management (Chapters 24–58). In preparing the fourth edition, we have endeavored to retain the format of the previous three editions but at the same time to incorporate new materials in a reader-friendly manner. To that end, a few chapters have needed minimal to no revision, some chapters have undergone extensive updates or have been rewritten completely, and some chapters have been divided into two to present the new materials better. There also have been a number of chapters written by new authors and chapters written on new subjects specifically for this edition.

Examples of chapters that are classics and required little to no rewriting include David Henick's chapter "Laryngeal Development," Ira Sander's chapter "Microanatomy of the Vocal Fold Musculature," and Jean and Patrick Abitbol's chapter "The Larynx: A Hormonal Target."

Chapters with extensive updates to keep pace with changes in knowledge include Jeffrey Laitman and colleagues' chapter "Formation of the Larynx: From *Hox* Genes to Critical Periods" and Kiminori Sato's chapter "Functional Fine Structures of the Human Vocal Fold Mucosa." Not surprisingly, expansion of information about the genome has led to better understanding of formative stages of embryogenesis; such information is now also becoming applicable to the structures of the vocal fold mucosa.

Examples of chapters with shifts in focus expressed through their revisions/rewrites include Ronald Baken and Robert Orlikoff's chapter "Toward a Dynamical Diagnosis of Vocal Function," Jamie Koufman's chapter "Laryngopharyngeal Reflux and Voice Disorders," and Steven Zeitels's "Glottic Carcinoma: Disease Presentation and Philosophy of Management." In these chapters, the authors show substantial changes in their approach to or understanding of the problem. For example, Ronald Baken and Robert Orlikoff postulate use of nonlinear vocal behavior models for diagnosis of discrete laryngeal pathology, Jamie Koufman approaches laryngopharyngeal reflux from a position akin to oncology, and Steven Zeitels reports on adjuvant therapies not even considered in the third edition.

In this edition, we have not only requested new authors for selected previous chapters but also expanded the book with a number of chapters on entirely new subjects. These additions are found in each section of the book. Some of the additions are paired with previous chapters, such as Jean-Paul Marie's chapter "Reinnervation: New Frontiers," paired with Harvey Tucker's chapter "Laryngeal Reinnervation: Traditional Approaches," and Barbara Houseman's chapter "The Role of the Voice Coach in the Treatment of Voice Disorders," paired with Linda Carroll's chapter "The Role of the Voice Specialist in the Nonmedical Management of Benign Voice Disorders." Some of the additions present new trends in clinical management such as Markus Hess and Susanne Fleischer's chapter "Office-Based Phonosurgery," Nancy Solowski and Gregory Postma's chapter "Transnasal Esophagoscopy," and Rupali Shah and Kenneth Altman's chapter "Cough and the Unified Airway." Particularly in the clinical chapters, evidence-based and clinical-based research is matched with step-by-step protocols and methods to avoid pitfalls.

Some of the new chapters offer insights and ideas not readily available at the time of the previous

edition. Examples might include John Rubin and Robert Sataloff's chapter "Telemedicine" or Orietta Calcinoni and Ewa Niebudek-Bogusz' chapter "Occupational Voice." We believe that some of the chapters will actually appear to the reader to be substantially ahead of the current time or at the very cutting edge. Examples might include Jonathan Fishman and colleagues' chapter "Emerging Approaches to Laryngeal Replacement and Reconstruction," Marie Jetté and Susan Thibeault's chapter "Vocal Fold Extracellular Matrix and Wound Healing," and Christie Ludlow's chapter "Laryngeal Neurophysiology."

In summary, this fourth edition of *Diagnosis and Treatment of Voice Disorders* provides a vibrant, up-to-date, accessible, and clear reference for the various professionals entrusted with the care of patients with voice disorders, be they laryngologists or phoniatricians, speech-language pathologists or logopeds, physical therapists, osteopaths or other practitioners of complementary medicine, singing or acting voice specialists, acoustic or voice scientists, psychiatrists or psychologists, gastroenterologists, pulmonologists, or neurologists, nurses, or other allied medical specialists. It is written in language intended to be accessible to an interdisciplinary readership, and we hope that the information presented will prove not only useful but also inspirational to all voice care professionals since each of us has the opportunity to add new knowledge to this exciting and rapidly advancing field.

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Unit 1

BASIC SCIENCE

1

Formation of the Larynx: From Hox *Genes to Critical Periods*

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Drew M. Noden
Thomas R. Van De Water

The human larynx is a compact and complex structure that must serve respiratory, protective, and vocalization functions. Although there have been several descriptions of the major histogenic and morphogenic events during laryngeal development in humans[1] and other mammals,[2] only recently have accurate fate mapping and molecular expression data become available.

The larynx arises at the interface of "head" and "trunk" regions of the embryo, and cells from both sides of this interface move to the site of laryngeal development. Also, it is the only musculoskeletal assembly intimately associated with the endodermal gut tube. These unique attributes make dissecting the cellular and molecular basis of laryngeal development especially difficult and, to date, neglected.

This chapter addresses two aspects of laryngeal development that are especially critical to understanding the structure-function relations both within this complex and between it and adjacent structures. First, we review early embryologic events and processes, including the genesis of laryngeal tissues and interactions, both cellular and genetic, which are essential for the normal histogenesis and morphogenesis of the larynx. Second, we identify and discuss significant critical periods in prenatal and postnatal laryngeal development in humans.

ESTABLISHING LARYNGEAL PRIMORDIA

Common Developmental Themes

Laryngeal development requires the determination and integrated movements of several cell lineages that converge beside the caudal aspect of the pharynx.

These epithelial and mesenchymal precursors of mucosa, loose and dense connective tissues, voluntary and smooth muscles, blood vessels, and nerves have greatly varied embryonic histories, and each cell lineage undergoes developmental programming that prepares its members to participate as chondrocytes, myocytes, and other components of laryngeal morphogenesis.

Achieving this programming requires a progressive series of interactions involving other cells and the extracellular milieu that alter the function of specific genes, which in turn changes the response characteristics of cells to subsequent interactions. These interactions affect rates of cell proliferation, pathways and speeds of cell migration, and both the commitment to and the expression of specific cell phenotypes. Clearly, such processes must be temporally and spatially coordinated in order for so many disparate progenitors to achieve an integrated outcome.

A multicomponent musculoskeletal laryngeal apparatus is absent in anamniotes, although some terrestrial amphibians do have cartilaginous rods that partially circumscribe an elongated glottis. This single skeletal element is often cited as being an antecedent to at least one of the laryngeal skeletal elements and is thought to have evolved from gill-associated cartilages. However, there is little direct evidence for either of these claims. However, among amniotes, many laryngeal precursor populations have sites of origin that are evolutionarily conserved. A key feature of this conserved plan is the presence in all vertebrate embryos of a *segmental organization* within many tissues that are developmentally related to the larynx. This is manifest especially in hindbrain, branchial arch, and trunk axial regions. Although the larynx is not generally viewed as a segmentally organized set of structures, tissues developing nearby, many formed from common progenitors, do exhibit a metameric organization during their development. And immediately caudal to the larynx, the tracheal rings present a metameric pattern.

The expression patterns of several members of gene families that are involved in lineage delineation and spatial programming of head and neck tissues similarly show a segmental organization. Abnormal expression of some of these genes, either as a result of germ line mutations in humans or experimental gene manipulation in transgenic mice, also results in disruptions of hindbrain, branchial, otic, and laryngeal morphogenesis.

The first objective of this section is to identify the origins of laryngeal precursors and document their movements to the site of laryngeal morphogenesis. The second goal is to identify when and where each of these populations become programmed to form tissues of the types and shapes appropriate to their final location, including the genetic bases for their decisions. The reader should be warned that laryngeal development has received little attention by experimental biologists. Thus, some hypotheses regarding laryngeal development presented here are by inference, based on properties of neighboring structures and experimental analyses in only a few model systems.

Origins of Laryngeal Precursors

Overview

The epithelial lining of the larynx forms close to the caudal margin of the embryonic pharynx, although this site is otherwise indistinct from the adjacent parts of the primitive endodermal tube. Rostral to this site, the pharynx forms a set of segmentally arranged, lateral endodermal outpocketings, the *pharyngeal pouches*, between which are located the *branchial arches* (also referred to as pharyngeal or visceral arches). Present within each branchial arch are precursor populations for connective tissues, skeletal muscle, blood vessels, and peripheral neurons. These may be segregated from their neighbors (eg, skeletal myoblasts) or fully interspersed (eg, endothelial precursors). Some vertebrates establish a large number of branchial arches, retaining many as gills, but amniotes (reptiles, birds, and mammals) form only 3 or 4 recognizable branchial arch swellings on each side of the head (Figure 1–1). True fifth and sixth branchial arches do not form in amniotes.

During the neurula stage, embryos establish sets of structures common to all developing vertebrates. The *neural tube* is located dorsally (posteriorly) and is flanked on each side by *paraxial mesoderm*. Along most of the body length, this mesoderm forms cuboidal epithelial blocks called *somites*. In the head, however, paraxial mesoderm fails to epithelialize and does not display an overt segmental organization. Ventrally, the endodermal sheet folds to form a gut tube, consisting of the pharynx, rostrally, that is continuous with the future fore-, mid-, and hind-gut passageways. When first formed, this endodermal tube is enveloped laterally and ventrally by *lateral mesoderm*. This sparse mesoderm becomes partially displaced by a secondary population of mesenchymal cells, the *neural crest*.

The neural crest brings a new population of connective tissue precursors to parts of the head in all vertebrates. Crest cells arise from the roof of the brain or neural folds and move en masse to fill the areas between each pharyngeal pouch and also circum-

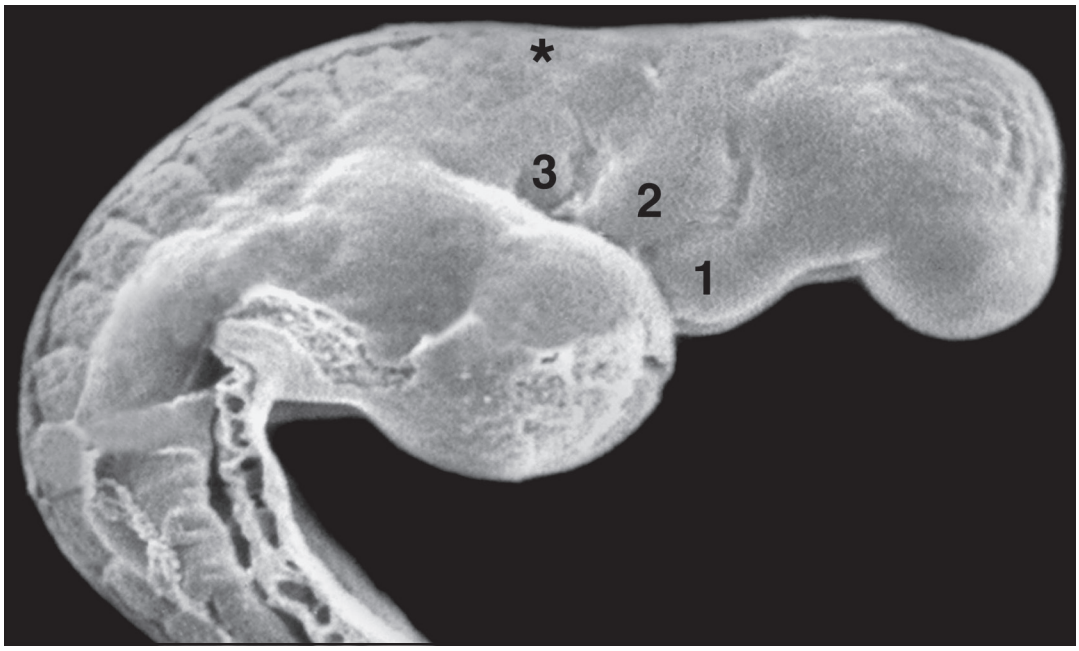

Figure 1–1. Scanning electron micrograph showing the swellings of the first (1), second (2), and third (3) branchial (pharyngeal) arches, which have formed by the movement of neural crest cells from dorsal, neural to ventral, pharyngeal regions. The grooves between each arch represent the sites of apposition between surface ectoderm and underlying pharyngeal pouches. Note the location of the prominent heart primordium, which at this stage has already begun to loop. The heart will subsequently shift its position caudally as the branchial arches and caudal pharyngeal region remodel. About 14 somites are visible; * indicates somite 1. The specimen is a 16-day, 22-somite domestic cat embryo, which corresponds to a stage 12 (30-day) human embryo.

scribe the prosencephalon (Figure 1–2). The hindbrain, from which the majority of branchial arch crest cells originate, is a segmentally organized tubular structure, and the crest cells that enter each branchial arch can be traced to specific segments.

Connective tissues of the larynx develop at the boundary of tissues derived from the neural crest and those derived from lateral mesoderm. Caudal (posterior) to this, all connective tissues associated with the endodermal tube—including tracheal rings—are of lateral mesoderm origin.

The preceding overview highlights the complexity of laryngeal embryology owing in large part to its association with the ventral endodermal tube and location at the head-trunk interface. The following sections provide detailed accounts of each component of the developing larynx.

The Respiratory Diverticulum

The epithelial lining of the pharynx, from which the *respiratory diverticulum* arises, is formed along with the endodermal lining of the pharynx and gut during early gastrulation stages. Cells within the epiblast, which is the superficial layer of the embryonic disc (inner cell mass), move internally beginning at the junction of the epiblast and early primitive streak: these establish a new, internal epithelial layer, the endoderm.[3] Once internalized, the endodermal sheet expands rapidly and forms the entire intraembryonic endodermal primordium. Shortly thereafter, the positional identities of most endodermal structures (eg, thyroid, thymus, stomach, pancreas) become specified.

Endodermal cells that will give rise to laryngeal mucosa are initially located beneath (ventral to) the future postotic hindbrain region. Analyses of dicephalic neonates reveal that only when the site of skull duplication occurs as far caudally as the occipito-atlanto-axial region, which flanks the caudal hindbrain, will there also be paired larynges. Duplications that extend only to the spheno-occipital (mid-hindbrain) level will have a single laryngeal apparatus.

The *respiratory diverticulum* (laryngotrachial groove, tracheal diverticulum) is first evident as a ventrally expanded trough projecting from the floor of the pharynx beginning at the level of the fourth (most

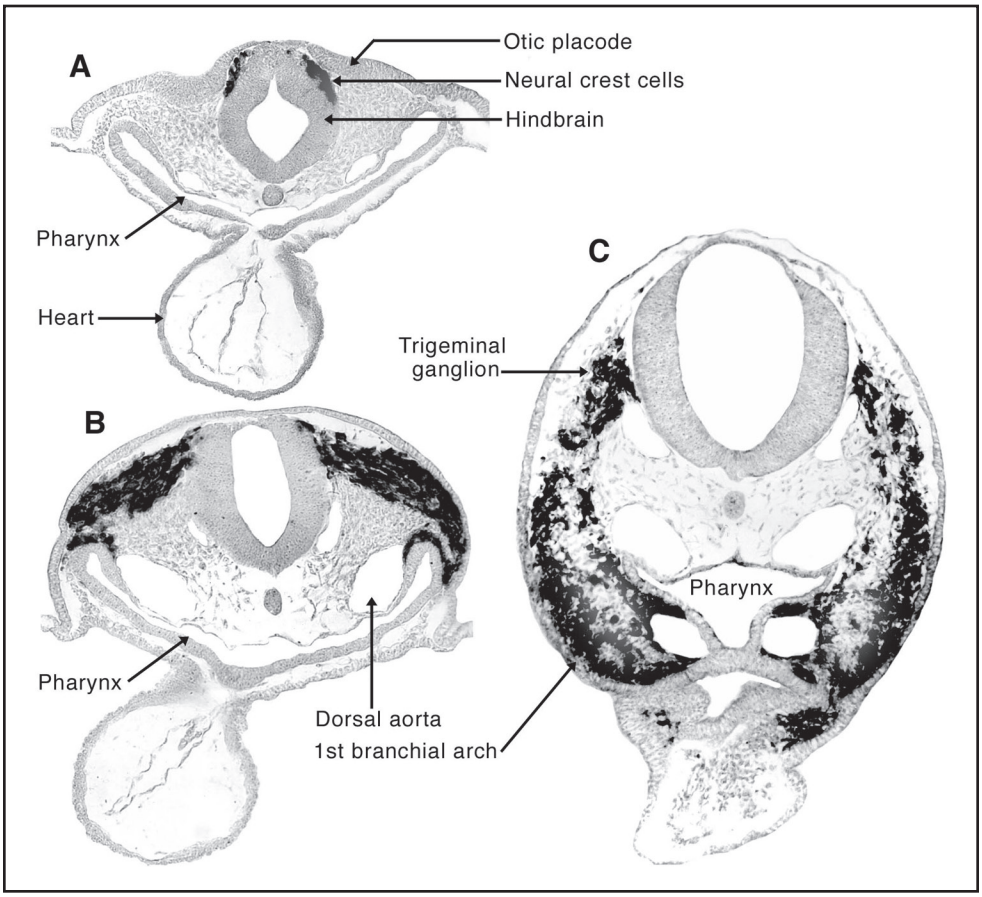

Figure 1–2. Transverse sections of chick embryos stained with an antibody to neural crest cells. **A** shows a 12-somite embryo at the level of the otic placode (inner ear primordium). Crest cells have recently emerged from the roof of the hindbrain. **B** is at the preotic (rhombomere 4), first pharyngeal pouch region of a 16-somite chick embryo; note the sharp boundary between crest and underlying paraxial mesoderm. **C** is a 25-somite embryo. By this stage, crest cells have completed their ventral movements and, after the outflow tract of the heart (O.T.) shifts caudally, will join in the midline to complete the formation of the lower jaw region. Unlabeled cells within the branchial arch are mesodermal cells that will form the jaw musculature.

caudal) pharyngeal pouch.[1] Shortly after this evagination forms, distinct lateral outpocketings emerge bilaterally from the caudal margin of this trough; these demarcate the future bronchial-pulmonary structures. Partial separation of the ventral (respiratory) from dorsal (esophageal) regions of the caudal pharynx occurs by a caudal-to-cranial dying off of intermediate endodermal epithelial cells.[4,5] This is followed by a rapid caudal elongation of both the respiratory diverticulum and the esophagus.[6,7] Subsequent stages in the development of the respiratory diverticulum are presented in greater detail in Chapter 2.

It is not known how the precise site at which the respiratory diverticulum forms is specified. Similar to several other endoderm-derived structures (eg, the thyroid and pancreas), the early histogenic remodeling of the respiratory diverticulum requires the presence of a cholesterol-associated growth factor called *sonic hedgehog*.[8] Reducing the level of sonic hedgehog biosynthesis by cells of the respiratory diverticulum, or disabling the ability of adjacent mesoderm cells to properly respond, results in defects of tracheoesophageal separation and tracheal chondrogenesis.[9] These dysmorphologies can be isolated, but in humans are more commonly syndromic (eg, Pallister-Hall, Smith-Lemli-Opitz, and VACTERL syndromes).[10,11]

Lateral Mesoderm

The onset of intraembryonic mesoderm formation follows the appearance of endoderm, but this mesenchymal population rapidly expands to fully overlie the

endodermal sheet. In human embryos, this process is complete by the end of the second week of gestation, and spatial relations established at these early stages remain constant throughout subsequent stages.

Fate mapping studies in avian embryos have identified lateral mesoderm located beside the first and second somites as the source of the arytenoid and cricoid cartilages (Figure 1–3A).[6] These data contradict previous assertions, based on descriptive studies, that all skeletal elements associated with the larynx are homologous to gill-associated skeletal structures in anamniotes and as such would be derived from branchial arch neural crest cells. Birds do not have structures homologous to thyroid and epiglottis cartilages, and thus the embryonic origin of this element could not be determined from these avian studies.

Lateral mesoderm located caudal to the laryngeal primordium forms the tracheal cartilages and associated connective tissues. Analyses of expression patterns of early chondrogenic genes such as *sox9* and *collagen 2A1* reveal that tracheal cartilage precursors are initially specified as a continuous longitudinal band within mesoderm located dorsolateral to the proximal (cranial) half of the respiratory diverticulum.[12] Later, this band becomes subdivided into discrete, regularly spaced chondrogenic foci, each of which subsequently expands ventrally.

A detailed molecular biography of laryngeal chondrogenesis is not yet available. Human patients and transgenic mice with haploinsufficiency of *sox9* expression have, among other skeletal defects, upper airway defects secondary to hypoplasia of laryngeal and tracheal cartilages.[13]

Lateral mesoderm located rostral to the laryngeal primordium is exclusively angiogenic and cardiogenic. Embryonic angioblasts are one of the earliest progenitor populations to be delineated and constitute more than one-third of the early mesodermal

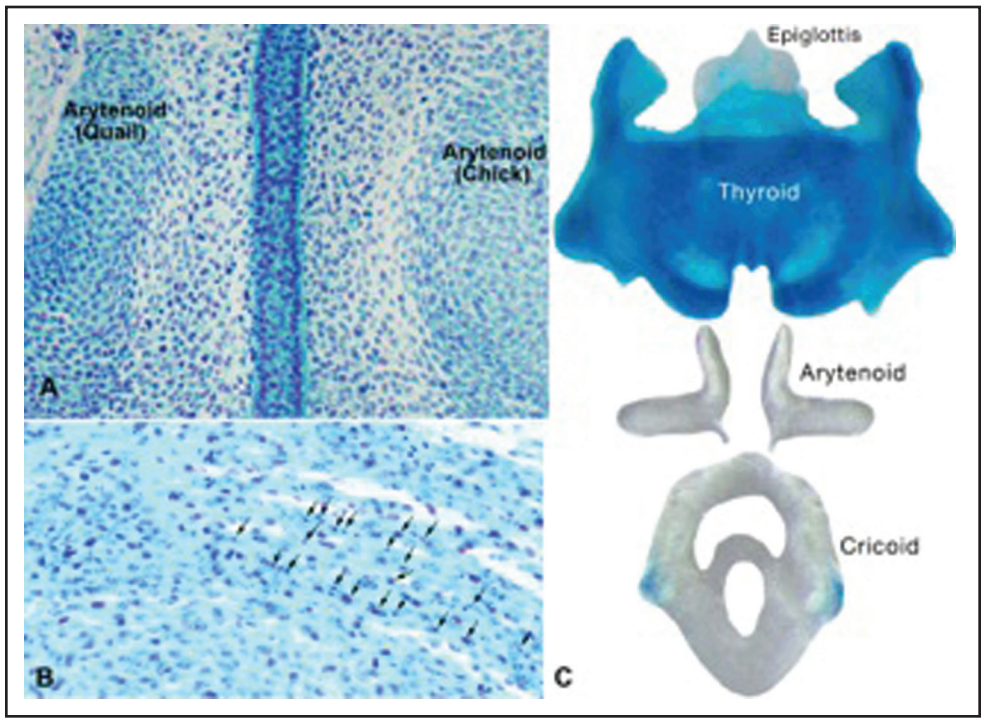

Figure 1–3. Origins of laryngeal cartilages and intrinsic muscles. **A** shows a transverse section of the larynx from a chick embryo that received a transplant of quail lateral mesoderm at an earlier stage. Quail cells are identified in the left arytenoid cartilage by their prominent dense nuclear marker, which is not present in chick tissues. **B** is from a chimeric embryo in which quail paraxial mesoderm cells were grafted. This section shows quail cells (*arrows*) contributing to an intrinsic laryngeal muscle, the dilator glottidis, but not to associated connective tissues. **C** shows the laryngeal cartilages, dissected apart for clarity, from a neonatal mouse in which all cells derived from the neural crest contain a reporter gene construct (*labeled blue*). The epiglottis and thyroid cartilages are derived from the neural crest; the other laryngeal cartilages are mesodermal in origin. *Sources:* A. Noden[51]; B. Noden.[18]