DEVELOPMENT OF CONCEPTS & THEORIES OF CRANIOFACIAL GROWTH

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Biological Basis for Dentofacial Orthopedic Treatment


CHAPTER 2

Craniofacial Biology as “Normal Science”

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Some people think that the philosophy a scientist accepts is not of very much importance; his job is to observe phenomena. This is a gross oversimplification and it involves the subsidiary hypothesis that all scientists are fully equipped with serendipity. A sensible philosophy controlled by a relevant set of concepts saves so much research time that it can nearly act as a substitute for genius. ... A scientist can have no more valuable skill than the ability to see whether the problem he is investigating exists and whether the concepts he is using are applicable.

Pirie (1952)

Orthodontic research has a long tradition of excellent symposia in which clinical and basic scientists have an opportunity to discuss common problems. Many of these have proved to be quite successful in addressing profound clinical problems while emphasizing the need for basic scientific research. Several symposia and edited volumes have also addressed more general topics within craniofacial biology. The first Vistas in Orthodontics, which represented clinical and scientific orthodontic thinking in 1962, was one of these (Kraus and Riedel, 1962). Now, 20 years later, we must examine “new vistas” in orthodontics—to summarize our progress and point the way toward future goals. It is the purpose of this paper to do so in one area that is central to orthodontics—research in craniofacial growth, or what many people refer to as craniofacial biology.

It is difficult to define craniofacial biology because it is nearly impossible to identify a core group of scientists recognized primarily as “craniofacial biologists.” For example, Johnston (personal communication) noted that there are few young individuals who profess to be craniofacial biologists and who do not, at the same time, practice some clinical specialty. There are many whom I would call craniofacial biologists who are in the early stages of their careers and who are doing excellent research, regardless of the extent of their clinical re-

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sponsibilities. The question remains, however, whether craniofacial biology exists as a distinct area of scientific inquiry independent of clinical orthodontics. If it does exist, one must define its parameters and identify its practitioners. If craniofacial biology does not exist as a distinct scientific discipline, the absence of a core group of researchers is not problematic because it means that young basic scientists do not recognize the field as a legitimate area of study and vocation.

With this question in mind, I will discuss three broad areas. The first will be certain aspects of the history and philosophy of science that help us understand the developmental processes by which scientific disciplines develop and mature. Second, I will apply some of these concepts to a personal view of the development of craniofacial biology, particularly over the past 20 years, and discuss its current concepts. I will conclude by explaining the relationship of craniofacial biology to clinical orthodontics.

Charles Kremenak (1972) in a paper, “Circumstances limiting the development and verification of a complete explanation of craniofacial growth,” asked, “What is the sense of a paper like this? Why bother with it?” He then noted that he did not “know enough to write this paper as it ought to be written, but perhaps none of us do.” I believe that reflecting on the philosophical underpinnings of our field, its current position, and its future goals helps us become better, more productive scientists. Ralph Waldo Emerson had a similar idea in mind when he said that “it is a good thing, now and then, to take a look at the landscape from between your legs” (Muller, 1943). I think we would also agree that, with due respect to contemporary workers, no one should presume to have sufficient experience, objectivity, and sagacity to give them a monopoly on insight as to where we have been, where we are going, and the best way to get there. This must be a joint effort.

NORMAL SCIENCE

My purpose is to introduce some terms and develop a logic that can be used as a research tool to discuss craniofacial biology. To do so, I will rely heavily on an elegant theory of the history of science put forward by Thomas Kuhn (1970) in his book, The Structure of Scientific Revolutions. I stress that history and philosophy as used here are techniques, not ends in themselves. Such an approach is not uncommon in philosophy. For example, as noted by John Locke in the eighteenth century (Muller, 1943):

It is of great use to the sailor to know the length of his line, though he cannot with it fathom all the depths of the ocean; it is well he knows that it is long enough to reach the bottom of such places as are necessary to direct his voyage, and caution him against running upon shoals that may ruin him. Our business is not to know all things, but those which concern our conduct.
Normal science, according to Kuhn (1970), refers to “research firmly based upon one or more past scientific achievements, achievements that some particular scientific community acknowledges as supplying the foundation for its further practice.” In other words, normal science is defined operationally as research that the members of a specific group of scientists recognize as central to their field. The research itself provides a model for related research, and its results are accepted and form a basis for subsequent research.

Closely affiliated with Kuhn’s definition of normal science is his concept of paradigm. Generally, a paradigm is thought of as a model or pattern. In terms of the theory of the history of science, however, paradigm has come to mean more. According to Kuhn, for example, paradigms are not only constellations of beliefs, values, and techniques shared by members of a given community but also concrete models that can serve as a basis for solving remaining problems. Even more simply, paradigms provide a coherent conceptual scheme for organizing observations and ideas, determining which observations are relevant, determining which problems are legitimate, and indicating how these problems probably should be solved. The precise manner in which relevant observations are interpreted and the predictive explanations that they provide may differ within a single paradigm without necessarily bringing the paradigm itself into question. Thus, a single paradigm may be the basis for many theories and certainly for numerous hypotheses, even if they are in conflict with each other (Fig. 2-1).

It is the study of the paradigms within a field of science that prepares a student for membership in a particular scientific community, and adherence to the scientific conduct dictated by the paradigm that maintains the credibility of a scientific community. By definition, then, a scientific community is a group characterized by its consensus about a paradigm and commitment to relate that paradigm to the rest of the natural world—in other words, to solve problems by conducting research that will elaborate on the paradigm itself and attract new members from competing paradigms.

Paradigms, and thus whole scientific communities, can and do come into direct conflict. One extreme example of this is the current debate between proponents of evolutionary biology and “creation science.” Without getting into any of the details of the arguments of either side, it is clear that, except during the process of formal adjudication, the facts that both groups hold to be true are not really important. At conflict are the paradigms adhered to by the communities of evolutionary biologists and creationists. The paradigm defines which data are relevant and which are not. In fact, it is not necessary to have any paradigm at all to gather data; however, in the absence of a paradigm, all data have equal importance and relevance. This does not mean, how-
ever, that just because creationism may be a paradigm, it is necessarily valid. Individually and collectively, scientists can decide that certain paradigms are wrong in their assumptions, explanations, and methods and can reject them. In fact, science progresses precisely because scientists make such decisions and abandon poor paradigms—those with too many inconsistencies—in favor of more profitable ones.

Normal science is, as the name implies, the norm. Paradigms can change, however. More correctly, alternative paradigms that conflict with the current concept of normal science may be proposed by one or more members of a scientific community. If this happens and if the competing paradigm attracts a reasonable number of members, either from the old scientific community or from new scientists just entering the field, what Kuhn calls a scientific revolution occurs (Fig. 2–2). Scientific revolutions are “tradition-shattering complements to the tradition-bound activity of normal science” (Kuhn, 1970, p. 6) that occur when the scientific community can no longer evade the anomalies that subvert the existing tradition. The new paradigm gains status simply by gaining adherents precisely because it is more successful than its competitors at identifying and solving the problems that the discipline’s practitioners see as most acute.

To summarize the points most salient to the discussion of craniofacial biology, a paradigm is a conceptual scheme that encompasses individual theories and is accepted by a scientific community as a model and foundation for further research. A change in paradigm...
brought about by inconsistencies within the old scheme or by technologic developments that permit scientists to ask new questions and gain new data is called a scientific revolution. This process does not in any way subvert more traditional concepts of the Hegelian dialectic.

During a period of normal science, when a single paradigm predominates, the dialectic is between competing hypotheses or theories (Fig. 2–3 A and B). During a period of scientific revolution, the dialectic is between competing paradigms (Harris, 1972).

**CRANIOFACIAL BIOLOGY AS NORMAL SCIENCE**

The following sections will attempt to answer some pertinent questions about craniofacial biology, including “Does craniofacial biology exist as a distinct area of scientific inquiry independent of clinical orthodontics?”; “What is craniofacial biology?”; “How is it distinct from other disciplines that deal with the head?”; “What are the current paradigms in craniofacial biology and how did they come about?”; “Who belongs to the scientific community involved with craniofacial biology?”; and “Is craniofacial biology in a period of normal science, scientific revolution, or transition between the two?”

**What is Craniofacial Biology?**

There have been few specific attempts to define craniofacial biology. Most authors simply assume its parameters are well known. The only specific attempt at defining craniofacial biology was undertaken by Pruzansky in 1968 as he traced the history of what has come to be known as the Craniofacial Biology Group of the International Association for Dental Research. Pruzansky noted that the Craniofacial Biology Group is the most recent manifestation of the International...
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A. Dialectic during a period of normal science.

B. Dialectic during a period of revolutionary science.

Fig. 2–3. During a period of normal science (A), there may be conflict between alternative hypotheses and theories that do not bring into question the paradigm that encompasses them. During a period of revolutionary science (B), however, the conflict is much more fundamental and involves argument between more than one paradigm.

Society of Craniofacial Biology, which was conceived in 1958 at the University of Michigan Orthodontic Workshop as the International Orthodontic Society for Research. Unfortunately, however, Pruzansky’s definition was limited: he noted only that craniofacial biology is concerned with the structure and function of the craniofacial complex. More recently, however, Pruzansky (1979) did describe craniofacial biology as a “relatively new hybrid” that has come about primarily as a result of clinical recognition that the craniofacial region is complex, that its various components are interrelated, and that, as a result, health services have become “a many-splintered thing that [do] not fulfill the needs of the patient.”
This perception of craniofacial biology clearly is weighted heavily toward clinical science and the direct clinical application of basic research. Because of its roots in clinical orthodontics, craniofacial biology certainly has a strong clinical orientation; however, craniofacial biology as a science is much more than multidisciplinary clinical research and treatment. Precisely because of its roots in orthodontics, craniofacial biology does not encompass all aspects of the biology of the head; however, it may include any tissues, functions, and biologic interactions that influence the growth and adaptation of the craniofacial skeleton. I define craniofacial biology as the study of the growth, function, and adaptation, both phylogenetically and ontogenetically, of the craniofacial skeleton and related structures. Particular emphasis within craniofacial biology is placed on the integration of the various biologic systems that maintain homeostasis or result in changes throughout the craniofacial complex. Thus, not every investigator who does all or part of his research in the cephalic region is necessarily a craniofacial biologist. The limiting factors in this regard are the focus on the growth and adaptation of the craniofacial skeleton and the integration of the systems comprising the craniofacial complex. This definition certainly does not preclude interest in nonskeletal tissues—in fact, it demands it. Rather, it focuses attention more clearly on those aspects of nonskeletal tissues that influence, directly or indirectly, the processes and mechanisms by which normal and abnormal skeletal growth and form come about.

From the standpoint of basic science, emphasis on the growth and adaptation of the craniofacial skeleton may involve all aspects of bone biology and many, but not all, aspects of neurophysiology, anthropology, paleontology, endocrinology, developmental biology, genetics, anatomy and cell biology, and biometrics and physiology. Emphasis on the growth and adaptation of the craniofacial skeleton clearly relates primarily to clinical orthodontics but also relates to certain specific aspects of other clinical specialties such as oral surgery, pedodontics, otolaryngology, ophthalmology, speech and hearing pathology, and pediatrics. Craniofacial biology is more than a regional, clinical specialization. Craniofacial biology has a specific orientation and emphasis that is rooted in its history and in the predilection of its current practitioners to analyze the growth and adaptation of the craniofacial complex in general and of the craniofacial skeleton in particular.

Paradigms in Craniofacial Biology

Craniofacial biology has had no shortage of theories regarding facial growth. Generally, these theories occupy a continuum ranging, on the one hand, from a complete emphasis on intrinsic genetic factors, such as the controlling mechanisms of facial growth, to a complete denial of
genetic factors and a total reliance on so-called “functional” determinants of facial growth on the other hand. Interestingly enough, this continuum also is closely correlated with time. Emphasis on the genetic predetermination of facial growth was prominent up to the middle of the twentieth century, at which time the emphasis changed to functional factors. The emphasis has continued to shift to the current focus on epigenesis. This temporal and conceptual continuum, characterized as it is by dichotomous positions, provides a convenient model for historical analysis in which the development of craniofacial biology can be traced with an eye toward evaluating general concepts as paradigms.

1920 to 1940

The early research into craniofacial skeletal growth, the central component of craniofacial biology, was reviewed by Krogman (1974). Krogman noted that craniofacial research from 1920 to 1940 was based primarily on the study of the structure of the craniofacial skeleton, with little or no consideration of function. This approach sprang from late nineteenth and early twentieth century anthropologic craniometry; however, a primary impetus was the racial analysis that was central to the socioeconomic structure of western Europe from the nineteenth century through the first half or more of the twentieth century (Carlson and Van Gerven, 1979). According to Krogman (1974, p. 53), it was during this period that an essentially static approach to craniofacial research was developed: “workers were content to say, ‘the craniofacial structures grow in a certain way,’ and they applied this thinking mostly to group data (‘standards,’ ‘norms’), rather than to the growing child.” In a recent essay on the dialectics of craniofacial growth research, Moss (1982) noted that this early period also can be subdivided into a preradiologic phase, when emphasis was placed on craniometry, and a radiologic period. The radiologic period, however, although characterized by a major technologic innovation, was not the start of a new era conceptually (Bookstein and Moyers, 1979). The development and early use of radiographic cephalometry, instead, initiated a more energetic period of data acquisition and quantification of growth and form, activities that continue in many laboratories. The major problems addressed by radiographic cephalometry at first were the same as those addressed by anthropologic craniometry. Only later, once “cephalometric” equipment became available to the clinician in his office, was this technique applied to individual patients. With the exception of promising recent developments in the area of morphometrics (Bookstein, 1978; Bookstein and Moyers, 1979; Bookstein, 1982), however, the research applications of radiographic cephalometrics has changed little up to the present time.
In addition to describing growth, early concepts concerning the factors controlling craniofacial growth were derived directly from studies of comparative anatomy, craniometrics, and radiographic cephalometrics. Anatomic intuition and extrapolation from other areas of the body led to the belief that the growth of the craniofacial skeleton was immutable and largely predetermined genetically (Charles, 1925; Sicher, 1947). The assumption that craniofacial skeletal growth proceeds in a manner identical to the growth of long bones led to what Moss (personal communication) has characterized as the "classic triad": (1) that sutures are primary growth sites; (2) that the growth of cranial vault occurs only by periosteal deposition and endosteal resorption; and (3) that all the cephalic cartilages, including the cranial base, nasal septum, and mandibular condyle, are primary growth "centers" under direct genetic control.

Clearly, the craniometric, radiographic, cephalometric, and comparative anatomic studies of the period from 1920 to 1940 were closely interrelated. Their broad assumptions and problems were the same; thus, it can be said that they were all maintained within the same paradigm. More specifically, the predominant paradigm of craniofacial biology through the first half of this century has been that craniofacial growth is determined by heredity—what is called the genomic paradigm. As a result of this paradigm, the search for "norms" and "standards" of craniofacial growth was quite reasonable, primarily because they could be used as tools to predict facial growth in individuals (Brodie, 1941a, 1941b; Hirschfield and Moyers, 1971). If, as was generally believed, craniofacial growth is genetically determined, its pattern should be nearly invariant. Recognition of facial type by comparison with growth standards would then imply a type-specific pattern of growth for individual patients. This approach would provide a means of predicting facial growth and thus of individualizing the choice of treatment. Accordingly, one can see both the scientific and applied clinical manifestations of the paradigm then current in craniofacial biology. The basic conceptual model of the primacy of heredity in the growth and form of the bones, sutures, and cartilages of the craniofacial complex provided a foundation for a clinical application that ignored treatment of the bones of the face and focused on the more plastic dentoalveolar region. If orthodontists believed that they could not alter facial growth, the best they could do would be to strive for an acceptable dental alignment.

1940 to 1960

Craniofacial biology during the 1940s and 1950s saw an increased emphasis on experimental animal research in an effort to account for the actual mechanisms of facial growth (Baume, 1961) (Fig. 2–4). This
Fig. 2-4. General model of craniofacial biology during the 1940s and early 1950s. Craniofacial growth research and orthodontics were characterized throughout this period by a single paradigm, the genomic paradigm. By the mid-1950s, however, partly as a result of influence from other biologic disciplines, a new approach—the structurofunctional approach—began to attract adherents, beginning a prerevolutionary period of development within craniofacial biology.

shift within craniofacial biology was both conceptual and methodologic in nature. Conceptually, investigators began to recognize not only that there is much more variation within the facial region than would be predicted if growth were predetermined genetically, but also that this variation could be the result of modifying influences during ontogeny.* In this manner, the concepts of function and adaptation to altered function were introduced conceptually.

The methodologic innovation associated with this conceptual shift was not profound, but it has had many ramifications. Specifically, the

* The view that genes control any aspect of development and form does not answer the question of how and why any given structure or complex of structures is the way it is. The statement that something is genetically determined simply begs the question of how the gene became encoded, how it is maintained in the gene pool, and how it operates, i.e., the mechanisms that control gene expression. Thus, the problem is removed to another level—the level of how the genetic variant came about, its selective value, and its expression—but no final solution is provided.
experimental method, so commonplace in other sciences, now could be used, in conjunction with animal models, to study the function and interrelationships of the various components of the craniofacial complex during growth. Emphasis on the use of laboratory animals led directly to specific technologic developments, including the use of radiopaque implants, vital dyes, autoradiography, and in vivo and in vitro transplantation, to name a few.

The significance of the beginning of a consideration of variation, function, and adaptation during growth was manifold in terms of what it signaled for craniofacial biology as a discipline because it was at this time that the foundation was laid for a major shift in paradigms. The mid to late 1950s, in particular, was a period that could be called prerevolutionary. According to Kuhn, prerevolutionary periods are characterized by a growing disenchantment with the current paradigm, which leads, ultimately, to the generation of a new paradigm. This disenchantment often results in a search for new methods, experimental techniques, and models—a process that also tends to be marked by frequent arguments within the scientific community. The discipline, in other words, begins to undergo an identity crisis.

One of the best and most tangible examples of this shift in thought occurring within craniofacial biology can be seen in the work of Moss during the early 1950s. Moss' experimental analysis of sutural growth established beyond any doubt that sutures within the cranial vault and face are sites of active, but compensatory, skeletal growth (Moss, 1954, 1961). Moreover, Moss established that sutural growth and the form of the individual bones of the vault are not genetically predetermined.

The importance of this research is threefold. First, experiments on sutural growth clearly established what Kuhn would call an anomaly. That is, the results differed significantly from those predicted by the existing paradigm. Remember, however, that paradigms are not hypotheses or theories. Thus, refutation of one of the tenets of the paradigm does not necessarily mean that the paradigm is incorrect or that it must be rejected; it merely raises doubts that may lead to a modification, but not outright rejection, of the paradigm. Second, Moss' interpretation of his results concerning sutures extended far beyond his experiments and began to provide a foundation within craniofacial biology for a change in paradigm. Moss interpreted, articulated, and extended van der Klaauw's concepts from comparative anatomy to craniofacial biology. Third, and perhaps most important for the consideration of paradigms in craniofacial biology, that research on sutural growth took place at all is significant. That it was done indicates that there was already some serious questioning of the current paradigm by at least a few craniofacial biologists.

By the end of the 1950s, there were two general, mutually compatible approaches within the single dominant genomic paradigm of
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craniofacial biology. These are what Krogman (1974) has called the comprehensive approach and the structurofunctional approach. The comprehensive approach continued the earlier tradition of cranio­metrics, albeit with more sophisticated hardware in the form of radiographs, x-ray units, and cephalostats and software in the form of statistical models. The structurofunctional approach focused primarily on cause-and-effect relationships within and among the biologic sys­tems of the craniofacial complex and subsequently on the effect of altered, or so-called "abnormal," function on form. The comprehen­sive approach is inherently descriptive, with concepts of process and the mechanisms of craniofacial growth being inferred from cross-section­al and longitudinal craniometric data. The problem associated with this approach, if one is looking for the factors controlling facial growth and their causal relationships, was well stated by Enlow (1973, p. 403), who noted that "We often confuse what happens for how it happens and are thereby deluded into believing that we understand and can account for the actual control mechanism itself." The structuro­functional approach, on the other hand, is inherently experimental and analytic. Even if the investigator only describes his results, given an experiment that is well designed and well documented, an edu­cated reader can infer from the data its major significance to an understanding of the mechanisms of facial growth. Accordingly, the comprehensive and structurofunctional approaches are not equal in their ability to provide answers concerning the control of cranio­facial growth.

By the end of the 1950s, the time was ripe for the development of an alternative to the dominant genomic paradigm. Whereas the dominant paradigm in craniofacial biology throughout the 1950s was character­ized by the view that all skeletal growth is genetically determined, anomalous results became apparent in the research of many, but not all, structurofunctionalists. For example, comparative and experimental anatomic research using animal models led to a questioning and eventual abandonment of the view that periosteal bone growth and sutural bone growth are under direct genetic control. Periosteal and sutural bone growth were, therefore, removed from the genomic para­digm and relegated to the status of secondary, compensatory, or adaptive phenomena. The essential feature of the paradigm, however, that genes are primarily responsible for craniofacial skeletal growth, re­mained intact and unquestioned by all except a small but growing community of experimental investigators. Because there was little reasonable empiric evidence at that time to suggest that the cephalic cartilages, including those of the cranial base, nasal septum, and mandibular condyle, are not under direct genetic control, the genomic paradigm continued to dominate craniofacial biology. The alternative view that "function" plays a major role during facial growth, however,
continued to gather momentum as a result of the confluence of the structurofunctional approach and concepts and empiric data from the fields of comparative functional anatomy, embryology, and even paleontology.

1960 to 1980

The early 1960s saw the formalization of an alternative paradigm and thus the beginning of a period of scientific revolution in craniofacial biology (Fig. 2–5). Many investigators using a variety of specific approaches were dealing with growth and adaptation and questioned the rationale of the long-standing genomic paradigm within craniofacial biology. For the most part, those who seriously questioned the genomic paradigm were basic biologists; relatively few were clinical scientists or practicing orthodontists. For a variety of historical as well as scientific reasons, however, the development of an alternative paradigm within craniofacial biology is almost completely associated with one individual, Melvin Moss. In fact, Moss’ “functional matrix hypothesis” is perceived by most craniofacial biologists to be the alter-

![Diagram](image-url)

Fig. 2–5. General model of craniofacial biology during the 1960s and 1970s. The 1960s were a period of scientific revolution within craniofacial biology, with the functional matrix hypothesis being articulated as the major alternative to the genomic paradigm. The more general structurofunctional approach, which encompassed the functional matrix hypothesis, evolved into the functional paradigm. The functional matrix hypothesis is still maintained within the functional paradigm.
native paradigm itself. I believe that the functional matrix hypothesis, taken in its broad context, is one component, a major component perhaps, of an even broader paradigm that has developed within craniofacial biology since 1950. Moreover, it is my opinion that two overriding factors have led to a great deal of the controversy regarding the functional matrix hypothesis. First, most investigators have failed to understand and consider the functional matrix hypothesis in the broad context of the paradigm of which it is a part, and, second, I believe that both protagonists and antagonists have interpreted naively the significance of the functional matrix hypothesis for the clinical treatment of craniofacial disorders.

The functional matrix hypothesis was first articulated by Moss and Young in a 1960 article published in the *American Journal of Physical Anthropology*. Although this benchmark article provided a unique way of looking at the skull as compared with conventional anthropologic craniology, it failed to generate much controversy. Concepts of function and adaptation are long-standing traditions in physical anthropology, a discipline whose roots in comparative anatomy and paleontology assured a warm reception for the notion that the skull is comprised of relatively independent functional components and skeletal units. Moss and Young simply applied the concept of functional cranial components to a theoretic evaluation of a discrete question of concern to physical anthropologists: why do certain human ancestors have a supraorbital torus? Their conclusion that large brow ridges are associated with a spatial separation of the facial complex from the cranial vault did not conflict with tradition in anthropologic craniology because Moss and Young ignored the issue of whether this relationship was due to functional factors during ontogeny or to inheritance of a particular morphologic pattern. The term functional adaptation, to the physical anthropologist, does not necessarily imply ontogenetic plasticity. Moss and Young spoke only of what they termed the biologic meaning of certain craniofacial features and their interrelationships and not of their efficient cause.

It was after the second major paper by Moss (1962), in which he introduced the functional matrix hypothesis to the clinical orthodontic community, that the real revolution within craniofacial biology began. Moss was one of three basic scientists who was included in the first *Vistas in Orthodontics* in 1962. The papers by Sicher on the periodontal ligament and by Reitan on alveolar bone remodeling during tooth movement were didactic. Moss, however, introduced the functional matrix hypothesis as a formal, alternative conceptual scheme for understanding normal and abnormal craniofacial growth. As noted by Moss 10 years later (1972, p. 482): "It seems fair to state that specific orthodontic interest in our work can be marked from the appearance of that article. However, this same article led to some ambiguities of
comprehension, not all of which are yet resolved in the minds of its readers.” Nevertheless, from this point on the functional matrix hypothesis became the flagship of the alternative paradigm, and Moss became its admiral.

The functional matrix hypothesis has been the subject, either directly or indirectly, of more theoretic debate, empiric experimental analysis, and just plain heated discussion than any single theory in the history of craniofacial biology. As noted by Koski (1977, p. 9):

“The functional matrix idea was, as we all know, not a really new, nor a very precise theory. However, by questioning as it did, the old beliefs, such as the supremacy of the craniofacial cartilages, it stimulated more research, perhaps, than any other idea in the recent history of craniofacial biology.”

According to Moorrees (1972, p. 147):

“We must acknowledge that the functional matrix concept has become the theoretical basis for craniofacial morphogenesis, with some aspects of its formulation existing perhaps as a working hypothesis, if you wish. The functional matrix concept has brought a fresh approach to studying facial growth. . . . functional interrelations can no longer be neglected in the methodological consideration of future experimentation or observation of the growth process.”

Taking the unusual position for the editor of a major journal of advocating a particular theoretic approach, Wayne Watson (1982, pp. 71–73) recently stated that

“The concept of the functional matrix hypothesis . . . has revitalized studies of growth and development and established a rationale for the orthodontic application of orthopedic forces as well as the surgical treatment of craniofacial anomalies. . . . Moss has taken a quantum leap with his functional matrix hypothesis to explain growth and development . . . [that] propels us beyond a pragmatic treatment approach and on into the field of prevention and correction through science.”

In an eloquent rebuttal of the functional matrix hypothesis, however, Johnston (1976, p. 159) stated that

“Unfortunately, much of the resulting experimentation has been done, not so much to study the mechanisms of facial growth, as to test some of the more extreme corollaries of a series of evolving hypotheses.”

According to Daniels and Kremenak (1971, p. 1498), in fact, the functional matrix hypothesis “has probably both stimulated and inhibited thinking and experimentation. It may be harmful in application.”

To a large extent, the debate surrounding the functional matrix hypothesis has been over semantics. Is the functional matrix hypothesis a hypothesis, is it a theory, or is it neither? What is a functional matrix?
What is a capsular matrix? What is a skeletal unit? These semantic issues are not trivial; a common vocabulary is essential for proper communication. Unfortunately, however, many arguments about the functional matrix hypothesis fail to go beyond semantics to the fundamental biologic issues.

To a large extent, also, the debate about the functional matrix hypothesis has not been about science but about personalities—about styles and egos. Again, this is not trivial; however, there comes a time when the fundamental basis of a model must be either accepted or rejected on its own merits, independent of its more vocal protagonists and antagonists. In fact, the inability to disassociate a theoretic model from its founder after a significant period of time is a mark of immaturity in the development of that discipline. This does not mean that credit should not be given where due for novel scientific ideas and applications. Rather, it means that ideas eventually must develop an existence of their own and that the scientific community is not necessarily obligated to agree in perpetuity with everything the originator of the idea says. The fact that Galileo, under extreme duress from the Vatican, repudiated his proof of Copernican astronomy does not mean that the proof was not there. On the other hand, with the exception of reasonable proof, an idea can have no greater allies than wise, forceful, articulate and energetic advocates.

As noted by Johnston (1976), analytic, scientific debate about the functional matrix hypothesis has tended to focus on two general features: (1) the rather extreme position that the cephalic cartilages have no intrinsic growth properties and (2) the mechanisms by which the capsular matrices—the oral, nasal, and pharyngeal cavities—assert “morphogenetic primacy.” Even these features, however, are relatively specific when compared with the conceptual model underlying the functional matrix hypothesis. According to Moss (1981, p. 370):

"...In summary form, the functional matrix hypothesis explicitly claims that the origin, growth and maintenance of all skeletal tissue and organs are always secondary, compensatory, and obligatory responses to temporally and operationally prior events or processes that occur in specifically related nonskeletal tissues, organs or functioning spaces (functional matrices)."

The emphasis is on all skeletal tissues as responsive, as having degrees of plasticity during their growth and development that reflect completely their environment. As a result, the focus of the functional matrix hypothesis is not on skeletal tissues per se but on the factors that influence their growth and development—in other words, on the skeletal tissues as reflections and direct products of their total environment. The functional matrix hypothesis is, in effect, simply a relatively extreme, although not radical, interpretation of the broader
alternative paradigm that has developed within craniofacial biology during the past three decades.

As previously mentioned, the advent of the structurofunctional approach within craniofacial biology following input from wider-ranging areas of anatomy, embryology, physiology, and paleontology led, in the early 1960s, to the development of a new paradigm that conflicted with the traditional genomic paradigm. The alternative paradigm, which I will call the “functional paradigm” for lack of a better term, states simply that the craniofacial complex is highly adaptable, ontogenetically and phylogenetically, to the functional demands placed on it and to its developmental environment. This statement of the paradigm does not preclude the influence of genetic factors on the growth and form of the craniofacial skeleton; however, the functional paradigm does state, implicitly at least, that the primary focus of craniofacial growth research should be on those factors that can be modified experimentally and treated clinically.

No rational scientist denies that genes are essential for normal development. The only argument concerns when the influence of the genotype ceases to be dominant and the epigenetic mechanisms take over. In my estimation, both the genomic and the alternative functional paradigm recognize this. Thus, why should these two paradigms be in conflict? Remember that paradigms are shared beliefs, values, and techniques, as well as concrete models that can serve as a basis for solving remaining problems. They are conceptual models that are used to define what problems are significant and what solutions are meaningful. The conflict between the genomic and functional paradigms, therefore, resides primarily in the foci of the two paradigms—in other words, in their recognition of legitimate problems, methodologic approaches, and in the nature of their solutions or their interpretations.

The genomic and functional paradigms are fundamentally dichotomous in their basic starting points. The genomic paradigm holds that a significant genetic influence is exerted on the growth and form of the craniofacial skeleton throughout development. According to this view, everything is genetically determined unless proven otherwise. In science, however, even the nature of proof is debatable because the paradigm itself dictates what constitutes significant data and, consequently, what constitutes proof. Thus, although most craniofacial biologists, regardless of the paradigm to which they subscribe, would accept the view that sutural and periosteal growth are not under direct genetic control, few adherents of the genomic paradigm would accept the view that the growth of the mandibular condyle is not under direct genetic control, and no adherent of the genomic paradigm would accept the view that the growth of the nasal septum and cranial base are not largely genetically determined.
The functional paradigm maintains that the burden of proof lies with those who believe that there is any genetic influence on craniofacial skeletal growth. The more extreme position within this paradigm, the position that Moss has tended to occupy, is what has come to be known as the epigenetic hypothesis. This hypothesis, as stated recently by Moss (1981, p. 369), is characterized by the view that

"Both structure and function evolve alterations in the biomechanical, biophysical, biochemical and bioelectric parameters of the developing organism, both intra- and intercellularly. These alterations of state (that is, new information) act significantly to regulate subsequent developmental stages, as well as to regulate genomic reaction to these altered environmental states. In this hypothesis, 'environment' is not just permissive and supportive but also regulative."

A less extreme position would hold that although virtually all components of the facial skeleton are alterable by environmental influence, they are hierarchically arranged from skeletogenic tissues that are most adaptable (e.g., periosteum and sutures) to least adaptable (e.g., the morphology of the teeth). I consider it axiomatic, however, that any member of the scientific community who believes in the functional paradigm must believe that all tissues of the craniofacial complex are adaptable; that is, given the proper epigenetic influences, all craniofacial tissues, even the most conservative, can be altered during growth and, therefore, in their final form. There is no aspect of craniofacial form that is absolutely genetically predetermined. Only the ability to grow and the capacity for adaptive change, given the appropriate epigenetic stimuli, are primarily genetically programmed.

It should be remembered that these are statements of the functional paradigm and that they conflict fundamentally with the genomic paradigm. Certain experimental studies purport to have found that alteration of the functional forces acting on the mandibular condyle do not stimulate growth but cause pathologic changes in the temporomandibular joint. Other researchers have concluded that nasal septum resection results in a deficiency of midfacial growth. Still other investigators have concluded that the growing cartilage of the cranial base resembles long bone epiphyseal cartilage morphologically and biochemically. Each of these studies, however, can be questioned as to their methods, designs, and interpretation of results by certain adherents of the functional paradigm. The point here is not that one paradigm is correct and the other is incorrect. The point is that the experimental design and the interpretation of results are influenced to a great extent by the paradigm maintained by the investigator.

Viewed in this manner, the major tasks of those who adhere to the genomic paradigm are threefold: (1) to describe facial growth as accurately as possible given existing techniques; (2) to use this description
to predict facial growth in the individual; and (3) to control the growth of those features that are technically feasible to control (Kremenak, 1972). The major tasks of the scientific community subscribing to the functional paradigm, on the other hand, are (1) to explain the epigenetic factors that influence facial growth and (2) to determine how the environment can be altered to produce a predictable alteration in facial growth. The third task is the same as that for adherents to the genomic paradigm—to control as precisely as possible those features of facial growth that are technically feasible to control.

I have stressed that the structurofunctional approach within craniofacial biology has been most common among basic scientists—those investigators doing research on the biologic mechanisms of craniofacial growth. Relatively few clinical orthodontists have adopted the structurofunctional approach. There is one good reason for this: the structurofunctional approach is a research strategy and not a health approach. Even today, acceptance of the functional paradigm by clinicians is not as widespread as it is among basic scientists. According to Moss (1981, p. 368), "While few clinicians might agree that 'the morphology of all the bones of the craniofacial complex is under the rigid control of hereditary forces,' most believe that the genome is primarily causative of some significant portion of craniofacial form." It is reasonable to question why it is that this belief predominates within clinical orthodontics and whether it is important.

Orthodontics historically has placed a great deal of emphasis on basic research. The rationale for this emphasis is that a proper understanding of biologic mechanisms will increase the effectiveness of clinical treatment. Why, then, do many clinicians tend to reject the functional paradigm?

First, the functional paradigm primarily deals with the mechanisms of craniofacial growth. Generally, the mechanisms for the growth of any single component of the craniofacial region are extremely complex. Growth of the entire region is made infinitely more complex by the incredibly large numbers of individual structures, functions, and interactions. All one has to do is glance at one of the elegant cybernetic models of mandibular growth that Alexander Petrovic and his associates (1975) have proposed to appreciate this fact. Second, for the most part, clinical orthodontics is not oriented toward prophylactic therapy but rather toward correction of an existing or developing craniofacial dysmorphology. Third, orthodontists must use the tools at their disposal prudently, including an understanding of the basic mechanisms of facial growth, in their treatment plans. For decades, orthodontists have known the basic principles underlying the movement and realignment of teeth. They also are sensitive to the detrimental influence of such factors as macroglossia, hyperactive masticatory muscles, thumb sucking, and other variations of oral func-
tion on facial growth. They have, in other words, implicitly accepted many aspects of the functional paradigm in terms of individual patients, even if they have not accepted the paradigm itself. Put another way, most clinical orthodontists have not failed to accept the functional paradigm; they merely have not rejected the genomic paradigm.

In the past, it has not been important that clinicians accept either the genomic or functional paradigm. In either case, it probably would not have altered individual treatment significantly. In fact, naive acceptance of certain of the major features of the functional paradigm, and of the functional matrix hypothesis in particular, could lead to significant treatment problems. For example, experimental data indicating that the mandibular condyle is not a primary growth center that carries the mandible downward and forward does not mean that the condyles are not important for normal mandibular growth and that they can be removed with impunity. Similarly, the assertion that the nasal septum does not pull the midface downward and forward does not mean that it is not a vital element in the growth and integrity of this region.

Clinical orthodontics in the United States recently has seen a remarkable increase in the use of “functional” appliances. Earlier, the application of orthopedic forces to the growing bones of the craniofacial complex by using fixed appliances had become commonplace. Clearly, both of these approaches are based on the assumption that facial growth can be changed significantly by altering the biomechanical and biophysical environment of the craniofacial complex. Thus, both treatment regimens are based primarily on the tenets of the functional paradigm.

The past 20 years of research in craniofacial biology can be characterized as a period of profound scientific revolution—of conflict between two conceptual models, or paradigms, the traditional genomic paradigm and the more recent functional paradigm. This conflict between paradigms has been dominated by Moss’ numerous expositions of the functional matrix hypothesis and counterarguments by his antagonists. It is unfortunate, however, that many craniofacial biologists have been unable to separate the functional paradigm from its major spokesperson. The functional matrix hypothesis is not synonymous with the functional paradigm. The functional matrix hypothesis is an extreme, but nevertheless legitimate, way of expressing the functional paradigm. It is not the only way, nor is it the most effective way if the goal is to articulate basic and clinical sciences within craniofacial biology.

CONCLUSIONS

If craniofacial biology was born of and nurtured by clinical orthodontics, it was fathered by such basic sciences as anthropology,
anatomy, biometrics, and physiology. Craniofacial biology emerged from the 1920s and 1930s with an existing conceptual model of how the face grows which held that all craniofacial growth and form—especially that of the skeletal tissues of the head—are genetically predetermined (Fig. 2-6). This is the same view that Wendell Wylie termed “orthodontic Calvinism” (Moyers, personal communication). I have called it the genomic paradigm. During the late 1940s and early 1950s, emphasis on the role of so-called functional factors on the growth of the craniofacial skeleton became noticeable among basic scientists, many of whom were engaged in experimental investigations of structure and function. Even by the mid-1950s, however, there was no consensual rejection of the genomic paradigm by structurefunctionalisats, but there was growing discomfort with it. It is my feeling, therefore, that this period was what Kuhn would call prerevolutionary. Soon afterward, in the early 1960s, craniofacial biology entered a period of scientific revolution as the functional paradigm, and the functional matrix hypothesis, in particular, came into direct conflict with the genomic paradigm.

Although the functional matrix hypothesis began to affect a relatively extreme posture, it was still well within the tradition of the functional paradigm. The functional paradigm focused attention on the relative plasticity of craniofacial growth. It emphasized those aspects of craniofacial growth that the basic scientist could alter experimentally and thus analyze using experimental methods. Similarly, the functional paradigm focused attention on those features of facial growth that potentially could be altered clinically given the appropriate treatment. In sum, the functional paradigm does not, by definition, preclude the influence of the genotype on craniofacial growth and form; it simply holds that the assumption that all or part of craniofacial growth cannot be altered experimentally and therapeutically is much less productive than the assumption that craniofacial growth is relatively adaptable. Viewed in this manner, the genomic paradigm is stifling in terms of its influence on both basic and clinical craniofacial biology.

At the present time, craniofacial biology is characterized by these two major paradigms. On the one hand, there is the genomic paradigm, which has survived the loss of periosteal, sutural, and condylar growth to the functional approach, and exists primarily on the strength of the belief that facial growth and form must be encoded genetically. This paradigm remains most popular among clinical orthodontists because it is more conservative and tends to be expedient in terms of individual treatment. On the other hand, there is the functional paradigm, which encompasses the functional matrix hypothesis and its logical extension, the epigenetic hypothesis. Because the functional paradigm emphasizes features that can be controlled by altering the envi-
Fig. 2-6. Summary of the development of competing paradigms within craniofacial biology from 1940 through the present.
Environment in which facial growth expresses itself, this paradigm is and will remain most popular with basic scientists interested in the evolution and function of the craniofacial complex and in the control mechanisms of facial growth. It also will remain popular with those clinical orthodontists who believe that the growth and form of the facial skeleton is a manifestation of a host of functions and physical interrelationships within the craniofacial complex.

The purposes and goals of the genomic and functional paradigms are distinctly different; thus, it is no wonder that there is conflict between them. Recognition of the existence of alternative paradigms—recognition that there are alternative ways to approach craniofacial research—should lessen this conflict, at least to the extent that the two scientific communities understand the basis of their differences. This becomes particularly important as the basic paradigms are applied clinically. It is in this respect that I believe the functional paradigm, in general, and the functional matrix hypothesis, in particular, are most misunderstood and here that the potential for misapplication is greatest.

In this chapter, I have argued that craniofacial biology is definitely not a clinical subspecialty. It is not even a subdiscipline of a clinical subspecialty, as Pruzansky implied. Nevertheless, craniofacial biology has maintained a close affiliation with clinical orthodontics for the past 50 years or more. This association has been extremely fruitful for both clinical orthodontists and basic scientists. I believe, however, that unless certain adjustments are made, this relationship is likely to falter. Specifically, although craniofacial biology has made relatively good scientific progress to date as a result of its strong clinical relevance, I question whether craniofacial biology will continue to be equally productive if this relationship continues. In fact, indications that the scientific progress of basic craniofacial growth research has slowed during the past decade or so have been apparent for some time. To a large extent, basic scientists within the field of craniofacial biology have become handmaidens to clinical orthodontists. Basic research on the mechanisms of facial growth has given way to after-the-fact scientific justification for a specific treatment procedure that frequently has been in use clinically for some years. The basic craniofacial biologist becomes, at worst, a "products liability tester" and, at best, a "fine-tuner" of a previously developed treatment approach.

There is no question that this relationship between clinical and basic science is to some extent necessary; however, my concern is that overemphasis on this particular relationship has led to a significant slowing of progress and often to plain "bad science." All too often, research in craniofacial biology has come to be simply thesis work toward a master's degree in orthodontics, usually on a problem with direct and obvious clinical relevance and often with little or no follow-
Craniofacial Biology as “Normal Science”

up research on the biologic mechanisms of facial growth. This problem was recognized by Krogman (1974, pp. 52–53), who suggested that

“Perhaps the alleged slowness of [research] ... progress has been that craniofacial biology has too often tried to shape basic findings into a too-rapid clinical application: dental research biologically oriented may have suffered from the ‘take-home-pay syndrome,’ the clinical demand that research results have a well-nigh immediate chairside implementation.”

What, then, should be the relationship between basic and clinical science within craniofacial biology and between craniofacial biology and clinical orthodontics? I believe that the dental and medical clinical specialties as a whole will continue to pose a large share of the important biologic problems; however, I believe that the most important scientific breakthroughs of the future will be in the basic sciences. The basic scientist within craniofacial biology should be concerned primarily with the most difficult problems—problems that promise to require long-term solutions—and secondarily with collaborating with the clinical scientists within craniofacial biology to find solutions to short-term, applied problems. If this relationship can be maintained successfully, if craniofacial biology is acknowledged as being more than research that must always have a direct and immediate clinical “payoff,” the discipline will continue to grow and be productive.

A greater breadth in craniofacial biology has the potential of again attracting young basic scientists to do research in craniofacial growth and adaptation. Basic nonclinical craniofacial biologists, however, will never reach a critical mass if there is no academic home for craniofacial biology itself. It is not enough for each orthodontic department to have a resident faculty member whose principal avocation is to direct the research of graduate orthodontic students. This is the model dental schools and orthodontic departments have tended to follow in the past, and I believe it is now found wanting. Basic research in craniofacial growth has developed and matured significantly during the past 50 to 60 years. Orthodontic departments and research groups, such as the Orthodontic Education and Research Foundation, have conceived and nurtured craniofacial biology during its formative years. The future of craniofacial biology, supported as it is by a firm historical foundation, will be best served if it is not constrained by a narrow emphasis on immediate clinical solutions. It is to the credit of American orthodontic programs that they have made craniofacial biology so strong. In effect, however, this success has alleviated the need for dental schools in general to support research in craniofacial biology as they do research conducted by their other basic science units. It is time to see within our dental schools greater concentrations of
New Vistas in Orthodontics

basic and clinical scientists interested in craniofacial biology. By continuing to support research and recognizing the diversity of craniofacial biology, we can ensure that the coming decades will see even more exciting developments.

REFERENCES


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GROWTH MODIFICATION:
FROM MOLECULES TO MANDIBLES

David S. Carlson

Historically, the field of orthodontics has been concerned with the correction of malocclusion, primarily by means of controlled movement of the developing and mature dentition into a desirable occlusal relationship. Control and modification of the growth of the skeletal structures of the craniofacial complex, especially via tooth-borne appliances, also has been a prominent but controversial area of interest and activity within the field of orthodontics since its inception (Lefoulin, 1840; Dewey and Anderson, 1935; Milch, 1938; Moore, 1985; Hamilton, 1998; Woodside, 1998).

As evidence of the predilection toward dentofacial orthopedics as well as traditional orthodontics, the name of the official journal of the American Association of Orthodontics was changed from the American Journal of Orthodontics, to the American Journal of Orthodontics and Dentofacial Orthopedics in 1986. This action itself was somewhat controversial within the orthodontic community. For example, L.R. Dermat, professor and chair of orthodontics at the University of Gent, Belgium, noted that "If 'facial orthopedics' stands for influencing facial growth, I wonder whether this addition is justified, referring to our limited ability in changing growth" (Moorrees, 1988:38). Similarly, Lyle E. Johnston, professor and chair of orthodontics at the University of Michigan, argued that "... something is severely amiss when the specialty concentrates on growing jaws (and changes the name of its journal to reflect this illusory preoccupation) without giving—or being forced to give—any serious thought to the basic mechanisms involved" (1990:81). The soundness of the rationale for the name change notwithstanding, these admonitions serve to underscore the importance of understanding concepts of craniofacial growth as they relate to treatment approaches of the contemporary orthodontists, especially as these

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1 It is interesting also that a similar change in name occurred recently at the National Institutes of Health, which is a principal supporting funding agency for all basic and clinical research in the area of the biomedical sciences. In order to emphasize its significantly broader scope, after 50 years the National Institute of Dental Research now is known as the National Institute of Dental and Craniofacial Research.

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of the environment ("nurture") on the overall process of ontogeny (see also Slavkin’s chapter in this volume). This apparent dichotomy is rooted deeply in the history of Western science and has influenced conceptual developments throughout the biological and social sciences (for an excellent review, see Weiss, 1973). In fact, Medawar and Medawar (1983) noted evidence of the "nature-nurture" controversy as early as the fifth century BC, and even in the literary work of Shakespeare. However, modern application of the "nature-nurture" concept probably is drawn from the now discredited concept of eugenics put forward by Sir Francis Galton (1874) in the late nineteenth century (Bynum et al., 1981).

As more is understood about modern developmental and molecular biology, it becomes apparent that nearly all arguments about "nature-nurture" among lay people and professionals alike are based on a false dichotomy rooted in a naïve understanding of genes, gene action, and the possible role of extrinsic factors in development and growth. On the one hand, the statement that a phenotypic trait is "genetic" and inherited often has led to the mistaken inference that it is "genetically predetermined," a kind of "biological Calvinism" (Moyers, personal communication). On the other hand, the logical extension of the view that the shape and size of a morphological feature is due primarily to the effects of the environment is that the underlying genomic basis for the feature is of little or no importance. In addition, it often is taken to mean that the shape and size of the feature can be changed significantly by alteration of environmental and "functional" factors, though the parameters of such morphological changes may not be considered. It is presumed that all one has to do is discover the environmental-functional factors that control growth, and will be is possible to alter form in a predictable way.

Form-Function

An offshoot of the "nurture" side of the "nature-nurture" equation is the "form-function" principal, which emphasizes the role of biological purpose, behavior, and the environment, i.e., "function," in the production of form. As a general biological concept, the "form-function" principal is attractive, but primarily so as a means of accounting for the...

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2 In the Tempest, act 4, scene I, Prospero describes Caliban as "a devil on whose nature nurture can never stick."
that paper is the premise that there is nothing in biological development and growth that does not have a genomic basis. However, this does not in any way mean that all biological tissues are genetically predetermined or immutable in their growth and form. All biological cells and tissues, and thus the growth and form of morphological structures and whole complexes, have a degree of plasticity at some stage of ontogeny during which they are capable of being influenced to a variable degree by factors extrinsic to the genome. In fact, some tissues, such as muscle and bone, require significant environmental interaction _via_ neural activity and mechanical load in order to develop normally. Other tissues, such as neural tissues, cartilaginous growth plates, and teeth, for example, are highly buffered from extrinsic environmental influences during much of their development and growth. As summarized by Dullemwijc (1974:224), “it is indeed easier to understand that cells [have the same] genetical constitution, the only difference being the factor of plasticity, than to suppose that for each shape or size specific factors are present. It remains a challenge to discover the specific condition determining the difference in plasticity of the various genomes.”

**CLINICAL ORTHODONTICS, DENTOFACIAL ORTHOPEDICS, AND CRANIOFACIAL BIOLOGY**

Orthodontics is based primarily on two major bodies of scientific knowledge—orthodontic biomechanics and craniofacial biology. Understanding both of these areas is essential for appropriate treatment of developing malocclusions and dentofacial deformities.

_Orthodontic Biomechanics_

Orthodontic biomechanics is the study of the forces applied to and derived from biological tissues, such as the facial skeleton and teeth, as well the specific manner in which they are applied. To a large extent, orthodontic biomechanics is concerned with three related areas: (1) the mechanical properties of biomaterials, (2) the technical means by which biomechanical forces are developed, and (3) the design of various appliances that will deliver forces to the skeletal structures and teeth _in_ a predictable manner.

_Craniofacial Biology_

Craniofacial biology is defined as the study of the development, growth, and function of the craniofacial skeleton, dentition, and related
surface at least, appear to be very disparate in approach is noteworthy. Perhaps because of this, many orthodontic philosophies have enjoyed longevity with little necessity for change in the fundamental orientation of their biological rationale (Johnston, 1990).

CONCEPTS OF CRANIOFACIAL GROWTH, ORTHODONTICS, AND GENETICS

Modern concepts of craniofacial growth and orthodontics can be viewed for heuristic purposes as a series of competing theories, each characterized by an emphasis on a particular biological issue or question of direct relevance to the mechanisms of skeletal growth in general and of craniofacial growth in particular. During the latter part of the nineteenth century through the middle third of the twentieth century, scientific investigation understandably proceeded quite slowly relative to current standards. The field of orthodontics, which ultimately provided the strongest single stimulus for craniofacial growth research, was still quite young intellectually throughout that time. However, even a cursory reading of events and meetings of the orthodontic societies indicates significant enthusiasm for independent research (Shankland, 1971); the numbers of orthodontic researchers and the resources available simply were not great. The same certainly is true for the field of genetics, which also was just emerging within the biomedical sciences.

During the latter part of the nineteenth century and the middle third of the twentieth century, the field of craniofacial biology witnessed development of a series of four or five relatively distinct, sequentially arranged, and competing theories of craniofacial growth. Each of these theories purported to explain the essential elements of craniofacial growth by focusing essentially on a particular factor as being the primary causal mechanism determining craniofacial growth and form. At the same time, the field of genetics was emerging from an emphasis on heredity as considered primarily with respect to transmission of units of inheritance between generations (i.e., Mendelian genetics) to an emphasis on the actions of genes and specific gene products during the developmental process (Raff, 1996).

Orthodontics, Race, and the Concept of Facial Type

The earliest foundations of modern orthodontics are intimately related to the concepts of beauty and ideal facial form developed within Hellenic Greek civilization. Concepts of facial beauty embodied by
quantitative approach to scientific racism . . . He became a villain of science when he tried to establish criteria for art.”
(Gould, 1991:238–240)

Regardless of the specific bias toward or against a particular facial form, for either social or other reasons, the artistic representations of facial form throughout the ages both reflected and reinforced early scientific concepts of discrete racial and social groups. Interestingly, these representations also related directly to emerging concepts of facial growth. According to the view shared by artists and scientists alike, faces could be classified and categorized into “types.” Within the realm of art, deviation from ideal facial form often was used as an indication of inferior social status (Olds, 1993). Among scientists and naturalists, facial types were classified further according to prevailing concepts of human races, which were believed to be pure and immutable.

The related concepts of racial typology, facial typology, and the relative immutability of facial types constituted the conventional wisdom throughout the various fields of biology and natural history during the late nineteenth century and first half of the twentieth century. This emphasis should not suggest that biologists as well as orthodontists and other health professionals, like any reasonably aware lay person, did not appreciate the fact that physical traits were passed down from one generation to the next. Rather, it was generally assumed that the very thing passed on through the generations is, in fact, the “type.” Further, it was believed that inheritance was particulate for complex morphological characteristics as well as for discrete traits. Admixture between racial types resulted in a new blend of typological-racial traits. From a clinical point of view, it would seem to make most sense to accept the mixture of inherited facial traits between parents of the same or widely different facial types, and to treat malocclusion and facial deformity within the limits presented by the blended type, understanding that the inherited form of the face could not be changed in any significant way.

It was within this conceptual milieu that Angle began his effort to develop the perfect orthodontic appliance (Moyers, 1990) and put forward the concept that “faces and occlusions should be brought into a condition of harmony according to type” (Angle, 1907, emphasis added). In fact, the Angle classification was established specifically to refine the concept of facial form by defining a series of types based on
Early Concepts of Bone Growth, Craniofacial Growth, and Heredity (circa 1800–1940)

Studies by Sir John Hunter in the eighteenth century (1771) on the growth of the jaws and eruption of the dentition are widely credited as representing the first rigorous scientific research on craniofacial growth. Following the work of Belchier and Duhamel, Hunter also performed experiments involving vital dyes and concluded that the growth of the maxilla and mandible takes place primarily by means of the addition of bone to their posterior aspects. This line of experimental research was extended using similar approaches with the work of Thoma (1848) and Humphrey (1864) in the nineteenth century, and Brash (1924a, b, 1934) and Scott (1938) among many others in the early twentieth century.

It generally is believed by craniofacial biologists today that this line of research initiated by Hunter and continued with the work of others through nearly the first half of the twentieth century was conducted primarily to increase understanding of the growth of the craniofacial skeleton. With closer analysis, however, it becomes apparent that elucidation of the process of craniofacial growth was actually only one, and most likely a secondary, goal. The rationale for this early research, which spanned well over 150 years, was primarily the nature of bone growth in general and specifically the issue of interstitial versus appositional bone growth. The craniofacial skeleton was used principally as a model system. We often fail to realize that it is only within the past 50 years that it has become completely understood and accepted that bone as a tissue does not grow interstitially, but grows only appositionally at bone surfaces. As late as 1946, in a lecture before the Forty-third Annual Meeting of the American Association of Orthodontists, Sicler stated that in spite of the unequivocal knowledge that bone grows only appositionally, "... almost every year an article is published in which the specter of interstitial bone growth is raised ... It is a pity that this should happen so often" (1947:30).

Remodeling Theory of Craniofacial Growth. The significance of the distinction between appositional and interstitial bone growth with respect to the goals of much of the early research in craniofacial growth is that it provided the theoretical foundation for the development of the first general theory of craniofacial growth—the remodeling theory. Once again, the major factor driving research on the growth of the craniofacial skeleton was not unique to that region; the essential issue
Hugo De Vries in the late nineteenth century and reintroduced by William Bateson in 1900. It was shortly thereafter, in 1905, that Bateson coined the term “genetics” as the new field of heredity (Dunn, 1963).

Of the many ideas regarding the material substance that carried the message for development of specific traits, Weismann’s concept of the *germ plasm* in the late nineteenth century (*Das Keinplasm*, 1892) was perhaps initially most influential. According to this idea, the cytoplasm found with germ cells is comprised of “determinants” that transmit traits from parents to offspring. Weismann asserted that the germ plasm is not affected by the life experiences of the parents, a clear contradiction of pre-Darwinian ideas of Lamarckism (*i.e.*, inheritance of acquired characteristics). Significantly, Weismann also maintained that the germ plasm is immutable (Bynum et al., 1981).

Several terms other than *determinant*, such as *character* and *pangen*, were used for the particulate units described mathematically by Mendel. In 1909, shortly after Bateson’s introduction of “genetics,” the Danish naturalist W.L. Johannsen used the term “gene” to refer to the presumed unit of heredity (R.A. Carlson, 1966). Even so, the concept of the gene remained theoretical but closely linked to the process of development. In fact, according to Johannsen, the gene represented the developmental “potentiality” of the organism rather than a discrete particle with a material basis for affecting the development and growth of individual phenotypic characteristics. With the discovery of the relationship between genes and the chromosome by the embryologist T.H. Morgan in 1910 and the first chromosome map by Sturtevant in 1912, however, “the gene was no longer an abstract unit but a segment of the chromosome” (Bynum et al., 1981:162).

Emerging into the twentieth century and even through the present time, the field of genetics was characterized by two principal foci. Transmission genetics, which is rooted in the Mendelian Laws of Inheritance and is characterized by a statistical approach, was readily accepted by and proved a highly useful quantitative tool for evolutionary biologists interested in the process of selection (*e.g.*, Haldane, 1924, 1927, 1932; Fisher, 1930; Wright, 1931, 1937, 1951). Important as Mendelian Laws of Inheritance were for understanding the process by which traits were passed on, however, “No knowledge of the nature of genes or their expression was required . . . Transmission genetics provided no theoretical foundation for the embryologist” (Raff, 1996:14).
less the precise role of the genome in the development and growth of complex morphological structures such as those comprising the craniofacial skeleton and dentition.

_Sutures, Cartilage, and the Structure of the Gene (1940–1960)_

*Disaffection with the Remodeling Theory.* The remodeling theory of craniofacial growth emphasized the role of differential deposition and resorption of bone to account for the growth of the craniofacial skeleton. However, this emphasis was related as much or more to competing hypotheses about the nature of bone growth as it was about the process of craniofacial growth. As earlier experimental studies indicated that bone deposition plays a significant role in the growth of the craniofacial skeleton, it tended to be assumed that bone remodeling played the preeminent role in this regard. However, a fundamental concern to many craniofacial biologists in the middle part of the twentieth century was the role that unique structures—such as sutures, cranial base synchondroses, and the mandibular condyle—play in the growth of the craniofacial skeleton. If these obvious sites of bone growth are not essential for normal craniofacial growth, then why are they present at all?

A second issue that emerged with more sophisticated studies of bone growth was the role of cartilage as compared to that of periosteum, the site of most bone remodeling activity, in the growth of bone. Specifically, it was understood that cartilage in the epiphyseal growth plates of long bones was capable of tissue-separating expansive growth, i.e., skeletal growth capable of pushing skeletal elements apart. The *remodeling theory* focused on the role of surface deposition and resorption in bone growth in general and growth of the craniofacial skeleton in particular. An alternative viewpoint emphasized the passive, secondary role of the periosteum and bone surfaces in skeletal growth and the primary expansive growth of cartilage in the production of skeletal growth and form. This view was reinforced by new experimental research demonstrating that Brash’s (1924) earlier studies of bone remodeling within the craniofacial skeleton used an inappropriate experimental design with respect to the choice and age of the animal model (pigs). As a result, it was determined that Brash arrived at erroneous conclusions about the importance of bone remodeling in craniofacial growth (Baer, 1954; Mednick and Washburn, 1956).

1940s: The Sutural Theory (Weinmann and Sicher). The *sutural theory* is identified most closely with the work of Weinmann and Sicher,
cept that growth of the face and jaws was essentially immutable. The
sutures, as well as the cartilages of the craniofacial skeleton, were es-
sentially the locations of centers of bone growth at which the inherited
pattern of craniofacial form and facial type, however determined, was
expressed; and the pattern could not be changed (Brodie, 1946).

1950s: The Nasal Septum Theory (Scott). Attractive as the sutural
theory was for craniofacial biologists and clinical orthodontists alike,
like the earlier remodeling theory, the sutural theory also appeared to
have numerous inconsistencies. For example, it had been clear for cen-
turies that a variety of major craniofacial deformities involving the de-
veloping central nervous system, such as those found with
anencephaly, on the one hand, and hydrocephalus, on the other, had
major effects on the development and growth of the cranial vault. Sec-
ond, it was understood that the early development of the bones of the
cranial vault and face have no direct cartilaginous precursor, unlike all
long bones and even flat bones elsewhere in the skeletal system. Third,
a major source of contention within craniofacial biology during the late
1940s and early 1950s was the description of the histomorphology of
the developing and growing suture. According to Weinmann and
Sicher (1947), the growing suture has three layers—a middle area of
proliferation of connective tissue bordered by two osteogenic layers
adjacent to the bone—thus, making sutures roughly equivalent in their
view to cranial base synchondroses and epiphyseal growth plates. An
alternative analysis of early suture development and growth put for-
ward by Scott and colleagues (Scott, 1956; Pritchard et al., 1956) con-
cluded that the osteogenic layers within the suture are actually
continuations of the osteogenic layer periosteum and dura within the
cranial vault and of the periosteum in facial sutures. As a result, ac-
cording to those investigators, sutural growth should be considered as
a specialized form of periosteal growth rather than akin to cartilagi-
nous growth. Finally, several experimental studies involving vital dyes
(Baer, 1954) and surgical manipulation (Moss, 1954, 1957) of cranial
sutures in appropriate animal models clearly indicated that although
sutures were major sites of craniofacial skeletal growth, they played no
determining role in that growth.

Each of these lines of evidence led many investigators to question the
validity of the sutural theory. Concomitantly, there was proposition of an
alternative explanation, the nasal septum theory, by the distinguished
Irish anatomist, James H. Scott, as the single and unified theory of cran-
iофacial growth (Scott, 1953, 1954, 1956). According to the nasal septum
ory, is essentially the same. The issue was not whether craniofacial growth and form are inherited, nor was it about whether craniofacial growth could be modified by means of dentofacial orthopedics. Similarly, the fundamental issue was not "do genes control growth of the craniofacial skeleton?" Based upon prevailing concepts about heredity and the gene, on the one hand, and about skeletal growth in general, on the other, it generally was assumed according to all three theories that craniofacial growth is largely inherited, intrinsically regulated, and predetermined. The major remaining question was about "where do heredity and the genes act—at sutures; within the cartilages of the cranial base, midface, and mandible; or at all three areas?"

Structural Basis of the Gene and Gene Action. Rediscovery of the Mendelian Laws of Inheritance and recognition of the particulate nature of inheritance early in the twentieth century set the stage for detailed analysis of the structure of the gene. As noted by Hays (1972:297), "From this point on, the problem of heredity involved a further reductive process, and as a result, chemistry and physics emerged to play a major role in the investigation of life." Subsequently, Waddington and others clearly established the conceptual linkage between embryology and genetics around 1940, and the field of developmental genetics was now attempting to address essential questions regarding the specific mechanisms that relate the mode and timing of gene activity. In fact, in a comprehensive review of the rise of developmental genetics, Raff noted that "The feeling that genetics was somehow crucial to developmental biology remained as a persistent, if uncomfortable and underdeveloped, theme throughout the first half of the twentieth century" (1996:15).

Two major breakthroughs in genetics during the 1950s greatly facilitated the ability of geneticists to develop and address questions of gene action. The discovery by Watson and Crick in 1953 that DNA is arranged structurally as a double helix provided a model for the understanding of gene replication and also was a benchmark in the development of techniques of molecular biology essential to the investigation of gene action. A second breakthrough, the operon theory of Jacob and Monod (1963), provided an explanation for how gene expression is regulated within the cell. According to this concept, genes and whole groups of genes operate within common regulatory sequences that can be turned on and turned off to control transcription of mRNA and gene expression.
little to resolve the issue of the degree to which and how growth and form of the craniofacial skeleton was determined via heredity in general and the action of specific intrinsic factors in particular. Baume's analysis focused the attention of later researchers more effectively on the locations within the craniofacial skeleton at which the presumptive forces of heredity, i.e., "true" primary growth centers, were active—whether at bone surfaces, within sutures, within cranial base synchondroses, and/or at the mandibular condyles. The issue that remained was not whether the growth and form of the craniofacial skeleton was inherited through the action of genes, the issue was where is this complex pattern of heredity expressed.

*Rise of the Functional Paradigm.* An alternative approach to the presumption of genetic predetermination of craniofacial growth had a long history in Europe and was especially noteworthy in what came to be known through the research of van der Klaauw (1945) and his students as the Dutch school of morphology. It was Melvin Moss, a dually trained dentist-anatomist, who carried the tradition of van der Klaauw and others to the United States initially in a classic paper published in the *American Journal of Physical Anthropology* in 1960 (Moss and Young, 1960). Moss then extended these concepts into the realm of clinical orthodontics as a new theory of craniofacial growth, called the *functional matrix hypothesis*, in another classic paper published in *Vestas in Orthodontics* two years later (Moss, 1962). These two papers were highly significant for both craniofacial biology and clinical orthodontics in terms of their impact on the next 40 years of craniofacial growth research. In fact, they should be considered as historic, benchmark events for all of craniofacial biology as they established a dialectic not between competing theories, but between competing paradigms of craniofacial growth (Carlson, 1985, 1997).

The earlier *genomic paradigm* emphasized the role of heredity and subsequently of genes in the growth of the craniofacial skeleton. As noted previously, the rationale for this predilection was based on fundamental assumptions regarding heredity as a determinant of growth and form that were derived logically from scientific investigations through the first half of the twentieth century. According to Moss (1976c,b), this earlier view can be summarized as the "classic triad" of craniofacial growth, which asserted that: (1) sutures, (2) bone surfaces, and (3) the cephalic cartilages are all primary growth centers capable of tissue-separating forces that control and shape the growth and form of the craniofacial skeleton.
about the *functional matrix hypothesis* was extremely spirited and often emotional. A further factor that fueled this debate was the fact that Moss introduced unfamiliar terminology to account for what he perceived as its fundamental propositions that was novel to most within the orthodontic community (Carlson, 1985).

According to the *functional matrix hypothesis*, the craniofacial skeleton, like all skeletal structures throughout the body, develops initially and grows in direct response to its extrinsic, epigenetic environment. As stated by Moss (1972), "bones do not grow; bones are grown." In order to understand the factors that affect bone growth in the craniofacial complex, therefore, it is most appropriate to understand both the local environment and the resultant skeletal structure in terms of their *functional cranial components*.

Each functional cranial component is comprised of two elements: (1) a *functional matrix* and (2) a *skeletal unit*. The *functional matrix* refers to all the soft tissues and spaces that perform a given function. The *skeletal unit* refers to the bony structures that support the functional matrix and thus are necessary or permissive for that function. Individual bones defined according to terms derived from traditional anatomy may be comprised of a number of overlapping skeletal units as the skeletal unit refers not to the individual bone directly, but to the function(s) that it supports.

There are two types of functional matrices. The *periosteal matrix* corresponds to the immediate local functional environment, typically associated with muscles, blood vessels, and nerves. The *capsular matrix* is defined as the organs and spaces that occupy a broader anatomical complex. Within the craniofacial complex, the capsular matrices would include such organs as the brain and globes of the eyes, as well as actual spaces such as the nasopharynx and oropharynx.

Similarly, there are two categories of skeletal units, *microskeletal* and *macroskeletal*. Functional variations in the periosteal matrix, such as muscle activity for example, may be expressed locally within the microskeletal unit as tuberosities and processes or ridges for muscle attachment (*e.g.*, the temporal line of the squamosal region of the perietal bone and the coronoid process of the mandible). Growth in size and shape of microskeletal units is typically associated with *transformational* bone growth, *i.e.*, transformation from an embryonic cell type to an osteoblast-osteocyte and periosteal deposition. Change in the size and shape of macroskeletal units, which include the neurocranium and maxillomandibular complex, for example, is the result primarily of ex-
and masticatory muscles, for example, could have no effect on dentofacial growth and form. The solutions that the functional matrix hypothesis presumes to provide relate not only to the factors regulating normal dentofacial growth, but also the efficient causes of abnormal growth and, by implication, the effects of appropriate treatment approaches to correct abnormal craniofacial growth (Moss, 1981, 1997a,b). The clearest example of this can be found in the general treatment approach of functional appliance therapy designed to "activate" the orofacial and masticatory muscles and to correct abnormal muscle function in order to "normalize" dentofacial growth (Andresen, 1936).

Serious debate during the 1960s and 1970s about the functional matrix hypothesis was considerable, primarily because it was antithetical to the established thinking of the genomic paradigm. As such, the functional matrix hypothesis presented an entirely new way to consider craniofacial growth (Carlson, 1985). In general, most of the criticism by thoughtful investigators was directed primarily at only two general points. First was what appeared to be unnecessarily ambiguous terminology and reliance on overly simplistic assumptions about "function." Second was the very extreme position taken by Moss with respect to the role of the cephalic cartilages on the growth of the craniofacial skeleton (Johnston, 1976). In these respects, the basic tenets of the functional matrix hypothesis and the ensuing arguments are reminiscent of the classic "nature-nurture" controversy and of the issues of "form-function" and "intrinsic-extrinsic" that were discussed previously.

Since its inception in the 1960s, the functional matrix hypothesis has been an evolving concept that warrants reconsideration and revision with the emergence of advances in science (Moss, 1997a). This is especially true in light of interpretations of recent advances in molecular biology and genetics. For example, as stated by Moss (1995):

Unfortunately... achievements in molecular biology in general, and molecular genetics in particular, often act as conceptual impediments to a correct comprehension of... the 'cause-effect' relationship exhibited in all aspects of craniofacial growth and development, normal as well as abnormal... Succinctly, many workers are caught up in a reductionistic genomic hypothesis; that is, they uncritically assume... that all of the developmental processes involved are unquestionably under direct genomic ("genetic") control.
Carlson

colleagues demonstrated that the growth of the mandibular condyle is highly adaptive and responsive to both extrinsic systemic factors and local biomechanical and functional factors, due primarily to the nature of secondary cartilage (Petrovic, 1974, 1984, 1986, 1991; Petrovic and Stutzmann, 1977, 1986, 1991; Petrovic et al., 1975, 1981a, 1981b, 1985a, 1985b; Stutzmann, 1979; Stutzmann and Petrovic 1979, 1990). Additional research by Stutzmann and Petrovic (1976) led to the conclusion that the growth of the primary cartilages of the craniofacial complex, such as the cranial base and nasal septum, could be influenced significantly less, especially by local functional factors.

The servosystem theory relies on the vocabulary of cybernetics in the development of a parsimonious model of the growth of the craniofacial complex. Most simply, the servosystem theory is characterized by two principal factors: (1) the hormonally regulated growth of the midface and anterior cranial base, which provides a constantly changing reference input via the occlusion, and (2) the rate-limiting effect of this midfacial growth on the growth of the mandible. While growth of the mandibular condyle and of the sutures may be affected directly and indirectly by systemic hormones, growth of these structures is clearly more compensatory and adaptive to the presence of extrinsic factors, including local function as well as the growth of other areas of the craniofacial complex.

The servosystem theory attempts to account for a very large and complex number of interrelated factors in the growth of the craniofacial complex, including: primary cartilage, the muscles of mastication, the tongue, sutures, growth and sex hormones, and neural proprioception among others. Reduced to its most fundamental principals, however, the servosystem theory can be summarized as follows. First, the midface grows downward and forward under the primary influence of the cartilaginous cranial base and nasal septum, influenced principally by the intrinsic cell-tissue related properties common to all primary cartilages and extrinsically by the endocrine system. As it does so, the maxillary dental arch is carried into a slightly more anterior position, resulting in a minute discrepancy between the upper and lower dental arches. It is the resulting occlusal discrepancy that constitutes what Petrovic calls the "comparator," i.e., the constantly changing reference point between the positions of the upper and lower jaws. Second, proprioceptors within the periodontal regions and temporomandibular joint perceive the occlusal discrepancy and tonically activate the muscles responsible for mandibular protrusion (i.e., the lateral pterygoid
larly, modern developmental molecular biology also began a major conceptual change in the early 1980s, with new discoveries relating to the role of neural crest cells (LeDouarin, 1983; Gans and Northcutt, 1983; Noden, 1983) and regulatory genetic factors in the development of mammals and of homeobox genes in the development of *Drosophila* (Lawrence, 1992). Subsequently, with the discovery of homologous homeobox and *Hox-like* genes in the mouse, molecular and genetic research focusing on the development of the craniofacial complex in mammals virtually exploded. As a result, many now believe that “Development of new technologies and their application in novel strategies . . . have generated new paradigms; determining the mechanisms controlling craniofacial development is no longer the intractable problem it was once thought to be” (Thorogood, 1997).

Homeobox genes, or Hox genes, contain highly conserved sequences of DNA comprised of 180 nucleotides that encode for 60 amino acids (homeodomain proteins). It now is understood that certain transcription factors and signaling molecules that regulate expression of other genes during development contain sequences whose expression is critical during early prenatal development of a number of craniofacial structures (Hunt et al., 1991, 1995; Thesleff, 1995). In particular, homeobox genes appear to express regulatory factors that control such basic properties as development of body plan and the presence, absence, and position of key elements of the body, including in particular areas associated with the rostral part of the central nervous system and craniofacial complex. In essence, within the context of the operon theory, the homeobox and other *Hox-like* regulatory genes can be considered as candidates for the master switches regulating development of fundamental elements associated with the presence and appearance of major body structures, such as those found in the craniofacial and dental region.

Since the discovery of Hox genes in vertebrates less than a decade ago, there has been an explosion of research on the developmental biology of the craniofacial complex (see reviews by Richman, 1995; Richman and Mitchell, 1996; Winter, 1996). Emphasis here has been placed primarily on the genetic screening of abnormal and mutant phenotypes, mapping of gene defects to specific homeobox domains, and development of animal models either lacking specific genes (*i.e.*, knockouts) or overexpressing genes (*i.e.*, transgenics) for key transcription and growth factors. With these tools, it then becomes possible to investigate the actual genetic mechanisms that regulate cellular ac-
very beginnings of what would become their modern understanding. Transmission genetics, which focused on a population approach to genetic traits and inheritance of complex traits, was most prominent within the field of genetics, and the linkage between the fields of heredity and embryology was just emerging to initiate the discipline of developmental genetics. There was no real knowledge of the nature of the gene, nor of the mechanisms of gene action. Rediscovery of Mendel’s experiments led to significant advances with respect to ideas about the mathematical laws by which traits were inherited. However, what traits were inherited, the specific particles of their inheritance, and how these particles acted to control or regulate the development of phenotypic traits were all unknown.

During the 1940s as the sutural theory became widely accepted, developmental genetics was in its infancy. At this point in time, the principals of transmission genetics were combined with concepts in embryology by Waddington and others to develop hypotheses about how genes might act to influence development of specific, usually discrete, phenotypic traits. Primarily using Drosophila, Waddington put forward ideas about gene regulation, ontogenetic adaptation, canalization of development, and the origin and assimilation of traits into the genome that formed the foundation for future advances; but these concepts were difficult to extend in specific fashion to other complex organisms, such as vertebrates. It is unclear how these experiments and even their underlying conceptual approaches could have influenced the concepts put forward in the sutural theory, except to invoke some vague and incomplete notion of inheritance of complex traits.

The nasal septum theory arose at a point in time when the structure of the gene and a concept for gene action, the operon theory, initially were described. Looking back, with these discoveries it was now possible, at least, to conceive of how genetic information could be encoded to result in developmental pathways leading to a specific phenotype that was passed between generations. Moreover, with its focus on the relatively immutable nature of cartilage growth, the nasal septum theory could have emphasized specific locations, primary growth centers, at which the genes for craniofacial growth might be expressed. However, even here it was unclear exactly what was being inherited. Was it the exact size and shape of the face? Did the genes act up until a certain point of development, as did the nasal septal cartilage, and then cease to influence growth and form? These are virtually the same questions that troubled T.H. Morgan decades before, in 1926.
of the functional matrix hypothesis, but did so with the obvious caveat that not all craniofacial tissues are alike in their ability to express intrinsic growth potential and to respond to functional, epigenetic, extrinsic factors. In this respect, without explicitly stating so, the servosystem theory addressed the expression of genes influencing the growth and adaptability of cells and tissues comprising the craniofacial complex.

Now, with the very recent initiation of a revolution in developmental genetics upon us, craniofacial biology is on a new threshold of research and discovery that already has affected scientific understanding of normal and abnormal craniofacial growth. There also can be no doubt that the emerging discoveries about the nature of the genome and of the specific action of the genes in the regulation of craniofacial development will continue at an unparalleled pace. In the relatively near future, the human genome will be mapped in its entirety. Basic scientists and clinicians alike will be able to identify the specific genetic factors that cause, at least in part, development of significant craniofacial dysmorphologies; and they will be able to point to the location of the genes responsible for these factors on the chromosome. A central question now is: How will these discoveries directly affect concepts and approaches to the treatment of abnormal or at least undesirable craniofacial growth and form in growing children?

GENETICS, CRANIOFACIAL BIOLOGY, AND ORTHODONTICS IN THE NEW MILLENIUM

For nearly all of the past 150 years, from the late nineteenth century through the 1980s, craniofacial growth research and orthodontics were completely consonant in their overall primary goals—to understand the mechanisms and specific factors that influence the growth of the craniofacial complex so that they might be used to improve treatment of dentofacial deformities. By the late 1980s and through the present time, the emphasis of much of craniofacial research shifted to a focus on morphogenesis, with concomitant emphasis on the methods of basic developmental genetics. As a result, there has been, over the past two decades, an unfortunate trend toward a separation between scientists interested in the basic mechanisms of morphogenesis, on the one hand, and clinically oriented craniofacial biologists and orthodontists interested in postnatal craniofacial growth, treatment, and growth modification, on the other. It may be argued that the scientific foundation of
toward morphogenesis and mechanisms of prenatal craniofacial development. Classical descriptive embryology gave way to experimental studies of cell and tissue interactions during development. The role of the neural crest population of cells in craniofacial development and of the factors influencing their migration and differentiation became primary areas of interest and research activity. The general area of teratology became focused on specific factors, such as retinoids, corticosteroids, vitamins, and ethanol, as developmental insults with specific effects on cell-tissue interactions and regulation of downstream developmental processes. Increasing numbers of specific regulatory factors, such as the family of transforming growth factors and homeobox genes, were discovered in mammals to have relatively discrete and highly significant effects on the morphogenesis and development of the craniofacial complex. Unfortunately, however, it is not immediately apparent how this emphasis on morphogenesis and mechanisms of prenatal development, while critically important for understanding the etiology of craniofacial anomalies and genetic syndromes, might relate to orthodontic treatment of a growing child. In particular, how does this relate to the possibility of modification of craniofacial growth?

As we move into the new millennium, at least three issues would seem to be clear as they pertain to craniofacial development and growth and to the possibility of modification of craniofacial growth. First, there is no question that there are a number of genetically encoded regulatory factors that have profound effects on the morphogenesis and prenatal development of the craniofacial complex. Second, it is clear that all of these factors operate within an epigenetic milieu, from the level of the position of genes on the chromosome to the interaction of cells and entire organisms with the external environment. Genes are turned on and off by factors both within and outside the genome. Third, there is no question that the morphogenesis, prenatal development, and postnatal growth of the craniofacial complex can be modified. There is a plethora of evidence from experimental embryology, teratology, and functional morphology to support this conclusion. However, this does not necessarily mean that craniofacial growth can be modified in a predictable, controlled, and clinically efficacious way. Major issues that must be considered regarding clinical efforts at craniofacial growth modification are: (1) What are the biological targets of treatment in the attempt to modify craniofacial growth, i.e., where is the growth-related problem located—in the midface, the mandible, the
tators that turn on regulatory genes and other morphogenetic factors improves, treatment of specific growth discrepancies will be precisely targeted, using orthopedic approaches alone or in combination with systemic and local interventions.

Scientists have made incredible headway in the understanding of the principles and regulatory mechanisms of craniofacial morphogenesis. During the coming decade or more, these same principles will be extended to the craniofacial complex postnatally, and we will see a further understanding of the processes and mechanisms of craniofacial growth specifically as they pertain to prospects for orthodontic growth modification. The foundation for this prognostication is provided by two fundamental conclusions. First, there is no question that it is theoretically and practically possible to modify the growth of the craniofacial skeleton, just as it is possible to modify skeletal growth elsewhere throughout the body. Second, there is no Holy Grail of craniofacial biology—no single theory of craniofacial growth. The development of the craniofacial region is complex and unique in some respects with regard to the origin of certain tissues and cell-tissue interactions, which makes it an ideal model system for basic research in developmental-molecular genetics. However, like all areas of the body, the craniofacial complex develops, grows, and adapts within an epigenetic milieu that includes both the genes themselves as they are arranged on the chromosome all the way up to broad environmental and functional factors, but within the parameters that are regulated and permitted by the genome. What remains now is to understand the genomic and epigenetic factors influencing the morphogenesis and growth of the craniofacial complex sufficiently that they can be engineered biologically and environmentally, and subsequently introduced into the treatment of individual patients at the appropriate times and in the appropriate measure in order to produce a biologically meaningful and clinically efficacious effect.

ACKNOWLEDGMENTS

This paper is dedicated to the memory of Dr. Robert E. Moyers on the occasion of the 25th anniversary of the Robert E. Moyers Symposium on Craniofacial Growth. I have been fortunate to have three principal mentors during my academic career, each of whom contributed greatly to the ideas presented in this paper. Ideas regarding the importance of understanding concepts of history, racial typology, and genet-
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Carlson

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Althought clinical modification of the growth of the bones comprising the maxillomandibular complex is of major interest to orthodontists, this treatment approach has remained controversial since its inception. Three related issues underlie the debate about orthodontic treatment designed to modify growth of the facial skeleton. Each, if true in most circumstances, would call into question the rationale of treatment designed to correct the orthopedic discrepancy via growth modification (ie, phase 1 treatment), whether or not it is followed by orthodontic correction of the occlusion (ie, phase 2 treatment). First, there is an ingrained assumption that growth of skeletal tissues generally cannot be altered in any clinically meaningful way, at least not by conventional fixed or functional orthodontic appliances. Second, clinical orthodontic experience and more formal studies, often using very different treatment approaches, times of onset and duration, and patient samples, have produced disparate outcomes. Third, there are significant concerns about the validity of the diagnostic criteria used to identify many true growth-related jaw discrepancies at an “early” age, especially in children who are believed to be otherwise normal.

This summary is a brief review of the biological foundation for consideration of early orthodontic treatment, with particular emphasis on growth modification to correct dentofacial deformities. Four areas are addressed: (1) the general processes of ontogeny, (2) the principles of ontogeny as they relate to understanding the potential for growth of sutures and the mandibular condyle, (3) the implication for dentofacial growth modification, and (4) future directions for research and clinical applications relating to orthodontic-orthopedic treatment of dentofacial deformities. Many of the concepts discussed here are developed more fully in monograph no. 35 of the Craniofacial Growth Series.1

Processes of ontogeny

Ontogeny—the life history of a person—can be considered at cellular through organismal levels in terms of the coordination and integration of the processes of development, growth, and adaptation (Fig 1). Development is a lifelong process that effectively begins with differentiation and ends with maturation. Once cells have differentiated, the process of growth leads to an increase in size and mass of tissues and organs through cellular activities. Adaptation refers to the potential for developmental plasticity and compensatory growth throughout the lifespan.

Considerable variation exists in the timing of the development of entire systems and their respective organs during ontogeny. Of particular note for craniofacial growth, the central nervous system and the associated neurocranium are very precocious in their development and growth, completing approximately 80% of total growth by 6 to 8 years of age. However, the midface and the mandible tend to follow a general or somatic growth curve similar to the skeletal growth of the limbs and, by age 8 to 10, have completed only about 50% of their total cumulative growth. Thus, the midface and the mandible have a considerable amount of their total growth remaining between the ages of 10 and 20 years; this makes it at least feasible to have a significant treatment impact on final size during that time period. Skeletal growth also is characterized by a significant decrease in rate beginning during the last
trimester of the fetal period and a hormonally mediated pubertal growth spurt during adolescence\(^2\) (Fig 2). Considerable research on facial growth in relation to the pubertal growth spurt in untreated persons and treated patients clearly indicates the significance of this period for orthodontic-orthopedic treatment.\(^3\)\(^\text{-8}\)
Growth potential of sutures and condylar cartilage

Critical to the process of organogenesis is the presence of precursor cells, which are undifferentiated mesenchymal stem cells. In some tissues, such as striated muscles, neurons, and glands, once the cells have differentiated and the tissue is functionally mature, significant populations of precursor cells are no longer available for tissue renewal and growth. However, skeletal tissues continue to have access to a ready supply of precursor mesenchymal cells throughout life through a specialized tissue—the periosteum.

The ontogenetic concordance among the periosteum, the sutures, and the mandibular condyle has been known for decades. Simply stated, the inner osteogenic layer of the bilaminar periosteum is homologous to the osteogenic tissue within sutures and the prechondroblastic-proliferative layer of the mandibular condyle. Proliferation of sutural tissue that will add to the advancing bone fronts while also contributing to suture maintenance and eventual synostosis is influenced during fetal development and the early postnatal stage by a variety of growth factors, including the TGF-β family and FGF-2. 9 In the mandibular condyle, mesenchymal cells in the prechondroblastic-proliferative layer differentiate into cartilage cells (membrane derived secondary cartilage), which then mature and are replaced by osteoblasts at the advancing bone front. Like sutures, the development and growth of the mandibular condyle are affected by the expression of a number of growth factors and signaling molecules and their receptors. Moreover, under controlled experimental conditions in postnatal animals, orthopedic appliances may have a significant effect on the rate and amount of growth of the condylar cartilage, and on the expression of specific growth factors. 10,11

Based on available biological evidence, it is clear that both sutures and the mandibular condylar cartilage can best be characterized as specializations of the periosteum, which is the essential element of intramembranous growth of skeletal tissues throughout ontogeny. Periosteal growth throughout the skeletal system can be greatly influenced by biomechanical factors, undoubtedly because of the effect of molecular mediators of differentiation of precursor cells into bone and cartilage, cartilage cell growth and maturation, and endochondral ossification. Also, the specific factors that might stimulate sutural and condylar growth, and therefore their potential to produce clinically meaningful outcomes, vary significantly throughout ontogeny and basically conform to the overall growth rate curve for skeletal tissues. As a result, although the local functional-biomechanical environment may be a significant factor in the process of adaptive, compensatory growth at certain stages of development, the actual potential for growth and adaptation of sutures and condylar cartilage should be expected to vary throughout the lifespan.

Implications for the modification of facial growth

Based on available biological evidence, there is no doubt that the growth of the skeletal tissues of the maxillo-mandibular complex can be modified with respect to amount and direction. However, this does not necessarily mean that the most significant questions and problems concerning the clinical efficacy of orthodontic-orthopedic treatment to correct a developing dentofacial deformity in individual patients have been solved. On the contrary, it may very well be that conventional orthodontics, including functional appliance treatment, may have reached (some might say exceeded) the limit of its ability to predictably influence facial growth. It is now necessary for craniofacial biologists and clinical orthodontists to take the principles of modern developmental biology as they emerge and target them toward specific therapeutic goals. With this in mind, the essential questions concerning modification of facial growth that should be addressed from both biological and clinical perspectives are as follows:

1. To what extent can facial growth and form be modified?
2. What is the best time to intervene, and for how long?
3. How feasible, effective, and predictable are specific treatment approaches with respect to modification of facial growth and form?

The phenotype of the craniofacial complex is a result of the combined effects of the genome and the intrinsic and extrinsic environment. As a result, the craniofacial phenotype in anyone comprises 2 general factors: (1) morphologic form and, (2) closer to the genome, the molecular factors whose presence and amounts regulate patterning of form and cellular growth. Assuming a basic pattern for normal craniofacial form, variation in craniofacial morphology is the result of subtle differences in the growth of the craniofacial tissues, including their ability to express intrinsic growth factors and to adapt to extrinsic fluctuations.

The orthodontic patient population represents a continuum that can be divided for heuristic purposes into 3 groups according to overall phenotype. These groups are characterized not only by morphology but also, and more importantly, by the presence, amount, and timing of their expression of signaling molecules and growth factors (Fig 3). At 1 extreme are abnormal patients who have at least 1 known or unknown defective gene that typically results in a definitive
malformation or dysplasia. In these people, the craniofacial phenotype is primarily the result of an intrinsic, genetic abnormality that affected the ability of certain cells, tissues, and structures to develop, grow, and adapt. Therefore, it should be expected that patients with abnormal genes affecting craniofacial tissues might not be capable of exhibiting a normal and predictable response to efforts to modify facial growth positively. At the other extreme of the orthodontic patient population are normal patients. This subgroup includes children who are normal genomically, but whose craniofacial phenotype may include a mild-to-moderate malocclusion and a minor skeletal jaw discrepancy. Efforts to achieve complete correction of the dental malocclusion and the jaw alignment in normally growing patients with conventional methods of orthodontic-orthopedic treatment are likely to be routinely successful, mainly because they have all the necessary molecular ingredients at the appropriate times.

The segment that is most difficult to characterize specifically, but that surely makes up a large percentage of an orthodontic practice, may be labeled the clinical patient population. The clinical patient population overlaps the abnormal and the normal segments and comprises patients who appear completely normal other than their undesirable craniofacial phenotype. However, these patients may be normal genomically but may tend to express unpredictable variations in growth responsiveness of the ontogenetic processes. According to this conceptual model, for example, subjects in the clinical patient pool may possess polymorphisms of normal genes for key signaling molecules and growth factors that limit the ability of the cells and tissues to respond in an expected way to dentofacial orthopedic treatment. Identifying patients who clearly have extreme craniofacial anomalies due to genetic abnormalities may be a challenge in some cases. Far more challenging, however, is the identification and the proper assessment of those in the clinical patient population who express intrinsic variations that may have major significance for the success of orthodontic-orthopedic treatment.

**FUTURE DIRECTIONS**

The most productive and important future directions for orthodontics as a specialty and for the possible treatment of orthodontic-orthopedic treatment of dentofacial deformities through growth modification will come from an amalgamation of the emerging principles of developmental biology with clinical treatment goals.

Within the past decade, an explosion of discoveries in developmental biology and genomics has direct relevance to understanding the development, growth, and adaptation of craniofacial skeletal tissues. Extensive research continues on early patterning and development of craniofacial form. Central to that effort is identifying and understanding the role of key intrinsic and extrinsic factors that influence gene expression and cell growth during the development of the craniofacial complex. That line of investigation is leading to major discoveries directly relevant for understanding and preventing certain types of craniofacial anoma-
lies.\textsuperscript{15-17} In the future, craniofacial research will focus more and more on the role of signaling molecules and growth factors as they interact with the environment, including biomechanical factors, with respect to postnatal craniofacial growth and treatment—a subject that is central to the field of orthodontics.

Once greater understanding of the molecular mediators of the growth and adaptation of skeletal tissues in the craniofacial regions and of their normal pattern of expression during the lifespan has been achieved, it will become possible to develop treatment methods to target specific tissues and time periods for growth modification. Initial progress in this therapeutic approach will most likely center on diagnostic methods to determine very precisely the developmental status of the patient and whether he or she possesses particular isoforms of key molecular mediators necessary for cell development and growth in specific regions of the craniofacial complex. Subsequent developments in this area may lead to local targeting of molecular mediators, quite likely in conjunction with conventional orthodontic-orthopedic approaches to modify facial growth and prevent or correct a developing dentofacial deformity.

**CONCLUSIONS**

1. The capability of cells, tissues, and organs to adapt via normal growth processes is greatest early in development and diminishes as maturation is approached.

2. The capability of the craniofacial skeleton to respond positively to orthodontic-orthopedic treatment depends on a number of factors, including:
   a. The availability of precursor mesenchymal stem cells (type of tissue)
   b. The capability of expression of growth factors (developmental age and sex)
   c. The local environment (treatment mechanics and duration)

3. The future of orthodontic-orthopedic treatment of dentofacial deformities will see an increased emphasis on the gene therapy combined with mechanotherapy.
   a. Molecular-genetic techniques will be used to determine the developmental status of patients by assessing the presence or absence and the characterization of genetic polymorphisms of key molecular mediators of growth.
   b. In the more distant future, methods will be developed for targeted use of molecular media-

**REFERENCES**


Theories of Craniofacial Growth in the Postgenomic Era

David S. Carlson

The controversies surrounding the use of dentofacial orthopedics to correct a developing maxillomandibular discrepancy—ie, growth modification—have been based to a large extent on evolving concepts concerning the biological mechanisms of craniofacial development and growth. At the start, these concepts were based on naive assumptions about the perceived competing roles of heredity and the environment, often framed within the context of the age-old "nature-nurture" controversy. Moreover, orthodontists and craniofacial biologists alike tended to believe that there was a single, overriding mechanism governing the growth of the craniofacial skeleton. As a result, much of the orthodontic research on the growth of the face and jaws tended to focus on a search for what might be called the "Holy Grail of Craniofacial Biology": a single theory of craniofacial growth that is both biologically accurate and clinically effective. This article traces the development of competing concepts and theories of craniofacial development and growth and relates these theories to concomitant developments in the field of genetics. The overall conclusion is that orthodontics is well-positioned to enter a new era through the incorporation of the principles of developmental-molecular genetics into the treatment of developing malocclusion and growth-related jaw discrepancies.

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Throughout its history, the field of orthodontics has been home to a number of competing but credible treatment approaches. Despite their obvious differences, virtually all these orthodontic approaches share at least one fundamental characteristic: their rationale is based on opinions regarding the biological mechanisms of the development and growth of the craniofacial skeleton and dentition, and on the etiology and natural history of malocclusion and dentofacial abnormalities. The foundation for some orthodontic treatment approaches emerged as long as 50 or even 100 years ago, well before the present level of sophistication with respect to biological research. Thus, it stands to reason that they may be based in part on incomplete or even archaic and incorrect understanding of the biological principals of development. Nevertheless, the apparent success of orthodontic treatment using techniques that appear to be very disparate in approach is noteworthy. Perhaps because of this, many orthodontic philosophies have enjoyed longevity with little necessity for change in the fundamental orientation of their biological rationale.

The goal of this article is to summarize the historical development of the major concepts of the growth of the craniofacial skeleton, with specific emphasis on concomitant developments in the field of genetics. The primary thesis is based on three principal arguments that were put forward in an earlier related paper. First, is the assertion that the various theories of craniofacial growth propounded over the past century or more are based primarily on incomplete and even erroneous assumptions about the nature of heredity and inheritance of skeletal and craniofacial growth. Second, it is maintained there was a significant lag time between discoveries in the emerging field of genetics and the incorporation of these discoveries into concepts of craniofacial growth modification and dentofacial orthopedics. Third, despite these apparent drawbacks, orthodontics is well-positioned to enter a new era through the incorporation of the principles of developmental-molecular genetics into the treatment of developing malocclusion and growth-related jaw discrepancies.

Early Concepts of Craniofacial Growth, Orthodontics, and Genetics

During the latter part of the 19th century and the middle third of the 20th century, the field of craniofacial biology
witnessed development of a series of four or five relatively distinct, sequentially arranged, and competing theories of craniofacial growth. Each of these theories purported to explain the essential elements of craniofacial growth by focusing essentially on a particular factor as being the primary causal mechanism determining craniofacial growth and form. At the same time, the field of genetics was emerging from an emphasis on Mendelian concepts of transmission of units of inheritance between generations to an emphasis on the actions of genes and specific gene products during the developmental process.

Orthodontics, Race, and the Concept of Facial Type

The earliest foundations of modern orthodontics are intimately related to classical concepts of beauty, ideal facial form, and facial types. In fact, it was one of the world’s most renowned classical statues, Apollo Belvedere, that was used by both Edward Angle in 1907 and by Andresen 30 years later to represent ideal facial form. Artistic representations of facial form throughout the ages both reflected and reinforced early scientific concepts of discrete racial groups and social hierarchy. Moreover, these representations also were intertwined directly with emerging concepts of facial growth. According to the view shared by artists and scientists alike, faces could be classified into relatively discrete “types” that, unfortunately, reflected opinions regarding both biological and social inferiority. Among scientists and naturalists during the late 19th century and first half of the 20th century, classification of facial types was based on prevailing concepts of human races, which were believed to be pure and immutable. It was within this conceptual framework that Angle put forward the concept that “faces and occlusions should be brought into a condition of harmony according to type” (emphasis added). According to Angle and his many followers, the goal of the treatment of malocclusion was to place teeth in the most harmonious position possible for a given facial type, thus compensating for an unchangeable facial form.

This theme of the inheritance and immutability of both normal and abnormal facial form was generally accepted by most members of the community of orthodontics and early craniofacial biologists. According to Sir Arthur Keith, the most prominent anatomist of the era, orthodontists have “…endeavored in their treatment to increase the maximum amount of bony tissue that nature has preordained, rather than to straighten the amount already predetermined” (emphasis added). More than 20 years later, Brodie stated the same view, asserting that facial growth “cannot be changed by treatment. The teeth and the alveolar process constitute the only area of the face whose change may be expected or induced” (emphasis added).

By the end of the first half of the 20th century, the field of orthodontics in the United States was dominated by the theme stated initially by Angle and reiterated by Brodie that craniofacial growth could not be altered in any significant way. Thus, the primary role of the orthodontist was to treat a malocclusion by moving teeth into a more harmonious position relative to the facial type; facial growth could not be affected by orthodontic treatment.

Bone Growth and Heredity

Studies by Sir John Hunter in the 18th century on the growth of the jaws and eruption of the dentition represent the first scientific research on craniofacial growth. This line of research using vital dyes continued throughout the late 19th and early 20th centuries primarily to study the nature of bone growth in general. This approach culminated in the research of Brash, which solidified understanding that bone only grows appositionally at its surfaces—bone does not grow interstitially through mitotic activity of osteocytes.

1930s: Remodeling Theory of Craniofacial Growth (Brash)

The research by Brash on bone provided the foundation for the development of the first general theory of craniofacial growth—the remodeling theory. The principal tenets of the remodeling theory were that (1) bone only grows appositionally at surfaces; (2) growth of the jaws is characterized by deposition of bone at the posterior surfaces of the maxilla and mandible, sometimes described as “Hunterian” growth of the jaws; and (3) calvarial growth occurs via deposition of bone on the ectocranial surface of the cranial vault and resorption of bone endocranially (Fig 1). Thus, the remodeling theory postulated that all of craniofacial skeletal growth occurs exclusively by bone remodeling—selective addition and resorption of bone at its surfaces; sutures and the cartilages of the craniofacial skeleton have little or no role in the growth of the craniofacial skeleton.

Heredity, Genetics, and the Gene

The concept that morphological traits were somehow transmitted between successive generations of living organisms has been understood for thousands of years. However, the
mechanisms by which traits are transmitted, the nature of the units of heredity, and the mechanisms of action by those units were not initially understood until the beginning of the 20th century. Mendel (1822-1884) is credited with performing benchmark research for much of genetics, but especially for questions regarding the mechanisms of inheritance and transmission of traits by demonstrating that specific traits were passed between generations in a particular, discrete manner from both parents according to a set of mathematical principals.

Of the many ideas regarding the material substance that carried the message for development of specific traits—i.e., the units of heredity—Weismann's concept of the germ plasm (Das Keimplasm) in the late 19th century was the most influential. According to this idea, determinants that contain the traits inherited from parents to offspring are located in the cytoplasm (germ plasm) of the gametes. Weismann further asserted that the germ plasm is immutable—it cannot be altered by life experiences. Weismann's term determinant was replaced by pan gene to describe particular units described mathematically by Mendel, and was then replaced again in 1909 by Bateson, who introduced the term genetics as the study of heredity. Johannsen then used the term gene to refer to the presumed unit of heredity, which provided the developmental ‘potentiality’ of the organism.

From this time forward, the field of genetics was characterized by two principal foci. Transmission genetics was based in the Mendelian Laws of Inheritance and was characterized by a statistical approach that required no understanding of the nature of genes or their expression. As a result, transmission genetics was of little help or consequence for the study of development and growth. The second focus within the new field of genetics concerned the nature of the gene itself and the mechanisms of gene action during development. It was these related emphasis that gave rise to modern developmental biology and the molecular biology of the gene.

Beginnings of Developmental Genetics
Analysis of the role of the gene in development began in earnest with the publication of Morgan's classic book The Theory of the Gene in 1926. Although, the tools necessary to investigate the nature of gene action would not be available until the rise of molecular biology almost 50 years later, numerous highly significant advances took place during the 1930s and 1940s that would have a profound impact on future discoveries in developmental molecular biology. In particular, research by Waddington clearly established the linkage between embryology and genetics by proposing to think of genes as organizers and "evocators" of development.

The Role of Sutures and Cartilage in Craniofacial Growth
The remodeling theory of craniofacial growth, which emphasized the role of differential deposition and resorption in the growth of the craniofacial skeleton, derived principally from competing hypotheses about the nature of bone growth in general, and not about the process of craniofacial growth per se. As experimental studies indicated that periosteal deposition plays a significant role in the growth of the craniofacial skeleton, it was assumed that remodeling played the preeminent role in this regard. However, this left unanswered the concern of many craniofacial biologists in the middle part of the 20th century, that is, the role that unique structures, such as sutures, cranial base synchondroses, and the mandibular condylar cartilage, provide in the growth of the craniofacial skeleton. If these obvious sites of bone growth are not essential for normal craniofacial growth, then why are they present at all?

An alternative viewpoint emphasized the passive, secondary role of the periosteum and bone surfaces in skeletal growth and the primary expansive growth of cartilage in the production of skeletal growth and form. The veracity of this view was reinforced by experimental research demonstrating that earlier studies of bone remodeling within the craniofacial skeleton by Brash had used an inappropriate experimental design with respect to the choice and age of the animal model, which led to erroneous conclusions about the importance of bone remodeling in craniofacial growth.

1940s: The Sutural Theory (Weinmann and Sicher)
The sutural theory is most closely identified with the work of Weinmann and Sicher, two prominent anatomists whose textbooks on skeletal growth, Bone and Bones and Oral Anatomy, became standard texts for medicine and dentistry. According to the sutural theory, the connective tissue and cartilaginous joints of the craniofacial skeleton, much like epiphyses of long bones, are the principal locations at which intrinsic, genetically regulated, primary growth of bone takes place. Growth of the cranial vault is caused by the intrinsic pattern of expansive proliferative growth by sutural connective tissue that forces the bones of the vault away from each other (Fig 2); indicating "the primacy of sutural growth for the determination of adult skull form . . . " Similarly, proliferation of sutural connective tissue in the circummandibular suture system surrounding the maxillary skeletal complex forces the midface to grow downward and forward. Thus, "the role of proliferating sutural connective tissue in cranial growth . . . is identical to that of the proliferating cartilage in basal synchondroses." The mandible was perceived as essentially a bent long bone, with the mandibular condylar cartilage being equivalent to the epiphyseal plates of long bones whose growth forces the mandible downward and forward, away from the cranial base, during normal ontogeny.

The sutural theory accounted for two major factors that were difficult to resolve within the remodeling theory. First, it was consistent with the established fact that periosteal remodeling of bone is under strong local influences by the functional environment, and thus is unlikely to be under strong intrinsic, hereditary control. Second, the sutural theory was consistent with the contemporary understanding of the importance of cartilaginous structures and skeletal joints.
in the development and postnatal growth of bones. The sutural theory also reinforced the concept that growth of the face and jaws was essentially immutable. Sutures as well as the cartilages of the craniofacial skeleton were the locations of centers of bone growth at which the inherited, immutable pattern of craniofacial form and facial type, however determined, was expressed.\textsuperscript{10}

**1950s: The Nasal Septum Theory (Scott)**

Like the remodeling theory before it, the sutural theory also appeared to have numerous inconsistencies. For example, it had been known for centuries that a variety of major disorders involving the developing central nervous system have major effects on the development and growth of the cranial vault. Second, it was understood that the development of the bones of the cranial vault and face have no direct cartilaginous precursor, unlike bones elsewhere in the skeletal system. Third, a major source of contention within craniofacial biology during the late 1940s and early 1950s was the description of the histomorphology of the developing and growing suture. According to Weinmann and Sicher, for example, the growing suture is roughly equivalent to cranial base synchondroses and epiphyseal growth plates.\textsuperscript{39} An alternative analysis of early suture development and growth by Scott and colleagues asserted that the osteogenic layers within the suture are actually continuations of the peristeum and dura within the cranial vault and of the periosteum in facial sutures.\textsuperscript{39,40} Thus, suture growth should be considered more properly as a specialized form of periosteal growth rather than analogous to cartilaginous growth. Finally, several experimental studies involving vital dyes\textsuperscript{39} and surgical manipulation\textsuperscript{41,42} of cranial sutures in an appropriate animal model clearly demonstrated that although sutures were major sites of craniofacial skeletal growth, they played no determining role in that growth.

Each of these lines of evidence led many investigators to question the validity of the sutural theory. Concomitantly, the Irish anatomist, James H. Scott, proposed an alternative explanation, the nasal septum theory, as the single and unified theory of craniofacial growth.\textsuperscript{43-45} According to the nasal septum theory, sutures play little or no direct role in the growth of the craniofacial skeleton. Rather, sutures are merely permissive, secondary, and compensatory sites of bone formation and growth. Primarily through comparative histological analysis, Scott concluded that the nasal septum is most active and important for craniofacial skeletal growth late prenatally and early postnatally, through approximately three to four years of age in humans. During that time, the anterior-inferior growth of the nasal septal cartilage, which is buttressed against the cranial base posteriorly, "drives" the midface downward and forward (Fig 3). The cranial base synchondroses, which are analogous to epiphyseal growth plates, were thought to have a longer lasting effect on craniofacial growth. Finally, Scott asserted that the cartilage of the mandibular condyles behaves similarly to cranial base and nasal septal cartilages, and directly determines the growth of the mandible as its "pushes" the mandible downward and forward.

Numerous descriptive and experimental studies were conducted during the 1950s and 1960s addressing both the sutural theory and the nasal septum theory of craniofacial growth. Through these studies, it became clear that sutures are, in fact, secondary sites of bone growth that are highly responsive to expansion of the contents of the cranial vault and to functional and orthopedic manipulations of the growing maxillary complex. Similarly, numerous experimental studies of the role of the nasal septal cartilage during early postnatal growth confirmed that normal growth of the nasal septal cartilage is extremely important for growth of the maxillary skeletal complex. However, the experimental designs at that time, which most often involved excision or otherwise gross disruption of the nasal septal cartilage, were relatively crude. Thus, the profoundly detrimental effects on the

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*Figure 2* Schematic representation of the sutural theory of craniofacial growth using the cranial vault as a model. Increase in the size of the cranial vault takes place via primary growth of bone at the sutures, which forces the bones of the vault away from each other. Growth of the midface takes place via intrinsically determined sutural expansion of the circummaxillary suture system, which forces the midface downward and forward. Mandibular growth takes place via intrinsically determined growth of the cartilage of the mandibular condyle, which pushes the mandible downward and forward.

*Figure 3* Schematic representation of the nasal septum theory of craniofacial growth. Growth of the nasal septal cartilage pushes the midface downward and forward relative to the anterior cranial base. This results in a separation of the midfacial suture system, which then fills in via secondary, compensatory sutural bone growth.
growth of the midface reported in many studies were almost always open to the criticism of surgical or other artifact. 46

It is important to note that the fundamental dialectic between the remodeling theory and the sutural theory, and then between the sutural theory and the nasal septum theory, is essentially the same. The issue was not whether craniofacial growth and form are strictly inherited; nor was it about whether craniofacial growth could be modified. Based on prevailing concepts about heredity and the gene and about skeletal growth in general, it was generally assumed by all three theories that craniofacial growth is largely inherited, intrinsically genetically regulated, and immutable. The major question was “where does heredity and the genes act—at the sutures; within the cartilages of the cranial base, midface, and mandible; or at all three areas?”

**Structural Basis of the Gene and Gene Action**

Two major breakthroughs in genetics during the 1950s greatly facilitated the ability of biologists to address questions of gene action. The report by Watson and Crick in 1953 that DNA is arranged structurally as a double helix provided a model for the understanding of gene replication and also was a benchmark in the development of techniques of molecular biology essential to the investigation of gene action. Second, the operon theory of Jacob and Monod provided an explanation for how genes and whole groups of genes operate within common regulatory sequences that can be turned on and turned off to control transcription of mRNA and gene expression. 47 These two essential discoveries led directly to the DNA recombinant technology 25 to 30 years later that forms the foundation of research in the mechanisms of gene action during development.

**Paradigm Shift in Craniofacial Biology (1960-1980)**

The major emphasis of research in craniofacial biology and its clinical application in orthodontics, especially in the United States, during the 1950s and 1960s was on the specific location(s) of the “center(s)” at which the inherited traits determining craniofacial growth and form were actually expressed. 48 Areas of the growing skeleton that exhibit “tissue-separating capabilities,” which included all the craniofacial cartilages that are primarily under the control of heredity, were referred to as growth centers. Locations at which active skeletal growth occurs as a secondary, compensatory effect were defined as growth sites. Growth sites lack direct genetic influence and are influenced by other factors, such as the remote primary growth centers and the environment. Sutures and periosteum were noted as clear and definitive examples of adaptive growth sites. Although this terminology did help to clarify some issues surrounding craniofacial growth research, it did little to resolve the issue of the degree to which and how growth and form of the craniofacial skeleton were determined via heredity. Attention thus focused on the locations within the craniofacial skeleton where the presumptive forces of heredity were active—such as at bone surfaces, sutures, cranial base synchondroses, and the mandibular condyles. The issue was not whether the growth and form of the craniofacial skeleton was inherited through the action of genes, but where is this complex pattern of heredity expressed.

An alternative approach to the presumption of genetic predetermination of craniofacial growth had a long history in Europe, and was especially noteworthy through the research of van der Klaauw. 49 It was Melvin Moss, a dually trained dentist-anatomist, who carried the tradition of van der Klaauw to the United States initially in a classic paper published in the *American Journal of Physical Anthropology* on functional cranioiogy. 50 Moss then extended these concepts to clinical orthodontics as a new theory of craniofacial growth, the functional matrix hypothesis. 51 These two papers were historic, benchmark events for all of craniofacial biology and clinical orthodontics as they established a dialectic not between competing theories, but between competing paradigms of craniofacial growth. 52, 53

Introduced in the early 1960s, at a time when emphasis was on the relative immutability of craniofacial growth and the location of growth centers within the craniofacial skeleton, Moss’ viewpoint was not merely contentious, it was heretical. 52 The functional matrix hypothesis was a principal catalyst of a new way of looking at craniofacial growth, which became known as the functional paradigm. 52 Whereas the genomic paradigm viewed craniofacial growth as primarily genetically predetermined and immutable, the functional paradigm emphasized the plasticity of development and growth of the craniofacial skeleton. Emphasis was placed on understanding the epigenetic interaction of intrinsic and extrinsic factors that result in variations in craniofacial form and on the potential of modification of craniofacial growth and form using the principals of orthodontics and dentofacial orthopedics. The historically older genomic paradigm emphasized the relative immutability of craniofacial growth and form; orthodontic treatment focused on tooth movement to correct malocclusion and to compensate for discrepancies within the maxillomandibular skeleton. The principles of the functional paradigm supported consideration of the use of dentofacial orthopedic techniques to correct a developing malocclusion or facial deformity.

**1960s: Functional Matrix Hypothesis (Moss)**

The basic tenets of the functional matrix hypothesis are simple. 54-59 Fundamentally, the functional matrix hypothesis maintains that, aside from setting into motion the initial process of development, heredity and the genes play no significant deterministic role in the growth of skeletal structures in general and of the craniofacial skeleton in particular. The craniofacial skeleton, like all skeletal structures throughout the body, develops initially and grows in direct response to its extrinsic, epigenetic environment. As stated by Moss, “bones do not grow; bones are grown.” 56 Therefore, to understand the factors that affect bone growth in the craniofacial complex, it is necessary to understand both the local environment...
and the resultant skeletal structure in terms of their functional cranial components.

Functional cranial components are comprised of the following two elements: (1) a functional matrix and (2) a skeletal unit. The functional matrix refers to all the soft tissues and spaces that perform a given function. The skeletal unit refers to the bony structures that support the functional matrix and thus are necessary or permissive for that function. Individual bones defined according to traditional anatomy may be comprised of a number of overlapping skeletal units as the skeletal unit refers not to the individual bone directly, but to the function(s) it supports.

There are two types of functional matrices (Fig 4). The periosteal matrix corresponds to the immediate local environment, typically muscles, blood vessels, and nerves. The capsular matrix is defined as the organs and spaces that occupy a broader anatomical complex. Within the craniofacial complex, the capsular matrix would include such organs as the brain and globes of the eyes, as well as actual spaces such as the nasopharynx and oropharynx.

There are also two categories of skeletal units: (1) microskeletal units and (2) macroskeletal units. Functional variations in the periosteal matrix, such as muscle activity for example, may be locally expressed within the microskeletal unit as tuberosities and processes or ridges for muscle attachment. Growth in size and shape of microskeletal units is typically associated with transformation from an embryonic cell type to an osteoblast-osteocyte associated with periosteal deposition. Changes in the size and shape of macroskeletal units, which include the neurocranium and maxillomandibular complex, are the result primarily of expansion of the capsular matrices and translational growth of associated skeletal structures. According to the functional matrix hypothesis, the craniofacial skeleton does not grow in primary fashion to permit expansion of the soft tissues, organs and spaces comprising the functional matrix. Rather, translation of skeletal units and associated local transformational bone growth of bone tissue occurs secondarily and in compensatory fashion to growth of the functional matrix, and in particular of growth-related expansion of the capsular matrices.

Debate about the functional matrix hypothesis was considerable during the 1960s and 1970s, primarily because it presented an entirely new way to consider craniofacial growth. Most of the criticism was directed primarily at only two general points. First was what appeared to be unnecessarily ambiguous terminology and reliance on overly simplistic assumptions about "function." Second was the very extreme position with respect to the role of the cephalic cartilages in the growth of the craniofacial skeleton.

1970s: Servosystem Theory of Craniofacial Growth (Petrovic)

The last major theory of craniofacial growth to emerge, the servosystem theory, was developed by Alexandre Petrovic, a physician-scientist interested in the extrinsic and intrinsic hormonal factors that affect cartilage growth. As a result of influences by many orthodontists throughout Europe and the North America, Petrovic's research came to focus on the nature of cartilage growth in the craniofacial complex, and especially the growth of the secondary cartilage of the mandibular condyle. Through a comprehensive series of in vitro and in vivo experiments using research approaches that were then state-of-the-art, Petrovic and colleagues demonstrated that the growth of the mandibular condyle is highly adaptive and responsive to both extrinsic systemic factors and local biomechanical and functional factors. He and his colleagues also demonstrated that the growth of the primary cartilages of the craniofacial complex, such as the cranial base and nasal septum, was influenced significantly less by local epigenetic factors.

The servosystem theory relies on the vocabulary of cybernetics to describe the growth of the craniofacial complex. Most simply, the servosystem theory is characterized by the following two principal factors: (1) the hormonally regulated growth of the midface and anterior cranial base, which pro-
vides a constantly changing reference input via the occlusion, and (2) the rate-limiting effect of this midfacial growth on the growth of the mandible. While growth of the mandibular condyle and of the sutures may be affected directly and indirectly by systemic hormones, growth of these structures is clearly more compensatory and adaptive to the action of extrinsic factors, including local function as well as the growth of other areas of the craniofacial complex.

Reduced to its most fundamental principals, the servosystem theory can be summarized as follows (Fig 5). First, as the midface grows downward and forward under the primary influence of the cartilaginous cranial base and nasal septum, influenced principally by the intrinsic cell-tissue related properties common to all primary cartilages and mediated by the endocrine system, the maxillary dental arch is carried into a slightly more anterior position. This causes a minute discrepancy between the upper and lower dental arches, which Petrovic referred to as the "comparator," that is, the constantly changing reference point between the positions of the upper and lower jaws. Second, proprioceptors within the periodontal and temporomandibular joint perceive even a very small occlusal discrepancy and tonically activate the muscles responsible for mandibular protrusion. Third, activation of jaw protruding muscles acts directly on the cartilage of the mandibular condyle and indirectly through the vascular supply to the temporomandibular joint, stimulating the condyle to grow. Finally, the effect of the muscle function and responsiveness of the condylar cartilage is influenced both directly and indirectly by hormonal factors acting principally on the condylar cartilage and on the musculature. This entire cycle is continuously activated as a servomotor as long as the midface-upper dental arch continues to grow and mature and appropriate extrinsic, hormonal, and functional factors remain supportive.

Unlike the functional matrix hypothesis, which precipitated a paradigm shift in craniofacial biology and rests primarily on alternative epistemological propositions about the nature of "causality" in explaining craniofacial growth, the principal feature of the servosystem theory is its reliance on experimental verification of detailed hypotheses. The servosystem theory, represented as a cybernetic model, describes the current state of available data and information and also provides insight into where to look to test relationships. In other words, the major strength of the servosystem theory is that it provides a road map for future experimentation.

**Revolution in Developmental Molecular Biology**

Modern developmental molecular biology began a major conceptual change in the early 1980s, with new discoveries relating to the role of neural crest cells and regulatory genetic factors during development. With the discovery of homeobox and other regulatory genes in the mouse, molecular and genetic research focusing on the development of the craniofacial complex in mammals virtually exploded. Homeobox genes, or Hox genes, contain highly conserved sequences of DNA that encode for certain transcription factors and signaling molecules that regulate expression of other genes during development. As predicted by the operon theory, homeobox and other regulatory genes are the master switches regulating development of fundamental elements associated with the presence and appearance of major body structures, including many of those found in the craniofacial complex.

Since the discovery of regulatory genes in vertebrates a little more than a decade ago, there has been an explosion of research on the developmental biology of the craniofacial complex. Emphasis has been placed primarily on the genetic screening of abnormal and mutant phenotypes, mapping of gene defects to specific domains, and development of animal models either lacking specific genes (i.e., knockouts) or overexpressing genes for key transcription and growth factors. With these tools, it then became possible to investi-
gate the actual genetic mechanisms that regulate cellular activity characteristic of a particular morphogenetic program.

Significant advances in our knowledge about normal and abnormal craniofacial development have come about as a result of very recent research involving homeobox and other regulatory genes. Clearly, the changes in our thinking about the mechanisms of craniofacial development and growth that will occur as a direct result of recent and future discoveries of the role of homeobox genes in development have only begun. However, it is important also not to assume that these genes, like the speculative units of heredity of the 19th century, are responsible for a predetermined specific phenotype involving complex characteristics. Clearly, understanding of homeobox genes and other regulatory factors, and of the additional genes and associated features whose expression they regulate, is fundamental to an understanding of the mechanisms of craniofacial development.93–81

Genetics and Craniofacial Growth Theories in the Modern Era

Revolutionary advances in the field of molecular biology and developmental genetics exemplified by discovery of Hox genes and other factors regulating development are quite recent. Intelligent as they may have been, the anatomists and orthodontists who dominated research in craniofacial growth over the past approximately 80 years could hardly be blamed for a lack of understanding about gene action and the function of genetically encoded regulatory factors. The discoveries about genes and gene action in mammalian development are themselves only very recent within the field of developmental genetics.

The concepts of heredity were only at their very beginnings when the remodeling theory was prominent in the 1920s and 1930s. Transmission genetics, which focused on a population approach to inheritance of discrete characteristics, emerged with the rediscovery of Mendel’s experiments with plant genetics. There was no real knowledge of the nature of the gene, nor of the mechanisms of gene action. Developmental genetics was in its infancy as the sutural theory became widely accepted during the 1940s. By combining the principals of transmission genetics with concepts in embryology, Waddington and others developed hypotheses about how genes might act to influence development of specific, usually discrete, phenotypic traits. Waddington’s ideas in the 1940s and 1950s about gene regulation, ontogenetic adaptation, canalization of development, and the origin and assimilation of traits into the genome formed the foundation for future advances; but these concepts were difficult to extend in specific fashion to complex organisms, such as vertebrates. It is unclear how these experiments and even their underlying conceptual approaches could have influenced the concepts put forward in the sutural theory, except to invoke some vague and incomplete notion of inheritance of complex traits.

The nasal septum theory arose at a point in time when the structure of the gene and a concept for gene action, the operon theory, were initially described. Looking back, with these discoveries it was now possible, at least, to conceive of how genetic information could be encoded to result in developmental pathways leading to a specific phenotype that was passed between generations. Moreover, with its focus on the relatively immutable nature of cartilage growth, the nasal septum theory could have emphasized specific locations, primary growth centers, at which the genes for craniofacial growth might be expressed. However, even here it was unclear exactly what was being inherited. Was it the exact size and shape of the face? Did the genes act up until a certain point of development, as did the nasal septal cartilage, and then cease to influence growth and form? These are virtually the same questions that troubled T.H. Morgan decades before, in 1926.27

Initial formulation of the functional matrix hypothesis took place at the same time as the nasal septum theory. Both Scott and Moss were interested in the role that sutures played in the growth of the craniofacial complex, and both came to the correct conclusion that sutures are secondary sites of bone growth. Scott then proposed that the intrinsic “motor” for craniofacial growth resided in the cephalic cartilages, including the mandibular condyles. Moss, however, became influenced by the totally different perspective of European functional morphologists and proposed that the soft tissues and spaces of the functional matrix are the principal factors controlling growth of the craniofacial skeleton. While this obviously should beg the question of what regulates the growth of the functional matrix, there have been few productive efforts to demonstrate mechanisms of genomic influence on the morphology of soft tissues themselves.

The relatively extreme position of the functional matrix hypothesis with respect to the role of the genome in craniofacial growth was a logical reaction to the prevailing but conceptually and operationally vacuous emphasis on genetic predetermination of craniofacial growth and form that characterized the first two-thirds of the 20th century. Derived as it was from the field of comparative functional morphology, the functional matrix hypothesis was best suited to considerations of phylogenetic significance, and was less applicable to issues of ontogeny. Nevertheless, the functional matrix hypothesis brought about a new approach to craniofacial biology and orthodontics; it shifted the paradigm from a reliance on genetic predetermination to an emphasis on the role of epigenetic factors in the postnatal growth of the craniofacial complex. As a result, the functional matrix hypothesis provided a conceptual framework for addressing questions about dentofacial orthopedics and the possibility of craniofacial growth modification.

Developmental genetics was in its infancy throughout the time that the functional matrix hypothesis was being debated, so it is reasonable to ask how vague and ambiguous concepts in the field of genetics could have provided meaningful answers to investigators and clinicians alike interested in the two central issues: what are the factors controlling facial growth and how can these factors be influenced therapeutically? It was in this regard that the servosystem theory was most significant. The major significance of the servosys-
tern theory stems from the fact that it clearly emphasized an approach to craniofacial growth research based in cell physiology and integrated biology. It brought to bear many of the concepts of the functional matrix hypothesis, but did so with the obvious caveat that not all craniofacial tissues are alike in their ability to express intrinsic growth potential and to respond to functional, epigenetic, extrinsic factors. In this respect, the servosystem theory provided a stimulus to research dealing with the expression of growth factors and signaling molecules that were the true gene products influencing the growth and adaptability of cells and tissues comprising the craniofacial complex.

With the recent initiation of a revolution in developmental genetics, craniofacial biology is on the threshold of research and discovery that has already affected scientific understanding of normal and abnormal craniofacial growth. There also can be no doubt that the emerging discoveries about the nature of the genome and of the specific action of the genes in the regulation of craniofacial development will continue at an unparalleled pace. The human genome is now mapped in its entirety. Basic scientists and clinicians alike will now be able to search for and identify the specific genetic factors that cause or increase susceptibility to significant craniofacial dysmorphologies. A central question now is: How will these discoveries directly affect concepts and approaches to the treatment of abnormal, or undesirable, craniofacial growth and form in growing children?

Genetics, Craniofacial Biology, and Orthodontics in the Postgenomic Era

For most of its history, the field of craniofacial biology, the primary scientific foundation of clinical orthodontics, has strongly emphasized research on postnatal craniofacial growth, from birth through skeletal maturity, for it is primarily within this developmental period that dentofacial orthopedics might be attempted to correct a developing malocclusion and skeletal discrepancy. The field of developmental biology, on the other hand, arose from the combination of the areas of heredity-genetics and embryology, with primary emphasis on the intrinsic, genetic, and epigenetic factors influencing morphogenesis and prenatal development. Up until approximately the late 1970s, for clinicians and experimental morphologists alike outside the specific field of developmental biology, the genetics of craniofacial development was essentially a "black box." The stages of prenatal development were well described by classical embryology, and it was understood empirically that teratogens have a significant effect on development of the craniofacial complex. However, the regulatory mechanisms of craniofacial morphogenesis were not understood.

By the mid-1970s to early 1980s and extending through the present time, many craniofacial biologists began to take greater notice of the exciting advances in the field of developmental biology and genetics. As a result, much of scientific research shifted noticeably toward morphogenesis and mechanisms of prenatal craniofacial development. Classical descriptive embryology gave way to experimental studies of cell and tissue interactions during development. The role of the neural crest population of cells in craniofacial development and of the factors influencing their migration and differentiation became primary areas of interest and research activity. The general area of teratology became focused on specific factors, such as retinoids, corticosteroids, vitamins, and ethanol, as developmental insults with specific effects on cell-tissue interactions and regulation of downstream developmental processes. Increasing numbers of specific regulatory factors, such as the family of transforming growth factors and homeobox genes, were discovered to have relatively discrete and highly significant effects on the morphogenesis and development of the craniofacial complex. Unfortunately, however, it is not immediately apparent how this emphasis on morphogenesis and mechanisms of prenatal development, while critically important for understanding etiology of craniofacial anomalies and genetic syndromes, could be related to orthodontic treatment of a growing child.

Now that we are in the postgenomic era, at least three issues would seem to be clear as they pertain to craniofacial development and growth and to the possibility of modification of craniofacial growth. First, there are a number of genetically encoded regulatory factors that have profound effects on the morphogenesis and prenatal development of the craniofacial complex. Second, it is clear that all of these factors operate within an epigenetic milieu, from the level of the position of genes on the chromosome to the interaction of cells and entire organisms with the external environment. Genes are turned on and off by factors both within and outside the genome to produce specific traits as well as to influence susceptibility to variations of development and growth. Third, there is a plethora of evidence from experimental embryology, teratology, and functional morphology to support the conclusion that morphogenesis, prenatal development, and postnatal growth of the craniofacial complex can be modified. However, this does not necessarily mean that craniofacial growth can be modified in a predictable, controlled, and clinically effective way. The following are major issues that must be considered regarding clinical efforts at craniofacial growth modification: (1) What are the biological targets of treatment in the attempt to modify craniofacial growth, that is, where is the growth-related problem located? (2) What is the amount of desired growth effect, that is, how much modification of craniofacial growth is reasonable to consider? (3) What are the most appropriate treatment approaches that may be used to bring about the desired growth effect? Only by understanding in detail the biological factors that influence the development and growth of craniofacial tissues can their growth be predictably modified and controlled.

The potential impact of advances in developmental biology for prevention and treatment of craniofacial deformities through the use of dentofacial orthopedics can be found in the essential question put forward initially by Thomas H. Morgan nearly 75 years ago concerning the timing of gene action. Morgan asked whether all genes were always active,
or whether genes were active only at certain time periods during development. A similar question can be raised now as it relates to the potential for refinement of orthodontico-dento-facial orthopedic treatment. We now are becoming increasing aware that a number of genes and gene products regulate craniofacial morphogenesis, and that these genes are turned on and off at critical times during development. These gene products do not determine growth and certainly do not determine specific form. Rather, they provide factors that may affect the receptivity and responsiveness of cells to intrinsic and extrinsic stimuli. Is it possible to activate these genes and produce growth factors that may have positive, targeted, and predictable effects on postnatal craniofacial growth? There are ample data from studies of wound healing, skeletal growth associated with distraction histogenesis and orthopedic forces, and alteration of neuromuscular function, just to name a few, to indicate that trauma, mechanical forces, and "function" may be the types of epigenetic factors that activate expression of regulatory genes influencing postnatal growth. Thus, the issue is not the fact that intrinsic factors within the genome regulate morphogenesis, but that the complex interaction of cells and tissues with remote extrinsic factors within both the body and the environment are triggers, or switches for gene expression that influences postnatal growth and responsiveness to clinical treatment.

Within the next several decades, orthodontists will be using molecular kits to diagnose growth-related problems and to determine precisely each patient's developmental status as well as the presence or absence of key polymorphisms for growth factors and signaling molecules. Advances in genetic engineering may provide a means for local introduction of novel isoforms of key growth factors as "molecular bullets." As understanding of the epigenetic factors that turn on regulatory genes and other morphogenetic factors improves, treatment of specific growth discrepancies will be precisely targeted, using orthopedic approaches alone or in combination with systemic and local interventions.

Scientists have made incredible headway in the understanding of the principles and regulatory mechanisms of craniofacial morphogenesis. During the coming decade or more, these same principles will be extended to the craniofacial complex postnatally, and we will see a further understanding of the processes and mechanisms of craniofacial growth specifically as they pertain to prospects for orthodontic growth modification. The foundation for this prediction is provided by two fundamental conclusions. First, there is no question that it is theoretically and practically possible to modify the growth of the craniofacial skeleton, just as it is possible to modify skeletal growth elsewhere throughout the body. Second, there is no Holy Grail of craniofacial biology—no single theory of craniofacial growth. The development of the craniofacial region is complex and unique in some respects with regard to the origin of certain tissues and cell-tissue interactions, which makes it an ideal model system for basic research in developmental molecular genetics. However, like all areas of the body, the craniofacial complex develops, grows, and adapts within an epigenetic milieu that includes both the genes themselves all the way up to broad environmental and functional factors, but within the parameters that are regulated and permitted by the genome. What remains now is to understand the genomic and epigenetic factors influencing the morphogenesis and growth of the craniofacial complex sufficiently that they can be engineered biologically and environmentally, and subsequently introduced into the treatment of individual patients at the appropriate times and in the appropriate measure to produce a biologically meaningful effect and a predictable and clinically efficacious result.

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TOWARD A MODERN SYNTHESIS FOR CRANIOFACIAL BIOLOGY: A GENOMIC-EPIGENOMIC BASIS FOR DENTOFACIAL ORTHOPEDIC TREATMENT

David S. Carlson

ABSTRACT

Understanding of the role of the genome, which includes both the individual genes and properties intrinsic to the chromosomes that affect their expression, in normal development has evolved greatly in recent years. In particular, it now is clear in this new “epigenomic era” that the epigenome, which refers to all the non-DNA encoded factors of the genome as well as extrinsic factors that control gene expression of regulatory proteins, plays a critical role in normal and abnormal development. As a result, understanding of both genomics and epigenomics is critical for understanding normal growth of the craniofacial complex, as well as the efficacy of treatment to correct a developing dentofacial deformity. Five sequentially related axioms serve as starting points for the idea of a modern synthesis of concepts from genomics-epigenomics and dentofacial orthopedic treatment of malocclusion and more profound craniofacial deformities. This approach is built on the premise that concepts regarding the efficacy of dentofacial treatment always have been based on contemporary understanding of the mechanisms of craniofacial growth (Axiom 1). Because phenotype, including the rate and amount of growth possible, varies both normally during ontogeny and as a result of the activity of normal and abnormal gene variants (Axiom 2), the capability of patients to respond to orthopedic dentofacial treatment should be considered as part of the phenotype (Axiom 3) that should be taken into consideration when planning dentofacial orthopedic treatment (Axiom 4). Finally, the possibility of underlying variation of normal genetic polymorphisms for key regulatory factors may be a significant factor affecting the outcome of clinical orthodontic research on the effectiveness of dentofacial orthopedics (Axiom 5).

KEY WORDS: genomics, epigenomics, dentofacial deformity, growth factors, orthodontics, craniofacial biology
With respect to clinical practice, is science useful merely because it is good science? The genome project, for example, may well revolutionize the treatment of schizophrenia or heart disease, but can the same be said of its potential impact on orthodontics? (Johnston, 2004)

The first Symposium on Craniofacial Growth at The University of Michigan, also known as both the Michigan Growth Symposium and the Moyers Symposium, was held in 1974. As it was established in honor of Dr. Robert E. Moyers, former chair of the Department of Orthodontics and then director of the Center for Human Growth and Development, from the onset the Symposium reflected Bob’s vision of a sustained intellectual environment in a major academic setting. The Symposium was designed to bring together experts in the fields of bio-medical/dental science and clinical orthodontics with scientists and scholars from a multitude other areas of academics, ranging from paleontology to psychology and sociology (Lucker et al., 1981) and even to the humanities, such as considerations of facial form and beauty as reflected through the history of art (McNamara, 1993). From its inception, the Moyers Symposium was more than a forum for scientific and clinical reports that typically would be found at the meetings of professional societies such as the annual meetings of the American Association of Orthodontists and the International Association for Dental Research. Rather, the Moyers Symposium provided a unique platform to present up-to-date scientific and clinical information in the context of advancement of new and innovative concepts about the current status and future prospects for craniofacial research and orthodontics.

There were few similar opportunities where scientists, scholars and clinicians actually were expected to put forward ideas of where the combined fields of craniofacial research and treatment of dento-facial deformities are, how they got there and where they are going in the future. In this respect, the Moyers Symposium was not just interdisciplinary—it was transdisciplinary (Lee, 2005; Medicus, 2005) as
it promoted insights into the full spectrum of biological, psychosocial and humanistic issues related to the causes, progression and treatment of dentofacial disorders and to the advancement of orthodontics as a learned profession.

The purpose of this chapter is to provide an overview of the development of modern concepts of genomics and epigenomics in the context of advances in craniofacial research and orthodontic-orthopedic treatment of developing dentofacial deformities through a series of five related axioms as focal points for discussion (Fig. 1). The overarching goal is to promote a more apparent synthesis within craniofacial biology between the modern science of genomics and approaches to dentofacial orthopedic treatment.

Figure 1. Axioms formulated as a basis for further discussion regarding the interrelationship of concepts and principles of genomics-epigenomics, craniofacial growth research and dentofacial orthopedic treatment.
WHY SYNTHESIS?

During its early years, the Moyers Symposium included a dinner open to all those attending the two-day event. As entertainment for the evening, Bob would recruit a distinguished member of the faculty of The University of Michigan—someone not associated with dentistry or medicine—to present a brief after-dinner lecture on a subject that might be of broad interest. The dinner speaker for the first Moyers Symposium was Frank H.T. Rhodes, professor of geology and at the time Vice President for Academic Affairs, who spoke about the life and contributions of St. Thomas Aquinas (1225-1274).

Aquinas was an Aristotelian who sought to “Christianize” Aristotle for the medieval world. Aquinas also was one of the most remarkable scholars of the Middle Ages who produced over 30 major works dealing with theology, science and philosophy. His monumental work, *Summa Theologica*, contains 60 volumes dealing with our perception of the universe through personal experience and science.

Rhodes noted that, “the real originality of Aquinas lies not so much in the discovery of the new but in the sheer boldness in tackling a synthesis of such monumental proportions” (1975, emphasis added). While acknowledging his “impudence of comparison,” Rhodes went on to observe that upon consideration of Bob Moyers’ vision for the Symposium on Craniofacial Growth combined with his life experiences in Greece during World War II and during his distinguished academic career, it is “… easy to draw parallels between the great success of Thomas Aquinas as a synthesizer, a committed academic statesman, and an individual with a lifelong dedication to the wider service of humanity…” (1975, emphasis added).

So, perhaps without realizing it, Professor Rhodes provided the perfect melding of Bob’s passions—Aristotle and Greece in general, academic life, philosophy, science and, of course, orthodontics. Bob also was a great synthesizer who sought to apply scientific and scholarly principles from wherever he found them to address his overarching interest in orthodontics through craniofacial research.

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1 Professor Rhodes later became president of Cornell University, where he retired as the longest serving president of any Ivy League university.
WHAT IS A SYNTHESIS?

A synthesis is simply a combination of two or more theses\(^2\) that together create something novel. A true synthesis is a transdisciplinary melding of ideas and approaches from two relatively separate areas or fields to create new concepts and approaches that incorporate the principles of the previously distinct components. For the purposes of this chapter, synthesis is used to relate and combine modern concepts explicitly in the relatively new field of genomics and especially of its more recent offshoot, epigenomics, with concepts of craniofacial growth and orthodontic research leading to insights about treatment of dentofacial deformities.

Perhaps the easiest way to explain the concept of synthesis in science is to use development of the “modern evolutionary synthesis” (Huxley, 1942) as an example. During the latter part of the 19th and first part of the 20th century, the study of evolution essentially became divided into three primary areas: 1) paleontology; 2) ecology, experimental biology and embryology; and 3) Mendelian genetics. The approach of paleontologists who worked in the field to discover fossil remains of extinct animals and then in the museum to assemble them characteristically inferred the process of evolution primarily through assembly of lineages representing progressive changes in morphology (phenotype) due to natural selection of morphological features and behavior/function. Embryologists, experimental biologists and ecologists focused on morphological variations in extant animals correlated with the environment to infer mechanisms for inheritance of gradual change over time (Morgan, 1926; Waddington, 1939, 1940, 1962). The emerging field of population genetics, on the other hand, accounted for evolution primarily through newer principles such as mutation and genetic separation (drift and flow) leading to changes in genetic fitness (Haldane, 1932; Dobzhanski, 1937). The synthesis between these groups occurred in the late 1930s when it became clear that gene change provides a basis for change in phenotype that then is acted upon by the process of natural selection. Thus, one group or idea was not supplanted by another; a synthesis of all of them was essential to explain the process of evolution.

\(^2\) Thesis: proposition maintained by argument; hypothetical proposition, especially one that is put forward without proof.
A Genomic-Epigenomic Basis

more fully and, thus, they merged to become the neo-Darwinian field of evolutionary biology.

CRANIOFACIAL BIOLOGY AND CLINICAL ORTHODONTICS

Opinions regarding the etiology and natural history of malocclusion provide the fundamental rationale for the treatment “philosophies” that characterize the field of orthodontics. (Robert Moyers, personal communication)

Craniofacial biology is defined as the study of the development, growth and function of the craniofacial skeleton, dentition and related tissues (Carlson, 1985). Basic research in craniofacial biology always has formed the foundation of orthodontic treatment and applied research in that area has been driven by clinical problems related to craniofacial deformities in general and orthodontic interest in dentofacial deformities in particular.

From the time of Edward Angle (1907), orthodontists have based their treatment “philosophy” on prevailing concepts regarding the effects of (bio)mechanical forces on growth and remodeling of craniofacial skeletal structures. The efficacy of remodeling of alveolar bone in response to forces applied to the dentition was demonstrated very early in the history of orthodontics. However, the ability to predictably modify skeletal growth at the sutures of the cranial vault and midface and through the cartilage of the mandibular condyle therapeutically has been debated for over a century.

The earlier view that the pattern of craniofacial skeletal growth and remodeling other than that associated with alveolar bone cannot be altered obviously affirms emphasis on treatment focused around orthodontic mechanics to bring about tooth movement, typically after most or all of growth is completed (Brodie, 1946). On the other hand, belief that craniofacial skeletal growth can be altered by treatment is the basis for use of “growth-modifying appliances” in an effort to correct

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3 It is interesting that even the modern evolutionary synthesis is, itself, “evolving further with the advent of advances in developmental biology and genomics/epigenomics into a new approach called evo-devo, which refers to the evolutionary developmental biology (Carroll, 2005).
skeletal malocclusions in younger, actively growing patients (Graber, 1983).

**CHANGING CONCEPTS OF GENETICS AND CRANIOFACIAL GROWTH**

For some time, attempts have been made to provide an overriding conceptual framework for all of craniofacial growth or, failing that, a neat synthesis of several “theories.” These efforts generally have not been successful yet because of the varied aspects and complicated nature of craniofacial growth...It is very important to remember that old ideas persist in the literature...long after they have been abandoned by craniofacial research biologists. (Moyers, 1988:48-50)

The history of research in craniofacial biology and orthodontics is characterized by five sequentially arranged and relatively distinct hypotheses or theories,\(^4\) to account for the mechanisms responsible for the growth of craniofacial skeletal structures and, concomitantly, the extent to which craniofacial growth might be influenced therapeutically with orthodontic treatment.\(^5\)

The first three of the principal theories of craniofacial growth, spanning the first six decades or more of the 20th century—the remodeling theory, sutural theory and the nasal septum/cartilage theory—are characterized by the view that development and growth of bone, sutures and all craniofacial cartilages, respectively, primarily are the result of intrinsic, inherited factors that essentially are immutable to any significant degree. Together that group of theories and the corollary proposition that dentofacial orthopedic treatment cannot affect craniofacial

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\(^4\) The terms “theory” and “hypothesis” are distinct formally, but often have been used as equivalent when characterizing the various concepts of craniofacial growth mechanisms.

\(^5\) Refer to Carlson (1985, 1999, 2005) for comprehensive discussions and references related to the historical development of theories and paradigms in craniofacial biology and orthodontics.
growth to any significant degree can be described as components of a larger conceptual framework referred to as the *genetic paradigm*.

Shortly after the mid-point of the 20th century, an alternative viewpoint was proposed that placed less emphasis on inherited “pre-determination” and immutability of craniofacial growth, but rather focused on the capacity for alteration of craniofacial skeletal growth in response to variations in biomechanical function, as well as in forces applied to craniofacial structures. The first and predominant theory of that era, the *functional matrix hypothesis*, provided a radical departure from the genomic paradigm as it focused on the role of muscle function as well as other soft tissues, organs and even spaces associated with the craniofacial region on the growth of the craniofacial skeleton. The subsequent general theory of craniofacial growth, the *servosystem theory*, also emphasized the role of muscle function with respect to altering craniofacial growth. However, the servosystem theory also focused on the role of hormonal factors affecting cell physiology as they relate to alteration of growth of the maxillomandibular skeleton. Because of the emphasis of these two theories on extrinsic “functional” factors, together they have been described as components of the *functional paradigm* of craniofacial biology.

**Genetic Determinism and the Genetic Paradigm**

At its birth, genetics was a science of similarities, not—as it would become later—a science of the mechanisms that produce these similarities. (Morange, 2001:12)

Considered in the light of current knowledge, the interpretation that all of ontogeny and in particular development and growth of the craniofacial complex leading to certain immutable types or classifications of morphologies could be considered “pre-determined” is naïve at best. However, craniofacial biologists and orthodontists in the early part of the 20th century obviously did not have the benefit of current knowledge of molecular biology and genomics on which to base their views about craniofacial growth and treatment. Moreover, even full knowledge of concepts in genetics as they were understood at the time would have

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6 *Ontogeny* refers to the “life history of the individual.” The process of ontogeny includes the mechanisms of development (differentiation-maturity), cell growth and adaptation or plasticity during growth (Carlson, 2002).
provided little benefit because they were so incomplete and the field was in such a fledgling state.

Modern concepts of genetics were only at their very emergence when the remodeling theory was prominent in the 1920s and 1930s (Brash, 1924, 1934). Transmission genetics, which focused on mathematical principles of inheritance of discrete characteristics within a population, began in the early part of the 20th century after rediscovery of Mendel’s experiments of heredity in plants. However, during the first half of the 20th century or more, there was no real knowledge of the nature of the gene and of the mechanisms of gene action.

The most widely held “pre-genetics” theory of inheritance in the early 20th century can be attributed to August Weismann (1834-1914), who many consider as the father of modern genetics. It was Weismann who demonstrated that only the germ cells—sperm and egg—carried the units that were responsible for heredity. An alternative prior belief was based on the assumption that somatic cells, such as muscle and bone, contributed directly to inheritance. That latter view of inheritance through somatic cells formed the basis of Lamarck’s principle of inheritance of acquired characteristics, which asserted that characteristics acquired during the parents’ lifetime could be passed on to offspring.

Weismann’s central argument about the role of germ cells in inheritance obviously was correct and provided a basis for refuting Lamarck’s ideas effectively as it supported the theory of evolution by natural selection as proposed by Darwin. However, perhaps in his zeal to refute Lamarck’s ideas about the inheritance of acquired characteristics, Weismann also made several corollary arguments that not only are incorrect, but also unfortunately were detrimental to advancement of understanding about the hereditary basis of development and growth for decades to come. Specifically, in rejecting the concept of inheritance of acquired characteristics Weismann (1892) also asserted that: 1) inheritance is based on a “pre-formative arrangement,” or blueprint, that is inherited through the germ plasm (cytoplasm) of the sperm and egg; and 2) the germ plasm contained “immutable determinants,” which later became known as “genes,” whose expression cannot be changed by the environment.
Concepts relating to the role of the gene during development remained in their infancy as the sutural theory of craniofacial growth became accepted widely by the middle third of the 20th century. According to the sutural theory, general surface remodeling of bone has relatively little impact on craniofacial skeletal growth, as assumed according to the earlier remodeling theory. Rather, the primary immutable determinants of craniofacial growth are active at the sutures as well as all the cartilaginous joints of the craniofacial skeleton. It was assumed, therefore, that the inherited and immutable pattern for craniofacial growth is expressed by intrinsically regulated skeletal growth at sutures, synchondroses and condyles (Weinmann and Sicher, 1947).

It was into this intellectual framework that the nasal septum/cartilage theory was reintroduced by James H. Scott (1953). According to the nasal septum/cartilage theory, intrinsically determined growth of the cartilages of the cranial base, including the nasal septal cartilage in particular, is responsible for downward and forward growth of the midface. Similarly, intrinsic growth of the mandibular condylar cartilage “pushes” the mandible downward and forward. Thus, according to the nasal-septum/cartilage theory, the cartilages of the craniofacial region are the primary tissues within which the genetically determined amount and pattern of skeletal growth leading to particular types of craniofacial form are expressed.

Significant advances in understanding the structure of the gene, as well as how genes are duplicated and passed on, came about through discoveries regarding the structure of DNA as a double-helix. Shortly thereafter, Jacob and Monod (1963) proposed a preliminary concept, the operon theory, which asserted that the timing and rate of gene action may be regulated by special classes of regulator genes (“operons”) that act as “switches,” much like a light switch, to activate or repress structural genes that actually code for a particular trait. However, translation and more widespread application of those concepts to understanding of gene expression during development of complex organisms would not be seen until the rise of molecular biology followed by development of animal models (typically mouse) several decades later. Thus, although each of the major early theories prior to the latter part of the mid-20th century emphasized inheritance of craniofacial development, growth and form, they all were formulated in an era when the nature and role of gene,
much less of the parameters and variability of gene expression, virtually were unknown even by scientific experts in genetics of the time.

**Functional Paradigm as a Response to Genetic Determinism**

Just as the genetic determinists of the 1920s looked always for confirmation of their ideas and never for falsification, so the environmental determinists of the 1960s always looked for supporting evidence and averted their eyes from contrary evidence, when they should have been actively seeking it...It is the experts who have taken extreme and absurd positions at either end of the spectrum. (Ridley, 2000:79-80)

Initial formulation of the functional matrix hypothesis by Melvin Moss occurred at approximately the same time that Scott advanced the nasal septum/cartilage theory. Both Scott and Moss focused initially on the role that sutures play in the growth of the craniofacial complex and concluded correctly that sutures are secondary sites of bone growth and, therefore, do not contribute in any deterministic fashion to cranial and midfacial growth (Scott, 1956; Moss, 1957).

While the nasal septum/cartilage theory asserted that the cephalic cartilages provided the intrinsic “motor” for growth, the functional matrix hypothesis proposed that the function of the soft tissues and growth of physiological spaces are the principal factors controlling growth of the craniofacial skeleton. According to Moss (1962, 1968), the soft tissues, organs and spaces comprising what he defined as the functional

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7 At approximately the time the functional matrix hypothesis initially was being articulated, Baume (1961) proposed that a clear distinction be made between skeletal growth centers and growth sites. The term growth centers was proposed to connote growth with “tissue separating capability,” which would include epiphyseal growth plates and the cartilages of the chondrocranium and nasal septal cartilage. Because they resisted the influence of environmental factors such as compressive load, skeletal growth centers were assumed to be regulated more intrinsically (i.e., genetic). Growth sites were locations of secondary and adaptive skeletal growth that were capable of being influenced greatly by their environment, including the intrinsic growth of adjacent growth centers. Examples of growth sites included periosteum and sutures, which were demonstrated to exhibit a specialized form of periosteal growth.
matrix are the primary objects that grow in the craniofacial complex; the associated sutures, cartilages and bones of the individual skeletal units develop and grow secondarily in response to the functional matrix (Moss and Salentijn, 1969).

The position of the functional matrix hypothesis that primary cartilage, especially the synchondroses of the cranial base and epiphyses of long bones, has no intrinsic growth potential was relatively extreme. The same is true for Moss’ view that genetics plays just a minor role only in embryonic differentiation and virtually none with respect to subsequent skeletal growth. However, both these ideas also can be seen as logical reactions to the prevailing emphasis on genetic pre-determination and immutability of craniofacial growth and form that had characterized craniofacial biology and orthodontics up to that time. As a result, the functional matrix hypothesis stimulated a whole new approach to craniofacial biology research and orthodontics by shifting emphasis on the causes of craniofacial disorders from a reliance solely on genetic pre-determination to consideration of the role of extrinsic, functional-behavioral and environmental factors in the development and growth of the craniofacial complex. Thus, the functional matrix hypothesis provided the conceptual framework for the shift from the genomic paradigm to the functional paradigm of craniofacial biology and provided a foundation for later expansion of concepts regarding the combined role of intrinsic as well as extrinsic epigenetic factors in craniofacial growth.

Historically, the last formal theory of craniofacial growth—the servosystem theory—developed almost serendipitously in the latter quarter of the 20th century and marks the beginning of a trend toward synthesis between craniofacial biology and genetics. The servosystem

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Legend has it that Petrovic’s friend and colleague, J.P. Charlier, an orthodontist in Strasbourg and advocate for the use of functional appliances, introduced Petrovic to the apparently unique growth properties of the mandibular condyle as a secondary cartilage derived from membranous skeletogenic connective tissue. Petrovic then began to look at the cell physiology of the condyle in the rat as a model-system. Thereafter, following significant interest by the orthodontic community, he focused his research almost exclusively on experimental studies of modification of the growth of the condylar cartilage with a focus on dentofacial therapy using functional orthopedic appliances.
theory, also referred to as the cybernetic model of craniofacial growth, was developed by Alexandre Petrovic and his colleagues from the Louis Pasteur University in Strasbourg, France (Petrovic, 1974, 1983; Petrovic et al., 1990).

Petrovic was an MD-physiologist with a specialty in endocrinology who was interested primarily in the effects of hormonal factors on the growth and adaptive properties of connective tissue; he was not concerned about the growth of the craniofacial complex specifically. However, because of his interest in the integrated role of hormones, muscle-biomechanical function and growth of a unique type of connective tissue—secondary cartilage such as comprises the cartilage of the mandibular condyle—Petrovic’s research was relevant to dentofacial orthopedics directly and especially to considerations of the modus operandi of growth-modifying functional appliances (Petrovic, 1985). Following considerable interest by orthodontists in his studies, Petrovic shifted his entire scope of research to studies of craniofacial growth, especially of the mandible, with emphasis principally on the roles growth hormones (e.g., somatomedin, somatotrophic growth hormone) and sex hormones, as well as muscle function play in alteration of mandibular growth.

Hormones are direct protein products of individual genes; therefore, they are direct expressions of genetic inheritance. Because of his background in therapeutic endocrinology, Petrovic understood that these genetic factors may have differential effects on different tissues, depending also on extrinsic influences, such as muscle function, at different stages of ontogeny. With its emphasis on muscle function, both directly and indirectly, the servosystem theory thus adopted many, but not all of the concepts of the functional matrix hypothesis.

The servosystem theory also extended these concepts into the more modern era with incorporation of endocrine factors as they affect normal growth and compensatory growth mechanisms in the craniofacial region. In this respect, the servosystem theory provided a bridge from traditional research on craniofacial growth as primarily a morphological science to introduction of emerging research dealing with the expression of growth factors and signaling molecules influencing the growth and adaptability of cells and tissues comprising the craniofacial complex.
CRANIOFACIAL BIOLOGY IN THE EPIGENOMIC ERA

Instead of thinking of the genome as a book, imagine it as a piano keyboard. (Shreeve, 2005:15)

If the DNA sequence is like the musical score of a symphony, then the epigenome is like the key signatures ...that show how the notes of the melody should be played. (Qiu, 2006:146)

Bateson introduced the term “genetics” in 1905 to refer to the study of genes, which would not be observed physically for another 50 years or more, as the theoretical units of heredity. The term “genome” was coined in 1920 by German botanist Hans Winkler (1877-1945) to refer to the integrated functions of an entire set of genes as opposed to the activity of single genes.

Genomics as the study of the interaction of entire sets of genes and chromosomes was not appreciated more widely outside the field of genetics until the initiation of the Human Genome Project just prior to 1990. Completion of the Human Genome Project in 2003 also marks the beginning of the “post-genomic era” in modern biomedical science, where the entire genetic makeup of an organism is being considered, especially insofar as individual genes and groups of genes, or haplotypes, are expressed and interact within a regulatory framework for gene expression.

Omic is a Greek word that essentially means “in the nature of.” Within the past decade the “-omic” suffix has been used widely in a variety of scientific fields to refer to study of all the genetic components responsible for a given system function (Baker, 2013). For example, proteomics refers to the study all the proteins in a given system; metabolomics to all the small molecules in a system; and interactomics to refer to all the molecular interactions is a given system. There now is even the term incidentalomes that refers to the study of incidental findings that occur during genetic diagnostic testing for other possible conditions.
Epigenetics\textsuperscript{10} also is a relatively old term, though its definition and nuances have changed considerably in recent years with improved understanding of the range of factors that control regulation of gene expression (Jablonka and Lamb, 2002; Ball, 2013). C.H. Waddington (1942) generally is credited with modern introduction of the term “epigenetics” to refer to all the factors, both inherited and non-inherited, that contributes to completion of the phenotype. By the end the 20th century, epigenetics became focused more on the genome and generally came to include all the factors, genetic and non-genetic, intrinsic and extrinsic to the chromosome, influencing expression of individuals genes and groups of genes during ontogeny (Holiday, 1990).

Within the field of craniofacial biology, the term “epigenetics” has been used previously in a meaningful way by only a handful of researchers, most notably by van Limborgh (1970, 1972, 1983) in a series of studies on craniofacial morphogenesis. While van Limborgh’s understanding of epigenetics may have been accurate for the time, it was extremely limited and does not reflect current understanding of the nature and scope of modern genomics and epigenomics fully. In van Limborgh’s parlance, influences on growth by associated anatomically adjacent structures are referred to as local epigenetic factors. General epigenetic factors include hormones that are produced at some distance from the target of growth and act systemically.\textsuperscript{11} Local environmental factors, which include muscle function, were considered to be distinct and apart from epigenetic factors.

The conceptual model put forward by van Limborgh was a harbinger of current understanding of the distinction between specific structures and traits, which he referred to as being the result of intrinsic genetic factors (i.e., genes) and the regulatory factors that influence the expression of the genes as part of the entire genome-epigenome. In this respect, van Limborgh’s analysis appropriately should have expanded the scope of the functional matrix hypothesis to a more comprehensive

\textsuperscript{10} The prefix \textit{epi} comes from the Greek to mean “around” and “in addition to.” The concept that development is not pre-determined goes all the way back to Aristotle’s \textit{On the Generation of Animals}, which described the process of development as an “unfolding” of the individual in concert with internal and external influences.

\textsuperscript{11} The role of growth factors and cytokines as gene products in the form of regulatory proteins was essentially unknown until the latter part of the 20th century.
level where genetic, epigenetic and local environmental factors all played complementary roles in craniofacial development and growth. However, his synthesis had little direct impact on the field aside from occasional and perhaps naïve use of the term “epigenetic” as essentially a synonym for “functional” factors (cf. Moss, 1985).

Defining the gene as the molecular unit of heredity comprised of DNA, current concepts posit that epigenetics refers to the action of “additions to the DNA and histones that are stably maintained [in the genome] and do not change the primary DNA sequence” (Feil and Fraga, 2012). In short, “the epigenome is the regulatory software for the genome” (C. Walker, personal communication). Epigenomics extends the scope of genomics through consideration of the interaction of the genes encoded to express a particular systematic activity, to the intrinsic structure of the chromosome, as well as to the non-genetic extrinsic factors that influence gene regulation and expression. In current usage, the concept of epigenetics has been extended further with the proposition of the possibility of heritable transgenerational changes in gene function that cannot be explained by changes in DNA sequence (Riggs, 1996; Ball, 2013; Grossniklaus et al., 2013) and even the possibility of somatic cell reprogramming (Buganim et al., 2013).

In the context of the present discussion, epigenomics refers broadly to the study of the entire scope of mechanisms, both intrinsic and extrinsic, by which the pattern of gene activity leading to development and growth is regulated and expressed. These mechanisms are based on the interaction of the genes comprising the genome as mediated by DNA methylation and chromatin structure as well as extrinsic, environmental factors that regulate gene expression in time, amount and duration (Smith and Meissner, 2013). Extrinsic, environmental factors would include, but not be limited to, mechanical forces and muscle function as typically might be associated with orthodontic treatment to correct a developing dentofacial deformity.

Thus, emphasis on the approach of epigenomics with respect to understanding the entire span of ontogeny, including its prenatal development, peri- and postnatal growth and capacity for phenomic plasticity and compensatory growth, is critical for understanding growth of the craniofacial complex and the potential for therapeutic modification.
SPECTRUM OF DENTOFACIAL DEFORMITIES: A GENOMIC-EPIGENOMIC PERSPECTIVE

Form is the visible expression of the formative processes that have been instrumental in its shaping. The end result is but the residual record of its formative history. Clearly, then, changes in the standard pattern of formative processes lead to deviations from the standard form: deformations end up as “deformities.” In this sense, “deformities” become valuable clues to the inner workings of formative processes. (Weiss, 1960:23)

The list of principal genes and protein products essential for regulation of normal as well as abnormal development and growth of the craniofacial complex has expanded significantly over the past several years (Rice, 2005; Spears and Svoboda, 2005). However, the significance of variation with respect to normal gene variants, or polymorphisms, in these and other key genes for ontogeny, including development, growth and adaptive capability of the craniofacial complex, has yet to be understood fully.

For heuristic purposes, craniofacial disorders with a probable direct or indirect genetic basis can be organized along a spectrum from the most severe and debilitating craniofacial anomalies, many of which are well defined with respect to mutation of key developmental genes, to less severe acquired deformities that also may have a genomic basis, but one that might be attributable to a haplotype of essentially normal gene variants or polymorphisms (Hefer et al., 1998; Fig. 2). At one end of the deformities spectrum are such conditions as mandibulofacial dysostosis, or Treacher Collins Syndrome, which is a major dysmorphogenesis syndrome caused by a mutation of a specific gene (Treacle, TCOF1) resulting in significant reduction in migration of neural crest cells into the first and second branchial arches during the first weeks of embryonic development.

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12 Genetic polymorphisms are “normal” gene variants. It now is believed that virtually all human genes have single nucleotide polymorphisms (SNP) due to alternative splicing, alternative promotors and post-translational modification (e.g., microRNA). Such polymorphisms may produce normal variations in phenotypic expression ranging from negligible, to minor but observable, to significant.
A Genomic-Epigenomic Basis

Figure 2. Heuristic model illustrating the spectrum of craniofacial deformities, from profound dysmorphogenesis syndromes associated with significant genetic anomalies to deformities with a heritable basis that may be acquired secondarily. Adapted from Hefer et al., 1998.

development. The lack of neural crest cells leads to a profound deficiency of mesenchymal tissues causing a significant hypoplasia of the mandible, malar-orbital structures, muscles of mastication and external and internal structures of the auditory system.

Embryonic disruption events represent a midpoint of the spectrum of genomic influencing craniofacial development and form. As an example, it has been proposed that isolated craniofacial microsomia, which is the second most common major non-syndromal craniofacial deformity after cleft palate, arises principally as a result of a hematoma that occurs during the transition in blood supply of the face from the stapedial artery to the maxillary artery at approximately five to six weeks’ gestation (Poswillo, 1988). Depending on its size, the blood clot is thought to disrupt formation and subsequent growth of the skeletal structures and muscle associated primarily with the ramus of the mandible and temporomandibular joint (TMJ), as well as with the ear and auditory structures.

Craniofacial microsomia may be unilateral or bilateral and also has a significant genetic basis as it occurs with other syndromic conditions.
However, there currently are no genes associated with isolated craniofacial microsomia (Luquet et al., 2011). Therefore, even though the apparent immediate precipitating event leading to disruption of the development of the lateral facial structures may be disruption of precursor neural crest cells or differentiated tissue development by the hematoma, it most likely is that isolated craniofacial microsomia has an epigenetically-modulated component characterized by a genetic predisposition or susceptibility related to problems with the developing blood vessels, at least in the face at a specific point in time during development.

At the other end of the spectrum in this heuristic model are craniofacial deformities that have a probable heritable basis, but in which the genetic basis is found not as much with the affected individual as with the genomic background of the pregnant mother. Examples of these deformities are idiopathic plagiocephaly due to craniosynostosis secondary to prenatal constraint of the calvarium and Pierre-Robin Sequence.

Pierre-Robin Sequence is an acquired severe dentofacial deformity that exhibits perinatal phenotypic similarity with Treacher Collins Syndrome. Like Treacher Collins Syndrome, Pierre-Robin Sequence is characterized by severe hypoplasia of the mandible as well as a complete cleft palate. However, the causes of these two deformities are completely different, which has profound implications for treatment of dentofacial growth. While Treacher Collins Syndrome is a neurocristopathy caused by a mutation either de novo or through inheritance of the Treacle gene, Pierre-Robin Sequence occurs as a secondary effect on the offspring thought to be caused principally by fetal restriction in utero.

Prior to six weeks’ gestation, the cephalic region of the human embryo is flexed downward with the developing face and mandible in close contact with the cardiac swelling and precociously developing heart. Soon thereafter, the embryo extends its neck, elevating the head and moving the face away from the cardiac swelling, thus freeing the mandible to move forward with anterior movement of the tongue. As the tongue thrusts forward, the palatal shelves are free to elevate as a first step in the process of palatal closure and the unconstrained mandible is free to grow anteriorly. In cases where the pregnant mother produces insufficient amniotic fluid, the embryo and fetus may be constricted such
that the head cannot be elevated and the face remains mechanically constrained against the cardiac swelling. As a result, the mandible is restricted severely in its early growth and the tongue remains between the palatal shelves causing complete cleft palate at birth. In this case, therefore, it is the epigenetic maternal uterine environment that leads to reduction in mandibular growth and resultant hypoplasia.

Each of these disorders has some degree of underlying genetic basis that affects craniofacial development and subsequent growth as well as possibilities for treatment. The deformities used as examples range from a definitive mutation of a single gene critical for normal craniofacial development as in the dysmorphology that characterizes Treacher Collins Syndrome; to the possibility of genetic susceptibility or predisposition for occurrence of a vascular accident in the developing face in isolated craniofacial microsomia; to an epigenetic, mechanical modification of normal development and growth of the mandible and palate in Pierre-Robin Sequence.

Thus, each deformity also presents a distinct biological rationale for different options for effective treatment based upon their underlying causes. For example, dentofacial orthopedic treatment designed to stimulate mandibular growth or even to correct the dentofacial deformity in a growing child with Treacher Collins Syndrome surgically and with distraction histogenesis are not successful primarily because of the profound deficiency in cells and tissues in the affected region, as well as the likelihood that the existing tissues are not capable of responding adequately to treatment fully (K. Salyer, personal communication; Gürsoy et al., 2007). Success of treatment options in isolated craniofacial microsomia depends in large part on the severity of the disruption event and the variable presence of normal cells and tissues (Harvold, 1983; Vig, 1988). Finally, the cells and tissues of the child affected with Pierre-Robin Sequence should be considered essentially if not completely normal; the mandible simply is profoundly hypoplastic due to physical constraint. Therefore, in principle, dentofacial orthopedic treatment designed to enhance growth of the mandible likely will lead to more favorable results in children with Pierre-Robin Sequence (Vig, 2002).
GENOMICS-EPIGENOMICS AND VARIATIONS IN CRANIOFACIAL DEVELOPMENT

...the epigenetic course of life, being decidedly not an automatic reeling off of a rigid chain of microprecisely concatenated events, offers man wide opportunity and the faculty for steering his course within that frame for better or worse...the general idea that “environment” enters the scene only when the bird hatches or the baby is born should be expunged. (Weiss, 1973:81)

Craniofacial anomalies due to genetic mutations represent development and growth gone awry and, thus, can be understood truly only as a complement to understanding of normal developmental and growth processes. Extrapolating from the previous examples of anomalous genetic and epigenetic influences on craniofacial deformities, it also is possible to gain insight into the potential roles that consideration of genomics-epigenomics might play in treatment to correct developing dentofacial deformities in patients who would not be characterized as “abnormal.”

Prospective orthodontic patients typically are evaluated based on a number of clinical criteria, with particular emphasis on dental models and cephalometric radiographs as the bases for diagnosis and treatment planning to correct dentofacial misalignment and related deformities. Maturational indicators, such as the status of dental eruption and ossification of the bones of the hand-wrist and cervical vertebrae, also may be used to assess maturational status and, thus, provide indirect evidence for the potential of further skeletal growth.

There are many other factors whose expression as isoforms of regulatory proteins from closely related genes may affect the process of skeletal growth and adaptation to dentofacial orthopedic treatment. In particular, there are many transcription factors, growth factors, cytokines and similar gene products that affect growth and remodeling of the craniofacial skeleton and related tissues that may be active to a variable degree throughout ontogeny (Fig. 3; see review by Spears and Svoboda, 2005).

All of those factors, when expressed at variable time periods during ontogeny, also directly influence the capacity for adaptation through
Normal variation in the degree of expression of these isoforms—from absence or insufficiency due to expression of only one allele as a result of haploinsufficiency and gene imprinting, to protein sufficiency, to protein overexpression—at critical time points during development and growth also are significant parts of the phenotype that will affect growth and responsiveness to treatment significantly.

The principal product of epigenesis is not so much the phenotypic trait itself as it is the developmental process that results in that trait. Expression of genes responsible for the processes of development and
growth is turned on and off by factors both within the genome and in the epigenetic environment to produce specific traits as well as to influence susceptibility to variations in the extrinsic environment. Development and growth of all cells and tissues are mediated within broad parameters by the activity of the genome of the individual. Therefore, normal individual genomic variation also may influence the rate, amount and timing of expression of gene variants for key molecular factors that regulate the normal growth process. Moreover, considering the linkage between growth processes and dentofacial orthopedic treatment, it is even more critical to consider the possibility that such normal genomic variation is likely to affect the degree to which the non-genomic effectors of growth will produce a desired effect.

It is within this conceptual framework that advances in the developmental biology and genetics of the craniofacial complex potentially can be most beneficial to the field of clinical orthodontics. Recent research on the development and growth of sutures and of the condylar cartilage of the mandible provide examples of how genomics-epigenomics could play a role in the future of treatment to correct developing dentofacial deformities.

**Sutures**

An essential prerequisite [to dentofacial orthopedic treatment] is a careful and thorough diagnostic study of all the factors that might influence growth regulation. Therapy then becomes a biological solution, not a mechanical compromise. (Graber, 1983:325)

There have been considerable advancements in understanding of the biology of suture development and growth since early reliance on histological descriptions led to the erroneous conclusion that sutures were intrinsic, genetically predetermined growth centers equivalent to epiphyseal growth plates in long bones. It subsequently was demonstrated that sutures, which are unique to the craniofacial complex, are passive sites of compensatory bone growth associated with membrane bones of the cranial vault and midface.

The principal concern in suture biology then focused on the specific extrinsic biomechanical factors that cause sutures to form, grow and
fuse. Initially, research studies principally addressed the effect of tensile forces brought about normally by expansion of organs such as the growing brain and eyes as well as the more intrinsically-regulated growth of the cartilage of the cranial base and midface. As a result of integration of advances in genetics, research in suture biology during the past decade or more has shifted to a primary concern with the expression and complex interplay of molecular factors that regulate sutural growth, maintain suture patency and promote suture fusion, both normally and prematurely as in craniosynostosis.

Studies in experimental animals have identified the presence, location and function of a number of key transcription factors and growth factors that are responsible for suture development (Fig. 4; Rice et al., 2003; Opperman et al., 2005; Rice, 2005; Martinez-Abadias et al., 2011). With the discovery of the existence of isoforms of certain of these growth factors and how they interact during suture development, experimental research began to address the potential for “rescue” of non-growing and even synostosed sutures by exogenous introduction of those factors that upregulate or repress expression of associated key isoforms.

Figure 4. Diagram illustrating expression of growth and transcription factors during development and maturation of a suture. A: Presumptive suture. B: Fully formed suture. C: Mature suture undergoing fusion. The growth and transcription factors known to be active principally at each of these stages are listed for each location within the suture. Adapted from Opperman et al., 2000.
of regulating proteins (Opperman and Ogle, 2002; Moursi et al., 2003; Opperman et al., 2005; Rice, 2005; Shukla et al., 2007).

Those studies clearly portend the possible longer-term goal of treatment approaches to correct and prevent syndromal and non-syndromal craniosynostosis, possibly as an adjunct to standard mechanical orthodontic treatment to stimulate sutural growth in both the cranial vault and midface. As a possibility for the short-term, assays of the presence and concentration of growth factor isoforms could provide critical diagnostic information related to whether or not sutures are more or less likely to grow further, under what conditions of mechanical influence and during what time period.

Mandibular Condylar Cartilage

If...the mandible is really the material cause of the Class II malocclusion, then it would be appropriate to ask whether any treatments effectively target it. Specifically, are you going to employ 1 or more of the so-called functional appliances? To answer yes, you must first ask why. What do you hope to accomplish and is there any proof that what you hope for is possible? (Johnston, 2002:552-553)

The condylar cartilage of the mandible is a secondary cartilage that is similar to a suture as both are derived from a skeletogenic membrane homologous to periosteum/perichondrium. As the condylar cartilage has periosteum-like properties, its growth is highly adaptive and responsive to a variety of environmental factors, including in particular muscle function and mechanical load (Carlson, 1994; Hinton and Carlson, 2005; Hinton et al., 2009; Solem et al., 2011).

Experimental research on the growth of the condylar cartilage in animal models has been prominent in craniofacial biology for many decades, principally due to its importance in overall mandibular growth and because of enthusiasm among clinicians for the possibility of altering growth of the mandible therapeutically. It should not be surprising that studies on the growth of the condylar cartilage have focused on those putative principal mechanisms thought to regulate the amount, rate and direction of mandibular growth therapeutically, especially to stimulate condylar growth as part of correction of Class II malocclusion.
Virtually all of the appliances designed to stimulate condylar growth have a number of overlapping characteristics in common, though with variable emphasis. These include: 1) increasing the neuromuscular activity and function of the muscles of mastication, generally by increasing bite opening; 2) repositioning of the mandible in a more forward, protrusive position, thus distracting the condyle from the glenoid fossa; and 3) relief of compressive forces on the condylar cartilage by mandibular protrusion as well as on the mandible as a whole by shielding of the perioral soft tissues.

Alteration of muscle function, jaw position and mechanical load generally represent attempts to change those components of the environment thought to be the principal mechanisms, themselves, that control growth of the condylar cartilage. However, it is important to emphasize that as elements of the therapeutic environment, those elements are not themselves “control mechanisms” of growth—rather they are possible effectors\textsuperscript{13} of condylar growth. Muscle function, jaw position and mechanical load are extrinsic, non-genomic epigenetic factors that potentially could influence regulation of genes responsible for expression of molecular factors that influence growth. Therefore, treatment approaches that alter these elements of the environment have the potential to alter such gene expression and, thus, alter condylar growth. However, the receptivity of the patient to alterations in these epigenetic effectors also is a function of their genome.

Similar to advances in genetics and molecular biology in the study of suture development, significant progress has been made in recent years in the study of the growth of the cartilage of the mandibular condyle. For example, it has been shown that expression of isoforms of fibroblast growth factor (FGF) and insulin-like growth factor (IGF) regulatory proteins and their receptors, as well as transcription factors such as core bonding factor and Sox 9 within the condylar cartilage, are critical for normal growth of the mandibular condylar cartilage (Fuentes et al., 2002; Rabie and Hägg, 2002; Visnapau et al., 2002; Rabie et al., 2004; Hinton and Carlson, 2005; Hinton et al., 2009).

\textsuperscript{13} An effector is an agent that mediates a specific effect. In biology, effectors are substances or activities that regulate gene activity by increasing or decreasing enzyme activity, gene expression and cell signaling.
It also has been shown that distribution of each of these factors varies within the several layers of the condylar cartilage during ontogeny (Hinton and Carlson, 2005; Shen et al., 2005; Fig. 5) and in response to experimental intervention that attempts to simulate therapy with a functional orthopedic appliance (Fuentes et al., 2002, 2003; Hajjar et al., 2003; Rabie et al., 2003; Delatte et al., 2004; Suzuki et al., 2004). In an experimental design using an intraoral appliance that created a crossbite and unilateral protrusive functional appliance, it was possible to determine significant differences in the expression of growth factors FGF-1, 2, 3 and IGF-1, as well as their receptors relative not only to control animals, but also to the different sides of the mandible within the same animal. For example, even within the experimental animals the protrusive and non-protrusive contralateral condyles showed altered gene expressions for FGF-2 and IGF-1 that essentially were in opposite directions (Fig. 6).

The significance of the experimental studies of the mandibular condylar cartilage cited above is not that key molecular factors related to growth of cartilage and bone are expressed in the condylar cartilage. The significance is, first, that their expression varies according to location and maturation in normal, genetically homogeneous strains of experimental animals and second, that variations in the extrinsic environment generally simulating dentofacial orthopedic treatment produce clear and discernible effects on that gene expression. Unfortunately, however, nothing is known about the presence and effects of normal variants or polymorphisms of growth factors for condylar growth in human subjects.

Understanding of the biology of suture development has been advanced considerably, principally because craniosynostosis is such a prominent characteristic in a large number of genetic anomalies for which tissue samples are available from surgery. Therefore, the mutations of key genes and expression of isoforms of key genes that affect sutural development and growth have been described relatively well. Similar assays are not available—nor will they be for ethical reasons—to determine the presence and amount of expression of growth factors specifically in the mandibular condyles of patients with a Class II malocclusion due to mild-to-moderate mandibular deficiency. However, it is reasonable hypothesize that variants of normal genes known to have an impact on sutural growth that are co-expressed in the growing
mandibular condyle could predispose to variations in the growth of the mandibular condyle and in the capacity for response to specific types of treatment and possible effectors.

**GENOMICS-EPIGENOMICS AND TREATMENT OF DENTOFACIAL DEFORMITIES**

*All orthodontic appliance systems succeed in correcting malocclusion in some circumstances, but are less successful or outright failures in other circumstances. Selecting the right approach for any given patient remains the key to success. (Proffit, 1985:63)*
Figure 6. Gene expression for FGF-2 and its receptors as a percentage of untreated controls in the mandibular condyle of animals that wore a tooth-borne unilateral appliance designed to create a unilateral crossbite. The crossbite caused an asymmetric shift of the mandible resulting in a unilateral protrusion of the condyle on the deviated side of the mandible. These data indicate that gene expression can be altered even in the same animal and at the same time with condylar protrusion. Adapted from Fuentes et al., 2003.

One of the major questions that has confounded orthodontic treatment and resulted in considerable debate among clinicians is why treatment outcomes in patients who present with similar dentofacial deformities and who are treated essentially in the same manner often are variable. Typically, such differences are ascribed to patient compliance. However, it also is likely that genomic differences related to the presence and regulation of individual gene variants and groups of variants are important in accounting for individual variation in treatment response.

Lisa Tedesco (1997), a principal program discussant at the Moyers Symposium on management of the non-compliant patient, noted that, “In spite of major improvements in diagnosis and great advances in orthodontic technologies, patient compliance remains the weak link in the chain between a good treatment plan and a successful outcome.”
As reviewed previously, patients exhibiting profound dentofacial abnormalities with a heritable genetic basis can be considered according to a continuum from craniofacial anomalies characterized by major mutations of key developmental genes to deformities acquired indirectly within the uterine environment (refer to Fig. 2). A similar model may be instructive to account for the genomic-epigenomic basis for variable outcome of clinical treatment to correct developing dentofacial deformities in patients who appear to be “normal.” While earlier discussion focused on individuals who clearly are affected, directly and indirectly, by severe-to-moderate genetic abnormalities, this segment of the discussion will take those principles and apply them to a spectrum of the orthodontic patient population where the influence of genomic-epigenomic factors may be considerably less obvious.

The dentofacial patient population can be divided conceptually into three overlapping groups; for lack of better terms these groups will be called Standard, Abnormal and Clinical (Fig. 7). Subjects in the Standard Group essentially provide the “norm” for how development and growth are supposed to proceed—the way craniofacial growth generally is described in textbooks and taught during graduate training. Individuals in this group would be expected to have unaltered, normal genes and an array of genetic polymorphisms and haplotypes to guide expression of craniofacial developmental and growth leading to normal craniofacial form.

Relatively minor variations in dentofacial form certainly exist within the Standard Group and naturally would lead to recommendations for orthodontic treatment. However, in the course of such treatment, dentofacial orthopedic patients in this group would tend to exhibit growth patterns and responses to growth effectors that are characteristic of the norm and, thus, would be expected in terms of the way the face and jaws are supposed to grow. Dentofacial orthopedic patients in the Standard Group also would be most capable of responding to treatment, perhaps even to a relatively wide range of different treatment approaches and appliances, in a more or less predictable and favorable fashion.
Figure 7. Heuristic model illustrating the three major subgroups of orthodontic patients and the hypothetical relationship between genomic background and likelihood of favorable orthodontic treatment for treatment for a developing dentofacial deformity. Standard Group patients with mild-to-moderate dentofacial malocclusion, such as a Class II malocclusion, have normal genomic structure and would be expected to respond favorably to treatment. Patients in the Abnormal Group have genetic abnormalities that generally preclude normal growth and response to standard treatment. Patients in the Clinical Group may be fully normal or may possess gene variants and haplotypes that could affect treatment response.

At the opposite end of the patient population spectrum is the Abnormal Group, representing subjects exhibiting profound craniofacial anomalies and deformities similar to those discussed previously. Patients in the Abnormal Group are characterized by genetic disorders ranging from significant mutations of key developmental genes responsible for major dysmorphogenesis malformations (A1); genes that predispose for major disruptions of craniofacial development (A2); and deformation of essentially normal tissues (A3). Because of abnormalities in genomic structure and concomitant cell-tissue deficiencies, another principal characteristic of these subjects especially in subgroup A1 and probably in A2 is a lack of capacity for normal growth. As a result, subjects in the
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Abnormal Group likely are incapable of responding to dentofacial orthopedic treatment that was developed on the basis of understanding of standard craniofacial growth and normal response to its effectors.

The most important group for the present discussion of the relationship between genomics-epigenomics, growth and treatment of dentofacial deformities according to this model is the Clinical Group, which lies intermediate to and overlaps with both the Standard and Abnormal Groups. The Clinical Group is comprised of the largest number of patients with moderate-to-minor dentofacial deformities most likely to be seen in an orthodontic practice. It also is assumed that a large component of subjects within the Clinical Group have a standard or normal intrinsic genomic background structure. Finally, this model proposes that a major component of the Clinical Group also may be characterized by unknown arrays of variants for individual genes and groups of genes that are normal, but may not be ideal for dentofacial growth; thus, they represent unfavorable, but not necessarily abnormal variants for dentofacial growth. This underlying genomic structure also would be expected to affect the response to treatment such that patients from the Clinical Group who fall in the normal range of gene variants respond favorably to treatment, while those outside the normal range would exhibit progressively less favorable and more variable responses depending on their degree of departure from standard genomic structure.

GENOMICS OF CRANIOFACIAL GROWTH TREATMENT AND CLINICAL RESEARCH

[Clinical research on control of craniofacial growth] is a study of averages. There is no evidence that any case or group of cases behaves in any way differently from the average except as a result of growth. (Mills, 1983:37)

The Median Isn’t the Message. (Gould, 1985; title of an article by Stephen J. Gould regarding the use of statistics in clinical research soon after he was diagnosed with cancer)
Discussion up to this point has emphasized the notion that greater understanding of genomics-epigenomics and particularly of variants of key genes and their effectors is increasingly important in order to understand craniofacial growth and, thus, to anticipate the likelihood of responsiveness to treatment of growth disorders related to dentofacial deformities more effectively. Understanding of the principles underlying a synthesis between the genomics-epigenomics of craniofacial growth and treatment also is significant for shedding light on a major confounding factor related to clinical research in orthodontics.

Discovery of genetic variations that underlie diseases and developmental deformities relies on DNA sequencing to determine the presence and location of individual genes and of whole groups of genes on the chromosomes (Fig. 8). That process begins with description and delineation of a well-characterized patient group that expresses a clearly defined disease, deformity or disorder with a strong likelihood of a definitive genetic basis. Biological samples taken from multiple members of the subject group then are screened with microarrays to look for shared variations in gene structure and loci. Once candidate genes are identified, cell-tissue studies and experiments on naturally occurring and genetically-engineered animal models are used to determine gene function related to the cascade of molecular interactions leading to the phenotypic features that characterize their expression (Hieter and Boguski, 1997).

Consideration of a well-characterized craniofacial anomaly with a known genetic basis, Crouzon Syndrome, provides an example of the process of discovery of abnormal genes in a well-characterized patient population. Crouzon Syndrome is one of a related series of craniofacial dysmorphogenesis syndromes that exhibit a number of features related to abnormal growth of sutures and the cranial base. DNA sequencing of Crouzon patients revealed that the primary genetic defects include mutations of the genes for FGFR2 and FGFR3 (Jabs et al., 1994; Jabs, 2002; Rice, 2005). Once identified, in situ hybridization in a mouse model was used to determine localization and timing of gene activity. Finally, with an essentially complete understanding of the mutated gene variants, information became available for use in diagnosis, prevention through genetic counseling and possible future treatment to prevent the deformity.
Figure 8. General overview of the various steps required to discover genes for key traits related to disease, disorders and deformities. An essential starting point for this process is delineation of a well-characterized subject group for a trait that has a clear genetic basis. Adapted from D. DePaola, personal communication.
Sequence analysis to discover candidate genes for diseases and developmental deformities is most useful and efficient when the underlying genetic basis of the disorder is relatively profound. It is considerably more difficult to determine minor genetic differences between subjects who express normal genes, gene variants and haplotypes, not only because of the gene array technique itself, but also more critically because it is nearly impossible to define well-characterized and discrete samples of affected subjects at the outset (Wilkie and Morris-Kay, 2001; Cheung et al., 2005; Justice et al., 2012).\(^{15}\)

It is well understood that malocclusion and minor dentofacial deformities, such as mild-to-moderate maxillomandibular discrepancies in otherwise apparently normal subjects have no simple and straightforward genetic basis related to mutation of key developmental genes. Rather, it has been well established that such deformities represent “multifactorial” expressions of continuous variation of normal dentofacial growth and form (Mossey, 1999\(^{a,b}\); Hartsfield, 2012). As a result, delineation of a subject pool of patients with a common dentofacial deformity, such as minor-moderate Class II malocclusion, for example, that is well characterized as being homogeneous for traits with a presumed genetic basis will prove to be difficult if not impossible. On the other hand, more profound malocclusions and certain classes of dentofacial deformities, such as skeletal Class III malocclusion, may be more amenable to such analysis (Xue et al., 2010\(^{a,b}\)).

A typical clinical orthodontic research paradigm as a randomized clinical trial is to define subject study samples on the basis of morphological indicators of facial form, such as type or classification of malocclusion, as well as age and sex, and then examine response to

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\(^{15}\) Genome-wide association analysis (GWA) attempts to analyze entire genomes in order to determine individual differences in common genetic variants such as single-nucleotide polymorphisms (Hinds et al., 2005). GWA generally is conducted to find associations and not causes of major diseases, not relatively minor phenotypic variations (Pearson and Manolio, 2008). GWA also is subject to the same concerns about selection of control and case populations for analysis. Therefore, GWA is not a likely solution for analysis of role of minor gene variants on craniofacial growth and dentofacial orthopedic treatment (Cheung et al., 2005).
treatment with one or more types of orthodontic appliance and/or protocol (Koletsi et al., 2012). Missing in this approach is recognition of the possibility that the study population is likely to be heterogeneous for normal variants of regulatory proteins that affect craniofacial growth. Orthodontic patients that appear to be similar with respect to general phenotype and especially dentofacial form and classification of malocclusion not only might have considerable variability with respect to expression patterns for normal gene variants that affect growth, but these gene variants also could influence the manner and degree of responsiveness to treatment as an epigenetic effector of growth. While patients with favorable genomics may respond well for a given standard treatment, patients lacking favorable gene variants may respond less well or even poorly. Thus, the combined results of the standard analysis of treatment outcome study regress to the average or median response, which could compromise the validity and applicability of findings significantly as they pertain to subgroups of patients if they could be delineated appropriately.

CONCLUSION: STARTING POINTS FOR A MODERN SYNTHESIS

Altogether, the complexity of structural variant-phenotype relationships calls for novel integrative and holistic approaches that involve the combined application of multiple models for well-phenotyped patients....This will form an essential prerequisite for improving predictions of disease onset and outcome, for developing therapeutic strategies and for facilitating translational molecular medicine research. (Weischenfeldt et al., 2013:136)

We need to spend less time talking about the median and more time talking about the tail. (Kalein, 2013; remarks at the Aspen Cancer Conference)

Five sequentially-arranged axioms were presented at the start of this review as starting points for consideration of a synthesis of concepts in orthodontics, dentofacial orthopedics and craniofacial research on the one hand and newly emerging advances in the field of genomics-epigenomics (refer to Fig. 1).
Axiom 1

Approaches to orthodontic treatment of dentofacial deformities are based on contemporary concepts regarding the mechanisms of craniofacial growth.

The foundation for advances in orthodontics always has been accepted scientific information and principles related to craniofacial biology, among other areas, that are available at the time. New scientific discoveries, often resulting from new technologies led to advances not only in this foundational information, but also to revision of the theories and paradigms used to organize and explain the relevance of that information for clinical treatment.

From the beginning of modern orthodontics at turn of the 20th century and for the subsequent 60 years, the prevailing scientific view was that virtually all development and growth (and thus form) of the craniofacial complex were a result of inherited genetic factors that were immutable. Thus, the growth of the face normally would not be subject to change in pattern to any great extent and also could not be changed with extrinsic factors such as orthodontic treatment.

The theories of craniofacial growth that prevailed through the middle of the 20th century as components of the genetic paradigm did not question so much whether this interpretation was correct. Rather, they focused on where the intrinsic, genetic influence as the motor that drives craniofacial skeletal growth was most active—was it in the periosteum and bone itself (remodeling theory), within sutures (sutural theory) or within the cartilages of the cranial base and mandible (nasal septum/cartilage theory)? The functional matrix hypothesis abrogated the role of genetic factors in craniofacial growth altogether and instead emphasized the role of muscle function and growth of organs and physiologic spaces to account for the forces driving the process of craniofacial development and growth.

The view that the functional matrix hypothesis caused a swing of scientific approach entirely too far away from considerations of genetic factors can be explained by the fact that the field of genetics was so incomplete and knowledge about genetics among craniofacial biologists was especially rudimentary. Genetics of development and growth, especially in higher organisms, essentially was a “black box” that would not
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begin to be understood reasonably in vertebrates until approximately the last two decades of the 20th century.

Variations in growth and form that could not be explained by variations in “function” typically were said to be “genetic,” as if that explanation was sufficient. As a result, many researchers and clinicians alike looked primarily for a “functional” explanation for all variations in craniofacial growth and form, perhaps with the view that it is possible to influence extrinsic, “functional” factors while little or nothing could be done therapeutically short of surgery to affect “genetic” factors. The servosystem theory, however, did provide a transitional and moderating influence in craniofacial research because of its emphasis on growth hormones, which are direct gene products, as mediators of craniofacial growth and treatment response.

Consideration of gene expression of regulatory protein growth factors advanced as research in developmental and molecular biology in general as well as elements of craniofacial biology entered the genomic era at the end of the 20th century with initiation of the Human Genome Project. The post-genomic era began following complete sequencing of the human genome, whereupon scientific attention turned to studies of the function of genes and their proteins important for development and disease.

In craniofacial research, this was the time period when discovery was made of the many transcription factors and growth factors that we now recognize as critical for normal craniofacial development (Slavkin, 2004). We now are in the “epigenomic era,” where the greatest emphasis is concentrated on understanding molecular-developmental biology as this relates principally to the combined role of intrinsic and extrinsic effectors that regulate expression of the genes identified as comprising the genome that are most important for development of disease and of normal development and growth.

Although of considerable value to understanding the history of craniofacial biology and orthodontics, in light of modern understanding of genomics in this “epigenomic era,” the differences between the genomic and functional paradigms now are blurring to the point where they no longer are exclusive mutually, but are complementary. The apparent dichotomy that was represented by earlier views that craniofacial growth was principally the result of intrinsic, unknown genetic factors on the one
hand versus non-genetic functional and environmental influences on the other no longer is useful except to explain the history of orthodontic science and craniofacial biology. The modern synthesis in orthodontics and craniofacial biology in this “epigenomic era” is based on the melding of current and emerging information, concepts and approaches from genomics-epigenomics with those of dentofacial orthopedic treatment.

Axiom 2

The phenotype, which includes the total result of all gene expression as well as the potential for producing or permitting morphological and physiological variation in response to extrinsic variables, changes normally throughout ontogeny in part as a result of expression of normal gene variants and regulatory proteins.

Differences in morphological form of the face and jaws arise as a result of variations, perhaps even minor differences, in craniofacial growth at critical time periods of ontogeny. It is well known that growth overall and also of the elements of the craniofacial complex varies significantly in rate and amount throughout prenatal and early postnatal life. What is less well appreciated is the fact that the presence of normal gene variants, especially those that affect the amount and timing of expression of proteins that regulate growth, provide an underlying basis for variations in growth and form that occur throughout ontogeny.

The issues most relevant with respect to a synthesis of principles of genomics-epigenomics and dentofacial orthopedics include the impact of normal variations of key genes and haplotypes with respect to susceptibility for dentofacial deformities early in development, predispositions toward certain patterns of craniofacial growth due to the presence of variations in key growth factors and the possibility of epigenetic modification of craniofacial growth in association with variations in genomic background during ontogeny.

Axiom 3

The capability of the orthodontic patient to respond to treatment to correct a developing dentofacial deformity is part of their phenotype.
To the orthodontist, phenotype most often exclusively refers to morphological appearance as assessed by facial appearance, as well as clinical assessment of radiographic cephalograms, dental models and maturational status. However, phenotypic traits include not only readily apparent morphological features, but also expression of growth mediators.

The presence of variants of regulatory proteins that mediate craniofacial growth through their degree or amount of expression at specific times of development is critical to understand variability in craniofacial growth and form. Variations in the presence and differential expression of these same gene products at various stages of development and post-natal growth undoubtedly are critical with respect to the capability of patients to respond in a predictable fashion to certain types of dentofacial orthopedic treatment. Normal gene products do not regulate craniofacial development and growth in the sense that they determine variations in form. Rather, they affect the receptivity and responsiveness of growing structures to intrinsic and extrinsic stimuli.

Axiom 4

Strategies to correct a dentofacial deformity should take into account the underlying gene variants and intrinsic epigenetic factors that contributed to the disorder and that may affect the ability of the patient to respond to specific treatment approaches.

In orthodontic parlance, some patients are considered to be “good growers,” while others might be considered “poor growers.” For “good growers,” this likely is due to the presence and normal expression of variants of key growth factors that are favorable in terms of response to dentofacial orthopedic treatment. Similarly, “poor growers” may have individual gene variants and haplotypes that are normal, but unfavorable to the kinds of biomechanical effectors used in standard dentofacial treatment.

Morphological description of dentofacial deformities and even modest success in prediction of facial growth within a relatively broad range based on individually appropriate population norms as averages are not difficult for normally growing subjects. However, in order to be most effective, dentofacial orthopedic treatment in the future will benefit not only from improved understanding of the underlying causes
of the deformity during growth at the level of variability in normal gene variants, but also from awareness of how those same gene variants could affect treatment designed to modify future growth.

The challenge to the field of craniofacial research is to advance understanding of the various gene variants alone and in combinations in order to assess responsiveness to treatment to correct dentofacial deformities and to develop biomarkers that can be used to determine which gene variants are present in individual patients. With this information in hand, clinicians will be in a better position to discern where an individual patient falls within the continuum of growth responsiveness and, thus, to prescribe their treatment accordingly. The genomics of the individual patient will be used as a key diagnostic indicator to predict, at least on a broad level, “good growers” from “poor growers” and to modify treatment accordingly at the start.

The underlying rationale for this approach is virtually the same as for the current emphasis in the medical community on pharmacogenomics and personalized medicine. Within the medical community, personalized medicine is focused appropriately at this time of its early development on diagnosis and treatment of major pathologies such as cancer, neurological disorders and cardiovascular disease; however, the same principles have been applied to treatment of dental disease and disorders such as oral cancer, periodontitis, dental caries and dental anesthesia (Eng et al., 2012; Garcia et al., 2013) and can be applied to dentofacial deformities (Carlson, 1999).

Simply stated, personalized medicine uses advances in molecular biology to target more precise clinical treatment based on the unique genomics of the patient in order to enhance the likelihood of successful treatment. This approach has two major goals. The first is to take into account individual gene variants as underlying causes of differential response to drugs in order to provide the right drug in the right dose with the minimum toxicity for each patient according to their genomic structure (Kornman and Duff, 2012). The second major goal is to develop diagnostic biomarkers for molecular testing in order to predict disease susceptibility, as well as patient response to treatment (Katsanis and Katsanis, 2013). In principle, these goals are exactly the same as those that clinicians should strive for in order to facilitate enhanced diagnosis and treatment of dentofacial deformities.
Using microarray technology, protein biochips are able to identify markers for certain diseases well before they are expressed more obviously in the phenotype. Similar technologies can be used to detect expression of proteins from key genes in the patient that are responsible for regulating growth of craniofacial skeletal structures. Although microarray technology generally has been too highly technical and cost-prohibitive in the past, this approach already is becoming increasingly available and less costly, especially now with availability of next generation sequencers.

As that trend continues, attention will turn from use of microarray analysis in just the most profound diseases in medicine to other areas, such as diagnosis and treatment to correct developmental and growth-related disorders, including dentofacial deformities (Nazmul-Hossain et al., 2008). When that occurs, the practicing orthodontist will have a technology suitable for determining whether or not individual patients in what has been described for the purposes of this discussion as the Clinical Group (refer to Fig. 7) have gene variants that likely are to be favorable or unfavorable with respect to treatment to modify growth and will be able to adjust the treatment approach accordingly. It would be of great value to know each patient’s expression profile of key growth factors and cytokines that will influence growth of the face and jaws. With that information, it may be possible to prescribe a treatment approach that best fits the patient in order to predict the likely response to treatment, rather than find after a significant period of treatment that a patient was or was not a “good grower.”

**Axiom 5**

*Clinical research in orthodontics has been limited by inability to characterize subject populations fully based on their complete phenotypic expression, which includes not only standard criteria for orthodontic diagnosis, but also expression of normally occurring gene variants.*

A central point of this chapter is that normal variation in the individual’s genome will influence not only growth, but also responsiveness to treatment. It follows, therefore, that delineation of subgroups of patients that exhibit favorable and unfavorable variants is critical in clinical orthodontic research to improve understanding of efficacy of dentofacial orthopedic treatment. Unfortunately, use of microarrays to discover
gene variants as described above has not been a practical approach in normal subjects (Wilkie and Morriss-Kay, 2001).

Malocclusion is not a disease with a clear and simple genetic basis. In addition, the standard classifications of malocclusion and dentofacial deformities are not precise sufficiently to define subject populations for the purpose of discovering normal gene variants that are responsible for their occurrence. A more practical approach to clinical research to determine the relationship between gene variants, growth and correction of a developing dentofacial deformity is the opposite approach; first determination of genes responsible for craniofacial development and growth using animal models, and then looking for normal variations in those gene products in such parameters as rate, timing and amount of expression of regulatory proteins in subgroups of patients. In the absence of more detailed information about individual genomic background, dentofacial patients and subjects in clinical trials become grouped together and critical information about the efficacy of various types of treatment to correct dentofacial deformities by altering growth is lost.

ENVOI

I do not believe that knowing whether there are fundamentally different underlying processes in morphogenesis and dysmorphogenesis will alter our clinical management of patients whose distorted dentofacial structures impair them either physically or psychologically. (Ackerman, 1988:219-220)

The comment above by Jim Ackerman was made as a final overview and reaction to the proceedings of the 1988 Moyers Symposium entitled Craniofacial Morphogenesis and Dysmorphogenesis (Vig and Burdi, 1988) over 25 years ago. It illustrates well the prevailing understanding about genetics and its relevance to treatment of dentofacial deformities, even about severe craniofacial anomalies with a certain genetic basis, at that time. While the commentary may seem short-sighted today, it reflects the fact that even in the latter part of the last century, the field of genetics had not developed to the point where even many informed practitioners could see its current and future relevance. As noted
previously as Axiom 1, dentofacial treatment is based on contemporary concepts of craniofacial growth.

The rhetorical questions posed by Lysle Johnston 16 years later in the forward of the proceedings of the Moyers Symposium on *Growth and Treatment: A Meeting of the Minds* (Johnston, 2004) quoted at the beginning of this review suggest similar concerns about the relevance of advances in genomics for orthodontics. Expanding on those concerns, Johnston further noted that while treatment of “real diseases” may benefit from advances in modern biology, “what about treatment of such non-diseases as Class II malocclusion, unilateral crossbite, or protrusion and crowding?”

Current understanding and future developments in the area of orthodontic-orthopedic treatment to correct developing dentofacial deformities have the potential for significant advancement in light of advances in genomics-epigenomics. The overall genomic structure, including both the genes themselves as well as the epigenome intrinsic to the chromosome, provides the foundation for the action of extrinsic epigenomic effectors, such as those that are part of clinical treatment.

In the more distant future, orthodontists and other clinicians treating dentofacial deformities will be using biomarkers to identify key gene variants and to introduce or enhance specific growth factors that either are deficient in expression or absent altogether, almost certainly in conjunction with standard orthodontic mechanotherapy. That approach will come after significantly more advances in personalized molecular medicine. In the relatively near future, however, clinicians principally will use molecular kits and biomarkers to determine the presence or absence of regulatory proteins in order to facilitate diagnosis of the molecular basis of the deformity and, more importantly, the likelihood of success of particular types of treatment approaches.

As many have pointed out, malocclusion and even moderate dentofacial deformities are not mortal diseases. Patients do not succumb to dental crowding, crossbite and Class II malocclusion, or even to relatively profound craniofacial deformities. Therefore, clinical treatment advances in personalized medicine initially have not been directed at orthodontic problems; they have focused on our most severe life-threatening diseases and disorders. There is no question that discoveries of critical biological processes, development of technologies to diagnose and treat diseases, and translation of these discoveries and technologies
Carlson

into patient care will find their way into the orthodontic clinic to improve treatment of dentofacial deformities, from simple Class II malocclusion to profound craniofacial anomalies.

An in-depth understanding of genomics-epigenomics probably is not important for treatment of unilateral crossbite, flared incisors and crowding. However, understanding of the relationship between modern concepts of genomics-epigenomics and of craniofacial development and growth is important critically for future advances in treatment of dentofacial deformities. It is essential, therefore, that orthodontists and especially new orthodontic residents have the knowledge, background and tools to understand these principles in order to recognize and use the potential of the modern, new biology in the development of the genomic-epigenomic perspective of personalized dentofacial orthopedic treatment.

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