# A Review of the Significant Findings in Growth and Development Since the Advent of Cephalometrics

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The task of reviewing the significant advances in growth and development since 1930 is a formidable assignment for the most scholarly of individuals. The field is so broad as to include the activities of cancer specialists seeking the basic mechanisms of cellular growth and of chemists, timing the appearance of various enzyme systems in the embryo and fetus. Indeed, growth and development is an integral part of all research into living processes. How then shall we approach this assignment in limited scope and yet achieve some perspective in this wide field?

It is clear to all of us that significant strides in knowledge are made in two main ways: one, by the invention of new tools of research which are the capital goods of the industry of creative thinking; two, by the formulation of some new concept or hypothesis which ties together existing disjointed information and points the way for the discovery of new facts. The abstract ideas are as essential as are the tools of research.

Let us then review our progress in terms of the invention of new and useful tools of research and at the same time observe the evolution of concepts catalyzing our progress. We shall examine the theories that have endured and even been strengthened by newer knowledge as well as those theories to which the test of time has

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been less kind.

## THE ADVENT OF CEPHALOMETRICS

New research tools set in motion slow, arduous gropings of research men who are then stimulated to search for new basic facts and to re-examine previous findings in the light of more critical observations. Thus we stood, in 1930, astride a vast accumulation of knowledge, but as yet no instrument had appeared with which to objectively examine many of our time-honored concepts.

At the risk of belaboring the importance of the cephalometer, which needs no further elucidation before this group, I should like to pay tribute to Dr. B. Holly Broadbent, who, had he done nothing else in the field of scientific achievement but develop the cephalometer, would have gained the honor of being one of the great scientists of the half century. It is through this excellently designed, precision instrument that we have been better able to explore the complex field of dentofacial development. It is from a serial study of the standardized x-rays, made possible by this machine, that many of the basic concepts of orthodontic thinking have evolved.

Let us examine the effect of the cephalometer a little more closely. The mechanics of the instrument are consistent with the mathematical laws that govern its operation, and it is comparable to the finest precision equipment available. But what does it do for us

as investigators? It gives us an extension of our senses so that we may visualize what is within the patient. However, mere familiarity with the use of a new research instrument offers no guarantee to the production of new or valid information. The instrument is only as good as the men who use it. They, in turn, are only as good as their intellectual backgrounds and their training in scientific discipline.

The cephalometer, as is true of all instruments, has its limitations; it is always the man who abuses the machine and not vice versa. Some of us would like the machine to do our thinking. Already in the few short years since its introduction, we have witnessed a great deal of misguided application in the search for a magic formula that will tell us what is wrong with the patient's face and denture, and what we as dentofacial orthopedists should do to correct the deformity. The men seeking such a simplified analysis are doomed to failure. In this frenzied search countless and perhaps useless angles have been analyzed as if we, like Erhlich, had to perform 606 different tests to find our "silver bullet."

But you may ask, "How shall the cephalometer be used?" Just as the true value of a Stradivarius can be demonstrated only by an accomplished musician, so the cephalometer has proved its value in the hands of those trained in the basic sciences. Thus Broadbent, Brodie, Bjork, Krogman and others used cephalometrics well because they had more than a research tool; they had the essential biological concepts. We shall critically examine some of the theories evolved by these men in an effort to determine if they are valid today in light of research findings in other fields as well as in orthodontics.

The cephalometer was not wholeheartedly accepted by the orthodontic profession when it was introduced by Dr. Broadbent in 1931<sup>1</sup>. No less a personage than Milo Hellman stated. "All progressive orthodontists were now being metamorphosed into pseudo-anthropologists by a so-called 'scientific method' for the improvement of orthodontic diagnosis2." Many new tools or concepts are born in the minds of men only to die in infancy or merely to exist in a state of suspended animation unless there is an intellectual readiness or a physical necessity for their being. This favorable atmosphere was not present until the value of the machine had been demonstrated. Broadbent. convinced of the ultimate value of records made through use of the cephalometer, proceeded with the establishment of the Bolton Study made possible by the generosity of Mrs. Francis P. Bolton, her son Charles, and the facilities of the Anatomical Laboratory of Western Reserve University. His convictions led to the finest serial collection of standardized cephalograms available, and many long range studies of the growth of the head are based on assessment of these records.

Dr. Brodie at once recognized the application of the cephalometer to research and, when the department of orthodontics was established in 1929 at the University of Illinois, insisted on the installation of a Broadbent-Bolton cephalometer. Thus in 1931 the Bolton Study placed the second cephalometer for conducting research. This proved to be a wise investment because this instrument was responsible for much of the research endeavor to come from that school.

While Broadbent was starting the Herculean task of accumulating serial records on a representative sample of nearly five thousand children in the Greater Cleveland area, the University of Illinois used the cephalometer largely for the study of clinical patients and unusual cases.

The stage was now set and the main actors were in the wings; only the raising of the curtain was necessary to get the show started. The wait was not a long one. In 1937 Broadbent published the first comprehensive report of the findings of the Bolton Study<sup>3</sup>. The most striking revelation was that when he compared representative composites of various stages in the growth and development of the face, an orderly and progressive pattern was apparent. This contradicted the previous studies made from the skulls of children which described growth as a series of "stops" and "goes" without progressive continuity of the whole process. This corroborated what Todd had long maintained: that a study of the skulls of dead children was largely a measure of defective growth4.

Although the Bolton group of healthy boys and girls did not show marked differences in the pattern of facial growth, there were differences of comparative size and variations in adult contours. For example, certain sexual differences were noted in that the supraorbital ridges and the external occipital protuberance were more prominent in the male than in the female. However, in certain instances the behavior of parts was found to be constant. Broadbent noted that the posterior nasal spine moved straight downward with growth and that the palate maintained a parallel relationship during the growth span. Thus with the publication of Dr. Broadbent's paper on "The Face Of The Normal Child<sup>3</sup>," the first suggestion of the pattern concept emerged, a concept which would guide and, according to some, mislead orthodontic thinking in the vears to follow.

The inquiring mind of the director of the Bolton Study was not content to limit his exploration of facial growth to the laboratory for he sought to extend the usefulness of his tools to clinical problems<sup>5</sup>. He sensed the importance of the cephalogram in establishing an anatomical diagnosis. Early defects and deviations in facial growth which led to later abnormalities in the denture itself could be detected and documented for future comparison. This was one of the first positive recordings of how closely good facial growth and normal tooth alignment were related but, most of all, it was a radical departure from the belief that occlusion could alter the facial conformation rather than the other way around.

Concurrently, but on an entirely different tangent, Brodie, Downs, Goldstein, and Myer from the University of Illinois published "A Cephalometric Evaluation of Orthodontic Results" in 19386. It was obvious from an analysis of the article that the orthodontist could well afford to be modest in his claims of accomplishment. This study dealt largely with changes in the denture resulting from treatment. Two conclusions of this work have bearing on the field of growth and development. First, the investigators found that a definite correlation existed between success in treatment and good facial growth, a point also stressed by Dr. Secondly, actual Broadbent. changes accompanying orthodontic treatment seemed to be restricted to the alveolar bone. This was a far cry from the days when orthodontists claimed they expanded the nasal passages and widened sella turcica. With these studies we began to think in terms of the limitations of orthodontics as well as its possibilities.

In the light of these findings the profession soon questioned how much influence the development of the denture had on facial growth. Thoma, in a study of six cases of anodontia<sup>7</sup>, stated that all showed normal mandibular proportions by clinical observa-

tion, but that half of the cases had under-developed maxillae due to nasal obstruction. This thinking was reinforced in a report by Brodie and Sarnat<sup>8</sup> who described a case of complete anodontia in which the facial proportions were found to be within the limits of normalcy. So the concept of the independence of facial growth and the formation and eruption of the teeth began to take shape.

Needless to say, there is considerable evidence to indicate that the above views are not universally accepted. Baker in 19379 removed the buccal dental apparatus from the maxilla of a pig and subsequently noticed that a pronounced effect was evident in the sutures as well as all the bones of the head. Baker later expanded his work to include rodents, carnivora and omnivora. In the latter study<sup>10</sup>, only the formative dental organs were removed, leaving the hard structures intact. Again he noted that experimental interference in the denture regions induced change in relatively remote facial areas. Baker concluded that the formative dental organs contained some mysterious growth-propelling force on the development of facial bone.

In reflecting on Baker's work, Wylie<sup>11</sup> noted that the dental apparatus is so important to the survival of the experimental animals studied that much of the cranial architecture is designed to house and support these organs. In man, of course, this is less true and therefore we may suspect a greater degree of independence between the biology of the denture and of the face of man. The studies conducted by Baker were, after all, acute academic experiments which did not simulate common clinical experience. Much closer to reality was the experiment performed by Whatt, Wellington and Williams<sup>12</sup>. These workers sought to determine the relationship between the functional activity of the masticatory apparatus and the growth of the facial skeleton. They selected two groups of young, growing rats of a single strain and endeavored to keep all variables constant with one exception. One group of rats was fed a hard diet, the other a soft. The animals were sacrificed after several months and the skeletons of the heads were retained for measurement. Their report demonstrated that the group subsisting on a hard diet, consistently developed larger and heavier supporting skeletal structures.

According to Pope "The proper study of mankind is man" and, inasmuch as there is always some question when the findings of laboratory animals are applied to man, it would be well to recall the conclusions of Hellman<sup>13</sup> and Broadbent<sup>14</sup>. Both men showed considerable evidence that faces with congenitally missing teeth also exhibited underdeveloped facial structures. Because of limited human subject matter perhaps the functional role of the masticatory apparatus as it affects facial growth and development remains to be further elucidated.

In 1941 a study was published which met the high criteria set by the best of basic science journals. This work, Brodie's thesis<sup>15</sup> on the growth of the head from three months to eight years, has become one of the most widely quoted in our entire orthodontic literature. The most important single finding resulting from this study was that the morphogenetic pattern of the head is established by the third month of post natal life, or perhaps earlier, and once attained does not change. An equally significant finding was the fact that the face did not change its axis in relation to the cranial base and that growth was an orderly progression without the stops and spurts frequently alluded to in the literature. The findings, such as the stability of the various planes and angles, as well as the constant proportions of the upper to the lower part of the face, became part of orthodontic theory. Order was developing in our thinking.

However, to assume that all was darkness and no light prior to 1941 would be fictitious. Other investigators had also attempted to establish an orderly approach to the growth of the face. Krogman as early as 193116 superimposed tracings of anthropoid skulls, using porion as a registration point, and recognized the development of a growth pattern. Hellman<sup>17</sup>, in studies, indicated the stability of the gonial angle when he questioned the progressive changes so frequently referred to by other men. Lastly, Broadbent, as we have stated previously, touched upon the stability and orderliness in the facial pattern. Brodie's special achievement was his systematic and imaginative approach to the study of growth and development and his ability to relate laboratory findings to the daily practical problems of orthodontics. Moreover, his gift as a teacher and his ability to inspire his students to continue along similar lines of investigation marks another of his special contributions to the field of orthodontics.

However, there was trouble in the making for the orthodontist as three ideas coalesced into one that was to place orthodontic thinking in a biological straight jacket. First, you will remember there was some evidence to suggest that facial growth proceeded independently of the denture. Secondly, the pattern of facial growth being genetically predetermined, could not be tampered with except to its detriment. Finally, cephalometric research indicated that the effects of orthodontic therapy were limited to a small area of the facial anatomy and that successful therapy was tied to the favorable growth of the pattern. Frustrating indeed was the outlook for the orthodontist for he was adrift in an open boat and at the mercy of biological variants. This pessimistic outlook was reflected in the research of the next decade. Everyone sought to map the unknown and this gave rise to the many analyses of the dentofacial complex published for the orthodontist's aid. What were these analyses? Were they maps intended for explorers into the unknown or were they charts to signify the reefs and shoals of orthodontics for the timid traveler? Let there be no mistake, these were valuable guides. They, also, reflected the age of pessimism and limitation.

A few recognized that the situation had gotten out of hand. The original statements of earnest investigators had been misappropriated and poorly applied in areas not intended by their proponents. The comfortable cradle of constancy was most reassuring to those who felt that we now had a blueprint to growth prediction. The Sunday supplement type of orthodontic reader erroneously interpreted Brodie's paper as an example of normal facial development, while the author, in the original thesis, stated that the sample used was based on the quality of the x-rays available, rather than on any specific type of occlusion or excellence of facial development. The automatic extension of the stability of the pattern through the entire growth span was beyond the author's sampling and intent. These same enthusiasts applied the constancy of the pattern to the individual whereas the concept was derived from a composite tracing of twenty-one males. Indeed, when the findings of the composite are applied to the individual, we are apt to fall into the same trap as the statistician who drowned while trying to walk across a river with an average depth of three feet.

While the orthodontic profession on

this side of the Atlantic was wholeheartedly embracing the pattern concept of growth, a prodigious investigation by a man across the sea was developing a slightly different theory of the growth behavior in the human. While Bjork accepted Brodie's pattern concept in principle, he did not subscribe to the rigid fixation of proportions as they had been proposed. His studies18, which included an age span twenty-one years, from twelve to showed that the facial axis did change its relationship to the cranial base, and that facial prognathism did increase with age. Although Bjork also based his conclusions on composites, he accepted the great variation to be found within the individual patient. Lande's19 work supports Bjork's contention that the mandible becomes more prognathic with advancing age, and this increase is associated with a decrease in the angulation of the lower border as well as a decrease in the angle of convexity. However, it is interesting to note that Lande19, as well as Bjork in later work, found the most significant changes occurred after seven years of age.

The specter of skepticism was beginning to stir and the contented individual investigators who were still clinging to the status quo were thrown into a schizophrenic type of confusion when Brodie<sup>20</sup> presented his findings on late growth changes to this group in 1951. It was becoming apparent to many that individual variation was the only finding that remained constant. The facial planes, all of which were remarkably stable in his first study, now began to show evidence of changes in relationships. An interesting corollary was the observation that the denture was not moving forward as rapidly as the supporting facial bones, and that great fluctuation could be found in the angulation of the incisor teeth during growth.

Needless to say, these findings were as disturbing as they were revealing. Did this mean that we were back where we started from many years ago? Did it mean that we should discard the pattern concept and begin to think only in terms of individual variation? Of course not. Those of you who have studied longitudinal series are aware that the stability of the growth pattern is still a workable hypothesis although many changes are occurring within the basic dentofacial complex. To think of the face as a fixed mold is also to think of the component parts as static in their proportions. This would considerably reduce the potential of the growing face. The pattern concept has its place in orthodontic theory, but it was never intended to be the termination of investigation into the variations of the growing face.

The disturbing revelation by Bjork which gave impetus to this new trend in orthodontic thinking was not immediately accepted by the profession, but the completeness of his investigation, which was summarized in "The Face in Profile18" and elaborated upon in subsequent papers21, 22, 23, 24, could not be ignored for long. He postulated that facial prognathism increased because mandibular growth was more active than that of the cranial base. A decrease in the angulation of the cranial base was also considered a significant factor in contributing to the increase of total facial prognathism. The rapid increase in ramus height was responsible for the relative prominence of mandibular over maxillary prognathism. The spatial relationship of these bones was somewhat equalized by the decrease in the chin angle. Bjork, in accord with Brodie, noted the decrease in alveolar prognathism. He attributed it to the decreasing chin angle along with widening of the jaws and crowding of the incisors, while Brodie<sup>20</sup> felt it was largely due to the restraining action of the facial musculature, mainly the buccinators. Bjork's reasoning at this point is open to question inasmuch as Schaeffer<sup>25</sup> showed that the incisal angulation may decrease, increase, or remain the same during the growth span. Nor did Woods<sup>26</sup> find an increase in the lower arch width after occlusion of the cuspid and molar was established.

Bjork<sup>27</sup>, in an attempt to analyze the variations in sagittal occlusion, decided that it was largely a matter of relative jaw size and position. This conclusion is not shared by many of the investigators in the field of morphological variation. Coben<sup>28</sup> concluded that due to the infinite variation in the cranial base and every structure in the dentofacial complex, it is doubtful that any rigid combination of factors can be associated with any particular type of malocclusion.

During the intervening years the director of the Bolton Foundation completed his task of accumulating records which cover the entire growth span of the individual. Dr. Broadbent's careful selection of material leading to his concept of normal dento-facial development has no equal. Those of you who have seen his composite of the growth of the face undoubtedly were impressed with the striking stability of the facial pattern and the marked similarity in growth between boys and girls. In comparing his own work with that of Bjork's, Dr. Broadbent indicated that their findings were similar and their differences were in degree and not in kind.

### VITAL STAINING

The cephalometrists have written a memorable chapter in the history of the growth and development of the human face. However, x-rays have their limitations and although quantitative growth was readily assessed from the cephalo-

gram, the question of qualitative growth could not be approached. Consequently, we returned to vital staining, a method long known for its ability to reveal growth sites. The interesting history of its discovery has often been told and the names associated with its utilization are part of the history of research methodology. The span of time which was assigned this essayist will permit only a partial review of this work.

It was during the very depth of the depression years in our country that Brash<sup>29</sup> published his now famous "Mechanics of Growth" in the Edinburgh Press. After analyzing the alizarine-stained pigs, he concluded that all changes in the size and form of individual bones occur by accretion and absorption of the surfaces. He relegated the influence of sutures on growth to a very minor role. However, there is some question as to whether or not all of his conclusions were sufficiently supported by his findings. His hypothesis was not completely accepted by the investigators in this country. Massler and Schour<sup>30</sup>, in their study of the growth pattern of the cranial vault in the rat, described generalized growth on all surfaces before seventy days of age, but determined that the most prolific after generalized growth ceased, was in the cranial sutures. When Moore<sup>31</sup> studied the cranial growth of an alizarinated monkey skull embedded in plastic, he concurred with the findings of Massler and Schour. Moore also pointed to the importance of the facial sutures and their influence in causing the face to grow downward and forward. It is interesting to note that stain was always present on the maxillary side of these sutures. He also found intense staining in the base of the cranium but he felt that this was an indication of reorganization and not interstitial growth.

All the findings of vital staining were under suspicion when Paff and associates<sup>32</sup> were able to stop bone growth in a tissue culture with Alizarine Red S. However, when they were unable to repeat the same feat in the living animal, the previous findings utilizing vital staining could be considered valid.

### Animal Experimentation

The role of sutural growth as an important determinant in the development of the face and cranium is as yet not fully clear. For example, Gibin and Alley<sup>33</sup> removed a plug of bone from the coronal suture area and rotated it 90°. Later observation revealed a new suture-like junction in the operated area and no distortion of the skull was observed. However, when this experiment was repeated with a solid plug of parietal bone, not including a sutural area, it was noted that complete fusion had taken place and that considerable alteration in the bony framework of the animal was evident.

Just when the evidence that the suture is a primary center of growth seemed conclusive, the interesting study by Moss appeared in the Journal of Anatomy. Moss<sup>34</sup> removed the parietal bones from the cranium of a rat less than seven days old and noted that the frontal bones showed over-growth into the parietal area. Thus the suture lines were displaced by bony growth. He then reasoned that the suture was not the primary predeterminer of the morphology of the individual bones, but that the usual location of the sutures is seemingly dependent upon the normal expansive growth of the individual bones adjacent to the sutures. These results were not repeated when the operation was performed on an older animal. Moss felt that expansion of the calvarium was initiated by brain growth as stated by Massler and Schour, but that peripheral extension of the

bones into the presumptive suture areas takes place. Thus the stain evident at the suture site is merely evidence of activity at the border of the bone. If the bones do not keep up this activity, wide sutures develop as can be seen in the hydrocephalic. Moss feels that the necessary biological structures are not present in sutures at the time of greatest growth and believes that the suture is largely an area of mechanical adjustment, thereby supporting Brash's contention that the sutures play a minor role. Moss observed that Massler and Schour's work was done during a period of rapid growth and reasoned that the sutures could only have been in what he termed their presumptive stage. Moss attempts to reconcile divergent points of view into a more coherent explanation of experimental phenome-

The work of Gans and Sarnat<sup>35</sup> neither supports nor discredits the role of the sutures as a primary growth site. These workers employed the technic of metallic implants which they placed at the suture sites. They subsequently noted considerable separation of the paired implants in the zygomatic temporal and zygomatic maxillary areas. However, it was evident that the rate of descent of the nasal and occlusal planes was faster than the degree of separation occurring at the frontal maxillary and frontal zygomatic sutures. This would indicate that absorption and accretion were playing an important part in the growth of the face.

Robinson and Sarnat<sup>36</sup> repeated Hunter's<sup>37</sup> classical study on the growth of the pig's mandible employing cephalomatic roentgenography as well as metallic implants. In the main they confirmed Hunter's original observations but added that considerable growth was evident in the anterior portion of the bone and less at the inferior border. The anterior growth,

or remodelling, was noted by Schaeffer<sup>25</sup> in his studies on the relationship of the lower incisor to its basal bone in man, when he began having difficulty superimposing the symphysis area in the late growth years.

The importance of condylar growth did not seem to be completely comprehended until several cases involving known histories of temporomandibular joint ankylosis were followed cephalometrically<sup>38, 39, 40</sup>. The vogelgeschihit, or the patient with unilateral temporomandibular joint involvement who developed marked dysplasias of the face, focused attention on the condyle as an important growth site. The marked lack of ramus height and pronounced ante-gonial notching was a common finding in these cases and one which was repeated when the condyles were removed in the monkey by Sarnat and Engel<sup>41</sup>. However, in the monkey experiment and the rat experiments by Jarabak<sup>42</sup>, there was evidence of regeneration along with the establishment of a false joint.

### Physiological Rest Position

No historical review of important milestones in the field of growth and development would be complete without reference to physiological rest position. Niswonger<sup>43</sup> and Gillis<sup>44</sup> both observed the muscular balance of the mandible, but Thompson<sup>45, 46</sup> deserves much of the credit for accurately documenting this important concept. Brodie<sup>15</sup>, in his thesis, stated that the mandibular rest position was established before the eruption of the teeth and was not later influenced by their presence. Thompson expanded this study<sup>47</sup> and in an extensive cephalometric examination of both edentulous and dentulous patients concluded that not only is physiological rest position highly constant but it cannot be permanently altered by prosthetics, operative dentistry, or orthodontic procedures. These findings constitute basic research in orthodontics and many important advances have emerged from this concept. This thinking led to the following conclusion: first, posture was all important, and the presence of teeth not a principal factor in physiological rest position; secondly, as the mandible closed, the center of rotation was in the middle of the head of the condyle and the path of closure was upward and forward. However, if in closing, malposed teeth interfered, the mandible was deflected into an abnormal position. If this interference were removed, there would then be spontaneous correction of many cases. Thus it seemed indicated that malocclusion should be analyzed from rest position rather than from the occlusal position. The advent of laminagraphy opened the temporomandibular joint for direct investigation in living man. Ricketts<sup>48</sup> made excellent use of the new tool and explored an area heretofore closed to orthodontic study. He found that rest position was not immutable but subject to change with alteration in anatomical relations induced by orthodontic therapy. Thus the constancy of rest position was challenged. Ricketts reasoned that physiological rest position is a conditioned position in the interest of speech mastication and not posture alone<sup>49</sup>. Also, it is constant only as long as the environment is unchanged. In reality his observation did not challenge the validity of Thompson's findings. Ricketts differed only with the interpretation placed upon the observed facts.

If this new concept of the mutability of muscle balance is valid, it leads to speculation as to what effect the change in skeletal architecture may have on muscle tensions and, in turn, the effect of altered muscle physiology on the future of skeletal growth. We know from Pratt's<sup>50</sup> experimental masseterec-

tomy that the cranium and mandible were distorted due to the change in muscle tension. Washburn<sup>51</sup> removed the temporal muscles in the rat and observed that certain bony prominences were resorbed. No distortion of the cranial bones could be seen unless the nuchal muscles were also removed. When he destroyed the seventh nerve unilaterally<sup>52</sup>, the lack of muscle tension on the operated side permitted the facial and cranial bones to be drawn toward the normal side. Needless to say, the alteration in muscle tensions caused by the simple changing of a Class II molar relationship is a minor operation compared to the removal of a masseter.

In closing, I should like to repeat that numerous significant articles have been mentioned in this paper which have been the building blocks in the foundation of orthodontic knowledge. Many other noteworthy papers were omitted in the interest of either time or continuity, and to these authors I extend my apologies. With your permission, I should like to indulge in a little crystal ball gazing. Time, further research, and practice have upheld some concepts; others have fallen by the wayside. With respect to some concepts, it would seem that we have made a complete circle and are now back where we started—the wiser for the trip. However, it is possible that we are on the threshold of two major advances that will have a profound influence on the future of our specialty. First, intensive studies are now underway, and others have been recently completed, in the field of muscle physiology. These studies will undoubtedly uncover important knowledge in areas heretofore unexplored. It next appears that growth prediction will command more of our attention in the field of cephalometrics and offer hope of direct practical application. The problems

are everywhere before us, for despite the advances on so many fronts, the sum of the unknown far exceeds the known even in our small sphere of scientific interest.

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