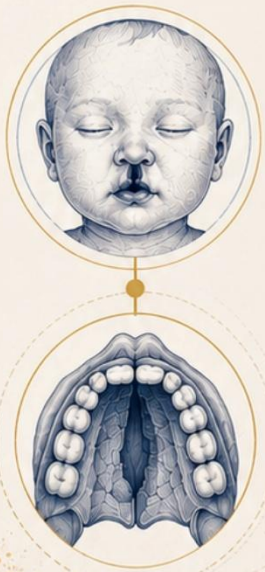
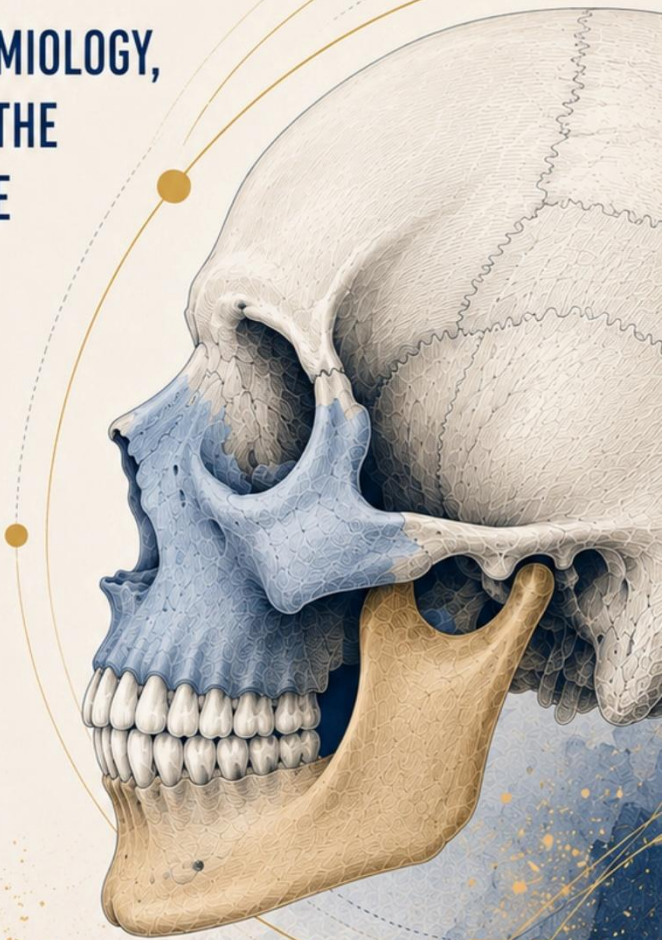
CLEFT LIP AND PALATE AND THE CRANIOFACIAL SKELETON:

CLASSIFICATION, EPIDEMIOLOGY, AND DEVELOPMENT OF THE MAXILLA AND MANDIBLE

AUTHOR:
ELİF SAĞIR





BİDGE

BİDGE Yayınları

CLEFT LIP AND PALATE AND THE CRANIOFACIAL SKELETON: CLASSIFICATION, EPIDEMIOLOGY, AND DEVELOPMENT OF THE MAXILLA AND MANDIBLE

Yazar: Elif SAĞIR

ISBN: 978-625-8821-86-4

1st Edition

Page Layout By: Gözde YÜCEL

Publication Date: 02.09.2026

BİDGE Yayınları

Certificate No: 71374

www.bidgeyayinlari.com.tr - bidgeyayinlari@gmail.com
Krc Bilişim Ticaret ve Organizasyon Ltd. Şti.
Güzeltepe Mahallesi Abidin Daver Sokak Sefer Apartmanı No: 7/9 Çankaya /Ankara

CONTENTS

PREFACE

Cleft lip and palate (CLP) is one of the most common congenital craniofacial anomalies, and its proper clinical understanding requires more than a single perspective. It requires, first, a clear and historically informed grasp of how the condition itself has been classified and communicated among clinicians and researchers over the past century, together with an understanding of how frequently it occurs and why it arises. It requires, second, a detailed understanding of the normal embryological development and adult anatomy of the craniofacial skeleton, and in particular of the maxilla and mandible, the two jaw bones whose growth and morphology are most closely bound up with the skeletal and functional consequences of CLP.

This book addresses these needs in turn. The first part traces the historical evolution of cleft lip and palate classification systems, from the earliest surgically oriented schemes of the 1920s to the genetically and syndromically informed systems of the present day, and closes with a review of the global epidemiology and genetic basis of CLP, situating the classification systems within the broader picture of how common the condition is and what is known about its causes. The second part turns to the jaws themselves, reviewing first the prenatal and postnatal development and growth of the maxilla, the bone within which the cleft itself lies, and then the embryological development, postnatal growth, and anatomical structure of the mandible, a bone with no direct embryological connection to the cleft, before returning specifically to how each jaw is structurally

affected in individuals with CLP, closing the circle between the two parts of the book.

Taken together, these two parts move from the clinical, historical, and epidemiological understanding of a craniofacial anomaly to the normal developmental and anatomical framework of a skeletal structure closely implicated in that anomaly, and finally to the specific skeletal consequences observed when the two intersect. It is our hope that this progression offers the reader a coherent and clinically grounded introduction to the classification, epidemiology, and craniofacial developmental consequences of cleft lip and palate, of particular relevance to orthodontics, oral and maxillofacial radiology, and craniofacial medicine.

Elif SAĞIR[1]

[1] [Uzm.Arş.Görevlisi]. Gaziantep Üniversitesi, Diş Hekimliği Fakültesi, Ortodonti Anabilim Dalı. ORCID: [0009-0002-6491-1973]

CLASSIFICATION SYSTEMS FOR CLEFT LIP AND PALATE: A HISTORICAL AND COMPARATIVE REVIEW

Cleft lip and palate (CLP) encompasses a remarkably wide range of phenotypic presentations, from an isolated notch in the vermilion border of the lip to a complete bilateral cleft extending through the lip, alveolus, and hard and soft palate. This phenotypic diversity has posed a persistent challenge for clinicians and researchers seeking a common language to describe, record, and compare cases across surgical practices, research centers, and countries. Over the course of the twentieth century, this challenge gave rise to a succession of classification systems, each reflecting the clinical priorities, anatomical understanding, and technological possibilities of its time. Early systems were devised chiefly to guide surgical planning; later systems incorporated embryological reasoning, functional and esthetic considerations, and eventually genetic and digital documentation needs. This part opens by describing the clinical spectrum of CLP and how the lip, palate, and maxilla normally develop, before tracing the historical progression of the classification systems built around that phenotypic variability, and closing with the global epidemiology and genetic basis of the condition.

Clinical Presentation and Anatomical Types of Cleft Lip and Palate

Before turning to how CLP has been classified historically, it is useful to set out the clinical vocabulary in which any classification system is grounded. A cleft of the lip is described first by laterality, as unilateral or bilateral, with unilateral presentations markedly more common and, among these, a left-sided cleft occurring roughly twice as often as a right-sided one; a smaller proportion of cases present bilaterally (Kosowski et al., 2012). Each lip cleft is further described by completeness: a complete cleft extends through the full height of the lip into the floor of the nostril, whereas an incomplete cleft leaves a band of tissue, however thin, bridging the gap. A cleft of the palate is described using an analogous vocabulary of laterality and completeness, together with its anteroposterior extent relative to the incisive foramen, and a distinct, often clinically inconspicuous variant, the submucous cleft palate, occurs when the oral mucosa remains intact over a defect in the underlying muscle or bone (Kosowski et al., 2012). Across large clinical series, isolated cleft lip, isolated cleft palate, and combined cleft lip and palate each account for a substantial share of cases, with combined presentations somewhat more frequent than either isolated form, underscoring that CLP is better understood as a family of related anatomical presentations than as a single uniform defect (Watkins et al., 2014).

These anatomical distinctions carry direct functional consequences that extend well beyond the visible cleft itself. Because normal closure of the soft palate against the pharyngeal wall is required to direct airflow and pressure into the oral cavity during speech, an unrepaired or incompletely functioning palate can leave this valve mechanism incompetent, altering the resonance and intelligibility of speech; three-dimensional airway imaging in patients treated for complete unilateral CLP has correspondingly demonstrated measurable postoperative changes in oropharyngeal

and velopharyngeal airway morphology relative to non-cleft controls, reflecting how closely the anatomy of this region is tied to its function (Chen & Zhang, 2022). A cleft extending through the secondary palate can also disrupt the normal action of the muscle that opens the Eustachian tube, predisposing affected children to recurrent middle-ear fluid accumulation and associated hearing difficulty until the palate is surgically repaired (Kosowski et al., 2012). These functional dimensions of CLP, distinct from but layered onto its purely anatomical description, help explain why the classification systems reviewed later in this part needed to evolve beyond simple anatomical description toward frameworks capable of supporting coordinated surgical, speech-language, and audiological management.

Embryological Development of the Lip and Palate

Before a phenotype can be classified, it is worth understanding how the structures it involves are normally formed and, correspondingly, where the process can go wrong. The upper lip takes shape between roughly the fourth and seventh weeks of gestation, as the medial nasal prominences, positioned beneath the developing nose, grow toward and merge with the maxillary prominences approaching from either side (Kosowski et al., 2012). This union establishes both the continuity of the lip and the vertical philtral groove at its midline. The mesenchyme populating these facial prominences is derived largely from cells that have migrated from the cranial neural crest, and the precise timing of this migration, together with adequate proliferation and merging of the prominences, is what allows an intact lip to form (Carlson, 2019). A cleft lip, unilateral or bilateral, results when this fusion fails at some point along its length; because the defect is one of fusion between adjacent prominences rather than the rupture of an already continuous structure, the resulting gap can range from a minor notch

in the vermilion to a complete separation reaching the floor of the nostril (Mossey et al., 2009).

The palate, by contrast, forms in two developmentally distinct stages. A small, triangular primary palate, lying immediately behind the position of the future incisors, arises from the same medial nasal tissue that produces the lip and is essentially complete by the seventh week (Kosowski et al., 2012). The much larger secondary palate, which becomes the remainder of the hard and soft palate, develops independently from a pair of shelves projecting from the maxillary prominences on either side of the tongue. These shelves initially point downward, and before they can meet at the midline they must reorient into a horizontal plane above the tongue, a repositioning that depends on the tongue dropping out of the space between them as the mandible itself grows (Bush & Jiang, 2012). Once elevated, the shelves grow toward each other, make contact, and fuse in the midline, a sequence that also requires their anterior edges to join the primary palate and their posterior edges to join the nasal septum, so that by around the twelfth week a single continuous partition separates the oral and nasal cavities (Kosowski et al., 2012; Bush & Jiang, 2012).

This entire sequence, outgrowth, elevation, contact, and fusion, is coordinated by an interacting network of molecular signals, among them sonic hedgehog, bone morphogenetic proteins, fibroblast growth factors, transforming growth factor beta, and Wnt signaling, which together govern how the neural-crest-derived mesenchyme within the shelves proliferates and behaves (Bush & Jiang, 2012). Completing the fusion additionally requires that the epithelial cells along the medial edge of each shelf be cleared away, principally through programmed cell death, so that the mesenchyme beneath can merge into one continuous tissue mass across the midline (Bush & Jiang, 2012). A cleft of the secondary palate can therefore arise from disruption at more than one point in this

sequence: shelves that fail to grow to sufficient size, elevation that is delayed long enough for the tongue or an unusually wide head to keep the shelves apart, or a failure of the medial edge epithelium to break down once contact has occurred (Kosowski et al., 2012; Bush & Jiang, 2012). Because the lip and primary palate share one embryological origin and the secondary palate another, cleft lip and cleft palate are best understood as related but mechanistically separable anomalies, capable of occurring together or independently.

Development and Growth of the Maxilla

The soft-tissue events described above take place within, and around, a bony framework, the maxilla, whose own developmental trajectory helps explain why the skeletal consequences of CLP extend beyond the cleft margin itself. Ossification of the maxilla begins during the seventh and eighth weeks of intrauterine life around a pair of discrete foci within each maxillary prominence, termed the maxillary primary growth centers, which radiological and histological study of fetal specimens has identified as the earliest ossification sites of the bone; these centers form a roughly trapezoidal arrangement, sometimes described as the maxillary trapezoid, that continues to enlarge steadily throughout the fetal period (Lee et al., 1992). Beyond approximately the twentieth week of gestation, further enlargement of the maxilla depends increasingly on intramembranous bone deposition around the periphery of this original trapezoid rather than on continued expansion of the primary centers themselves, which by then have largely completed their own maturation (Lee et al., 1992).

After birth, the maxilla continues to enlarge through a combination of sutural growth, surface remodeling, and passive displacement, a framework most fully articulated by Enlow, in which the maxilla is carried downward and forward largely as a passive consequence of growth in the structures to which it is

attached, particularly expansion of the nasal septal cartilage and the cranial base, while new bone is added at the sutures connecting it to the surrounding facial skeleton to maintain these articulations as the displacement proceeds (Enlow & Hans, 2008). The paired maxillae themselves remain separated at the midline by the midpalatal suture for an extended period after birth; the structure, maturation, and eventual reduction in growth potential of this suture, documented in detail through histological study of the human midpalatal region, is of particular relevance to the timing of orthopedic and orthodontic maxillary expansion procedures (Latham, 1971). A further midline structure, the septo-premaxillary ligament, links the growing nasal septum to the premaxillary segment of the maxilla anteriorly and has been proposed as a mechanical link through which septal growth is transmitted to forward displacement of the anterior maxilla (Latham, 1970).

This growth mechanism has direct relevance to the deformity associated with CLP. Latham proposed that, in unilateral CLP, the septo-premaxillary ligament and the abnormal muscular environment created by the cleft itself distort the normal transmission of nasal septal growth to the maxillary segments, contributing to the characteristic skeletal deformity, including a rotated and often laterally displaced premaxillary-vomerine segment, observed even before any surgical intervention has taken place (Latham, 1969). In bilateral CLP, a related but distinct pattern is seen: with the premaxilla no longer restrained by continuous lateral maxillary segments on either side, unopposed growth at the vomeropremaxillary suture can carry the premaxillary segment into a conspicuously protrusive position ahead of the two lateral maxillary segments (Latham, 1969). These theoretical accounts of impaired or redirected maxillary growth in CLP complement, from the maxillary side, the mandibular findings discussed later in this book, and together they indicate that the altered growth environment

created by a cleft is not confined to the immediate margins of the defect but reshapes the growth mechanics of the jaws more broadly.

The Surgically Based Classification of Davis and Ritchie (1922)

In 1922, Davis and Ritchie proposed a three-group system that is widely regarded as a landmark in the classification of CLP (Davis & Ritchie, 1922). Responding to the terminological confusion that characterized the literature of their time, the authors evaluated the lip, alveolus, and palate as distinct anatomical units and organized their classification accordingly, distinguishing Group I (prealveolar clefts, affecting the lip only), Group II (postalveolar clefts, affecting the palate only), and Group III (clefts involving the alveolar process). In this system, the alveolar process was treated as the central anatomical reference point, since its involvement was considered the principal determinant of surgical approach. Although influential, the system was criticized by some contemporary surgeons as being oriented too narrowly toward surgical planning rather than underlying anatomy, raising concerns that its clinical utility might diminish as surgical techniques evolved (Davis & Ritchie, 1922).

The Morphologically Based Classification of Brophy (1921-1923)

Truman W. Brophy was among the surgeons who considered the Davis and Ritchie system insufficient. Drawing on his experience with 7,752 surgical procedures performed between 1921 and 1923, Brophy developed a classification that divided clefts of the lip and palate into sixteen distinct morphological forms (Brophy, 1923). Brophy argued that a satisfactory classification needed to account for every affected muscular and osseous structure, and his system was correspondingly detailed. However, this same thoroughness made the classification cumbersome, and its complexity limited its adoption in routine clinical practice (Brophy, 1923).

Veau's Simplified Classification (1931)

In 1931, in his monograph Division Palatine, Victor Veau proposed a markedly simpler, morphologically based alternative to Brophy's elaborate system. Veau's classification comprised four types: Type I, cleft of the soft palate only; Type II, cleft of the hard and soft palate extending to the incisive foramen; Type III, cleft of the hard and soft palate with a unilateral alveolar cleft; and Type IV, cleft of the hard and soft palate with a bilateral alveolar cleft (Wu et al., 2017). By deliberately excluding fine anatomical detail from the classification itself, Veau produced a system that was straightforward, easily communicated, and readily applied in clinical morphological assessment, and elements of this classification, and its correlation with clinical outcomes, continue to be referenced in the contemporary literature (Wu et al., 2017).

Fogh-Andersen's Embryologically Based Classification (1942)

In 1942, Fogh-Andersen challenged the alveolar-process-centered reasoning of Davis and Ritchie, arguing instead that the incisive foramen represented a more embryologically accurate anatomical reference point for classification. His system distinguished four categories: cleft lip (unilateral or bilateral); combined cleft lip and palate; isolated cleft palate; and atypical or rare clefts, such as median cleft lip. Fogh-Andersen proposed that a cleft of the alveolar structure is frequently accompanied by cleft lip, implying a shared embryological origin between the two, and he further emphasized that clefts of the palate proper do not extend beyond the incisive foramen, grounding his classification firmly in embryological development (Allori et al., 2017).

The Developmentally Based Classification of Kernahan and Stark (1958)

In 1958, Kernahan and Stark argued that classification should be founded on the stages of embryological development rather than

on morphology alone. Noting that the primary and secondary palatal structures involved in the formation of cleft lip and palate arise at different developmental time points, the authors contended that purely morphological classifications were inherently inadequate, and proposed instead that classification be organized around the embryological origins of the cleft, placing the distinction between primary and secondary palate formation at the center of the system (Zimmerer et al., 2023). This developmental framework, and its later graphic representation as a "striped Y," proved highly influential and served as the conceptual basis for several of the systems that followed.

The Elsahy Classification (1973)

In 1973, Elsahy and colleagues built upon Kernahan's "striped Y" classification to produce a more functionally oriented system. Their modified model incorporated the nasal floors and the posterior and premaxillary pharyngeal walls into the classification diagram, extending its scope beyond purely anatomical description to include functionally relevant structures. The Elsahy classification is regarded as an important step toward clinical frameworks capable of guiding the assessment of velopharyngeal function (Elsahy, 1973).

Millard's Modified Y Classification (1977)

Millard considered Kernahan's Y-shaped diagram to be incomplete and, in 1977, introduced a modification that incorporated triangular areas representing the nose and nasal floor into the schema. This extension broadened the classification beyond the cleft region itself to include structures of esthetic and functional importance, such as nasal support, and Millard's system was subsequently adopted by many plastic surgeons of the period for its value in facilitating surgical planning (Mitts et al., 1981).

The Friedman Classification (1991)

In 1991, Friedman and colleagues proposed a new system intended to overcome the visual and documentation limitations of earlier diagrammatic classifications. Their approach incorporated additional structures, including velopharyngeal closure capacity and the prolabium, and replaced traditional graphic symbols with a numerical coding system suited to digital record-keeping. The Friedman classification thereby enabled more systematic recording of clinical observations and represented a notable advance in the digital archiving of cleft phenotypes (Friedman et al., 1991).

The Kriens LAHSHAL Classification (1991)

The LAHSHAL system, developed by Otto Kriens in 1991, was designed to provide a universally applicable notation for CLP suitable for clinical, surgical, and research use. The system records the status of the lip (L), alveolus (A), hard palate (H), and soft palate (S), arranged from the patient's right side to the left, using an uppercase letter to denote a complete cleft, a lowercase letter to denote an incomplete cleft, and a dash to denote the absence of a cleft in that position. Owing to its diagrammatic simplicity, anatomical precision, and compatibility with digital data recording, the LAHSHAL system has become one of the most widely accepted classification systems in contemporary practice (Koch et al., 1995).

The Schutte and Murray Classification (1999)

In 1999, Schutte and Murray proposed an influential model that introduced a genetic and syndromic perspective into the classification of CLP. Rather than describing cleft morphology directly, this system groups affected individuals according to the presence or absence of an associated syndrome, distinguishing four categories: non-syndromic cleft lip and palate; non-syndromic isolated cleft palate; syndromic cleft lip and palate; and syndromic isolated cleft palate. By foregrounding syndromic status, this

classification has made a substantial contribution to genetic counseling, research stratification, and the modern multidisciplinary clinical follow-up of individuals with CLP (Schutte & Murray, 1999).

Comparative Discussion

Viewed as a chronological sequence, these ten systems trace a clear conceptual evolution in the classification of CLP. The earliest systems, those of Davis and Ritchie and of Brophy, were grounded primarily in surgical experience and anatomical description, differing chiefly in how much morphological detail they attempted to capture-three broad groups in one case, sixteen specific forms in the other (Davis & Ritchie, 1922; Brophy, 1923). Veau's system marked a deliberate return to simplicity, prioritizing clinical usability over exhaustive detail, while Fogh-Andersen's and Kernahan and Stark's systems shifted the conceptual foundation of classification from surgical or morphological convenience toward embryological accuracy, using the incisive foramen and the timing of primary versus secondary palate formation, respectively, as organizing principles.

The subsequent graphic systems of Elsahy, Millard, and Friedman each extended the Kernahan "striped Y" concept to incorporate structures and information not captured by the original diagram (Elsahy, 1973; Mitts et al., 1981; Friedman et al., 1991). The LAHSHAL system of Kriens can be understood as the culmination of this trajectory toward simplicity combined with digital compatibility, offering a compact alphanumeric notation capable of representing the full range of cleft phenotypes without requiring a graphic diagram (Koch et al., 1995). Finally, the classification of Schutte and Murray represents a departure from purely descriptive or diagrammatic approaches altogether, reorienting classification around syndromic status and thereby

aligning it with the genetic and multidisciplinary orientation of contemporary craniofacial care (Schutte & Murray, 1999).

No single system has proven universally sufficient for every purpose. Systems oriented toward surgical planning or fine morphological detail are of limited value for genetic counseling or large-scale epidemiological comparison, while systems oriented toward syndromic classification do not by themselves convey the specific anatomical extent of a cleft. In contemporary practice, this has led many centers to use complementary combinations of these systems, for example employing the LAHSHAL notation to record the precise anatomical extent of a cleft alongside a syndromic classification to capture its genetic context, rather than relying on any single historical system in isolation. The syndromic perspective introduced by Schutte and Murray also raises a further question left unanswered by classification alone: how common is CLP, and what is actually known about why it occurs? The remainder of this part turns to that question.

Global Epidemiology of Cleft Lip and Palate

Reported birth prevalence of CLP varies considerably across populations, diagnostic criteria, and study periods, but converges on a broad global estimate of approximately one in every 700 to 1,000 live births (Babai & Irving, 2023). A comprehensive systematic review and meta-analysis pooling data from more than 55 studies and over 17.8 million live births found a global pooled prevalence of combined cleft lip and palate of approximately 0.45 per 1,000 live births, with cleft lip alone at approximately 0.3 per 1,000 and cleft palate alone at approximately 0.33 per 1,000 live births (Salari et al., 2022). Substantial regional and ethnic variation is well documented within this overall picture: prevalence has consistently been reported as highest among Asian populations, intermediate among populations of European descent, and lowest among populations of

African descent, a pattern that has remained stable across successive epidemiological reviews spanning several decades (Mossey & Modell, 2012; Watkins et al., 2014). A modest male predominance in combined cleft lip and palate, and a corresponding female predominance in isolated cleft palate, have also been consistently reported across populations (Watkins et al., 2014).

Genetic and Environmental Basis of Cleft Lip and Palate

The etiology of CLP is complex and multifactorial, reflecting the interaction of genetic susceptibility with environmental exposures during the critical embryological period of facial fusion (Babai & Irving, 2023). Approximately 70% of cases of non-syndromic cleft lip with or without cleft palate are believed to arise from this kind of multifactorial, gene-environment interaction, while the remaining cases occur as part of a recognized genetic syndrome, consistent with the syndromic-versus-non-syndromic distinction introduced by Schutte and Murray's classification (Schutte & Murray, 1999; Babai & Irving, 2023). Genome-wide association studies conducted over the past two decades have identified numerous genetic loci contributing to non-syndromic CLP susceptibility, with genes involved in craniofacial developmental signaling pathways, including several implicated directly in lip and palate fusion, showing the most robust and widely replicated associations across populations (Babai & Irving, 2023). Recognized environmental risk factors acting on this genetic background include maternal smoking, alcohol consumption, folic acid deficiency, and certain teratogenic medications taken during early pregnancy, findings that have informed public health approaches to primary prevention even though the precise mechanisms of gene-environment interaction remain incompletely understood (Watkins et al., 2014; Mossey & Modell, 2012). This combination of high global prevalence, wide population variation, and multifactorial genetic and environmental causation underscores why the

classification systems reviewed above, spanning purely morphological to explicitly syndromic frameworks, have needed to evolve in parallel with an expanding understanding of the condition's underlying epidemiology and biology.

From Classification and Epidemiology to Craniofacial Structure

The classification systems and epidemiological and genetic evidence reviewed above provide the vocabulary, the population-level context, and the causal framework through which cleft lip and palate is recognized, recorded, and studied. Yet none of this, however precise, explains the skeletal structures that CLP affects or how those structures come to acquire their normal form in the first place. Among the craniofacial bones whose growth and morphology are of particular relevance to CLP is the mandible, a structure whose prenatal development, postnatal growth trajectory, and adult anatomical configuration must be understood before the specific alterations observed in individuals with CLP can be meaningfully interpreted. The following part turns to this task, reviewing the embryology, growth, and anatomy of the mandible in detail, before returning directly to its relationship with CLP.

THE ANATOMY AND EMBRYOLOGY OF THE MANDIBLE: FROM THE FIRST PHARYNGEAL ARCH TO ITS INVOLVEMENT IN CLEFT LIP AND PALATE

The mandible is the largest and only mobile bone of the facial skeleton, and its development and structure are of central and enduring importance to orthodontic, orthopedic, and orthognathic practice. Its embryonic origin lies in the first pharyngeal (mandibular) arch, the most rostral of the series of paired mesenchymal swellings that appear on the lateral surface of the embryonic head and pharynx and that give rise, together with their associated cartilaginous, muscular, arterial, and neural components, to the greater part of the face and jaws (Graham & Richardson, 2012). The mesenchyme of the first arch is populated principally by cranial neural crest cells, which migrate from the developing neural tube and differentiate into the chondrocytes, osteoblasts, and connective tissue of the future jaw skeleton, and the arch is uniformly innervated by the mandibular and maxillary divisions of the trigeminal nerve (cranial nerve V), which supplies both general sensation to the face and motor innervation to the muscles of mastication that arise from the same arch (Graham & Richardson, 2012).

Unlike most other bones of the craniofacial skeleton, which form largely through endochondral ossification of a preformed cartilaginous model, the mandible develops chiefly through

intramembranous ossification of mesenchymal connective tissue, occurring alongside, but largely independent of, a transient cartilaginous rod known as Meckel's cartilage. This dual character, membranous bone formation guided by, but not directly replacing, an adjacent cartilaginous template, has made the mandible a long-standing subject of embryological interest, and contemporary developmental biology continues to refine understanding of the precise contribution of Meckel's cartilage to the definitive bone (Svandova et al., 2020). This part reviews, in turn, the prenatal embryological development of the mandible, its postnatal growth and remodeling across childhood, adolescence, and adulthood, and the anatomical structure of the mature bone, before closing with a direct account of how mandibular development and morphology are altered in individuals with cleft lip and palate.

Prenatal Development of the Mandible: Neural Crest Origin and the First Pharyngeal Arch

The skeletal, connective, and much of the muscular tissue of the mandible originates from cranial neural crest cells that migrate into the first pharyngeal arch during the fourth week of intrauterine life. Within this arch, the neural-crest-derived mesenchyme condenses to form a central cartilaginous rod, Meckel's cartilage, which extends bilaterally from the region of the developing middle ear toward the anterior midline and serves as a spatial and morphogenetic guide for the mandible that will form around it (Graham & Richardson, 2012; Svandova et al., 2020). Because the first arch also gives rise to the muscles of mastication, the mylohyoid muscle, and the anterior belly of the digastric muscle, all under the motor control of the mandibular division of the trigeminal nerve, the developing mandible and its associated musculature share a single embryological origin and a single pattern of innervation from the earliest stages of development (Graham & Richardson, 2012).

Intramembranous Ossification and Formation of the Mandibular Body

The mandible is the second bone, after the clavicle, to begin ossification in the developing embryo (Kantomaa & Rönning, 2018). The lower jaw develops largely through intramembranous ossification of the connective tissue lying lateral to Meckel's cartilage, rather than through direct ossification of the cartilage itself. Between approximately the sixth and seventh weeks of intrauterine life, a single ossification center appears within this connective tissue on each side of the developing mandible; these paired centers rapidly extend along the length of the cartilage and form the structural basis of the mandibular corpus and ramus (Kantomaa & Rönning, 2018). As ossification proceeds, the growing bony sheath surrounds increasing portions of Meckel's cartilage, though it does not directly incorporate the cartilage itself into the definitive bone.

Secondary Cartilages of the Developing Mandible

In addition to the ossification centers associated with Meckel's cartilage, several secondary cartilaginous islands appear within the mandibular connective tissue at the condylar process, the coronoid process, the angle of the mandible, and the dental arch. Unlike Meckel's cartilage, these secondary cartilages ossify independently and are considered distinct developmental entities that progressively unite with the growing mandibular body to complete the definitive shape of the bone (Kantomaa & Rönning, 2018). Among these, the condylar cartilage is of particular long-term significance, since it persists as an active growth site well beyond the prenatal period and continues to contribute to mandibular lengthening throughout childhood and adolescence.

The Fate of Meckel's Cartilage and Associated Structures

Shortly before birth, one or two small ossicles, termed ossicula mentalia, form within the connective tissue at the anterior midline where the two developing mandibular halves approach one another; these ossicles fuse with the mandible shortly after birth to form the mental protuberance of the chin (Rosas & Bermúdez de Castro, 1998). Meckel's cartilage itself follows three distinct fates along its length. Its posterior (proximal) end, situated near the developing ear, is transformed into two of the three auditory ossicles, the malleus and the incus. Its anterior (distal) end fuses with the mandibular bone and contributes to the development of the anterior mandibular region and, at the midline, to the mandibular symphysis. The intervening middle portion of the cartilage undergoes resorption, and its perichondrial connective tissue sheath persists postnatally as two structures of continuing anatomical and clinical significance: the mylohyoid groove, which marks the original course of the cartilage along the internal surface of the mandible, and the sphenomandibular ligament, one of the principal passive supports of the mandible and the temporomandibular joint (Graham & Richardson, 2012; Svandova et al., 2020).

Postnatal Development: The Neonatal Mandible and Symphyseal Fusion

At birth, the mandible does not yet exist as a single bone: it consists of two separate, symmetrical halves joined at the midline by the mandibular symphysis, a fibrocartilaginous joint rather than a bony union. In humans, this symphysis typically ossifies during the first year of postnatal life, at which point the two halves fuse and the mandible becomes a single, continuous bone (Kantomaa & Rönning, 2018). The neonatal mandible differs markedly from its adult counterpart: the gonial angle is quite obtuse, on the order of 175 degrees, reflecting the shallow ramus and small muscular attachments of infancy; the cortical bone is thin; the associated masticatory musculature is still weak; the condyle is attached to the

temporomandibular fossa by loose, poorly developed capsular tissue; and the mental foramen lies in an anterosuperior position, at approximately the level of the canine or first molar tooth germ, considerably higher than its eventual adult location.

Growth Mechanisms: Membranous and Endochondral Processes

Postnatal mandibular growth proceeds through a coordinated combination of membranous and endochondral ossification, together with extensive surface remodeling. Cartilaginous growth at the condylar region is a principal driver of the downward and forward translation of the mandible as a whole, while the coronoid process develops in a superior and posterior direction under the traction of the developing temporalis muscle. Along the ramus, a well-documented pattern of surface remodeling occurs, with bone resorption on the internal (medial) surface and apposition on the external (lateral) surface; this coordinated process not only widens the ramus but also progressively displaces it posteriorly, creating the space required for the eruption of the second and third molars within the mandibular corpus. The corpus itself increases in both length and width over time, and remodeling at the chin produces the more pronounced anterior curvature characteristic of the adult mandible in place of the receding infantile profile. With the sequential eruption of the primary and then permanent dentition, vertical growth of the alveolar process accelerates correspondingly. Overall, the different dimensions of the mandible do not complete their growth simultaneously: growth in width is generally completed first, followed by growth in length, and finally by growth in height (Moxham, 2001).

Growth Timing and Completion

Mandibular growth is not linear but shows distinct periods of acceleration linked to dental eruption and to puberty. A noticeable

acceleration occurs at approximately six years of age, coinciding with the eruption of the first permanent molars, and a further acceleration accompanies the eruption of the second permanent molars later in childhood. Growth velocity reaches its overall maximum during the pubertal growth spurt. Following this peak, the rate of growth gradually declines, and mandibular growth is generally considered to be completed at approximately 17 to 18 years of age in females and somewhat later, in the early twenties, in males (Ülgen, 1999). This sex difference in the timing of growth completion parallels the well-documented earlier onset and completion of the pubertal growth spurt in females relative to males and is of direct relevance to the timing of orthodontic and orthopedic interventions intended to influence mandibular growth.

Age-Related Changes in the Adult and Aging Mandible

Mandibular remodeling does not cease once adult stature is reached but continues, more subtly, throughout adult life, and becomes particularly pronounced in advanced age, largely as a consequence of tooth loss. As teeth are lost and the alveolar process is no longer subjected to functional occlusal loading, progressive resorption of the alveolar bone occurs. This resorption brings the mental foramen into closer proximity to the superior (alveolar) border of the mandible than in the dentate adult, and the gonial angle, having reached its most acute configuration in the dentate adult, becomes progressively more obtuse again, approaching the wider angle characteristic of the edentulous infantile mandible. The condyle also tends to tilt posteriorly with advancing age. This overall rotational pattern of mandibular growth and remodeling across the lifespan is governed by the combined influence of cranial base morphology, sutural growth at the cranial base and midface, apposition and resorption at the condyle, and the vertical development of the dentoalveolar structures, all acting together rather than in isolation (Moxham, 2001).

Table 1 summarizes the principal embryological and postnatal developmental milestones of the mandible discussed above.

Table 1. Timeline of Key Embryological and Postnatal Developmental Events of the Mandible

Developmental stage	**Key event(s)**
6th-7th intrauterine week	Paired ossification centers appear in connective tissue lateral to Meckel's cartilage; onset of intramembranous ossification of the mandibular corpus and ramus.
Prenatal (variable)	Secondary cartilages form independently at the condylar and coronoid processes, the mandibular angle, and the dental arch; each ossifies separately and unites with the main body of the mandible.
Shortly before birth	One or two mental ossicles (ossicula mentalia) form at the anterior symphyseal midline.
Birth	Mandible consists of two separate, unfused halves joined by the mandibular symphysis; mandibular (gonial) angle is obtuse (~175 degrees); mental foramen lies anterosuperiorly.
Within the 1st postnatal year	Symphyseal fusion is completed, and the mandible becomes a single continuous bone; mental ossicles fuse to form the mental protuberance.
~6 years	Eruption of the first permanent molars accelerates mandibular growth.
Late childhood	Eruption of the second permanent molars produces a further acceleration of growth.
Puberty	Mandibular growth rate reaches its maximum.
~17-18 years (females) / early 20s (males)	Mandibular growth is essentially completed.
Older adulthood	Tooth loss leads to alveolar bone resorption, superior migration of the mental foramen, an increasingly obtuse gonial angle, and posterior tilting of the condyle.

Kaynak: Yazarlar tarafından oluşturulmuştur.

Anatomical Structure of the Adult Mandible: General Morphology of the Corpus

The mandible is classified anatomically as a flat bone, and within it, the corpus is generally thicker than the ramus. Maximum cortical thickness within the corpus is observed along the oblique line externally and at the level of the mylohyoid line internally,

regions that correspond closely to the areas of greatest concentration of masticatory force during function. The compact bone of the mandible is notably dense overall, and the internal and external cortical laminae show pronounced thickening specifically at the base (inferior border) of the mandible, an area subjected to substantial bending stresses during mastication. As with all bones subject to functional loading, the detailed morphology of the mandibular corpus is shaped by the muscles and ligaments that attach to it, with areas of greatest muscular pull and occlusal load generally corresponding to areas of greatest cortical reinforcement (Radlanski et al., 2003).

The Ramus and Its Processes

The ramus of the mandible is broadly quadrilateral in outline and bears two processes at its superior border: the coronoid process anteriorly and the condylar process posteriorly, with the two separated by a distinct concave notch, the incisura mandibulae (mandibular or sigmoid notch) (Kaczkowski et al., 2012). On the lower portion of the lateral surface of the ramus lies the masseteric tuberosity, a roughened area that serves as the principal attachment site of the masseter muscle. On the corresponding medial surface lies the mandibular foramen, the entry point of the inferior alveolar neurovascular bundle into the mandibular canal, together with, in some individuals, one or more accessory foramina. The mandibular foramen is bounded anteriorly by a small bony spine, the lingula of the mandible, which serves as the principal attachment site for the sphenomandibular ligament, the fibrous remnant of the middle portion of Meckel's cartilage described earlier (Fabian, 2006). Because the lingula and mandibular foramen together define the point of entry of the inferior alveolar nerve, their precise anatomical position, which shows recognized individual variation, is of direct clinical importance in the accurate localization of inferior alveolar

nerve blocks in dental practice (Peixoto Ennes & Monteiro de Medeiros, 2009).

The Mandibular Canal and Associated Foramina

The mandibular canal originates at the mandibular foramen on the medial surface of the ramus, travels anteriorly through the body of the mandible beneath the roots of the posterior teeth, and terminates in the region of the mental foramen, typically in the premolar area, where it transmits the inferior alveolar neurovascular bundle. The internal diameter of the canal is not uniform along its course, narrowing progressively as it approaches the mental region medially before terminating or continuing as the incisive canal (Juodzbalys et al., 2010). Immediately inferior to the origin of the mandibular canal, on the medial surface of the ramus, lies the mylohyoid groove, marking the original course of Meckel's cartilage and the associated nerve and vessels supplying the mylohyoid muscle; this groove extends inferiorly toward the pterygoid tuberosity, the attachment site of the medial pterygoid muscle (Fabian, 2006).

The Anterior Ramal Border, Retromolar Region, and Coronoid-Condylar Complex

The anterior border of the ramus is continuous with the oblique line of the mandibular corpus and terminates, behind the position of the third molar, at the retromolar trigone, a triangular area bounded laterally by the buccinator crest, the attachment site of the buccinator muscle. This region is of surgical relevance both in third molar extraction and in the assessment of retromolar pathology. As noted above, the superior border of the ramus bears the coronoid process anteriorly, which serves as the principal attachment site of the temporalis muscle, and the condylar process posteriorly, which articulates with the temporomandibular fossa of the temporal bone to form the temporomandibular joint; the mandibular notch

separating these two processes is a consistent and readily identifiable anatomical landmark on both clinical palpation and panoramic radiographic examination (Kaczkowski et al., 2012).

Mandibular Development in Individuals with Cleft Lip and Palate

Having reviewed the normal embryological development, growth, and adult anatomy of the mandible, it is now possible to return, as this book's preface promised, to the question with which it began: how is this structure affected in individuals with the condition reviewed in Part One? Although the maxilla is the skeletal structure most visibly and directly affected by CLP, cephalometric studies comparing adult patients with cleft lip and/or palate to non-cleft controls have consistently found that the mandible itself is also structurally altered. In a cephalometric study of 229 adult patients with unilateral cleft lip and alveolus, complete unilateral cleft lip and palate, or isolated cleft palate, compared with 65 non-cleft controls, da Silva Filho and colleagues found that all three cleft groups displayed a significantly shorter mandibular ramus and corpus than controls, with no significant difference in mandibular size among the cleft types themselves, indicating that a smaller mandible is a structural feature common to CLP in general rather than to any one specific cleft type (da Silva Filho et al., 1993). The same study found that clefts involving the palate specifically, as opposed to clefts of the lip and alveolus alone, were associated with a significant downward and backward rotation of the mandible and a more obtuse gonial angle, indicating that the spatial position and rotational pattern of the mandible, and not only its size, are influenced by the specific anatomical extent of the cleft (da Silva Filho et al., 1993).

More recent three-dimensional imaging studies have extended these classic cephalometric findings to the temporomandibular joint itself. A cone-beam computed tomography study comparing temporomandibular joint parameters across

growing and non-growing patients with unilateral and bilateral CLP found significant differences in anterior joint space and glenoid fossa roof thickness between growing and non-growing unilateral cleft patients, together with significant asymmetry in articular eminence angle between the cleft and non-cleft sides within the growing unilateral group, findings that underscore the importance of age- and growth-stage-specific considerations when planning orthodontic and orthopedic treatment in this population (Abdelkarim et al., 2024). Taken together with the anatomical and embryological framework reviewed earlier in this part, these findings indicate that the structural consequences of CLP for the mandible are not confined to the immediate region of the cleft itself, but extend to overall mandibular size, spatial position, and even the morphology of the temporomandibular joint, reinforcing the view that comprehensive craniofacial assessment in CLP must include careful evaluation of the mandible alongside the maxilla.

Conclusion

This book has traced a deliberate progression: from the historical classification of cleft lip and palate and the global epidemiological and genetic evidence describing how common the condition is and why it arises, through the embryological development and postnatal growth of the maxilla and the mandible, to the specific structural consequences that CLP produces in each of these bones. Read together, these two parts illustrate a broader principle in craniofacial medicine: that the clinical understanding of a congenital anomaly rests not only on its accurate classification and epidemiological characterization, but on a detailed knowledge of the normal developmental and anatomical framework of the structures it affects, since it is only against that normal framework that the specific skeletal consequences of the anomaly, whether Latham's account of redirected maxillary growth or the mandibular findings of da Silva Filho and colleagues and of Abdelkarim and colleagues,

can be meaningfully identified and interpreted. When applied together, the classification systems, epidemiological and genetic evidence, and developmental and anatomical knowledge reviewed in this book provide a coherent foundation for the clinical and research study of cleft lip and palate and its consequences for the craniofacial skeleton.

REFERENCES

Abdelkarim, A. Z., Almeshari, A. A., Ozen, D. C., Khalifa, A. R., Rezallah, N. N., Duman, S. B., & Khurana, S. (2024). Comparative evaluation of temporomandibular joint parameters in unilateral and bilateral cleft lip and palate patients using cone-beam CT: focus on growing vs. non-growing subjects. *Healthcare, 12*(16), 1563.

Allori, A. C., Mulliken, J. B., Meara, J. G., Shusterman, S., & Marcus, J. R. (2017). Classification of cleft lip/palate: then and now. *Cleft Palate-Craniofacial Journal, 54*(2), 175-188.

Babai, A., & Irving, M. (2023). Orofacial clefts: genetics of cleft lip and palate. *Genes, 14*(8), 1603.

Brophy, T. W. (1923). Bone surgery essential in the treatment of complete cleft palate. *The Journal of the American Dental Association, 10*, 3-18.

Bush, J. O., & Jiang, R. (2012). Palatogenesis: morphogenetic and molecular mechanisms of secondary palate development. *Development, 139*(2), 231-243.

Carlson, B. M. (2019). *Human Embryology and Developmental Biology* (6th ed.). Elsevier.

Chen, B., & Zhang, H. (2022). The study on the morphological changes of oropharynx in patients with complete unilateral cleft lip and palate after palatopharyngeal closure. *Frontiers in Neuroscience, 16*, 997057.

da Silva Filho, O. G., Normando, A. D. C., & Capelozza Filho, L. (1993). Mandibular growth in patients with cleft lip and/or cleft palate-the influence of cleft type. *American Journal of Orthodontics and Dentofacial Orthopedics, 104*(3), 269-275.

Davis, J. S., & Ritchie, H. P. (1922). Classification of congenital clefts of the lip and palate: with a suggestion for recording these cases. *The Journal of the American Medical Association, 79*, 1323-1327.

Elsahy, N. I. (1973). The modified striped Y: a systematic classification for cleft lip and palate. *Cleft Palate Journal, 10*, 247-250.

Enlow, D. H., & Hans, M. G. (2008). *Essentials of Facial Growth* (2nd ed.). Needham Press.

Fabian, F. M. (2006). Observation of the position of the lingula in relation to the mandibular foramen and the mylohyoid groove. *Italian Journal of Anatomy and Embryology, 111*(3), 151-158.

Friedman, H. I., Sayetta, R. B., Coston, G. N., & Hussey, J. R. (1991). Symbolic representation of cleft lip and palate. *Cleft Palate-Craniofacial Journal, 28*(3), 252-260.

Graham, A., & Richardson, J. (2012). Developmental and evolutionary origins of the pharyngeal apparatus. *EvoDevo, 3*, 24.

Juodzbalys, G., Wang, H. L., & Sabalys, G. (2010). Anatomy of mandibular vital structures. Part II: mandibular incisive canal, mental foramen and associated neurovascular bundles in relation with dental implantology. *Journal of Oral & Maxillofacial Research, 1*(1), e3.

Kaczkowski, H., Porwolik, K., Porwolik, M., Noga, L., Woyton, H., & Domagała, Z. (2012). Anatomical analysis of preangular mandibular notch in humans. *Folia Morphologica, 71*(2), 100-104.

Kantomaa, T., & Rönning, O. (2018). Growth mechanisms of the mandible. In D. H. Enlow & M. G. Hans (Eds.), *Fundamentals of Craniofacial Growth* (pp. 189-204). CRC Press.

Koch, H., Grzonka, M., & Koch, J. (1995). Cleft malformation of lip, alveolus, hard and soft palate, and nose (LAHSN): a critical view of the terminology, the diagnosis and gradation as a basis for documentation and therapy. *British Journal of Oral and Maxillofacial Surgery, 33*(1), 51-58.

Kosowski, T. R., Weathers, W. M., Wolfswinkel, E. M., & Ridgway, E. B. (2012). Cleft palate. *Seminars in Plastic Surgery, 26*(4), 164-169.

Latham, R. A. (1969). The pathogenesis of the skeletal deformity associated with unilateral cleft lip and palate. *Cleft Palate Journal, 6*, 404-414.

Latham, R. A. (1970). Maxillary development and growth: the septo-premaxillary ligament. *Journal of Anatomy, 107*(3), 471-478.

Latham, R. A. (1971). The development, structure and growth pattern of the human mid-palatal suture. *Journal of Anatomy, 108*(1), 31-41.

Lee, S. K., Kim, Y. S., Lim, C. Y., Chi, J. G., & Yang, K. H. (1992). Prenatal growth pattern of the human maxilla. *Acta Anatomica, 145*(1), 1-10.

Mitts, T. F., Garrett, T. F., & Hurwitz, D. J. (1981). Cleft of the hard palate with soft palate integrity. *Cleft Palate Journal, 18*(4), 239-244.

Mossey, P. A., Little, J., Munger, R. G., Dixon, M. J., & Shaw, W. C. (2009). Cleft lip and palate. *Lancet, 374*(9703), 1773-1785.

Mossey, P. A., & Modell, B. (2012). Epidemiology of oral clefts 2012: an international perspective. *Frontiers of Oral Biology, 16*, 1-18.

Moxham, B. (2001). Craniofacial development, 5th edn: G.H. Sperber [Book review]. BC Decker Inc.

Peixoto Ennes, J., & Monteiro de Medeiros, R. (2009). Localization of mandibular foramen and clinical implications. *International Journal of Morphology, 27*(4), 1305-1311.

Radlanski, R. J., Renz, H., & Klarkowski, M. C. (2003). Prenatal development of the human mandible: 3D reconstructions, morphometry and bone remodelling pattern, sizes 12-117 mm CRL. *Anatomy and Embryology, 207*(3), 221-232.

Rosas, A., & Bermúdez de Castro, J. M. (1998). The Mauer mandible and the evolutionary significance of Homo heidelbergensis. *Geobios, 31*(5), 687-697.

Salari, N., Darvishi, N., Heydari, M., Bokaee, S., Darvishi, F., & Mohammadi, M. (2022). Global prevalence of cleft palate, cleft lip and cleft palate and lip: a comprehensive systematic review and meta-analysis. *Journal of Stomatology, Oral and Maxillofacial Surgery, 123*(2), 110-120.

Schutte, B. C., & Murray, J. C. (1999). The many faces and factors of orofacial clefts. *Human Molecular Genetics, 8*(10), 1853-1859.

Svandova, E., Anthwal, N., Tucker, A. S., & Matalova, E. (2020). Diverse fate of an enigmatic structure: 200 years of Meckel's cartilage. *Frontiers in Cell and Developmental Biology, 8*, 821.

Ülgen, M. (1999). *Ortodonti: Anomaliler, Sefalometri, Etiyoloji, Büyüme ve Gelişim, Tanı*. Yeditepe Üniversitesi Diş Hekimliği Fakültesi.

Watkins, S. E., Meyer, R. E., Strauss, R. P., & Aylsworth, A. S. (2014). Classification, epidemiology, and genetics of orofacial clefts. *Clinics in Plastic Surgery, 41*(2), 149-163.

Wu, R., Cheraghlou, S., Parsaei, Y., Travieso, R., & Steinbacher, D. M. (2017). Does cleft palate width correlate with Veau

classification and outcome? *Journal of Craniofacial Surgery, 28*(6), 1369-1374.

Zimmerer, R. M., Sander, A. K., & Lethaus, B. (2023). Classification of orofacial clefts. In *Fundamentals of Craniofacial Malformations, Volume 2, Treatment Principles* (pp. 67-78). Springer.