Introduction

Deformations and malformations: the history of induced and congenital skull deformity

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The human skull is amazing in its design. Although it matures into a solid, protective casing for the brain, it begins as a softer, more malleable structure that allows for the enormous growth of the brain in the child's early years. During this period, there are numerous biological and environmental forces (intentional and unintentional) that can affect the shape of the human skull. This issue of *Neurosurgical Focus* brings together the internal biological mechanisms that can alter the shape of the skull and the external forces that can do likewise.

External forces that can contribute to deformations of the skull, in its broadest sense, may depict evolutionary trends. Indeed, the skull has been "deforming" for over 500 million years, from the days when the first vertebrates developed a bony encasement for the brain and several important organs that support life such as the special senses and aerodigestive organs. As animals evolve, skulls represent one of the most prominent manifestations of an animal's phylogenetic development.

Humans are no different. Comparison of specimens of various anthropological morphologies has reflected this relative change in the neurocranial (braincase) component and the viscerocranial (facial) component over the course of human evolution. These changes, for the most part, reflected functional (and assumed survival) advantages. It is not surprising, although fascinating that the development of the brain and its size relative to the organism has had a major impact on the ultimate evolutionary shape of the modern human skull.[1] Interestingly, as humans became more adept at changing their environment, they became adept at changing their own appearance. Whereas evolutionary changes in the skull were associated with functionality (and likely survival advantage), the induced changes are for cosmesis or "communication."

Intentional deformations of the skull have been practiced since approximately 45,000 BC as noted in the anthropological record. The written records date back to the Hippocratic writings of 400 BC. It is believed that among other reasons, intentional deformation of the skull was a means of denoting social status. Several authors in this issue provide the reader with carefully researched, succinct information about this topic. Ayer et al. begin by describing the implications of skull deformation in ancient Peru and Egypt, and bring it forward to the modern era where skull deformity, though previously suggestive of high stature in certain cultures, may actually be deleterious in modern Western cultures. Romero-Vargas et al. revisit the Mayans and provide excellent insight into a methodology that seemed to change and evolve over time as well as to the significance of such skull deformations. Enchev at al. reveal the many fascinating aspects of proto-Bulgarian culture and the complex role skull deformations had in that culture. Most interestingly, although most believe skull deformity is a thing of the ancients, Dr. Gump presents a very intriguing look at the practices of skull modification through the use of implants and the potential implications for neurosurgeons.

Skull deformations are not necessarily just induced. Neurosurgeons in general and pediatric neurosurgeons in particular are experts in the biological and indeed the environmental forces involved in skull deformity. Pediatric neurosurgeons and our basic science colleagues continue to study and learn about these factors, ranging from hydrocephalus, to the craniosynostoses, to benign positional molding. Mehta et al. provide an excellent survey of the history of the diagnosis and treatment of craniosynostosis. The article authored by Maher et al. presents to us Cushing's limited but some may say seminal work in deformity surgery of the skull. Manjila et al. provide an excellent historical perspective and modern therapy for Kleeblattschadel deformity, giving the reader a surgical strategy for treatment of this rare disorder. The reader is then invited to consider the future of the treatment of all cranial bone deformities, iatrogenic and otherwise, by looking at future bioactive technology for new implants.

Indeed, this issue of *Neurosurgical Focus* is unique in many respects. It provides a different look and a newfound respect to that structure through which all of us have had the privilege of entering. Understanding the skull, civilization's fascination with it and its pathology is what this issue will provide the reader. *(DOI: 10.3171/2010.12.FOCUS.Intro)*

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The sociopolitical history and physiological underpinnings of skull deformation

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In this report, the evidence, mechanisms, and rationale for the practice of artificial cranial deformation (ACD) in ancient Peru and during Akhenaten's reign in the 18th dynasty in Egypt (1375–1358 BCE) are reviewed. The authors argue that insufficient attention has been given to the sociopolitical implications of the practice in both regions. While evidence from ancient Peru is widespread and complex, there are comparatively fewer examples of deformed crania from the period of Akhenaten's rule. Nevertheless, Akhenaten's own deformity, the skull of the so-called "Younger Lady" mummy, and Tutankhamen's skull all evince some degree of plagiocephaly, suggesting the need for further research using evidence from depictions of the royal family in reliefs and busts. Following the anthropological review, a neurosurgical focus is directed to instances of plagiocephaly in modern medicine, with special attention to the conditions' etiology, consequences, and treatment. Novel clinical studies on varying modes of treatment will also be studied, together forming a comprehensive review of ACD, both in the past and present.
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Key Words • skull deformation • plagiocephaly • brachycephaly • Egypt • Peru

Nichter and colleagues[21] suggested that the idiom "heads of state" might have derived from the practice of the political elite's molding the heads of their offspring to differentiate themselves from the rest of a populace. Studies of human remains from ancient Peru and Egypt have not drawn attention to the political implications of artificial skull deformation, whether artistic or real. These perceptual or structural cranial characteristics can be derived from a variety of factors that will be elaborated upon throughout the course of this paper. First, physical evidence from ancient Peru and Egypt is reviewed. Second, the discussion draws attention to ways in which the politics of a society might help to explain the rationale behind ACD. Ancient Peruvian and Egyptian evidence suggests that physical or artistic manipulation of skulls was undertaken not just to reinforce social distinctions, but also to entrench political power. It is argued that approaching perceptions and portrayals of skulls could also complement discussions of artificially deformed crania. The techniques used in ACD will then be elaborated upon, with a discussion of the physiological basis, consequences, and treatments of plagiocephaly.

Abbreviation used in this paper: ACD = artificial cranial deformation.

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Artificial Cranial Deformation by Region

The earliest evidence of the practice of ACD comes from remains of the Mousterian people from Shanidar in Iraq and dates from the Middle Paleolithic period (approximately 300,000–30,000 years ago).[30] The practice in ancient Peru and Egypt shall be addressed here, because evidence from the latter society greatly differs from that of the former in terms of frequency. Anthropologists studying the 2 societies, nonetheless, have accounted for the practice in similar ways.

Ancient Peru

The first evidence of an artificially deformed skull in Peru was found near Uricocha, dated to the period between 6000 and 7000 BCE, suggesting that the ancient Peruvians introduced the practice on the continent.[7,26] A collection of 500 Peruvian skulls in Paris only contains 60 free of deformation (Figs. 1 and 2).[5] In some cases, dig sites yielded human remains with 90% of the skulls deformed.[3,5,26] Head shape appears to have demarcated membership within a group in a large, complex society, whereas in smaller societies, head shape demarcated social group differences. There is a "complex" archaeological record in the region according to Dingwall,[5] which Imbelloni[13] divided into 7 distinct regions according to, among other things, the method used. Intentional defor-

Fig. 1. Lateral view of ancient Peruvian skull. Courtesy of the Université Libre de Bruxelles (Bruxelles, Belgium).

mation was accomplished either by compression of the front and back of the head with boards and pads, tightly bandaging the head and progressively adjusting the bandages, or by restraining the child against a cradleboard.[26]

Anthropologists have explained ACD as a method of defining membership of social or ethnic groups. Tommaseo and Drusini[29] argued that the practice could enforce a hierarchy or signify membership in a warrior class. Social distinctions, however, could also give the individual political power. In ancient Peru it has been suggested that as the ruling class became comfortable in power, they permitted some noble families to shape the skulls of their children, imitating the distinct features of the ruler's skull.[5,8,26] While this may have entrenched the ruler's power, permitting an individual to show such allegiance would require the individual to take on a political role. Conversely, this privilege could have resulted in a proliferation of claims to rule the society. With more nobles eliciting the cranial characteristics of the ruler, the populace would no longer be able to differentiate between ruler and noble based upon that criterion.

Ancient Egypt

Although there is little archaeological evidence of ACD in Egypt before 600 CE, notable exceptions exist from the reign of Akhenaten (1375–1358 BCE) in the 18th dynasty. Studies of the morphology of Akhenaten's skull suggest that an acromegalic or macrocephalic disease may have deformed it.[3,5] Akhenaten's queen, Nefertiti, is notably portrayed in busts and reliefs with apparent anterior plagiocephaly, although her mummy has not been discovered to verify this trait. The mummy of another of Akhenaten's consorts and the mother of Tutankhamen, the so-called "Younger Lady" mummy, also possesses a cranial deformity.[11] Finally, the mummy of Tutankhamen, Akhenaten's apparent successor, was discovered at the

Fig. 2. Posterior view of ancient Peruvian skull. Courtesy of the Université Libre de Bruxelles.

start of the 20th century with a deformed cranium (Fig. 3).[5] Although no current study addresses the methods that might have been used, the skulls elicit deformations characteristic of frontooccipital deformation.

Akhenaten ushered in a great religious, political, and artistic upheaval: the Amarna revolution. Government was centralized as the pharaoh dissolved local cults and turned Egypt into a monotheism worshipping Aten. Stylistic changes in depictions of the royal family were so drastic that it is believed they could only have occurred at the suggestion of the pharaoh.[1] In particular, the cranial shape of the royal family and officials was distorted.[3,5]

Dingwall's[5] claim that no physical evidence exists from the period surrounding Akhenaten's reign appears to be disproven by the skulls of the "Younger Lady" and Tutankhamen. Yet the artistic evidence should not be discredited. Depictions of members of the royal family, such as Nefertiti, may have deliberately been distorted so that they became linked to Akhenaten's growing power. Further research into the causes of Tutankhamen's deformed cranium may reveal that Akhenaten decided to physically deform his heir's head to legitimize his claim to the throne. The importance of distorting head shape, artistically or physically, may have been politically significant for Akhenaten.

Fig. 3. Artistic reproduction of Tutankhamen's head shape based on a CT of his skull.

Plagiocephaly in Modern Medicine

Though societies may no longer manipulate the heads of their offspring to augment their political power, plagiocephaly continues to be a problem in developing children. Plagiocephaly refers to an asymmetrical head, wherein part of the head is flattened and part is round (Figs. 4, 5, and 6). In this section, we will review the mechanisms, intentional or unintentional, of skull deformation, physiological consequences, and treatment options.

Mechanisms

Deformation occurs by an alteration of the direction of intrinsic growth of the human head. Physiologically, as the brain grows, the developing bones are pushed outward by its expansion, while osteogenic membranes at the sutures produce bone equal to this displacement. This functions to increase bone size but maintain surrounding articulations.[8] Occasionally helping to fill the space are intercalary, "wormian" bones, compensating for the increased surface area.[6,23] Once fused, the sutures remain in their position.

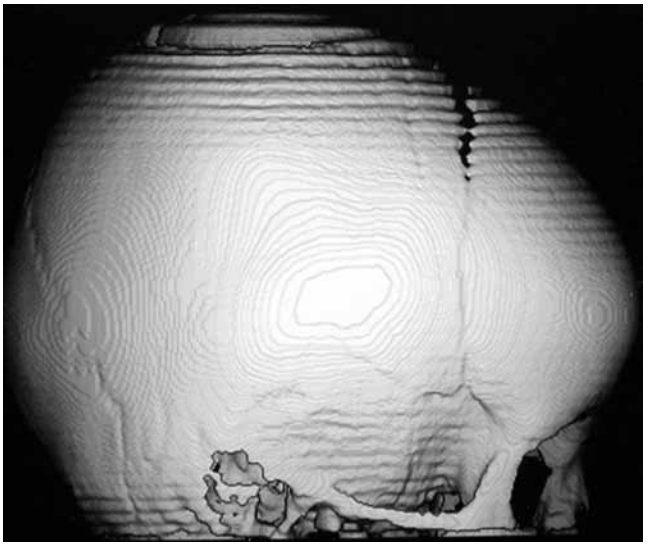

Fig. 4. Lateral view of 3D CT reconstruction of plagiocephalic skull.

Artificial Deformation

According to Imbelloni,[13] the skull may be artificially shaped through either tabular or anular deformation. Tabular, or "flat-head" deformation involves skull manipulation by compressing the frontal and occipital parts of the head with oblique or erect fixed boards and pads. This produces frontooccipital flattening and lateral bulging of the head. Oblique deformation occurs when oblique boards compress the skull at the inion, whereas erect deformation is accomplished with vertical boards centered on the lambdoid suture.[26] The deforming apparatus can prevent blood flow to the developing areas and cause necrosis of the occipital bone.[9] Anular deformation

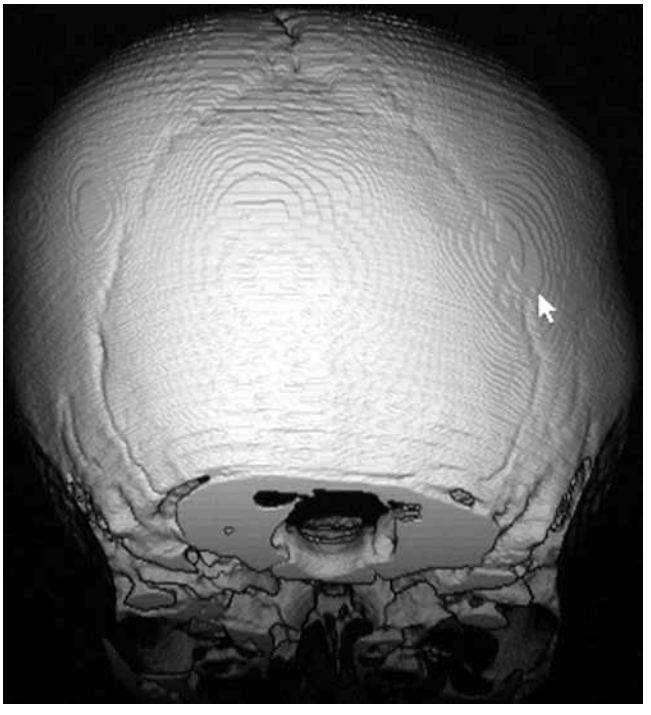

Fig. 5. Posterior view of 3D CT of plagiocephalic skull.

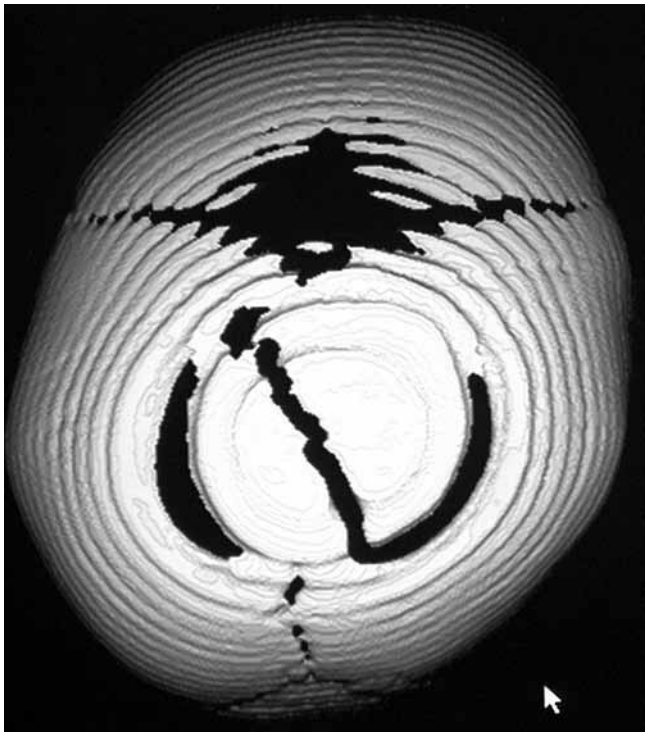

Fig. 6. Inferior view of 3D CT of plagiocephalic skull.

is the consequence of wrapping a compressive bandage around the skull, leading to a conical cranium.

Pathological Deformation

Plagiocephaly continues to affect nearly 10% of all children, with a large rise in incidence beginning in 1992 corresponding with the initiation of the "Back to Sleep" campaign by the American Academy of Pediatrics. This campaign urged parents to position their children supine during sleep to decrease the incidence of sudden infant death syndrome.[2,15,18] The impact of this initiative can be seen in the near elimination of frontal plagiocephaly (attributed to prone sleeping) and a concomitant rise in the incidence of posterior plagiocephaly. In addition to a supine sleep position, the uterine environment has been implicated in the development of plagiocephaly.[19] Intrauterine factors may compromise neck musculature or be the primary cause of skull malformation, leading to a positional sleep preference that may exacerbate plagiocephaly. Maternal primiparity, multiple births, and congenital torticollis are all associated with the development of plagiocephaly due to constraints of the maturing fetus.[14] Factors compromising fetal movement may lead to pressure on a specific cranial area, thereby conferring plagiocephaly on the newborn. In addition, many infants suffering from neurological impairment, oligohydramnios, or undergoing forceps- or vacuum-assisted delivery may also have plagiocephaly.[10,22] Interestingly, posterior deformational plagiocephaly has a right-sided prevalence, perhaps due to the fetus's descent into the pelvis, which may limit growth of the right occiput and left frontal areas. In addition, males have a higher risk of developing plagiocephaly, which is suggested to be due to the larger cranial size and comparative inflexibility of the male fetus.[22]

Sequelae

The consequences of cranial deformation are generally resolved if the infant is positioned so that he or she is lying on the side opposite to the plagiocephalic side. However, without positional maneuvering off the flattened area, the problem may perpetuate or worsen. Deformities may persist into adolescence, but such occurrences are rare, with few current cases acknowledged by patients.[4] One frequent comorbidity is torticollis, or "wryneck," which is most commonly due to an imbalanced tightness of the sternocleidomastoid muscle. A 371-patient prospective case series correlated congenital muscular torticollis with deformational plagiocephaly ($p = 0.043$), and suggested that the incidence of "torticollis/sternocleidomastoid imbalance in deformational plagiocephaly" may be underreported.[25] Fortunately, muscular torticollis can be successfully managed with physical therapy in nearly all cases. Several other conditions have been reported to be associated with plagiocephaly, but it is important to recognize that none have been demonstrated to have a causal relationship. For example, a recent small case-control study compared motor development in infants with and without positional plagiocephaly, and suggested a possible risk of motor delay in infants with this condition.[17] In addition, a 470-patient case-control study assessed neurodevelopment in infants with and without plagiocephaly at 6 months of age. Deformational plagiocephaly was associated with a decrement in Bayley Scales of Infant Development scores ($p < 0.001$), most significantly evident in motor functions.[27] It is likely, however, that any difference in motor development between these 2 groups is simply due to spending less time in the prone position, and not due to the positional plagiocephaly. In addition to motor development, a 1259-patient retrospective study showed a trend correlating deformational plagiocephaly with otitis media, possibly because of plagiocephalic developmental alteration of the eustachian tube.[24] Lastly, strabismus has been reported to be associated with frontal plagiocephaly, possibly due to traction on the ocular globe from underlying cranial malformations.[4] Fortunately, deformational frontal plagiocephaly has been nearly completely eliminated since the initiation of the Back to Sleep program. Overall, despite several studies demonstrating associations between positional plagiocephaly and other conditions, no good-quality evidence supports the hypothesis that plagiocephaly is the cause.

Treatment

Due to parental concerns about appearance and the perceived comorbidities associated with plagiocephaly, treatment is often sought for these conditions. Suggested care for affected patients include reassurance, positioning, and, on occasion, external orthotic devices.[4] Positioning refers to the facilitated placement of an infant's head on the nonflattened side when lying down; this fixation occurs with the use of wraps, foam wedges, or strategic positioning implemented by the caregiver. A recent randomized controlled trial used a Safe T Sleep device compared with positioning strategies, with no significant dif-

ference found.[12] External orthotic devices, such as skull bands or helmets, use strategically placed pads to guide the intrinsic growth of the skull. These devices are worn for about 23 hours per day and are custom-fit to the child's head.[4] Some studies have shown that these skull-molding helmets, which work in a fundamentally similar mechanism to the tabular artificial deformation method, may be more effective in the treatment of plagiocephaly than positioning methods, as measured by improvements in the cephalic index score.[28] However, controversy surrounds these helmets because of their significant expense and the lack of controls and long-term follow-up in most studies.[4] Helmets have been shown to be effective in short-term studies, with a 114-patient prospective study reporting a 17% correction of transcranial asymmetry ($p < 0.001$).[20] Another study recently compared parental opinion to the results of topographic laser head scans, assessing real versus perceived improvements with skull-molding therapy. Interestingly, parents reported more improvement post-therapy than was identified with topographical scanning, suggesting that parental bias plays a significant role in reported outcomes.[16]

Conclusions

From its origins in ancient Peru and ancient Egypt to the increasing prevalence in modern times, skull deformation continues to exhibit relevance in anthropological and medical contexts. Recent medical studies detailing consequences of skull deformation should inform future anthropological studies of ancient remains. A discussion of the rationale behind the practice in the light of political contexts might broaden our understanding of this worldwide practice of ACD, and could provide comfort for patients affected by skull deformation. Researchers should determine whether membership within a particular group, for example, also brought with it certain political responsibilities that may help to explain the rationale behind deforming the head of one's offspring. Further research may yield more fruitful results if, in investigating the political implications of head shape, researchers account for the wider cultural significance of head shapes and not merely those that have been intentionally deformed during infancy.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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A look at Mayan artificial cranial deformation practices: morphological and cultural aspects

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Induced deformation of the cranial vault is one form of permanent alteration of the body that has been performed by human beings from the beginning of history as a way of differentiating from others. These procedures have been observed in different cultures, but were particularly widespread in Mesoamerica. The authors examined and reviewed the historical and anthropological literature of intentional deformation practices in Mayan culture. The Mayans performed different types of cranial deformations and used different techniques and instruments to deform children's heads. The most remarkable morphological alteration is seen in the flattening of the frontal bone. Some archeological investigations link deformation types with specific periods. This article provides a glance at the cultural environment of the Mayans and demonstrates the heterogeneity of this interesting cultural phenomenon, which has changed over time. *(DOI: 10.3171/2010.9.FOCUS10200)*

Key Words • Mayan culture • artificial cranial deformation • archaeology

Permanent alterations of the body (such as dental modifications, scarification, mutilation, tattooing, body piercing, and other types of body art and ornaments) have been part of human culture from the beginning of history and have served as a way of differentiating oneself and one's tribe or clan from others. Lip piercing was practiced among African and American tribes and was a sign of social status. Vikings employed dental modification in order to look fearless and for aesthetic purposes. Induced deformation of the neonatal cranial vault is another example of these types of practices.

Artificial (also known as intentional) cranial deformation results from manual manipulation of the skull and/or from the application of a deforming apparatus. It is manifested in morphological changes to the cranial vault.[1] Artificial deformation can take many forms; Gerszten and Gerszten[7] discuss as many as 14 unique cranial shapes resulting from different methods of deformation. The practice of artificial cranial deformation has been documented on nearly every continent and may have begun as many as 30,000 years ago.[19] The practice of deforming newborn heads was present in the whole of the American continent[4] from North America to Patagonia, but cranial molding in neonates was most widely practiced in Mesoamerica. The Maya was the main Mesoamerican civilization, noted for its development of written language, architecture, and mathematical systems.[2]

The Mayans are among the most studied ethnic groups in the world. In many collections of Mayan skulls recovered by archaeologists, artificial cranial deformation is a common feature, and some collections show a diversity of deformation styles.[3] When Columbus saw some of the natives in the New World, he wrote that they had "foreheads and heads much broader than any people."[6]

In this paper, we analyze the historical precedents, mechanisms, different types, and role of cranial vault modification among the Mayans.

Methods

To gain perspective on this issue, we examined the historical and anthropological literature on intentional deformation practices in Mayan culture in the collections of the National Institute of Anthropology and History

in México and the National Autonomous University of México. Evidence of different types of artificially deformed skulls was sought from archaeological collections and previous anthropological investigations.

In the 16th century, Spanish chroniclers provided numerous detailed descriptions of cranial deformation, methods, and materials popular among the Mayan people. Some fascinating fragments of these records are translated and shared with the neurosurgical community in this article.

For purposes of illustration, we also provide images of ancient Mayan art and figurines that represent cranial deformation.

Results

The Mayans lived in what is now the southeastern part of Mexico and northern parts of Central America.[18] Pre-Hispanic Mayan culture is divided into 4 main periods: the Early Preclassic, Late Preclassic, Classic, and Postclassic. The Early Preclassic Maya is considered to date from 1400 to 1000 BC, the Late Preclassic period from 500 to 300 BC, the Classic period from AD 300 to 900 (when the Mayan cities reached their highest development), and the Postclassic period from AD 900 to 1540. We do not know at present precisely how the Mayan civilization originated. It almost appears as if it suddenly sprang into being, flourished, and then decayed just as suddenly. The practice of skull deformation seems to have been known from the earliest times.[8] Among Mayans, the meaning of deformation was not only aesthetic but also religious and social.[18]

Gonzalo Fernández de Oviedo,[11] a Spanish chronicler, reports an interesting conversation about deformation between one Mayan and an early Spanish missionary, who questioned the Mayan about the meaning of the custom. The native was asked why the heads of his countrymen were not like those of the Christians. He replied that when the children were born, their skulls were plastic and so they could easily be molded into shape, thus producing a boss on each side and a great depression in the middle of the head extending from one side to the other. "This is done because our ancestors were told by the gods that if our heads were thus formed we should appear noble and handsome and better able to bear burdens." According to Dembo and Imbelloni,[4] the Mayans used hard implements in their deformation techniques. Several techniques existed, but the shaping of the head in neonates was carried out mainly in 2 ways: by compression of the head with pads and adjusted bindings and by restraining the child on specially designed cradles.[10]

The Spanish Franciscan Diego de Landa described how the Mayans deformed the heads of their children in 1572. He describes the women as bringing up their children with the greatest roughness and says that as a rule the children went naked. Scarcely 4 or 5 days after birth the child was stretched out upon a sort of little bed made of reeds or strips of other material, and then the head was placed between two boards, one at the back and one at the front. These were then pressed together and fastened. For days at a time the child was thus left in suffering; Landa adds that sometimes so much pain was caused that the children died, and that he himself saw one who had openings behind the ears, a condition that, it was reported, was not uncommon (Fig. 1).[5]

According to experts, 2 main head shapes existed: erect deformation and oblique deformation.[17] Erect deformation (Fig. 2) is associated with cradle-boards, a deforming device that affected corporal mobility. The child was placed in a decubitus position, which is associated with lambdoidal flattening. The lambdoidal flattening was associated with erect deformation as a secondary, unintentional effect because of the position of the child in the cradle-board. The occipital flattening was often asymmetrical and was not limited to a single side but was noted on both the left and right sides.[15]

Oblique deformation (Fig. 3) was attained without affecting the mobility of the child. Instead, paddles were applied directly to the head. This type of deformation had several variants. The pseudoanular, bilobulated, and trilobulated variants were all obtained when a frontal board was employed together with a system of bandaging.[17]

Some archeological investigations link deformation types with specific periods. Oblique deformation began during the Preclassic period (500–300 BC). During the Classic period, both the oblique form (with its pseudoanular variant) and the erect form are present. In the Postclassic period, the erect form was dominant, and it seems that the technique was widespread within the Mayan territory and had few variants.

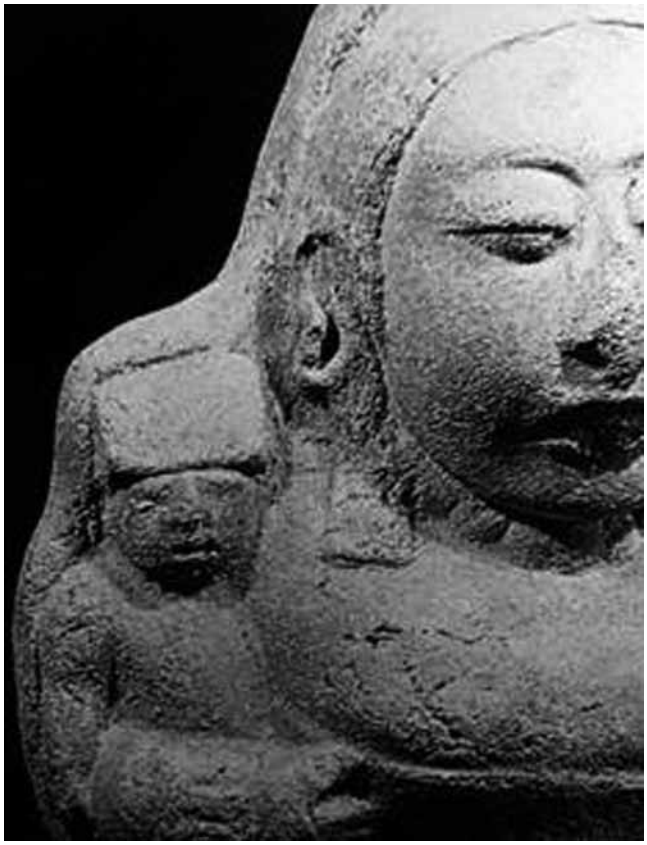

Fig. 1. Photograph of Mayan figurine representing a woman with a child. The child is wearing a board on the forehead, which is part of a deforming device. (Figurine from Museo del Popol Vuh, ciudad de Guatemala. Catalog number 0379.) Photograph courtesy of V. Tiesler Blos.

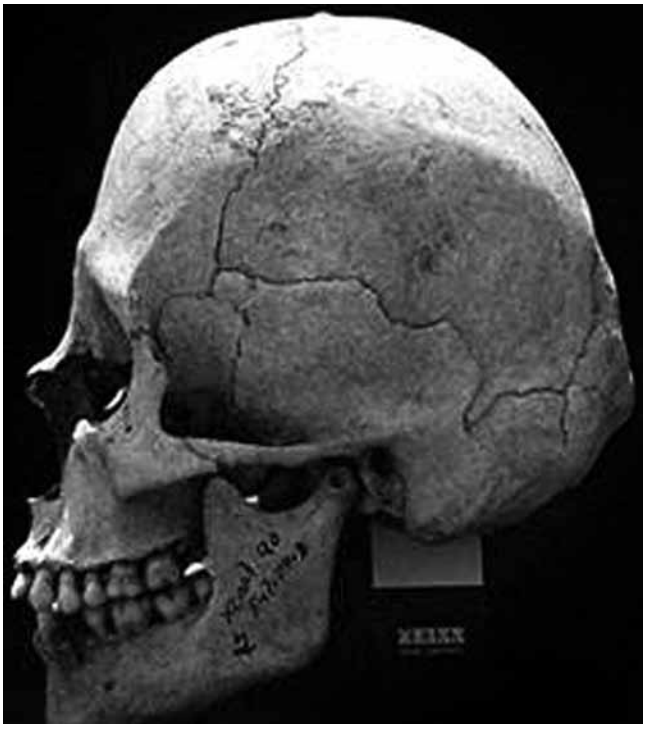

Fig. 2. Photograph of Mayan skull exhibiting a typical erect deformation with its characteristic lambdoidal flattening. Reproduced with permission from V. Tiesler Blos.

During the Classic period, evidence shows that skull deformation was characterized by a distinct social pattern (Fig. 4). The general population could only perform erect deformations. However, if children were destined to become governors, priests, or warriors or attain another high-status position, they were given oblique deformations. High-ranking Mayan families of the Classic period differentiated themselves from the lower classes with their head shape. This social hierarchy can be seen in pottery, figurines, drawings, monuments, and architecture, where characters with oblique deformation are dominant.[10] After the Classic period, this pattern was less pronounced, probably because of the influence of neighboring cultures.[12,17] According to some authors and based on the analysis of artistic representations, oblique deformation was meant to shape a child's head to resemble the head of a jaguar, a sacred animal and symbol of power for the Mayans.[13] Another hypothesis, based on analysis of paintings, is that the Mayans were trying to shape heads to resemble the head of the maize god, who was the symbol of fertility.[16] Vera Tiesler performed one of the largest studies of Mayan skulls. She examined 175 deformed pre-Columbian Mayan skulls and was able to determine gender in 140 (69 female and 71 male). She found that 127 of these had the erect deformation and confirmed that the oblique shape was linked to elevated social standing. The obliquely deformed skulls were frequently accompanied by a postcoronal sulcus caused by bandages used to constrict the paddle against the forehead.[17]

The most remarkable morphological alteration is seen in the flattening of the frontal bone. The Mayas were naturally a brachycephalic people, and the custom

Fig. 3. Photograph of Mayan skull exhibiting a typical oblique deformation with the frontal bone sloped backward in a continuing oblique line with the nasal bones. Reproduced with permission from V. Tiesler Blos.

of anteroposterior compression would promote this racial characteristic, causing the skull deformation to be displayed throughout life. The flattened skull is higher than nondeformed skulls of comparable age at death. Based on the figurines, paintings, and skulls that have been discovered, it seems that the greatest pressure seems to have been exerted upon the forehead. In many cases, the fron-

Fig. 4. Photograph of Mayan relief (originally painted) showing characteristic oblique deformity among governors.

tal bone sloped backward to an amazing extent, causing the nose to be in line with the retreating forehead, modifying the appearance of the entire face.

In the more isolated modern Mayan settlements, this custom is still practiced, though not to the same extent.

Discussion

Cranial deformation practices are common in many areas of the world and are practiced for many reasons. The practice has mainly been documented in Egypt, Japan, South America, Mesoamerica, and some places in Europe.[1]

Anthropologists and other scientists have extensive knowledge of cranial deformation practices among ancient cultures. Some of the available information has been known for centuries. Although it is impossible to know the precise cultural environment, social organization, and religious conceptions that have led to this practice, it is clear that the practice is culturally influenced.[1]

Because of the plastic characteristic of the skull in newborns, skull modification was initiated during the first days of life and lasted for 2 or 3 years. This is done around the world to achieve specific adult head shapes.[3]

The first descriptions of cranial deformation among the Mayans were made by Spanish chroniclers in the 16th century. These descriptions (some of which are translated above) are historically invaluable,[5,11] but most are superficial, highlighting the "primitive" parts of the custom, and are indeed interpretations. There is a lack of primary information directly from the Mayan culture.

The cranial deformation practice was forgotten in the literature from the 16th century to 1843, when John L. Stephens published *Incidents of Travel in Yucatán*.[14] Stephens describes an artificially deformed skull that he found during an excavation. Based on skull collections and writings about the Mayan practice of cranial deformation, it is clear that the custom was at one time widespread.

The deformations were not uniform, probably because of the physiological responses of the children, the duration of the compression, and the particular characteristics of the deforming device. Despite the variety of forms found in the osteological evidence, Romano[12] says that only the oblique deformation is represented in the paintings of the classical Mayan period. This confirms that the cranial deformations were a permanently visible symbol of social affiliation.

Neurosurgeons have recently focused on the neurological effects of the deformations, but there is no scientific evidence of their having caused any neurological disability.[9]

From the point of view of the present, cranial deformation could seem to be a primitive practice. It may not be easy to understand why this custom was performed, but its practitioners found it socially and religiously appropriate. Doubtless, to the Mayans, the skull was a fundamental part of an individual's identity, and cranial deformation was elevated to the level of art.

Conclusions

With this paper, we are only providing a glance at the Mayan culture and are trying to present this valuable information to the neurosurgical community. Artificial cranial deformation constitutes a biocultural process. Our investigation describes the main deforming techniques and the resulting morphological expressions. This article demonstrates the heterogeneity of this interesting cultural phenomenon, which has changed through time. In the past century, interest in this ancient custom has surged, and neurosurgeons should not be excluded from this fascinating discussion.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Paleoneurosurgical aspects of Proto-Bulgarian artificial skull deformations

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Paleoneurosurgery represents a comparatively new developing direction of neurosurgery dealing with archaeological skull and spine finds and studying their neurosurgical aspects. Artificial skull deformation, as a bone artifact, naturally has been one of the main paleoneurosurgical research topics. Traditionally, the relevant neurosurgical literature has analyzed in detail the intentional skull deformations in South America's tribes. However, little is known about the artificial skull deformations of the Proto-Bulgarians, and what information exists is mostly due to anthropological studies. The Proto-Bulgarians originated from Central Asia, and distributed their skull deformation ritual on the Balkan Peninsula by their migration and domination. Proto-Bulgarian artificial skull deformation was an erect or oblique form of the anular type, and was achieved by 1 or 2 pressure bandages that were tightened around a newborn's head for a sufficiently long period. The intentional skull deformation in Proto-Bulgarians was not associated with neurological deficits and/or mental retardation. No indirect signs of chronic elevated intracranial pressure were found on the 3D CT reconstruction of the artificially deformed skulls. *(DOI: 10.3171/2010.9.FOCUS10193)*

Key Words • **paleoneurosurgery** • **artificial skull deformation** • **Proto-Bulgarian**

The eternal striving of humans to be discernible from the others in the crowd has provoked the development of many different techniques for changing their bodies. Throughout the history of humankind, humans have constantly invented new methods to change their external appearance. Some of the methods, such as body painting, make-up and hairdressing, produce temporary effects. Other, permanent examples of body modification include tattooing, circumcision, clitoridectomy, foot binding, uvulectomy, body piercing, intentional scarring, and most recently plastic surgery.[7] Some of the most extreme forms of body modification are those that alter not only the humans' soft tissues, but also their skeletons. These include dental mutilation, trephination, and artificial cranial deformation. The historical geographical distribution of body modification and in particular of intentional skull deformation is ubiquitous; it occurs in all continents of the world[16] and is a part of many cultures, including that of Proto-Bulgarians[3–5,10,11,13] (Fig. 1). All dates in this paper are from the Common Era.

Abbreviation used in this paper: ICP = intracranial pressure.

Who Were the Proto-Bulgarians?

The modern Bulgarians are descended from 3 ancestral groups: Slavs, Thracians, and Proto-Bulgarians. In the postulated "homeland" region (present-day Ukraine), Slavs had had contacts with Sarmatians and Goths. After their subsequent spread on the Balkans, in the early 6th century, they had begun assimilating non-Slavic, paleo-Balkan peoples, such as Thracians and Greeks. Having lost their indigenous culture due to persistent Hellenization and the Roman conquest, everything that had remained from the Thracians had been completely absorbed into the Slavic tribes.

Traditionally, historians associated the Proto-Bulgarians with the Huns, who had migrated from Central Asia. However, the evidence for this has not been definitive, and the debates have continued up to the present. Genetic and anthropological researchers have shown that the large steppe confederations of history had not been ethnically homogeneous, but rather had been unions of multiple ethnicities.[3] In the first third of the 6th century, the Proto-Bulgarians, originally from Central Asia, had formed an inde-

Fig. 1. Map of the world showing historical geographical distribution of artificial skull deformations.

pendent state that had become known as Great Bulgaria. Its territory had extended from the Donets River to the north, the Black Sea and the Azov Sea to the south, the lower course of the Danube to the west, and the Kuban River to the east. Khazars had subjugated Great Bulgaria in the second half of the 7th century. Proto-Bulgarians had migrated to the region known as Ongal and conquered Moesia and Scythia Minor from the Byzantine Empire, expanding the new kingdom farther into the Balkan Peninsula. A peace treaty with Byzantium in 681 and the establishment of the Bulgarian capital of Pliska south of the Danube River had marked the beginning of the First Bulgarian Empire. Proto-Bulgarian invaders had mingled with the Slav tribes and had imposed their traditions and rituals, including artificial skull deformation.

Proto-Bulgarian Artificial Skull Deformations

In the territory of contemporary Bulgaria were found 56 cases of Proto-Bulgarian artificial skull deformations in 4 excavations, and 1 intentionally deformed Pecheneg skull. The finds were dated from the 4th to the 11th century.

An artificially deformed skull from the Late Antiquity period (4th–6th century), belonging to a man more than 60 years old, was excavated from a Christian necropolis in Kabile, in southeast Bulgaria[5] (Fig. 2). Some morphological changes of the neurocranium, like a strongly flattened, elevated, and elongated frontal bone; shortened occipital bones; and a flattened lower part of the squama occipitalis with a smooth relief show that the deformation must have been caused by a combined circular bandage that had exerted pressure in the direction from front to back and from the upper to the lower part. The imprint of the bandage was notable on the fontal, parietal, and occipital bones. The bandage had caused shortening of the skull and had enlarged its height; an oblique form of the so-called anular type. In the crossing point of the sagittal and the coronal sutures a rare anatomical variation—os bregmaticum—was observed. The identified changes of the nasal bones most likely had been caused by an additional tightening bandage, which had flattening of the nose as its aim. According to the racial analysis, the skull had belonged to a member of the European race, with prevailing Proto-European racial features.

Another artificially deformed skull, dating back to the Late Antiquity period (4th–6th century), was excavated in the city of Varna, in the Black Sea region[13] (Fig. 2). The skull had belonged to a 25- to 30-year-old woman, and had an erect form of the anular type cranial deformation. It had been encircled by a 4-cm-wide bandage, which had been tied around the forehead, the parietal bones, and the squama occipitalis. Due to the circular pressure, the head had grown upward and had aquired an approximately cone-shaped form, with an apparent depression in the middle of the squama frontalis and a flattened squama occipitalis. Based on racial analysis, the skull could be assigned to the European race, with slight Mongoloid traces.

Two skulls with artificial deformation of the anular type were examined (of a total of 23 skeletons), from the Early Medieval non-Christian necropolis with 2 burial sites in the village of Kyulevcha, Shumen region (8th–9th century)[11] (Fig. 2).

The first skull had belonged to a 22- to 25-year-old woman. The traces from the tightening bandages (with a width of approximately 4.5–5 cm), were clearly detected immediately above the frontal eminences. Over the parietal bones and the squama occipitalis, however, the imprint of the pressure bandages could be noted, although this was slightly indistinct. Most likely, the artificial skull deformation, which is an oblique form of the anular type, had been produced by combined circular bandages with frontooccipital and parietooccipital pressure directions.

The second skull had belonged to a 40- to 45-year-old man. Traces from the tightening bandages (with a

Fig. 2. Maps showing geographical distribution of the Proto-Bulgarian artificial skull deformation in Bulgaria. The symbol ▲ designates excavations in Kabile, in southeast Bulgaria (4th–6th century; see Cholakov). Finds: 1 artificially deformed skull. The symbol ▼ designates excavations in the city of Varna, in the Black Sea region (5th–6th century; see Minkov and Boev). Finds: 1 artificially deformed skull. The symbol ► designates excavations in the village of Kyulevcha, in the Shumen region (8th–9th century; see Kondova et al.). Finds: 2 artificially deformed skulls. The symbol ◄ designates excavations near the city of Devnja, in the Black Sea region (end of the 9th century; see Kadanoff and Jordanov). Finds: 52 artificially deformed skulls. The symbol • designates excavations near Krivina village, in the Rousse region (11th century; see Boev and Minkov). Finds: 1 artificially deformed skull.

width of approximately 5 cm), were found on the squama frontalis, on the parietal bones over the lambda, and on the upper part of the squama occipitalis. These signs indicated that the deformation had been caused by circular pressure with upward-downward and forward-backward directions, resulting in the so-called erect form of the anular type skull deformation. In the region of the squama occipitalis, pronounced sutura mendosa, which is a rare anatomical variation, was observed, and also noted was a well-defined interparietal bone (a large wormian bone at the lambda craniometric point, often referred to as an Inca bone [os incae], due to the relatively high frequency of occurrence in Peruvian mummies).[18]

According to the typological racial analysis of the skulls, the female one was classified as a contact racial type—gracile Mediterranean—with strongly defined Mongoloid features. The male one was identified as an Iranian variant of the Northern race, with slight Mongoloid traces. Those data have connected the studied population with both the supposed Turkic and the Alanian origin of the Proto-Bulgarians.

In 1976, Kadanoff and Jordanov[10] reported on a series of 18 skulls with pronounced asymmetry, which they selected from a total of 52 artificially deformed and accordingly restored skulls from all age groups (from toddlers to elderly adults; Figs. 3 and 4). The finds were excavated in a circular tomb near the city of Devnja (Fig. 2), dating back to the end of the 9th century. In each individual skull, the artificial deformation was verified by serial measurements of linear and arched distances between several craniometric points; namely the glabella, bregma, inion, lambda, sphenion, asterion, and porion. Precise quantitative analysis of the skull asymmetry was achieved in both the occipitoparietal and temporoclinoidal parts of the specimen (compensatory and persisting asymmetry). The authors demonstrated that the discrepancies among some of the size values established in individual skulls, and the skull asymmetry, recorded scopically with other measurements, are due to displacements of the craniometric points (sphenion, asterion, inion), produced by differences in the growth rate and size of bones. Within the artificially deformed skulls, the pressure bandages produced arrested development of the bones and depressions along their surfaces.

A unique find for our country, an artificially deformed Pecheneg skull was discovered at the excavations near Krivina village, Rousse region (Fig. 2), and dated back to the 11th century.[4] The skull had been shaped with an oblique form of anular deformation, and belonged to a 40- to 45-year-old man. The imprints of the pressure bandage, with a width of approximately 4 cm, were evident in the middle of the forehead. Archeological finds played a crucial part in determining the ethnic origin of the skull, because anthropological data alone do not yield sufficient evidence to distinguish a Proto-Bulgarian from a Pecheneg skull.

Discussion

Definition, Classification, and Techniques of Artificial Skull Deformation

The skull deformations basically could be divided into artificial (also known as intentional or cultural) and unintentional types.[15] The intentional type of skull deformation results from a ritual of artificial modification of the primary, natural head shape in newborns to a desired, unnatural

Fig. 3. Photographs and 3D CT scans of an artificially deformed Proto-Bulgarian skull from the circular tomb near the city of Devnja, dating back to the end of the 9th century (see Kadanoff and Jordanov). The artificially deformed skull had belonged to an adult woman, and displays an oblique form of anular intentional cranial deformation. The artificial cranial deformation had been a result of the tightening of 2 pressure bandages: one in front of and the other behind the coronal suture. **A:** Photographs of the skull: anterior, lateral (notice the imprints of the pressure bandages—*arrows*), posterior, and superior. **B:** Series of 3D CT scans of the skull: anterior, lateral (notice the imprints of the pressure bandages—*arrows*), posterior, superior, and inferior (notice the absence of bony signs of elevated ICP). **C:** Plastic head reconstruction made by Professor J. Jordanov (Institute of Experimental Morphology and Anthropology with Museum, Bulgarian Academy of Sciences), anterior and lateral views.

form.[1,2,6,7] Artificial head deformation is achieved by application of different techniques, including bandages, pads, boards, stones, or a combination of these to the neonate skull throughout the 1st year of life or longer.[6] In contrast to desired cranial modifications, unintentional cranial deformation could be caused by numerous medical factors,[8] some peculiarities of the habitual sleeping posture, and by nutritional factors.[6]

In the literature, artificially deformed skulls are classified in 2 general types: anular (also known as circumferential or circular) and tabular (or frontooccipital or anteroposterior).[6,7,9] These 2 types can be subdivided into oblique (Fig. 3) and erect (Fig. 4) forms, which can be further subdivided into numerous subtypes.[15,16]

Anular skull deformation is achieved by constriction of the head with pressure bandages, resulting in a lengthened, conical cranial vault, with narrowed medial-lateral dimensions. Typical for the craniometric vault measurements are the decreased width and increased height.[1,2,15,16]

Tabular skull deformation, also known as a "flat-head" deformation or "artificial brachicephaly," is characterized by anterior and posterior vault compression along the sagittal plane, resulted in flattening at the front and back and lateral expansion of the head. Typically, the cranial vault width increases, whereas the cranial vault height is variably affected.[1,2,15,16]

Artificial Skull Deformation in the Scientific Literature

The practice of artificial skull deformation traditionally has been an object mainly of anthropological,[1–6,9–11,13–15]

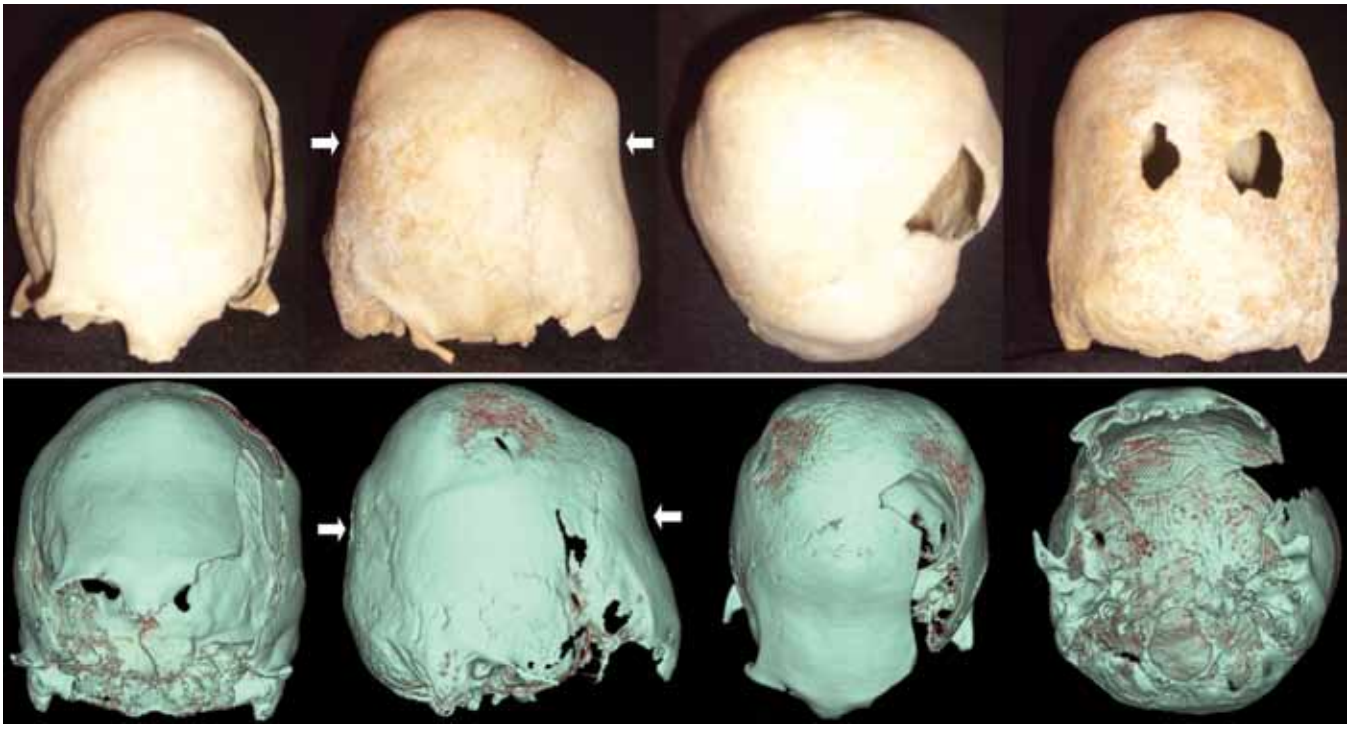

Fig. 4. Photographs and 3D CT scans of an artificially deformed Proto-Bulgarian skull from the circular tomb near the city of Devnja, dating back to the end of the 9th century (see Kadanoff and Jordanov). The artificially deformed skull had been shaped with an erect form of anular intentional cranial deformation, caused by the tightening of one pressure bandage that encircles the forehead and the occiput. **A:** Photographs of the skull: anterior, lateral (notice the imprints of the pressure bandage—*arrows*), superior, and posterior. **B:** Series of 3D CT scans of the skull: anterior, lateral (notice the imprints of the pressure bandage—*arrows*), superior, and inferior (notice the absence of bony signs of elevated ICP).

archaeological, and historical studies and publications. The problem was not investigated from a neurosurgical point of view until the past 2 decades, when the first so-called paleoneurosurgical papers were published in neurosurgical journals.[7,12,16,17]

Artificial Skull Deformation in the Neurosurgical Literature

The neurosurgical literature concerning artificial skull deformations is surprisingly scarce.[7,12,15,16] Several papers initiated the development of a quite new direction of neurosurgery; paleoneurosurgery.

The term paleoneurosurgery (from the Greek word "paleon" [old] combined with "neurosurgery") could be defined as a branch of neurosurgery dealing with the recovery and identification of human skull and spine remains from archaeological and anthropological contexts, their use for the nosological reconstruction of past populations (paleonosology), and the evolutionary history of diseases, with a bearing on the evolution of neurosurgery in general.

Artificial Skull Deformation as a Heritage of the Proto-Bulgarians

In Bulgaria, Gothic artificially deformed skulls were discovered in the necropolis of the Roman cities of Abritus (in the province of Moesia Inferior) and Augusta Traiana (in the province of Thrace) dating back to the era of the so-called Great Barbarian Incursion (3rd–5th century) in the Roman empire.[11] The rite of artificial cranial deformation had not been practiced by Thracians and Slavs. The custom had been transferred to the Balkans by the Hun tribes and mainly by the Proto-Bulgarians. Consequently, artificial cranial deformation had become widely applied; the most numerous findings of intentionally deformed skulls in our lands were from the medieval period. The most recent artificially deformed skulls in

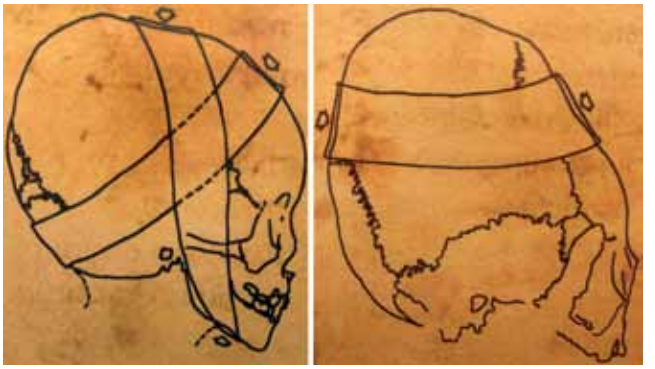

Fig. 5. Drawings illustrating the technique of Proto-Bulgarian artificial skull deformation (Institute of Experimental Morphology and Anthropology with Museum, Bulgarian Academy of Sciences). **Left:** Technique performed with 2 pressure bandages, resulting in an oblique form of anular skull deformation (notice the imprints of the pressure bandages—*arrows*). **Right:** Technique performed with 1 pressure bandage, resulting in an erect form of anular skull deformation (notice the imprints of the pressure bandage—*arrows*).

Bulgaria were discovered in a necropolis from the 15th century, but as a remnant.

Why Did Proto-Bulgarians Perform Artificial Skull Deformation?

Currently, the reason Proto-Bulgarians had performed artificial skull deformations is a matter of speculation. Unfortunately, no historical records referring to the practice have been found. However, most Bulgarian anthropologists have accepted that in the beginning of the tradition, artificial skull deformation had emphasized the upper social status of the tribal leaders and their relatives (social belonging). Later, artificial skull deformation spread among the other members of the ethnic group and became a sign of ethnic belonging.[3–5,11,13]

Technique of Proto-Bulgarian Artificial Skull Deformation

The morphological changes of the neurocranium in the Proto-Bulgarian artificially deformed skulls had been caused by 1 or 2 circular bandages made from textiles, leather, or other soft materials, exerting pressure in the desired direction[3–5,11,13] (Fig. 5). In the cases with 1 pressure bandage, the bandage had been positioned behind the coronal suture or had encircled the forehead and the occiput. In the cases with 2 bandages, the bandages had been fixed in front of and behind the coronal suture, crossing each other above the porus acusticus externus. The imprint of the tightening bandages frequently could be observed on the skulls. The Proto-Bulgarian artificial skull deformation in general is an anular (also known as circumferential or circular) type of skull deformation with oblique (Fig. 3) and erect (Fig. 4) forms.

Neurological Consequences of Proto-Bulgarian Artificial Skull Deformation

In the lands of contemporary Bulgaria were discovered Proto-Bulgarian artificially deformed skulls belonging to individuals from almost all age groups—from toddlers to elderly adults[3–5,10,11,13]—which indirectly means that the pressure bandages causing the artificial cranial deformation did not injure the underlying brain, at least not to a degree that can cause death. On the contrary, most of the intentionally deformed skulls had belonged to adult persons with long survival, which could be difficult in the presence of permanent neurological deficit and/or mental retardation. These facts correspond to the data in the literature.[7,12,16,17]

Evaluation of Proto-Bulgarian Artificially Deformed Skulls With 3D CT Scanning

Computed tomography represents an exceptionally valuable tool in paleoneurosurgery, improving the reconstruction of fragmented skull specimens and allowing the anatomical and morphological analysis of the inner structures (endocranium, paranasal sinuses, semicircular canals, teeth, diploë, and so on).[17] The bony signs of chronic elevated ICP are well known and include diffuse beaten-copper pattern, dorsum sellae erosion, suture diastasis, abnormalities of venous drainage that particularly affect the sigmoid–jugular sinus complex, and elevation of the bregma region. The existence of these signs of elevated ICP in the Proto-Bulgarian artificially deformed skull specimens was examined using 3D CT studies. The data obtained demonstrated the absence of signs of chronic elevated ICP (Figs. 3 and 4).

Conclusions

Artificial skull deformation logically represents one of the main research objects of the newly developing branch of neurosurgery—namely, paleoneurosurgery. That rite of intentional cranial deformation had been traditionally practiced by the Proto-Bulgarians. Their technique had included 1 or 2 pressure bandages, tightening around the newborn's head during the first 1–2 years of life. Typically, the resulting intentional cranial deformation had been an erect or oblique form of the anular type. The practice of artificial skull deformation in the Proto-Bulgarians had not caused neurological deficits and mental retardation. The 3D CT reconstruction of the artificially deformed skulls, which was used to evaluate the internal cranial surface, rejected the existence of indirect bony signs of elevated ICP.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Enchev. Acquisition of data: Enchev, Nedelkov, Atanassova-Timeva. Analysis and interpretation of data: Enchev, Nedelkov, Atanassova-Timeva. Critically revising the article: Atanassova-Timeva. Study supervision: Jordanov.

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Modern induced skull deformity in adults

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The practice of induced skull deformity has long existed in numerous disparate cultures, but for the first time in history it can be applied to adults. While extremely limited in application, some ideas have persisted in the far fringes of modern Western culture with remarkable tenacity. Practitioners of extreme body modification undergo procedures, outside the sphere of traditional medical practice, to make striking, permanent, nontraditional esthetic tissue distortions with the goal of transgressing societal norms. The International Trepanation Advocacy Group represents another example of a fringe cultural movement, whose goal, rather than being purely aesthetic in nature, is to promote elective trepanation as a method for achieving a heightened level of consciousness. Both movements have relatively short and well-defined histories. Despite their tiny numbers of adherents, neurosurgeons may be called on to address relevant patient concerns preprocedurally, or complications postprocedurally, and would benefit from awareness of these peculiar subcultures. *(DOI: 10.3171/2010.10.FOCUS10203)*

Key Words • **skull deformity** • **trepanation** • **skull modification**

Historically, skull modification has essentially been limited to infants in cultures in which this practice occurred.[4] These traditions have been documented extensively in the anthropology literature and have been carried out at some time on every inhabited continent.[1,3,5,7–12] Study of the history of neurosurgery supports the hypothesis that, until modern times, most cranial procedures in adults were undertaken to relieve mass effect from such entities as hematoma, abscess, or depressed skull fracture. This limited scope of cranial intervention, especially on an elective basis, was primarily due to technological constraints. These constraints have largely been overcome, and a wide spectrum of cranioplasty procedures is now standard in the modern neurosurgical armamentarium.

Interestingly, there has been some movement in the past few decades, within some far-fringe elements in society, toward applying this technology outside the bounds of traditional medicine. There are 2 new general perspectives on the role of cranial modification that have emerged in 20th century Western culture and that may represent the first time that elective skull deformity procedures have been applied to adults. These ideas include the concept of extreme body modification, and the position promoted by the International Trepanation Advocacy Group. Both movements have relatively well-defined modern histories.

Body Modification

Deliberate alteration of the human body for nonmedical reasons has a lengthy and rich history in human culture.[3] These practices can be carried out for religious reasons, aesthetic purposes, sexual enhancement, as a rite of passage, to denote affiliation, or for shock value or self-expression. Male circumcision and ear piercing represent 2 of the more common and socially accepted practices today. One views these particular examples as one end of a spectrum, whereas at the other end one sees the psychopathology known as apotemnophilia, a disorder in which an otherwise rational individual has a strong and specific desire for the amputation of a healthy limb or limbs.

Although deliberate deformation of the skull has historically been restricted to infants, modern science now allows us to realistically consider previously impossible feats of modification. These boundaries have been explored and expanded outside the context of medical practice. The foremost practitioner of this extreme body modification is former piercer Steve Haworth.

Haworth is the body modification artist credited with inventing and popularizing techniques that facilitated such creations as the infamous "Metal Mohawk" on client Joe Aylward (Fig. 1).[14] This particular project was completed in 1996 and remains one of Haworth's more notorious accomplishments. Among his many contributions to the advancement of body modification are techniques for subdermal and transdermal implants that alter the appearance of the individual's head. (Figs. 2–4) (http://www.stevehaworth.com/wordpress/index.php/archives/category/modify-blog). The very limited but consistent demand for such procedures suggests that more radical cranial modifications will emerge in the future. Haworth and others continue to push back the boundaries of what is technically achievable. To date, no medical complications of procedures such as these have been reported in the neurosurgical literature.

Fig. 1. Photograph showing metal spikes screwed into bases that have been embedded in the skull. From http://www.piercingsntattoos.com/?cat=24, accessed November 15, 2010.

Fig. 2. Photograph showing how subdermal implants can be used to modify head shape. From http://www.piercingsntattoos.com/?cat=24, accessed November 15, 2010.

Trepanation

The history of the International Trepanation Advocacy Group can be traced back to a Dutch medical student and admitted polysubstance abuser named Bart Huges, who was ultimately denied his medical degree by the University of Amsterdam at least in part for his vocal advocacy of marijuana use. During one particular episode in the early 1960s while under the influence of recreational psychoactive drugs, Huges came to believe that drilling a hole in one's head would allow blood to more freely pulse around the brain, reproducing the state of an infant's brain prior to closure of the cranial sutures. He was aware that by adulthood, the brain is denied an elastic bony covering against which to expand; in addition, he proposed that gravity gradually robbed the brain of some of its blood volume.[12]

Trepanation, as his theory went, had the potential to reverse both of these processes. Huges felt that prolonged standing on one's head could yield the same result, albeit temporarily, but only with trepanation could a long-term so-called "permanent high" be attained. He eventually delineated his ideas in a 1962 monograph alternately entitled either *Homo Sapiens Correctus*, named for what he believed would describe a new species of humans with holes in their skulls, or *The Mechanism of Brainbloodvolume (BBV)*. He later also authored the book, *Trepanation: the Cure for Psychosis*, and an autobiography, *The Book With the Hole*. Although never finishing medical school, he did in 1965 successfully self-trepan, and, based on what he felt was an excellent benefit from this procedure, later convinced others to do the same.[2]

Huges met his first trepanation converts, Englishman Joe Mellen and his companion Amanda Feilding, in Spain in 1966. Three years later, Mellen was the second, after Huges, to self-trepan, with the goal of reaching an elevated state of consciousness. Unfortunately, his process was not at first successful; he made several bloody, botched attempts himself with a twist drill over several weeks before finally breaking through the inner table with a power drill. He apparently survived these traumas with minimal morbidity.[12] Now an art dealer and publisher in London, Mellen described this series of actions in graphic detail in his autobiography entitled *Bore Hole*.

However, it was Amanda Feilding who was to become the standard-bearer for this procedure.[2] Shortly after Mellen's ultimately successful trepanation, she decided to undergo the procedure herself and, perhaps moved to greater caution from his series of attempts, searched for over a year to find a physician who would perform the trepanation. None could be found, so in 1970 she also performed her own self-trepanation. In addition, she had Mellen film it. The footage was used to create the short film, *Heartbeat in the Brain*, which clearly documents her making an incision in the middle of her forehead, drilling through her skull with a power drill, and then wrapping her head in a turbanlike bandage and mopping the copious blood from her face and white gown, all while standing in front of a mirror.

Fig. 3. Photograph showing a subdermal implant. From http://www.piercingsntattoos.com/?cat=24, accessed November 15, 2010.

Feilding claimed that she first felt the beneficial effects about 4 hours later, describing the sensation as, "a lifting upwards, like the tide coming in, and at the same time a feeling of relaxation and silence in the head, a peace, a stopping of that voice in the head." Feilding was so convinced of its beneficial effects that she twice ran for Parliament in the late 1970s under the banner, "Trepanation For the National Health." She and Mellen remained companions for many years, had two sons together, but eventually split.

Feilding and Mellen later both remarried, and fascinatingly, each convinced his or her spouse to undergo trepanation as well. Feilding's husband, Lord James Neidpath, was a former Oxford professor who, it turns out, taught an international relations course attended by Bill Clinton during his Rhodes Scholarship. Neidpath's trepanation was performed by a surgeon in Cairo in 1995. Feilding herself had her own trepanation redone by a surgeon in Mexico in 2000.[2,12]

In 1997, the case of a 65-year-old Englishman who self-trepanned using a power drill was reported.[13] He apparently had been inspired by a recent BBC documentary featuring Feilding and Neidpath. He presented to a local emergency department several hours after successfully drilling through his skull with a power tool, with the initially profuse bleeding mostly stopped, but a CSF leak was still active. On presentation, the authors described a "curious ambivalence to the unusual nature of his actions." Surgery was performed: the blood clot was evacuated, the dura mater closed, and the wound debrided; recovery was described as otherwise uneventful.

Feilding has used some of the substantial fortunes of her and her husband's families to establish the Beckley Foundation, with the goal of funding scientific research

Fig. 4. Photograph showing a subdermal implant. From http://www.stevehaworth.com/wordpress/index.php/archives/category/modify blog, accessed November 15, 2010.

in nontraditional avenues of the study of consciousness, including the effects of LSD on the brain. One 2008 publication by a Russian research group, funded by the Beckley Foundation, claimed to offer empirical evidence of cerebral hemodynamic benefit from trepanation but failed to attract much attention in the scientific community at large.[6]

The Beckley Foundation also helped to fund the International Trepanation Advocacy Group, which was founded by American Peter Halvorson, who himself self-trepanned in 1973, inspired by the successes of Huges and Feilding, after his own unsuccessful search for a physician who would perform the procedure for him. The International Trepanation Advocacy Group currently estimates that over a dozen people worldwide have undergone trepanation since Bart Huges.

Halvorson himself was the center of controversy some years later when, in 2000, he allowed a camera crew from the American news magazine show *20/20* to film him and an assistant perform a trepanation on a willing adult subject. This ultimately led to criminal charges against Halvorson for practicing medicine without a license, although the "patient," Englishwoman Heather Perry, suffered no overt complication and made no complaint herself; in fact, she reported relief from her chronic depres-

sion and fibromyalgia since the trepanation.[2] Given that this procedure is not available in any sanctioned medical context, the majority of these have been self-performed.

Discussion

The increasing popularity of body modifications such as piercing and tattoos pushes those who wish to defy social norms to more radical lengths to achieve desired shock value. Given this small but persistent demand, as well as the existence of neurosurgical cranioplasty technology, it is only a matter of time before complications from these procedures are brought to the attention of our profession.

At least one such instance has already been documented from the practitioners of self-trepanation. Although highly unlikely to ever become a popular or widespread practice, Amanda Feilding and the International Trepanation Advocacy Group demonstrate that this idea resonates deeply with a small number of people. Given modern communications technology, their opportunity to share their vision with the rest of the world has never been greater. It remains a responsibility of the medical community to keep aware of practices such as these, for which the potential risks and consequences remain to be defined.

Disclosure

The author reports no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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The evolution of surgical management for craniosynostosis

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Craniosynostosis, the premature closure of cranial sutures, has been known to exist for centuries, but modern surgical management has only emerged and evolved over the past 100 years. The success of surgery for this condition has been based on the recognition of scientific principles that dictate brain and cranial growth in early infancy and childhood. The evolution of strip craniectomies and suturectomies to extensive calvarial remodeling and endoscopic suturectomies has been driven by a growing understanding of how a prematurely fused cranial suture can affect the growth and shape of the entire skull. In this review, the authors discuss the early descriptions of craniosynostosis, describe the scientific principles upon which surgical intervention was based, and briefly summarize the eras of surgical management and their evolution to present day. *(DOI: 10.3171/2010.9.FOCUS10204)*

Key Words • **craniosynostosis** • **surgical management** • **suture**

Early Descriptions of Cranial Deformity

The aberrant congenital deformities of the skull have been known to exist for centuries and were well-recognized and described as early as the time of antiquity. In the Iliad, Homer describes the warrior Thersites as "the ugliest man who came before Troy…his head ran up to a point..," a description characteristic of oxycephaly.[20] The recognition of cranial vault deformities by the ancient physician Galen, and some early understanding of the role of cranial sutures by Hippocrates, have also been reported.[6,55] By the 16th century, it appears that anatomists appreciated the existence of cranial sutures and had documented a broad range of the characteristics of the deformity, from an appreciation of suture pattern and premature suture fusion in a variety of configurations by Hundt,[21] specific abnormal varieties of sagittal and coronal sutures by Dryander,[13] and what would now be described as oxycephaly and brachycephaly by della Croce[10] and Vesalius[58] (Fig. 1). However, von Sömmering[61] in the late 1790s was the first to go beyond simple descriptions and apply scientific principles to the study of abnormal cranial suture growth. He recognized the importance of sutures in active skull growth and the consequences of premature fusion, thus laying the foundation for our modern understanding of craniosynostosis and the subsequent surgical and nonsurgical interventions.[62,63]

Early Scientific Exploration

In his first scientific descriptions of craniosynostosis, von Sömmering sought to not only describe the primary defect and the cosmetic consequences, but also to elucidate the secondary global cranial impact. He aimed to develop a unifying mechanistic theory describing the pathogenesis with a clear intent on developing a treatment. Soon after von Sömmering, Otto[43]—based on his observations in humans and animals—proposed that a consequence of premature suture fusion was a compensatory cranial expansion along another trajectory in the skull, providing the first explanation for the global cranial abnormalities observed. In 1851, Virchow[59] published a landmark paper in the history of craniosynostosis in which he described the fundamental aberrant growth patterns in this condition, which he termed Virchow's law. Virchow's law stated that the observed deformities occurred as a result of "cessation of growth across a prematurely fused suture," with "compensatory growth" along nonfused sutures in a direction parallel to the affected suture, causing obstruction of normal brain growth.[3] This was the first accurate and generalizable principle applicable to all patterns of premature suture fusion.

Virchow[59] initially described this disorder in 1851 as craniostenosis, meaning a structured or narrowed skull, but was convinced by Sear[47] to instead call this entity

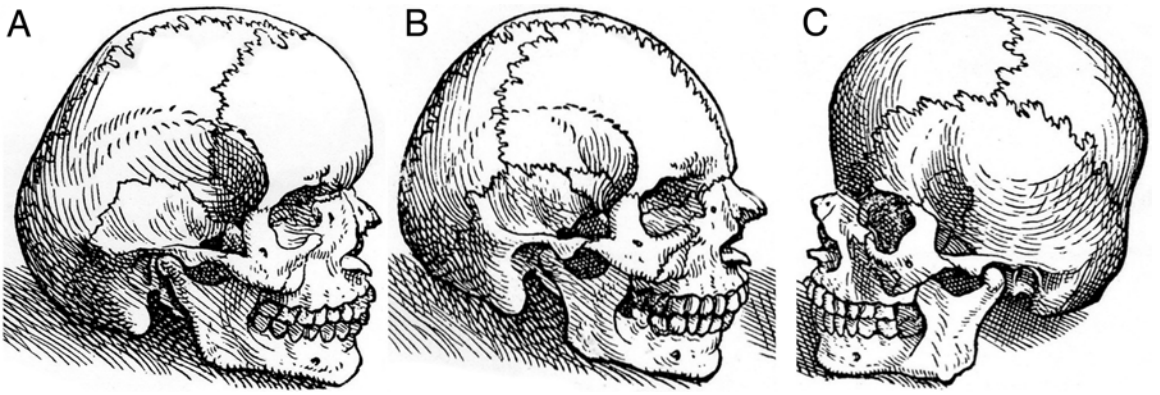


Fig. 1. Illustrations of abnormal skull shapes by Vesalius in 1543 in *De Humani Corporis Fabrica.* Abnormalities were described in terms of prominences, not sutures. **A:** Loss of posterior eminence. **B:** Loss of anterior and posterior eminence. **C:** Loss of eminence at sides. Image credit: William H. Welch Medical Library, Johns Hopkins Medical Institutions.

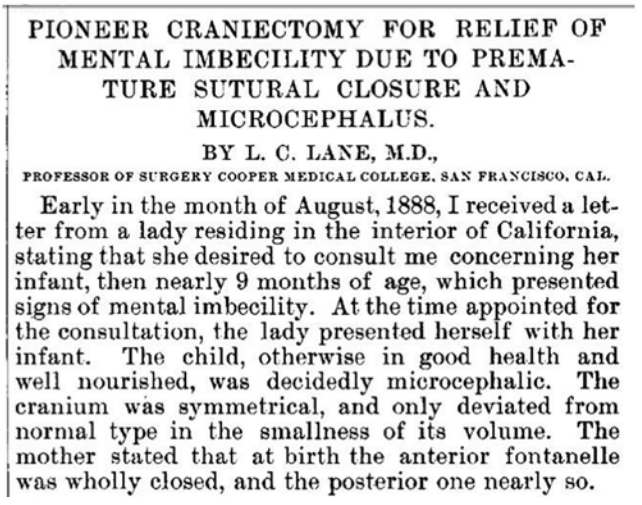
craniosynostosis, which more accurately indicated suture involvement and encompassed all varieties of suture disease. Virchow's impact was significant, as the first surgical interventions and subsequent iterations were based directly on his observations and principles. By the early 1900s, craniosynostosis was recognized as one component of complex syndromic deformities, most notably by Apert[4] in 1906 and Crouzon[7] in 1912, whose names bare two of the most well-known syndromic deformities, of which there are now more than 60.

Nearly a century later, Moss became very interested in craniosynostosis but categorically rejected Virchow's law. Instead, in an attempt to unify all types of craniosynostosis, he proposed that the cranial base, not the suture, was the primary site of abnormality, with suture fusion being a secondary consequence.[12,40,41] He based this theory on 4 observations: 1) sutures were often patent at surgery, even when there was a high degree of preoperative suspicion of suture fusion; 2) there were characteristic abnormalities at the cranial base that occurred with certain suture fusion patterns; 3) excision of the fused suture did not always improve the cranial shape; and 4) embryologically, skull development occurred after cranial base development.

Moss' theory fell out of favor as surgical treatment in humans directed at the prematurely fused sutures demonstrated reversal of the deformity. Unfortunately, some surgeons attempted complex cranial base expansion based on these theories. Moss's theory was later definitively disproven when it was shown that the suture itself was the primary site of abnormality in craniosynostosis, that cranial base and facial abnormalities responded to opportunities for suturing,[44,46] and that abnormalities in the cranial base could resolve completely with suture release.[36] However, a lasting contribution of Moss' work was his recognition that the active growth of the underlying brain dictated the passive cranial growth along the suture lines. He termed this the "functional matrix theory" and it would later form part of the justification for the minimally invasive approach early in life.

Early Attempts at Surgical Intervention

By the late 1800s, the understanding of sutures and the consequences of premature fusion was growing, but surgical intervention was not attempted until it was reliably recognized that craniosynostosis could lead to impaired neurological and cognitive growth, blindness, and hydrocephalus.[18] The first reported surgical interventions for craniosynostosis were strip craniectomies, first by Lannelongue in Paris in 1890[33] followed shortly by Lane in San Francisco in 1892.[31] Lannelongue performed bilateral strip craniectomies for sagittal synostosis and strongly advocated for release, not resection, of the fused suture. Lane reports being approached by the mother of a child who pleaded to him: "Can you not unlock my poor child's brain and let it grow?" Lane performed a strip craniectomy with removal of a stenosed sagittal suture along with lateral strip of parietal bone bilaterally (Fig. 2). However, the patient died 14 hours postoperatively, reportedly from complications of anesthesia. Despite these isolated reports with limited outcome data, it appears that this technique was quickly adopted and used for the treatment of craniosynostosis. An atlas with figures demonstrating a variety of craniectomies for craniosynostosis was published just 5 years after Lannelongue's first report,[11] along



PIONEER CRANIECTOMY FOR RELIEF OF MENTAL IMBECILITY DUE TO PREMATURE SUTURAL CLOSURE AND MICROCEPHALUS.

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Early in the month of August, 1888, I received a letter from a lady residing in the interior of California, stating that she desired to consult me concerning her infant, then nearly 9 months of age, which presented signs of mental imbecility. At the time appointed for the consultation, the lady presented herself with her infant. The child, otherwise in good health and well nourished, was decidedly microcephalic. The cranium was symmetrical, and only deviated from normal type in the smallness of its volume. The mother stated that at birth the anterior fontanelle was wholly closed, and the posterior one nearly so.

Fig. 2. Lane's early report of surgical repair for presumed craniosynostosis published in the *Journal of the American Medical Association.* Reproduced with permission from Lane LC: **JAMA XVIII:**49–50, 1892.

with many surgical texts illustrating techniques for treatment of fused sutures.[32,34]

However, the outcomes of these early interventions were limited by 2 major challenges. First, it later became clear that many of the children operated on at this time were more likely to have microcephaly, rather than craniosynostosis, a distinction that was either not diagnosed or considered at that time. Second, in patients with true craniosynostosis, these procedures were performed late in the course of the disease after neurological deficits developed. Their outcomes were therefore accompanied by significant reossification, and only served to temporize the constriction for a short period of time. At this time, Jacobi,[23] the father of American pediatrics in this era, reviewed a series of 33 children treated for presumed craniosynostosis, and found alarming results of surgery with a high mortality rate (15 of 33 children dying), and publicly denounced the practice to an audience at a meeting of the American Academy of Pediatrics, marking the end of surgery for nearly 3 decades. He famously said:

> The relative impunity of operative interference accomplished by modern asepsis and antisepsis has developed an undue tendency to, and rashness in, handling the knife. The hands take too frequently the place of brains…Is it sufficient glory to don a white apron and swing a carbonized knife, and is therein a sufficient indication to let daylight into a deformed cranium and on top of the hopelessly defective brain, and to proclaim a success because the victim consented not to die of the assault? Such rash feats of indiscriminate surgery…are stains on your hands and sins on your soul. No ocean of soap and water will clean those hands, no power of corrosive sublimate will disinfect the souls.

Revival of Surgical Treatment

Surgical intervention for craniosynostosis was revived decades later when Mehner[39] reported on the first successful craniectomy for complete removal of a fused suture. A few years later, Faber and Towne[15]—now presumably with the capability to accurately differentiate microcephaly from craniosynostosis—also reported excellent preservation of neurological function with minimal morbidity and mortality. Additionally, based on their observations of outcomes, they pioneered the concept of early and prophylactic linear synostectomy for preservation of neurological function and improvement of cosmesis, commenting "it is probable that the evil effects of synostoses are largely preventable by a suitable operation performed sufficiently early in life."[16] By the 1940s, strip craniectomies and suturectomies were once again widely accepted and the critical importance of early intervention—which they describe as the period before 2 months of age—leading to better functional and cosmetic outcomes was beginning to be appreciated. However, despite advances in surgical management in this era, a new challenge in the management of these children became apparent. In older children, reossification with rapid bridging of the artificial suture was a commonly observed complication, which often required multiple extensive cranial vault remodeling procedures with limited efficacy.[25] The outcomes in these complex patients with mature and delayed fusion led Harvey Cushing to question the indication of late linear craniectomies in these patients[8] and presented surgeons of the next era with major challenges to solve.

Advances at Children's Hospital Boston

Once an effective approach for early craniosynostosis was in widespread use, much of the research focus, which was primarily taking place at Children's Hospital Boston, shifted to addressing the limitations of surgical intervention for children who presented late in the disease course or in children who had experienced reossification at the synostectomy site. The primary concern was that surgery at suture sites that have recurrent fusion required extensive and difficult secondary cranial reconstruction operations that were technically challenging and associated with high morbidity and mortality rates.

In one of the first attempts to minimize reossification, Donald Matson and Frank Ingraham[22] proposed the use of a polyethylene film at the edges of cut bone following strip craniectomy. One year prior to Matson and Ingraham's report of polyethylene film, Simmons and Peyton[49] reported on the use of tantalum foil between the newly cut bone, but both techniques fell out of favor due to reports of infection and reossification. However, these techniques became widespread as more effective modern surgical options became available. Interestingly, Anderson and Johnson[2] developed a technique in 1956 in which Zenker's solution was applied directly onto the dura. This served to cauterize the ossifying elements within the meninges and increased the incidence of suture patency, but was found to cause seizures.[35] Matson and Ingraham's simple craniosynostectomy became widely popular and replaced strip craniectomies as the treatment of choice in most pediatric neurosurgery texts and was one of the most common approaches of this era.[37,42] Their technique consisted of removing a 1-cm strip of bone at the site of the involved suture, extending the craniectomy across the adjacent normal sutures, and excising the pericranium to prevent reossification. The importance of restoring natural skull shape early to allow a proper rate of expansion for normal brain development was again recognized in this era, particularly by Shillito and Matson.[48]

By the mid-1950s, there had been significant advances in anesthesia, blood transfusion, and surgical technique at high-volume centers such as Children's Hospital Boston, and surgery for craniosynostosis became very safe. In one of their largest series, Shillito and Matson reported only 2 deaths in 394 operations, a stark contrast to the results reviewed by Jacobi just decades prior.[63] This allowed the consideration of cosmesis (which Shillito and Matson strongly argued for) as a primary indication for surgical intervention,[48] inviting Paul Tessier and other craniofacial surgeons to pioneer techniques with more focus on cosmesis and the correction of associated facial anomalies.[52–54] Although simple craniosynostectomy and strip craniectomy produced excellent results in very young infants, these were inadequate approaches for older children with advanced disease, and the pioneers of the next era were challenged to develop procedures to treat their disease.

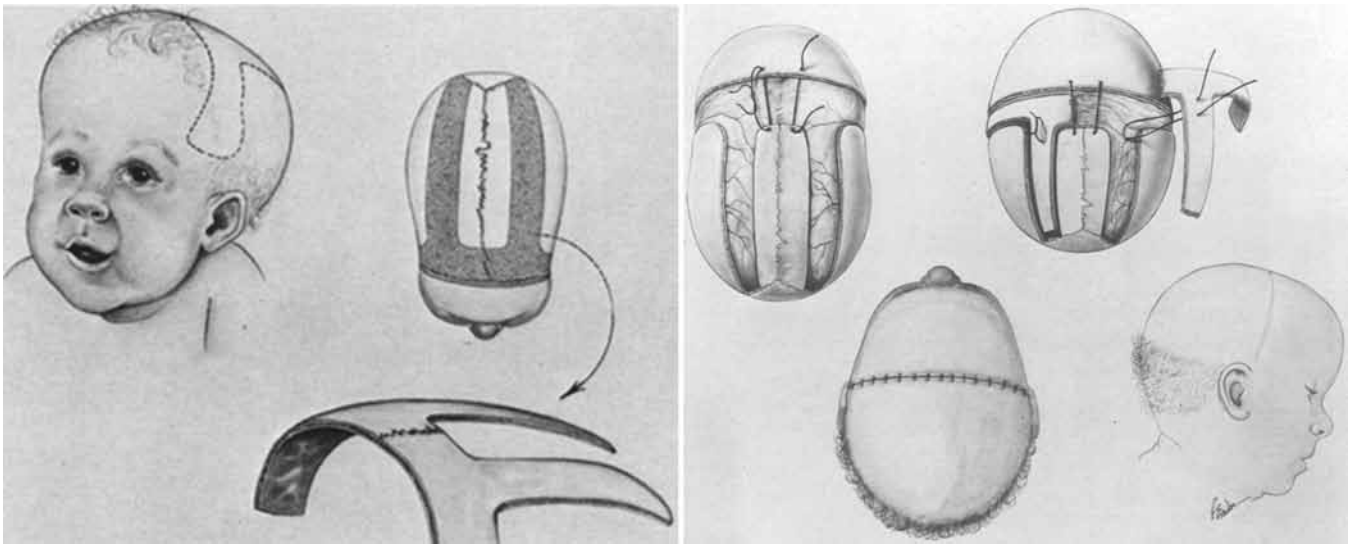

Fig. 3. Illustrations of the pi procedure developed by Jane and colleagues. **A:** Schematic of site and shape of bone removed. **B:** Schematic depicting the technique to replace bone flap to reduce anterior-posterior diameter. From Jane JA et al: **J Neurosurg 49:**705–710, 1978.

Extensive Calvarial Remodeling

The early 1960s to mid-1990s marked an era in which the limitations of simple suturectomies and strip craniectomies for advanced late disease were recognized, challenging surgeons to develop novel procedures for complex calvarial vault remodeling. The innovation of these procedures was driven by the need for immediate deformity correction to prevent impending neurological dysfunction in nonneonates, as well as the need to treat the secondary compensatory changes at sites away from the diseased suture that had taken place. Also fueling this movement was the discovery by Jane et al. that the major cause of the global cranial deformity was compensatory overgrowth at adjacent sutures.[9] Some of the most popular procedures included wide-strip craniectomy with bilateral wedge parietal craniectomy,[1] sagittal craniectomy with biparietal morcellation,[19] extended vertex craniectomy, midline craniectomy with occiput resection,[57] and complete calvarial remodeling via the pi procedure for advanced sagittal synostosis and orbitofrontal advancement for metopic, unicoronal, or bicoronal synostosis. For the most common form of craniosynostosis—isolated sagittal synostosis—Jane and colleagues[5,24] developed the pi procedure, named after the shape of bone that is removed (Fig. 3). In this technique, the sagittal, bilateral coronal, and lambdoid sutures are first removed and the parietal bones are outfractured to increase the skull width. The sagittal suture is then removed and used as a strut to maintain the outward position of the parietal bones. Finally, the frontal and occipital bones are secured to the parietal bones with adjustments of anterior-posterior dimension and frontal bossing. The pi procedure and its variations and modifications have the advantages of addressing the primary suture fusion and also the global cranial deformity, including anterior-posterior dimension and frontal bossing, and providing immediate correction without the need for a postoperative helmet.

In 1982, Epstein et al.[14] described total vertex craniectomy, a hybrid of the midline craniectomy procedure of Stein and Schut[51] and the occipital and coronal prominence excision of Venes and Sayers.[57] Epstein et al. further modified this approach by extending the width of bone removed to 6–8 cm, which eliminated the need for interpositional Silastic, a common technique of the time. They reported excellent cosmetic and functional outcome without any morbidity and deaths.[14] Summarizing the experience of this era, McComb and colleagues at Children's Hospital Los Angeles published one of the most significant articles on contemporary surgical management in the journal *Pediatrics*, describing their institutional experience with 250 patients over 6 years.[50] Of the many important findings, they describe the prevalence of fused suture patterns, the morbidity and mortality of extensive calvarial remodeling, and describe a novel 7-category outcome classification system for more scientific analysis of outcomes. Additional contributions during this era from Children's Hospital Los Angeles include McComb's approach for management of sagittal synostosis in the older infant, in which a reduced rate of brain growth provides an insufficient force for passive cranial vault expansion. In this technique, termed "occipital reduction–biparietal widening," the occipital protuberance is reduced, the biparietal diameter widened, and the height of the vertex is lowered (Fig. 4). Employing this technique in a large series of infants > 6 months of age, McComb[38] reported excellent cosmetic outcomes, no bone defects, and no need for reoperation.

As the efficacy of these procedures became apparent, they gained widespread acceptance as the preferred method of treatment for nonneonates, despite the perioperative limitations. Another significant advance during this era was the contributions of Paul Tessier, who is widely regarded as the father of craniofacial surgery. He developed the principles that define modern craniofacial surgery, as well as sophisticated techniques and tools that

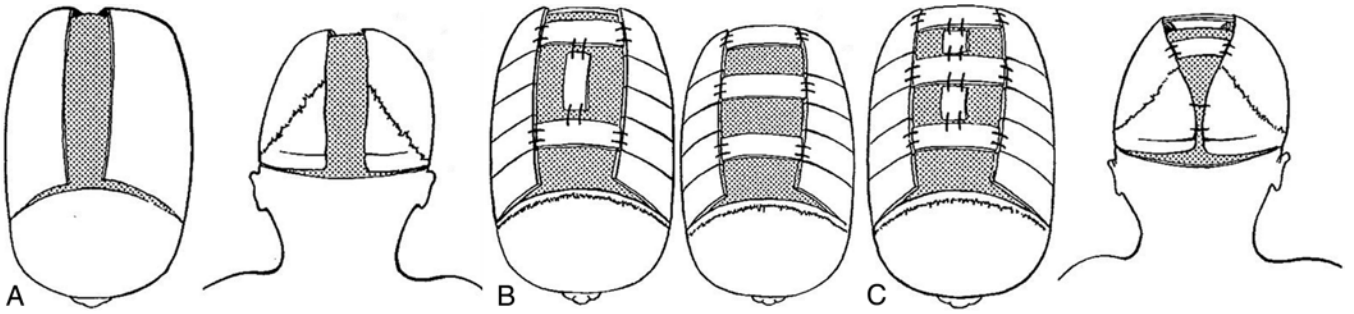

Fig. 4. Schematic illustrations of McComb's occipital reduction–biparietal widening technique for sagittal synostosis. **A:** Posterior and vertex view of midline bone strip removed and cuts parallel to the skull base in the occipital bone. **B and C:** Vertex **(B)** and posterior **(C)** views of methods to graft the midline bone removed. Reproduced with permission from McComb JG: **Pediatr Neurosurg 20:**99–106, 1994, S. Karger AG, Basel.

led to significant improvements in cosmetic outcomes, particularly for those with facial abnormalities.[52–54] The advances of extensive calvarial remodeling allowed for normal neurological development and excellent cosmetic results, particularly for those with the most complex of multiple-suture disease.[60] However, these advances were associated with significant operative time, hospital stay, blood loss requiring transfusion, and complications that were well described even in modern literature of the 1990s.[17,30,56] These limitations became the impetus for the most recent endoscopic advances.

Modern Endoscopic Strip Craniectomy

In the early 1990s, Jimenez, a pediatric neurosurgeon, and Barone, a plastic surgeon, recognized the limitation of the approaches of the past quarter century, including extensive operations in young children, prolonged operative time, blood loss and need for blood transfusion, significant scalp mobilization, and need for subsequent reconstructive procedures. They proposed a novel technique: simple suturectomy via an endoscopic approach (Fig. 5). The success of this approach can be attributed to

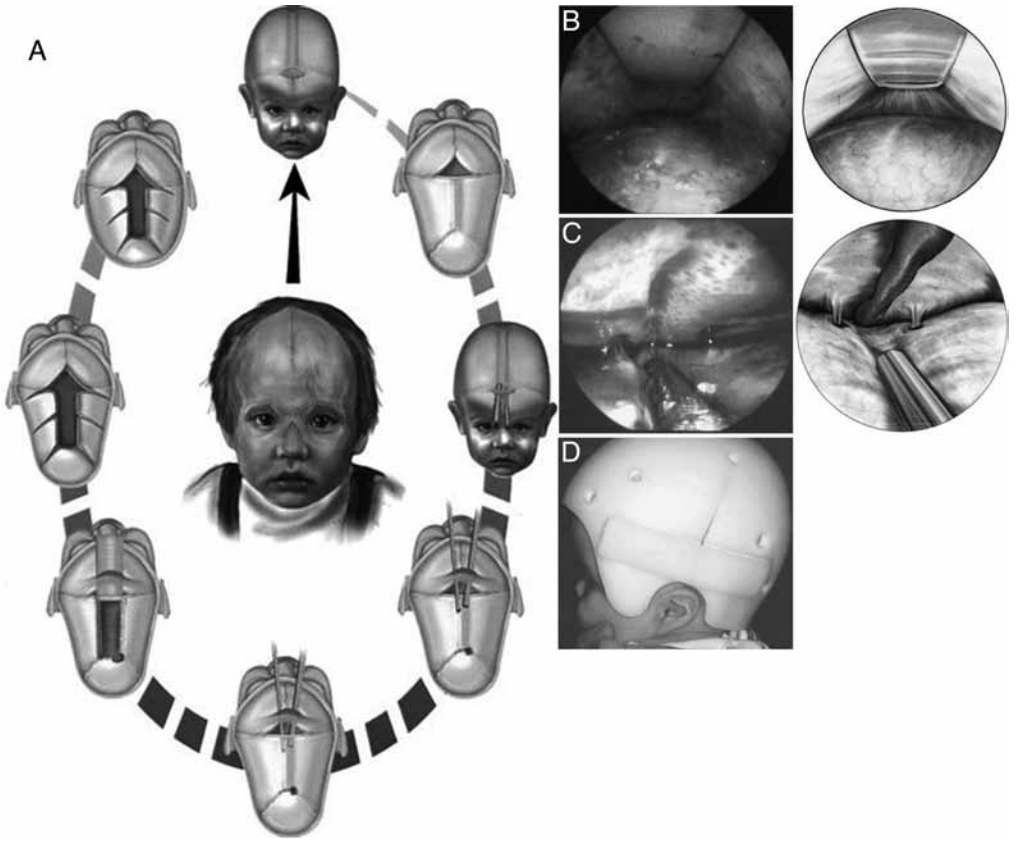

Fig. 5. Images from the work of Jimenez and Barone on endoscopic craniectomy for early surgical correction of sagittal craniosynostosis. **A:** Schematic of sequential steps in endoscopic strip craniectomy. **B:** Endoscopic *(left)* and schematic *(right)* views of the subgaleal space. The scalp is retracted superiorly away from the cranium. **C:** Endoscopic *(left)* and schematic *(right)* views of the stenosed sagittal suture. **D:** Photograph of a postoperative molding helmet that partially restricts anteroposterior growth and allows bitemporal and biparietal expansion. From Jimenez DF and Barone CM: **J Neurosurg 88:**77–81, 1998.

Jimenez and Barone's consideration of 3 basic principles of craniosynostosis. First, as recognized by Farber and Towne, they recommended surgery early in life. Second, as described by Moss's functional matrix theory, they recognized that if timely intervention occurred, the rapidly growing brain would cause expansion of the skull into a normal shape. Third, to counteract the tendency of the cranial vault to revert to a premarid shape as described by Otto and Virchow, they employed an adjunct vault remodeling helmet introduced by Persing et al. in 1986,[45] into which the brain would shape the skull. They first presented this work in a small series of 4 patients, all with sagittal synostosis, treated with early endoscopic strip craniectomy with adjunct postoperative cranial molding helmets. They were able to demonstrate minimal blood loss, short operative times, early hospital discharge, and excellent functional and cosmetic results, although with limited follow-up.[26] Subsequent studies with progressively larger patient samples and a wide variety of fused suture patterns with long-term follow-up confirmed the efficacy and safety of this approach.[27–29]

The collective outcomes from these studies show remarkable results with short operative times, minimal blood loss, early hospital discharge, and minimal operative and perioperative risks, including extremely rare cases of infection, dural sinus tears, CSF leaks, or neurological injury. A collective review of their technique from the past 11 years in infants with a variety of multiple-suture nonsyndromic craniosynostoses demonstrates results superior to those achieved with more invasive procedures of the prior era.[28] This most recent advancement, founded upon the principles of the natural history and pathophysiology of craniosynostosis, has led to dramatically improved outcomes and has fundamentally changed the treatment of these patients.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Bettegowda, Mehta, Ahn. Acquisition of data: Bettegowda, Mehta, Ahn. Analysis and interpretation of data: Bettegowda, Mehta, Ahn. Drafting the article: all authors. Critically revising the article: Bettegowda, Jallo, Ahn. Reviewed final version of the manuscript and approved it for submission: Bettegowda, Jallo, Ahn.

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Harvey Cushing's experience with cranial deformity

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Surgery for cranial deformity was associated with significant surgical morbidity during the early part of the 20th century. For this reason, Harvey Cushing was initially not in favor of surgical treatment of craniosynostosis. Later in his career, Cushing began to operate on these children, although it never became a major focus of his practice. Several examples of his patients with cranial deformity are presented, and his limited role in the development of this field is discussed. *(DOI: 10.3171/2010.9.FOCUS10191)*

Key Words • history of neurosurgery • history of craniosynostosis • cranial deformity • surgical correction • Harvey Cushing

Although there are numerous premodern descriptions of craniosynostosis, the scientific basis for the surgical correction of craniosynostosis dates to the early 19th century. Early pioneers in this work included Samuel von Sömmerring (1755–1830) and Rudolf Virchow (1821–1902). In 1800, von Sömmerring's description of cranial sutures and their role in cranial vault development and growth suggested that premature suture closure would lead to subsequent cranial deformity.[18] In 1851, Virchow published his paper, giving rise to Virchow's law: "When premature fusion of the cranial vault occurs there is an inhibition of the normal growth of the skull in a direction perpendicular to the suture which is fused, which gives a compensatory growth in a direction parallel to the fused suture."[1,15] It was in this same publication that Virchow coined the term craniostenosis.[3]

Progress with the surgical correction of this disorder lagged several decades behind the early pathophysiological descriptions. In August 1888, strip craniectomies were performed in a child with craniosynostosis in San Francisco by L. C. Lane (1830–1902). Unfortunately, the child died of anesthetic complications.[12] In 1890, the novel use of a double parasagittal linear craniectomy was reported by Lannelongue with an excellent outcome.[13] For every surgical success, however, there were numerous failures that led to open verbal attacks on those surgeons who would perform such operations. Abraham Jacobi (1830–1919) was a well-known New York pediatrician who openly criticized craniectomies:[11]

> The last subject I dare to discuss before you is that of linear craniotomy… such rash feats of indiscriminate surgery, if continued, moreover in the presence of fourteen deaths in thirty-three cases, are stains on your hands and sins on your souls. No ocean of soap and water will clean those hands, no power of corrosive sublimate will disinfect the souls.[11]

The high mortality rate associated with craniectomy for craniosynostosis during this period made this operation especially controversial during the early years of Harvey Cushing's practice.

Cushing's Early Opinions on Cranial Deformity Surgery

Secondary microcephaly, resulting from primary brain abnormalities rather than craniosynostosis, was often incorrectly diagnosed as craniosynostosis during the early years of Cushing's practice. Cushing described the introduction of linear craniotomy as "a lamentable instance of the juror operandi running away with surgical judgment."[5] Cushing believed that "educational rather

than surgical or medicinal measures are indicated…" and furthermore, "only when epilepsy or hydrocephalus is superadded to the defect can we have any expectation—and that a remote one—of benefiting the condition…"[5] By 1908, the improper surgical treatment of microcephalic patients led to this warning from Cushing on the indiscriminate performance of craniectomies:

> It is unaccountable that an idea should have arisen attributing microcephalus and other conditions of congenital imperfection, as well as those of development arrested by disease, to premature closure of the cranial bones. All of our knowledge goes to show that an early closure of fontanel and suture is due to a primary failure of growth of the encephalon; not the reverse, a failure of growth due to a primary closure. Experiments by d'Abundo and others show that animals whose skulls in early life have been firmly enclosed, so that there is no possibility of cerebral expansion, cannot survive. Even firmly closed sutures may give way before the pressure of growth. We see this even in young adult life, as a separation of sutures in acquired hydrocephalus, and in cases of tumor growth.

Perhaps Cushing's opinion at that time is best summarized by his remark, "There has been a high mortality in these operations, and though death cannot be lamented, the surgeon is not a barbarian to execute the helpless."[5] Since surgical and anesthetic techniques were in their infancy at this time and the methods of blood transfusion were rudimentary, children with limited blood volume were especially at risk in such operations, which often involved significant blood loss due to manipulations of the adjacent dural sinuses.

Controversy surrounding the use of craniotomies delayed further development in the surgical management of craniosynostosis until the early 1920s when Mehner in 1921 advocated the use of simple extirpation of the synostosed suture and successfully used strip craniectomy to remove a fused suture.[2,6] At that time, further recognition of the risk to normal brain function and vision associated with craniosynostosis was used to justify these early surgeries.[1,8]

Cranial Deformity in Cushing's Practice During the 1920s

We present photographs of 4 patients treated by Dr. Harvey Cushing at the Peter Bent Brigham Hospital between 1921 and 1924 (Figs. 1–4). Photographs of 2 of these patients (Figs. 3 and 4) have been presented previously without discussion,[4] and the other patients (Figs. 1 and 2) are presented now for the first time. The first patient in this series (Fig. 1) was an infant admitted to the Brigham with an appearance consistent with secondary microcephaly. The primary cause of the microcephaly is not known. Images of the child seem to demonstrate an overriding of the coronal sutures, which would be consistent with the type of primary failure of growth of the encephalon described by Cushing. This child was not treated surgically, which is not surprising given Cushing's recorded opinions on unnecessary surgery for this condition.

The second patient in this series presented to Dr. Cushing with an appearance consistent with a craniofacial syndrome (Fig. 2). The almost conical appearance of the calvaria is consistent with a diagnosis of oxycephaly. In addition, given the midface hypoplasia, oxycephaly, exorbitism, broad great toes, and subtle syndactaly or webbing of the toes, a diagnosis of Pfeiffer's syndrome may be considered. Such a precise syndromic designation was difficult or impossible in Cushing's day. Pfeiffer's syndrome was not described until 1964, although Crouzon's (1912) and Apert's (1906) syndromes had been recently described at the time that Cushing was treating this patient.[7] We are fortunate in that the surgical treatment of this child was recorded in great detail. Although his diagnosis is not recorded, the careful photography of the toes suggests that Cushing appreciated the syndromic nature of this child's condition. From an examination of Cushing's skin incisions as well as the preserved pieces of removed cranial bone, it is evident that Cushing performed multiple small craniectomies on this child. Craniectomies were carried out over the lateral sphenoid wing bilaterally as well as over the bregma. It is difficult to say with precision the exact rationale for the specific craniectomies performed by Cushing; however, the removal of bone at the lateral sphenoid wing could have been an attempt at addressing the patient's proptosis due to the exorbitism while simultaneously increasing intracranial volume. Although the patient's aesthetic appearance at extended follow-up would be considered disappointing by the standards of a modern practice, the postoperative result was quite favorable in an era when mortality was still a common outcome of this surgery. It is

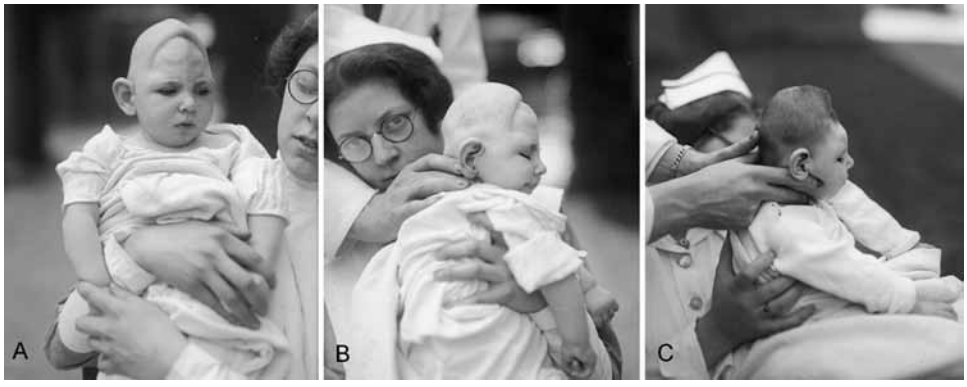

Fig. 1. Photographs of a child with secondary microcephaly **(A and B)** admitted to the Peter Bent Brigham Hospital in the summer of 1923. Surgical treatment was not recommended for this child. The cranial defect had progressed 1 month later **(C)**. Photographs courtesy of the Cushing Brain Tumor Registry at Yale University.

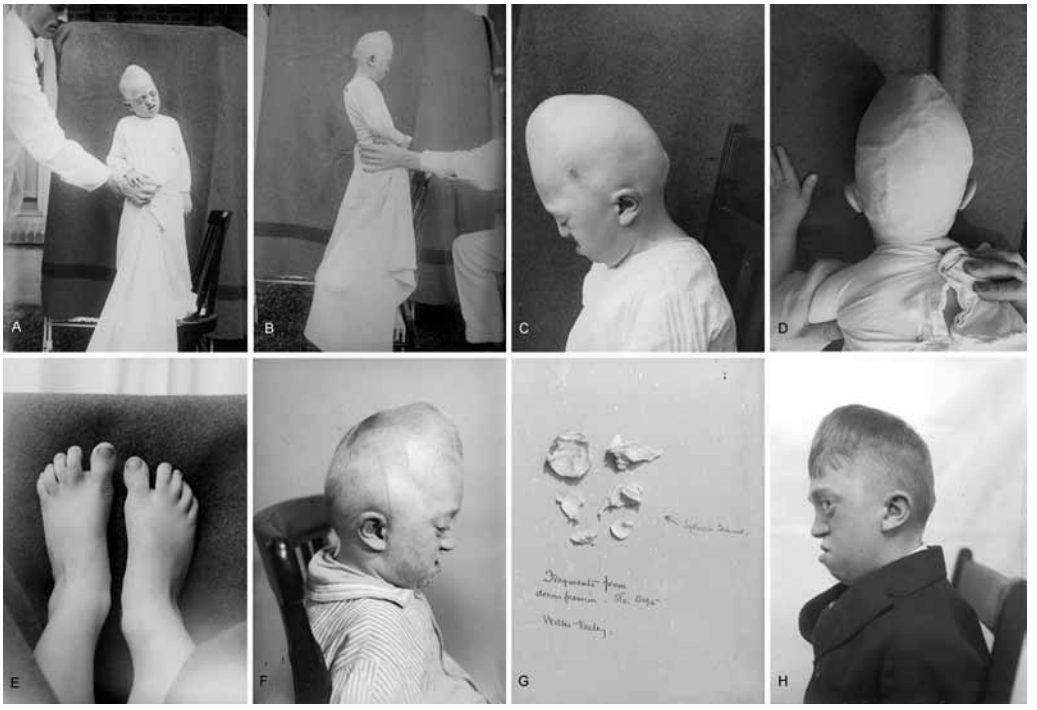

Fig. 2. Photographs of a boy with evident oxycephaly admitted to the Peter Bent Brigham Hospital in 1921. Dr. Gilbert Horrax helps position the child for the photographer **(A and B)**. Preoperative photographs show an appearance that could be consistent with Crouzon or Pfieffer syndrome, including midface hypoplasia **(C and D)**. The child's feet show webbing of the toes **(E)**, suggesting Pfieffer syndrome as the most likely diagnosis. A photograph taken shortly after surgery shows an unusual incision extending from the anterior tragus toward the superior temporal line and a second incision over the convexity in the location of the sylvian fissure **(F)**. The extent of bone removal was recorded photographically **(G)** and evidently included the lateral sphenoid wings bilaterally as well as the skull surrounding the bregma at the junction of the coronal and sagittal sutures. A photograph of the same child obtained 3 years postoperatively **(H)** shows significant cosmetic improvement since the time of surgery. No attempt was made to correct the associated facial deformities, and the postoperative photograph shows the expected persistent midface hypoplasia. Photographs courtesy of the Cushing Brain Tumor Registry at Yale University.

interesting that this child was older than the typical child undergoing craniofacial surgery today. This likely reflects both a reluctance to perform surgery until it was obviously necessary, as well as the relative safety of operating on an older child with a larger blood volume.

In contrast with the previous example, the third child in this series presented to Dr. Cushing at a very early age (Fig. 3). The cranial shape is most consistent with plagiocephaly due to left unicoronal synostosis. Note the recessed supraorbital rim and flattened forehead on the left side. The patient also demonstrates a classic "C" deformity with deviation of the nasal root and chin point to the opposite side. Such a finding represents the facial manifestations of the compensatory changes in this condition. A small craniectomy was performed, and multiple postoperative photographs were taken. Despite the fact that this craniectomy would not be recommended today for coronal synostosis, the operative result would have been considered satisfactory under the circumstances. The follow-up photographs of this child do seem to demonstrate somewhat of a diminished progression of the deformity. Given this child's small blood volume, hemostasis would have been a principal concern during this surgical procedure, as methods to control intraoperative bleeding were quite primitive at that time. Cushing began his initial work with intraoperative electrocautery several years after this child underwent surgery.[14,19]

The fourth child in this series also presented to Dr. Cushing at a very young age (Fig. 4). Although no preoperative photographs of this patient are known to exist, it is evident from photographs taken immediately postoperatively that this patient had a Kleeblattschädel-type deformity with associated exorbitism. Such children often demonstrate multiple suture synostoses and are often syndromic. This child underwent small bilateral craniectomies. Photographs obtained 10 days after surgery show significant swelling at both sites. We may speculate that this child suffered from increased intracranial pressure, whether as a direct result of a severe cranial suture deformity or due to associated hydrocephalus. No outcome information is available for this patient, a fact that is sadly telling, given Dr. Cushing's normally fastidious recording of follow-up data.

Craniosynostosis Surgery After Cushing

Since the middle of the 20th century, surgical treatment of craniosynostosis utilizing linear craniectomies has become a well-established treatment with progressive refinements and increasingly good results. In 1948,

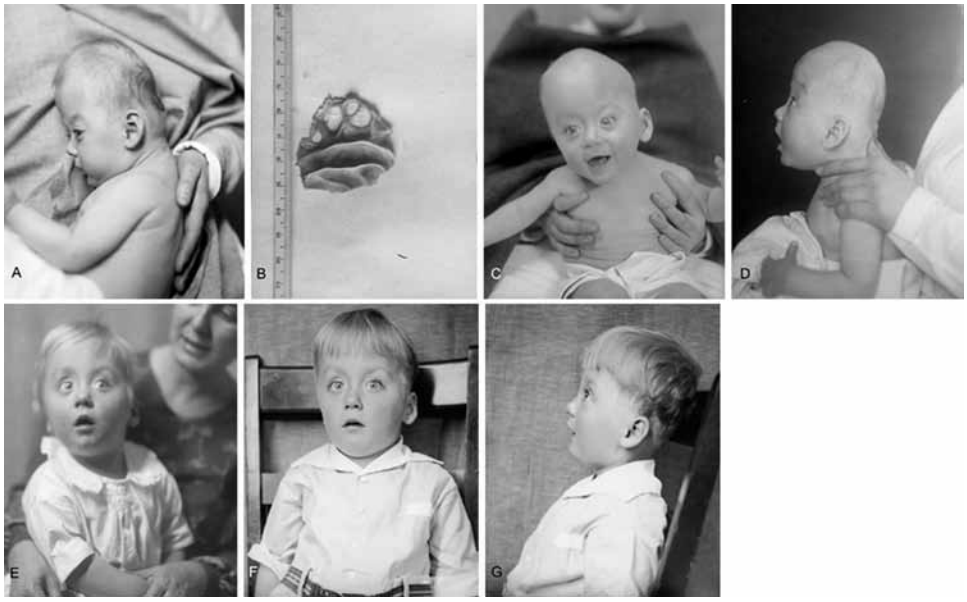

Fig. 3. Photographs of an infant with plagiocephaly presumably resulting from unicoronal synostosis **(A)** who was treated by Harvey Cushing. A craniectomy was performed centered on the bregma but including the medial portions of both coronal sutures **(B)**. Photographs obtained 3 weeks postoperatively show a large incision was made over the convexity **(C and D)**. The craniofacial deformity is still apparent postoperatively, especially at the left orbit. At 1 year **(E)** and 3 years **(F and G)** postoperatively, the cranium achieves a more normal shape, although some deformity persists even at the last follow-up. Photographs courtesy of the Cushing Brain Tumor Registry at Yale University.

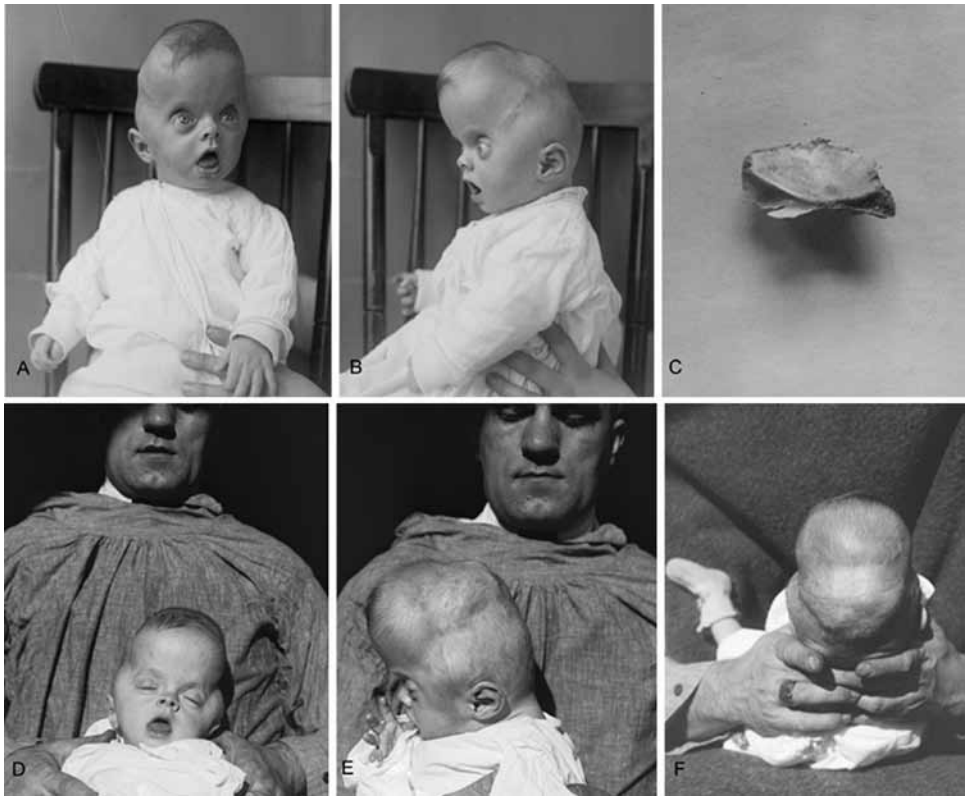

Fig. 4. Photographs of an infant with a head deformity most consistent with Kleeblattschädel with exorbitism. Although multisutural syndromic craniosynostosis is possible, the fingers appear normal in the available images and there are no associated midface anomalies. In the immediate postoperative photographs, bilateral incisions can be seen in front of the ears **(A and B)**. Bilateral craniectomies were carried out at both of these sites **(C)**. Two weeks later, significant swelling is noted at the operative sites **(D–F)**, most likely the result of persistently elevated intracranial pressure or associated hydrocephalus. Dr. Cushing's orderly, Adolf Watzka, can be seen holding the baby for the photographer. Photographs courtesy of the Cushing Brain Tumor Registry at Yale University.

Ingraham and coworkers[9] described 50 patients, 44 of whom were treated surgically, and reported that "mortality for operation on infants with craniosynostosis is negligible when proper supportive measures are provided." In 1954, Ingraham and Matson[10] included aesthetic benefits as an indications for surgery in their textbook on pediatric neurosurgery; thus, the modern era of craniofacial surgery was born.

Cosmetic indications for craniosynostosis began to receive emphasis only after the safety of surgical correction could be assessed as minimal. This evidence came in 1968 with a review of 519 patients with craniosynostosis who were surgically treated between 1930 and 1966 with a reported morality rate of 0.39%, a morbidity rate of 14%, and lasting undesirable sequelae of 0.58%.[16] With the safety of surgical procedures established, cosmetic benefits as indications for surgery received increasing emphasis in the 1960s and 1970s.[2] In 1976, Venes and Sayers[17] noted that "it is generally accepted that scaphocephaly does not significantly alter brain growth and consequently the single indication for operative correction is cosmetic improvement." It is this emphasis on cosmetic improvement that lead to the development of many new techniques to replace the simple craniectomy.[17]

Conclusions

Harvey Cushing's contributions to craniosynostosis surgery were modest in comparison with his major contributions in nearly all other areas of neurosurgery. Nevertheless, his dominance of orthodox neurosurgical opinion for many decades did influence the evolution of the surgical treatment of this condition.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Conception and design: Maher, Cohen-Gadol. Acquisition of data: Cohen-Gadol. Analysis and interpretation of data: Maher, Buchman, Cohen-Gadol. Drafting the article: Maher, O'Hara. Critically revising the article: Maher, Cohen-Gadol. Reviewed final version of the manuscript and approved it for submission: all authors. Study supervision: Maher, Buchman, Cohen-Gadol.

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History of the Kleeblattschädel deformity: origin of concepts and evolution of management in the past 50 years

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The history and evolution of surgical strategies for the treatment of Kleeblattschädel deformity are not well described in the medical literature. Kleeblattschädel anomaly is one of the most formidable of the craniosynostoses, requiring a multidisciplinary team for surgical treatment. The initial descriptions of this cloverleaf deformity and the evolution of surgical treatment are detailed in the present report. Two illustrative cases of Kleeblattschädel deformity, syndromic and nonsyndromic craniosynostoses treated by the senior authors, are also described along with insights into operative strategies. *(DOI: 10.3171/2010.9.FOCUS10212)*

Key Words • Kleeblattschädel deformity • craniosynostosis • cloverleaf skull syndrome • chondrodystrophic hydrocephalus • hindbrain herniation

The cloverleaf skull, or Kleeblattschädel, is a rare skull deformity resulting from premature fusion of multiple cranial sutures and characterized by a trilobar skull with bossing of the forehead, temporal bulging, and a flat posterior skull.[20,24,40] Inconsistent patterns of suture fusion have been reported, with the coronal and lambdoid sutures most often involved.[1] The condition is further characterized by cosmetic facial deformity and micromyelia and can be further complicated by increased intracranial pressure, hydrocephalus, hindbrain herniation, skull base dysplasias, and impaired neurological function.[2,10,28,38] The etiology of Kleeblattschädel syndrome is unknown; it has been attributed to abnormalities of both the calvaria and the skull base, making it one of the most complex craniosynostoses to treat. The Kleeblattschädel anomaly has been reported to occur in patients with both syndromic and nonsyndromic forms of craniosynostosis.[39]

Anatomical observations made in previous case studies involving the Kleeblattschädel anomaly have included inconsistent patterns of craniosynostosis, with the coronal and lambdoid sutures most frequently implicated.[3,7] Other authors have also observed a shortened anteroposterior dimension of the cranial base, particularly affecting the anterior cranial fossa. The superior leaf of this deformity arises from a widely diastatic sagittal suture and/or metopic suture. If the sagittal suture is closed, a grossly expanded anterior fontanel is noted. The anterior cranial fossa has a shortened anteroposterior dimension and steep upward inclination, which extends to its posterior border at the sphenoid ridge. Correspondingly, the lesser wings of the sphenoid have been seen to have a steep upward inclination. It is suggested that these anomalies of the cranial base may transmit forces to the dura mater, which result in stenosis of the overlying cranial sutures.

Origin of Concepts: the Holtermüller-Wiedemann Collaboration

In 1849 Vrolik described a craniofacial malformation he called "dyscrania" that probably resembled a cloverleaf deformity. However, the name "Kleeblattschadel Syndrom" was given by Holtermüller and Wiedemann in their paper published in the journal *Medicinische Bild* in 1958 and subsequently included in the second edition (1959) of the *Dictionary of Clinical Syndromes* by Leiber. Karl Holtermüller, born in 1915, had practiced as a pediatrician in several cities in Germany, including Bonn, Berlin, and Hagen, prior to becoming head of the Children's Clinic in Neunkirchen Kohlhof (1953) and later Kinderklinic Saarbrucken, located at the Bürgerhospital, Saarbrücken. He consulted Hans-Rudolf Wiedemann (1915–2006; Fig. 1) regarding a newborn with an unusual head shape and circumference, which led to their 1960 article in *Medizinische Monatsschrift*.[18,44] Wiedemann was at that time a well-

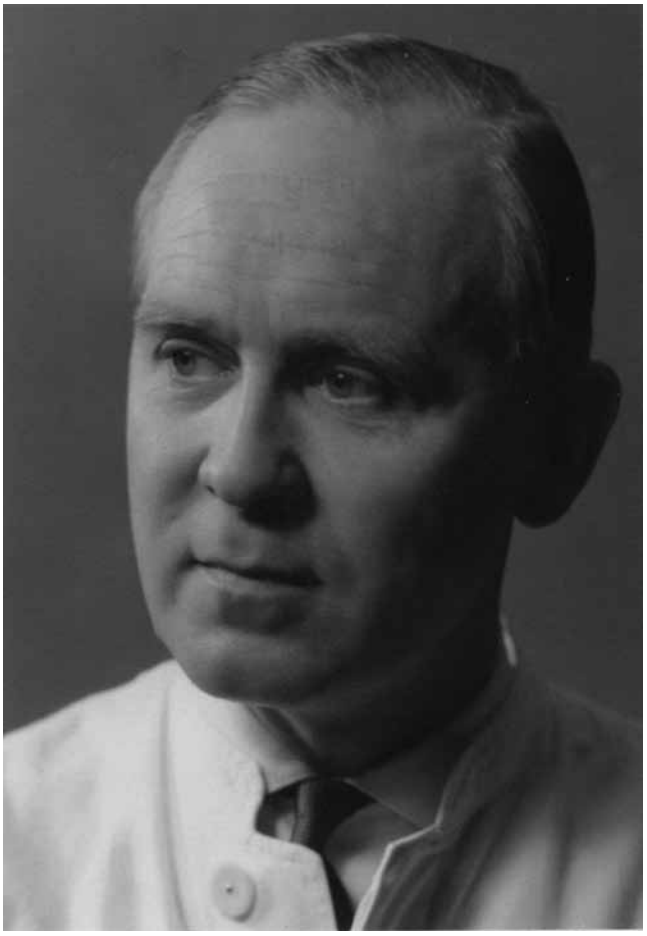

Fig. 1. Photograph of Hans-Rudolf Wiedemann, who collaborated with Holtermüller to describe the Kleeblattschädel deformity.

known scholar, teacher, and administrator in the Department of Pediatrics in Krefeld and later in Kiel, Germany.[29] Having been trained in Jena with Jussuf Ibrahim, who influenced him to do neuropediatrics and clinical genetics, Wiedemann was first recognized for his documentation of a malformation epidemic in 1961, which was later understood to occur from thalidomide. Beyond the classic eponym Beckwith-Wiedemann syndrome (exomphalos-macroglossia-gigantism syndrome), Wiedemann was also known for phenotype descriptions in various lipidoses, mucopolysaccharidoses, hereditary skeletal dysplasias, and gonosomal aneuploidies. Furthermore, he harbored a keen interest in progeroid syndromes and defined a neonatal pseudohydrocephalic progeroid syndrome, referred to as "Wiedemann-Rautenstrauch syndrome." In addition to receiving several national and international awards,[44] he was the recipient of the Otto Heubner Prize awarded by the German Society of Pediatrics, the highest distinction and honor bestowed by that society. In the 1990s, Wiedemann suffered a major stroke that left him aphasic and hemiplegic for the last decade of his life; he died on August 8, 2006.

The classic paper by Holtermüller and Wiedemann compiled 13 cases; 12 were previously called "chondrodystrophic hydrocephalus" (Table 1).[18] The original description of this new cloverleaf skull deformity included the following: a trilobar skull configuration with downward displacement of the ears, facial deformity with hypertelorism, nasal flattening, jaw abnormalities, micromyelia and skeletal abnormalities, radiological documentation of cloverleaf skull, and hydrocephalus. An original published photograph and a radiograph featuring an infant with Kleeblattschädel deformity are shown in Fig. 2. Chondrodystrophy was implicated in several of the initial cases prior to the description of Kleeblattschädel anomaly; however, the Kleeblattschädel deformity lacked the genetic inheritance seen with the chondrodystrophies, and thus, patients with Kleeblattschädel often lacked the associated chondrodystrophic body habitus.

Neurological Manifestations: Current Understanding

Pathologically, the Kleeblattschädel specimen reveals patent sagittal and squamosal sutures with a circumferential ring of bone joined at the junction by the upper and lower leaves of the cloverleaf, dividing the upper part into 2 halves, with abundant endocranial molding (honeycomb pattern of the inner vault) and a small crowded posterior fossa often associated with tonsillar herniation. Bony deformities include a foreshortened anterior cranial fossa; flattened occiput; and thickened, sclerosed sphenoid wings. The neurological sequelae of the Kleeblattschädel deformity arise mainly from 1) hydrocephalus, 2) hindbrain herniation, and 3) venous hypertension.

Hydrocephalus Association

The origin of hydrocephalus in patients with Kleeblattschädel is often debated.[14,26] All of the initial published reports on the deformity have cited hydrocephalus as an invariable association.[11,13,16] Angle et al.[1] reported basilar deformity causing fourth ventricular outflow obstruction, and Partington et al.[30] suggested basilar impression documented at autopsy as a cause for hydrocephalus

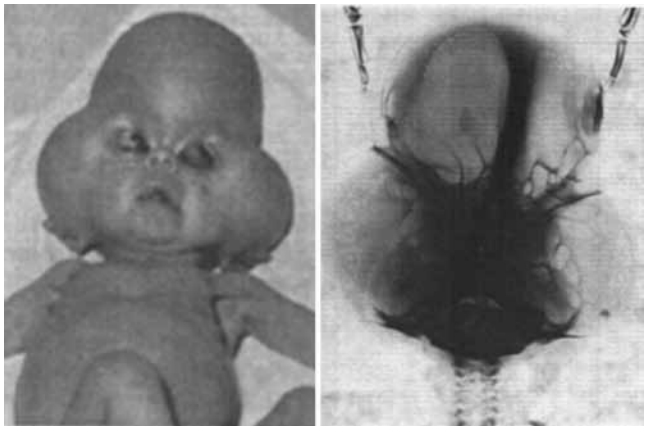

Fig. 2. Left: The Kleeblattschädel anomaly. Photograph demonstrating an infant with a cloverleaf skull, or trilobar cranial vault, frontal bossing, pronounced temporal bulging, and exophthalmos. **Right:** Anteroposterior radiograph demonstrating the constriction band believed to contribute to the formation of a trilobar skull. Both images reproduced with permission from Holtermüller K, Wiedemann HR: Kleeblattschadel-Syndrom. **Med Monatsschr 14:**439–446, 1960.

TABLE 1: Initial cases reviewed by Holtermüller and Wiedemann*

Author & Year	Cited Diagnosis	Brief Patient History	Additional Cranial Pathology	Systemic Malformation
Vrolik, 1849†	hydrocephalus chondrodystrophicus	1 infant: 17-wk-old M, footling breech birth	downslanting palpebral fissure; occipital encephalocele (vs biparietal bone)	foreshortened extremities; possible abdominal hernia
Mayer, 1912 & 1924	hydrocephalus chondrodystrophicus	2 infants: 1 M, 40 cm; 1 F, 36 cm	occipital encephalocele versus biparietal bone; cleft palate; downslanting palpebral fissure; tribasilar bone (chondrodystrophic shortening of the chondrocranium)	
Gruber, 1926	hydrocephalus chondrodystrophicus	5 infants: 1, 36 cm; 2, F, 45 cm; 3, referenced from Gottingen; 4, originally described by Rudolphia, 1824; 5, originally described by physician at University of Vienna	biparietal bone; downslanting palpebral fissure; tribasilar bone shortening	consistent w/ chondrodystrophy (chondrodystrophia fetalis)
Dietrich-Weinnoldt, 1926	hydrocephalus chondrodystrophicus	1 infant, stillbirth	biparietal bone; coronal synostosis; constriction of the foramen magnum	consistent w/ chondrodystrophy
Welter, 1936	hydrocephalus chondrodystrophicus	1 infant, F, 46 cm	biparietal bone w/ osseous propulsion along posterior fontanelle w/ tuberous rim; tribasilar bone; coronal & lambdoid synostosis; abnormal CSF flow; jugular foramen constriction	pathological confirmation of chondrodystrophia fetalis; hepatomegaly
Krauspe, 1958	hydrocephalus chondrodystrophicus	2 infants, unknown birth length	skull base narrowing; multiple craniosynostoses	consistent w/ chondrodystrophy
Holtermüller & Wiedemann, 1960‡		1 infant, M; ultimately died due to hydrocephalus	occipital "buckelschadel" (tuberous skull); extreme exophthalmos; elevated palate; rudimentary parietal bones merging into osseous formation w/in fontanel; underlying parenchymal maldevelopment	

* Prior cases (translated from German) of chondrodystrophy that may represent Kleeblattschädel. See Holtermüller and Wiedemann, 1960.
† Believed to be chondrodystrophy by Mayer and Gruber.
‡ First case ultimately described as Kleeblattschädel.

in cloverleaf skull deformities. Feingold et al.[9] described a case of aqueductal stenosis with hydrocephalus in a case of Kleeblattschädel deformity. Shiroyama et al.[37] documented 2 cases and reviewed 21 other cases of this deformity; communicating hydrocephalus was seen in 8 patients and noncommunicating hydrocephalus in 15 patients. The most common causes of noncommunicating hydrocephalus were basilar invagination, aqueductal stenosis, compression by a midline occipital bone crest, and posterior fossa deformities. Communicating hydrocephalus, when present, is thought to have resulted from venous hypertension and CSF flow obstruction at the constriction band of bone (Fig. 3).[46] However, in 1980 Turner and Reynolds[42] reported a case of cloverleaf skull without associated hydrocephalus, suggesting that hydrocephalus is not an invariable accompaniment to the Kleeblattschädel deformity.

Venous Hypertension

Intracranial obstruction can reroute venous drainage via the scalp veins, and such an interruption can lead to serious brain swelling and infarcts.[25] Prominent veins in the scalp, sclera, and periorbital region are described in several reports on the Kleeblattschädel deformity, arguably a remnant of persistent embryonic cranial circulation. There are also case reports of severe proptosis leading to corneal ulcerations, often treated with tarsorrhaphies.[12,35] Enlarged emissary veins, stenosis of the jugular foramina, and the presence of high-pressure, intraosseous, cranial venous sinuses communicating with a collateral scalp venous system lead to venous hypertension associated with the Kleeblattschädel deformity, according to Thompson et al.[41] This observation was validated by the fact that their patient required shunt placement despite adequate release of the supratentorial constriction band of bone. Hence, the venous obstruction at the jugular foramen level was held at fault.

The role of venous hypertension and the development of hydrocephalus seem to be linked.[12,23] Portnoy et al.[32] postulated that the venous hypertension is dependent on the status of cranial sutures (open or closed) and the re-

sultant ICP that acts over the sagittal venous sinus pressure, the rate-limiting factor in CSF absorption. With the multiple cranial synostoses that occur in the Kleeblattschädel deformity, the chances of venous hypertension developing are high. The presence of venous collaterals were documented by Pierre-Kahn et al.,[31] which eventually led to an extracranial-intracranial bypass in a patient with Crouzon syndrome, whose hydrocephalus resolved postoperatively. We believe that a shunt surgery or vault expansion surgery could be a less invasive initial approach in treating these patients.

Hindbrain Herniation

The hindbrain herniation in syndromic craniosynostosis was first reported by Saldino et al.[36] Venes[43] also described hindbrain herniation in a case of cloverleaf skull deformity and advanced the concept of an acquired Chiari malformation. It has been postulated that the venous hypertension, small posterior fossa, and hydrocephalus would be contributing variables in the development of hindbrain deformation/herniation. Cinalli and colleagues[5,6] posit that the chronic tonsillar herniation in craniosynostosis is a result of venous hypertension and cephalocranial disproportion (brain growth and small posterior fossa). This theory applies to all the complex craniobasal craniostenotic states, such as cloverleaf skull deformity.

Associated Conditions

There are reports of an association between the Kleeblattschädel deformity and achondroplasia, Crouzon craniofacial dysostosis, and Apert syndrome (acrocephalosyndactyly). Available reports reveal that 20% of cloverleaf malformations are associated with Pfeiffer syndrome (acrocephalosyndactyly Type V).[22] Cohen[8] has proposed 3 clinical subtypes of Pfeiffer syndrome and has attributed a poor prognosis to those associated with Kleeblattschädel deformity. It has been noted that an isolated Kleeblattschädel deformity without an associated craniofacial syndrome is relatively rare.

Several postulates are available for the pathogenesis of the Kleeblattschädel: abnormal membranous bone ossification,[1] abnormal endochondral ossification,[4] and generalized chondrodysplastic process.[4] The first classification of Kleeblattschädel deformity was proposed by Partington et al.[30] in the following 3 groups: Type I, cloverleaf skull associated with generalized chondrodystrophy or thanatophoric dwarfism; Type II, cloverleaf skull with localized skeletal lesions such as bony ankylosis of elbows and subluxation of radial heads or hips; and Type III, cloverleaf skull deformity without any skeletal deformity.[30]

The current neurogenetic grouping of the Kleeblattschädel deformity is under thanatophoric dysplasia Type II—whereas Type I is more common and patients classically present with curved femur bones that look like telephone receivers and a flattened spine (platyspondyly). The term "thanatophoric" is Greek for "death bearing," and infants with thanatophoric dysplasia are usually stillborn or die of respiratory failure shortly after birth.[17,33,45] This type of dysplasia arises from mutations in the *FGFR3* gene, which has been mapped to chromosome band 4p16.3 and is involved in the development and maintenance of bone and brain tissue. Note that *FGFR3* is part of the tyrosine kinase receptor family and that mutations in this gene cause the FGFR3 protein to be overly active, which leads to the severe disturbances in bone growth that are characteristic of thanatophoric dysplasia, which often shows an autosomal dominant pattern of inheritance. Germline mosaicism has not been clearly documented but remains a theoretical possibility. In the existing medical literature, all patients with thanatophoric dysplasia Type II (Kleeblattschädel deformity) have a single point mutation, p.Lys650Glu, with an A→G nucleotide transition in the tyrosine kinase domain of *FGFR3*, also known as K650E. This occurs in 99% of patients with Type II dysplasia and remains the only reported gene mutation in Kleeblattschädel deformity. Thanatophoric dysplasias Type I and II may both carry a cloverleaf skull deformity, although it is extremely rare in Type I. However, they do not share common *FGFR3* gene mutations.[19] Sequence and targeted mutation analysis of *FGFR3* is currently available to assist with diagnosis when clinical concerns are high.[27]

Surgical Strategies in Kleeblattschädel: Evolution in the Past 5 Decades

Early reports documented death of the affected infant soon after birth,[1,2] with an overall poor prognosis. In 1972 Arseni et al.[2] first described surgical treatment in the form of linear craniotomies along the coronal, lambdoid, and temporoparietal sutures in 2 stages at intervals of 4 and 7 weeks. These patients had survived to 6 years and 3 months of age because of a milder form of hydrocephalus. In both patients, the authors described improvement in symptoms such as headaches and agitation; however, the trilobar cranial deformity was not corrected in either patient.

In 1975 Muller and Hoffman[25] described the use of a 2-stage craniectomy in a 4-month-old child to correct a cranial deformity. A preoperative lumboperitoneal shunt was inserted to achieve decompression of the hydrocephalus. In the first stage, the bony constricting band separating the cephalic and lateral leaves of the skull was removed and cut back to the transverse sinuses. In a second stage 3 weeks later, an occipital craniectomy was performed, resulting in a circumferential bony decompression. The patient was alive and well at 9.5 years of age; however, there was significant intellectual and growth retardation.

Subsequent authors in larger series advocated early subtotal craniectomy with preoperative shunting of hydrocephalus to achieve internal decompression. Heeckt et al.[16] described early subtotal craniectomy combined with frontoorbital advancement to decrease intracranial pressure, preserve vision, and increase patency of the upper airway. Because of the high mortality rate (3 of 11 patients) following early radical surgery, however, the authors suggested that early total craniofacial mobilization before 3 months of age should be reserved for severe cases in which the natural history of the disease would result in death without immediate intervention.

In their series, Resnick et al.[34] described a similar high morbidity with the use of initial radical decompres-

sive craniectomy. In their experience with 4 patients, at least 50% of the cranial vault was removed in early infancy to relieve high intracranial pressures. Of these 4 children, however, only 1 child had a neurologically normal outcome. These authors reported better results utilizing a staged approach with anterior and posterior craniectomies and bone morcellation and replacement.

Because of the uniformly poor outcomes achieved with early subtotal craniectomy, staged release of the involved sutures has evolved to become the surgical technique of choice. Lodge et al.[23] described initial excision of the coronal ring of sutures before 6 months of age, followed by staged combinations of frontoorbital advancement and lambdoid craniectomies in a series of 10 patients. Staged surgery allows calvarial remodeling, expansion of the brain, and orbital decompression between surgeries. Crouzon syndrome (6 patients) followed by Pfeiffer syndrome (4 patients) was diagnosed in the majority of patients in their series. Nine of the 10 patients in the study required ventriculoperitoneal shunting for the treatment of hydrocephalus following initial calvarial decompressive procedures. These authors also emphasized the importance of managing the airway due to midfacial retrusion restricting patency of the upper airway.

Gosain et al.[15] reported a similar approach in a 2-month-old patient, with the initial decompressive craniectomy involving both coronal sutures and the right lambdoid suture to release the constricting calvarial ring, followed by subsequent frontoorbital advancement and cranial vault remodeling at 8 months and 2 years of age to correct the anterior cranial deformity, respectively. The patient eventually required a ventriculoperitoneal shunt at 9 months of age for decompression of the hydrocephalus. The authors noted the presence of progressive turricephaly after the initial decompressive craniectomy and early frontoorbital advancement due to continued growth of the brain in the presence of a shortened anterior cranial fossa, but they asserted that there was no solution for the problem at that time.

Jarrahy et al.[21] analyzed a series of 14 patients who had staged correction with a ventriculoperitoneal shunt in early infancy, frontoorbital advancement between 3 and 6 months of age, and posterior vault expansion at 1 year of age. They, like other authors, concluded that patients who underwent early cranial vault remodeling experienced more complications such as pneumonia, meningitis, bleeding, and seizures and required longer stays in the intensive care unit. Patients who underwent early cranial vault remodeling also had delays in intellectual development and performed worse on preschool tests. In contrast, in the group that underwent staged surgical correction, 85% of the patients had normal IQ scores at 4 years of age. Based on their experience, the authors advocate staged correction with initial placement of a ventriculoperitoneal shunt in the neonatal period, followed by frontoorbital advancement between 3 and 6 months of age and posterior vault remodeling at around 1 year of age. Frontoorbital advancement both corrects the trilobar head shape and reduces the development of turricephaly while providing intracranial space for the growing brain, whereas posterior vault remodeling corrects the occipital flattening, reduces turricephaly, and provides additional space for the brain in the posterior cranial vault. Good aesthetic results were achieved using their technique, with the restoration of a normal cranial shape. A substantial number of these patients did subsequently require monobloc or midfacial advancement in later childhood; however, this result concurs with findings in other patients with craniosynostosis and is not unusual.

Illustrative Cases

Case 1: Kleeblattschädel Anomaly With Syndromic Craniosynostosis

History and Examination. This 1-month-old boy with Apert syndrome presented with bitemporal and frontal bossing resulting in a trilobed skull. He also had a palpable bicoronal ridge and profound exorbitism. Closed bilateral coronal and right lambdoid sutures were noted on CT.

Operation. The child subsequently underwent craniectomy of the stenotic coronal sutures bilaterally and the right lambdoid suture at 2 months of age, releasing the point of fusion of the cephalically displaced sphenoid ridge with the bicoronal synostosis. Multiple bone spicules extending from the region of the bicoronal synostosis pushed the dura mater inward to cause impressions on the underlying brain (Fig. 3).

Postoperative Course. Following the craniectomy, there was gradual resolution of the bitemporal bossing. A repeat CT scan 3 months after the craniectomy demonstrated release of the fusion between the sphenoid ridge and the stenotic coronal sutures. Releasing these constricting elements led to a more rounded contour of the superior

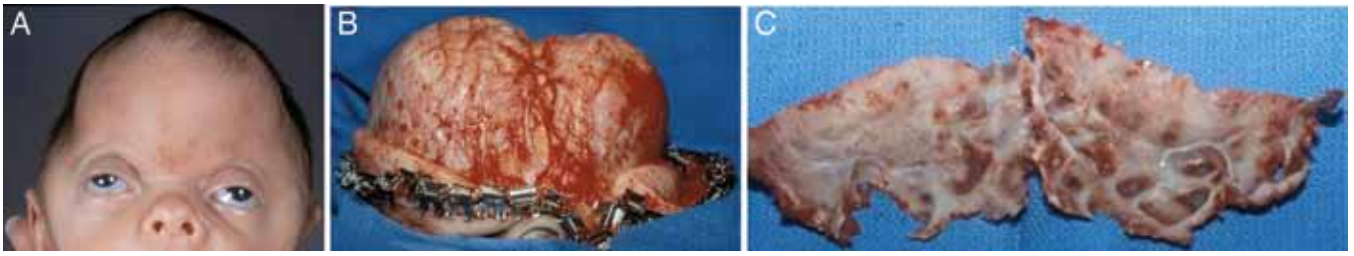

Fig. 3. Case 1. **A:** Photograph of 1-month-old boy with Apert syndrome demonstrating the classic findings of Kleeblattschädel with frontal bossing, temporal bulging, and a trilobar cranial vault as well as exophthalmos apart from syndactyly. **B:** Intraoperative photograph showing impressive frontal bossing as well as the characteristic tension band. **C:** Photograph of removed frontal and temporal skull showing the characteristic "honeycomb pattern" of inner-table irregularities.

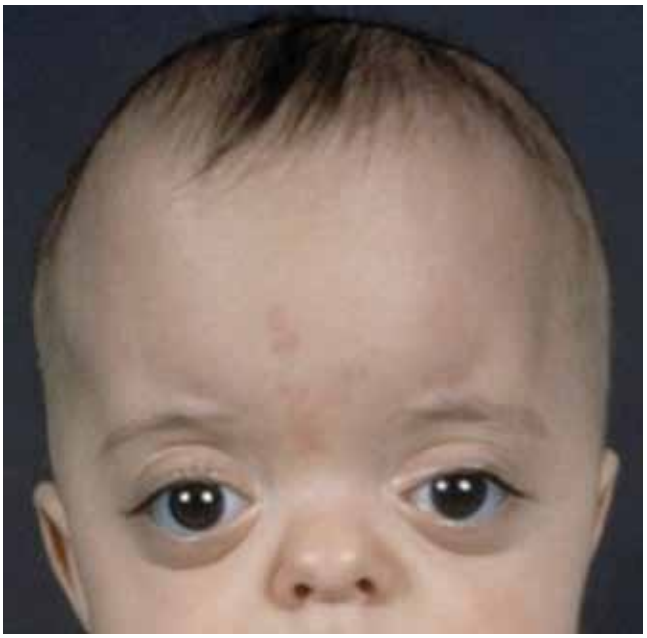

Fig. 4. Case 1. Postoperative photograph taken when the patient was 13 months of age demonstrating marked improvement in the frontal bossing and temporal bulging.

portion of the skull. Four months after craniectomy, the trilobed skull began to show correction in shape, with persistent deformity observed in the forehead contour.

At the age of 8 months, the patient underwent frontoorbital advancement and cranial vault remodeling to correct the anterior cranial deformity. Follow-up examination 1 month postoperatively demonstrated resolution of the trilobed skull configuration. A ventriculoperitoneal shunt was placed for the postoperative worsening of hydrocephalus.

By 2 years of age, however, the patient's calvarial growth demonstrated progressive turricephaly with exorbitism. Therefore, repeat frontoorbital advancement and cranial vault remodeling were performed. Although correction of the frontofacial deformity remained good, with improvement in exorbitism 16 months after surgery (age 40 months), the patient demonstrated gradual progression of anterior turricephaly characteristic of patients with Apert syndrome (Fig. 4).[15]

Case 2: Kleeblattschädel Anomaly Without Syndromic Craniosynostosis

History and Examination. This 1-year-old boy with a trilobed skull and prominent frontal bossing was referred for evaluation because of an abnormal head shape, a developmental delay, and multiple medical problems. The child was the second born to a gravida 2 para 2 healthy mother and was delivered via Cesarean section at 38 weeks gestation due to polyhydramnios. He had medical comorbidities including pulmonary artery stenosis, hypertension, hepatomegaly, chylothorax, and mitral valve regurgitation. He had undergone Nissen fundoplication for gastroesophageal reflux disease and suffered cardiopulmonary arrest at 8 months of age. On examination, he had an occipitofrontal circumference of 41 cm (< 3rd percentile) with brachyturricephaly and prominent scalp veins. Additionally, bilateral exophthalmos, a bifid uvula, and diffuse hypotonia were noted. Three-dimensional CT revealed the absence of bilateral coronal sutures and the right lambdoid suture (Fig. 5).

Operation and Postoperative Course. The patient underwent bifrontal cranioplasty with bilateral coronal synostectomy and flattening of the parietal bones superiorly (Fig. 6). This procedure led to significant aesthetic improvement, although the patient remained seriously debilitated from his multiple medical comorbidities.

Conclusions

Advances in surgical technique, anesthesia, and intensive care management have rendered a previously untreatable craniofacial condition, the cloverleaf skull syndrome, treatable, with the potential for decent neurological and aesthetic outcomes. Historically, surgical treatment involved simple decompression in the form of craniotomy or craniectomy or early radical subtotal calvariectomy, with uniformly poor results. Treatment has evolved over the past 5 decades toward the performance of staged surgeries, with much better outcomes. An initial ventriculoperitoneal shunt or simple craniectomy of the coronal sutures allows decompression of the hydrocephalus or release of the constriction ring around the skull, respectively. These temporizing measures allow the delay

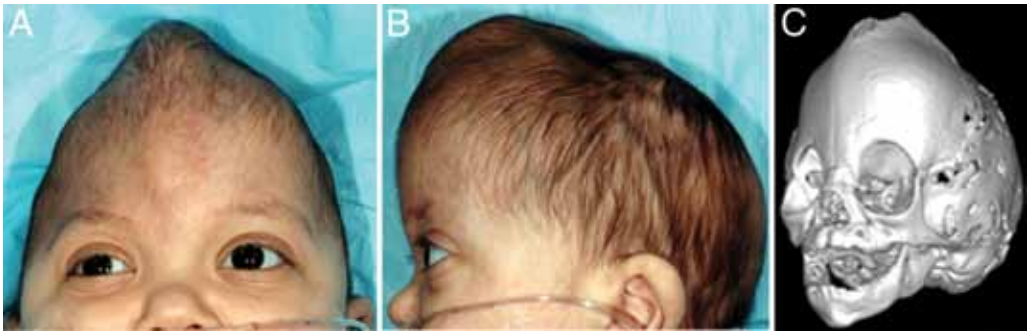

Fig. 5. Case 2. Anteroposterior **(A)** and lateral **(B)** photographs of a 1-year-old infant who presented with Kleeblattschädel deformity. Note the prominent frontal and mild bitemporal bossing as well as the pronounced engorgement of scalp veins. Computed tomography reconstruction image **(C)** demonstrating the absence of coronal sutures with typical porous skull abnormalities seen in the setting of elevated intracranial pressure.

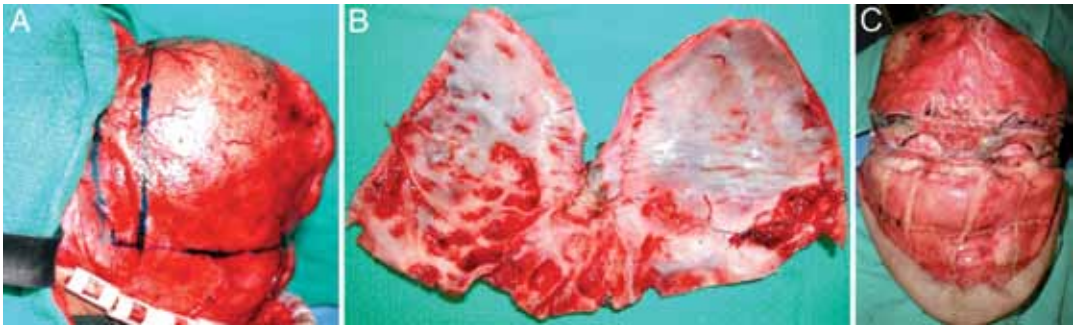

Fig. 6. Case 2. **A:** Intraoperative photograph revealing bony abnormalities in cloverleaf skull deformity. **B:** Photograph of excised frontal and temporal bone demonstrating irregularities of the inner table and changes in the cranial sutures. **C:** Intraoperative photograph taken following bony remodeling and replacement of skull bones.

of definitive surgical intervention until the child is older and better able to tolerate the stresses of surgery and anesthesia.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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Cranial bone defects: current and future strategies

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Bony defects in the craniomaxillofacial skeleton remain a major and challenging health concern. Surgeons have been trying for centuries to restore functionality and aesthetic appearance using autografts, allografts, and even xenografts without entirely satisfactory results. As a result, physicians, scientists, and engineers have been trying for the past few decades to develop new techniques to improve bone growth and bone healing. In this review, the authors summarize the advantages and limitations of current animal models; describe current materials used as scaffolds, cell-based, and protein-based therapies; and lastly highlight areas for future investigation. The purpose of this review is to highlight the major scaffold-, cell-, and protein-based preclinical tools that are currently being developed to repair cranial defects. *(DOI: 10.3171/2010.9.FOCUS10201)*

Key Words • **cranial bone defects** • **bone-tissue engineering** • **scaffold** • **bone healing**

Bony defects in the craniomaxillofacial skeleton can occur as a result of congenital defects (for example, in 2001, 37,732 children underwent surgery to repair birth defects) or acquired injuries (for example, in 2001, 24,298 patients required maxillofacial surgery for injuries to the face and jaw) (www.surgeryencyclopedia.com). Regardless of their cause, bony defects are functionally debilitating, socially incapacitating, and biomedically and economically burdensome.

The war on terrorism has brought a myriad of new challenges to maxillofacial surgeons, plastic surgeons, and neurosurgeons: combat-associated craniomaxillofacial injuries. Wars in Iraq and Afghanistan have resulted in the greatest incidence of head trauma since the Vietnam conflict. Increased survival because of body armor and advanced battlefield medicine, as well as the increased use of explosive devices, has contributed to the increased incidence of craniomaxillofacial combat injuries. Patients once not considered amenable to reconstructive surgery are now being aggressively treated and are surviving devastating head trauma. This unique patient population ultimately requires reconstruction of the cranial skeleton for protection of the brain as well as aesthetic and functional restoration of the calvaria or the bones of the face. These patients require countless procedures and are often left with poor aesthetic and functional results.

Abbreviations used in this paper: ADMSC = adipose-derived mesenchymal stem cells; BCP = biphasic calcium phosphate; BMMSC = bone marrow–derived mesenchymal stem cell; BMP = bone morphogenetic protein; HA = hydroxyapatite; OCP = octacalcium phosphate; rhBMP = recombinant human BMP; TCP = tricalcium phosphate; VEGF = vascular endothelial growth factor.

It is now well known that successful spontaneous calvarial reossification only occurs in infants younger than 2 years of age.[27] Thus, a variety of materials and methods have been proposed to restore such defects including autogenous bone grafts and allogeneic banked bone, demineralized matrix pastes, ceramic scaffolds, and even synthetic materials and bone substitutes such as calcium ceramics. More recently, cell-based alternatives and BMPs have also been used.[26] The multitude of methods reflects both the inadequacy of each technique, as well as the pressing need to adequately reconstruct the skeleton. While each method may achieve craniofacial reconstruction, each possesses inherent limitations, such as donor-site morbidity, an obligatory graft resorption phase, contour irregularities, insufficient autogenous resources, disease transmission, graft-versus-host disease, immunosuppression, structural failure, and foreign body infection. These limitations preclude most large defects from being repaired with these materials. Therefore, the need for new and improved treatment options is urgent.

To solve these issues, scientists, physicians, and engineers are collaborating to design new tissues to repair cranial defects. Because bone formation is an intricate and dynamic process, an interdisciplinary team effort is a requirement for the generation of functional tissue. Many strategies have been employed including cell-based therapies, cellular and acellular scaffolds, recombinant gene therapy, and topical small molecule therapies among others. Although bone-tissue engineering for the treatment of cranial defects is a multistep and multicomponent process, for clarity we will separately highlight every major tool that is currently being developed to solve common craniofacial problems.

TABLE 1: Characteristics of currently used animal models

Animal Model	Size of Critical Defects	Pros	Cons
mouse	5 mm	small size, easy maintenance, low cost	small size, poor surgical precision
rat	8 mm	slightly larger than mouse: still relatively affordable w/ more surgical precision	similar to mouse model but more expensive
rabbit	15 mm	not much larger than rat but has larger critical defect so more surgical control	more expensive than rats; few benefits other than larger defect size
monkey	15 mm	closely related to humans so most translational model	expensive, ethical concerns
canine	20 mm	larger defect size for more surgical precision & control	expensive, ethical concerns
sheep	22 mm	larger defect size for more surgical precision & control	expensive, ethical concerns

In Vivo Animal Models Of Cranial Defects

The in vivo regeneration of bone for healing critical-size calvarial defects is an ongoing area of active research. Physicians and scientists are generating novel methods and combination treatments for addressing cranial defects, and these strategies abound in the literature. Animal models have the limitations of recreating only limited cranial defects but are our best option currently available. We will first focus on describing small-animal models and then shortly describe larger-animal models that are used less frequently (Table 1).

Small-Animal Models

Mouse. The mouse is currently the most commonly used animal model in basic science research owing to its ease of maintenance and relatively low cost. Additionally, sophisticated molecular and cellular biology analytical tools are readily available and yield highly reproducible results.[1] In the mouse, a critical-size cranial defect is defined as a bony deficit greater than or equal to 5 mm.[63,67,80] Such a defect, if left untreated, will not heal in the life of an animal.[102] Generally, a critical-size defect in the mouse calvaria is created by using a trephine that makes a circular defect in the cranial skeleton[16] (Fig. 1). The challenge in using this particular model is the small size of the mouse. Because of the intimate relationship of the cerebral cortex, the dura mater, and the calvaria, a dura-sparing craniotomy is technically challenging. Sparing the dura mater is in fact critically important since several studies have shown that the dura is instrumental in bony regeneration of the skull.[1,35,117]

As previously noted, humans up to 2 years of age have the capacity to spontaneously heal cranial defects that would be "critical" in an adult human. In 2003, Aalami et al.[1] reported similar findings in a mouse model of juvenile and adult cranial defect healing: in the juvenile mice (6 days old) a significantly greater portion of critical-size calvarial defects was healed than in the adults (60 days old). The authors were particularly careful in sparing the dura mater in these procedures. Prior studies have shown that although juvenile animals have the capacity to spontaneously heal critical-size defects, this ability is negated if the dura mater is compromised.[17] Further support of the observation that the dura mater is influential in bony healing is the finding that critical-size bony defects in adult guinea pigs can be rescued by allotransplantation of juvenile guinea pig dura mater to the adult defect.[41] To preserve the dura mater, craniotomies in mice should to be performed with the aid of a dissecting microscope. The other option, of course, is to use a larger-animal model such as the rat.

Rat. The rat is another commonly used animal model for studying critical-size defects. In the rat, a critical-size cranial defect is defined as a bony deficit greater than or equal to 8 mm.[103] In 1982, Takagi and Urist[110] determined that 8-mm-diameter cranial defects in Sprague-Dawley rats healed to 5 mm by 4 weeks and by 12 weeks no further healing was noted; however, the first to examine critical-sized defects in the rat were Freeman and Turnbull[30] 10 years earlier.[113] Benefits of the rat over a smaller animal to study cranial defects are its larger size and the consequence that one is thereby permitted to perform technically sound craniotomies.

Larger-Animal Models

Larger-animal models have also been used, and there are pros and cons to using these animals. On the one hand, the primary benefit is the greater control and precision that the larger size allows intraoperatively. Larger animals such as the rabbit, guinea pig, dog, sheep, and monkey provide the opportunity for more control in the surgical area. On the other hand, these animals are more expensive to purchase and maintain, and they also take up a lot of space.

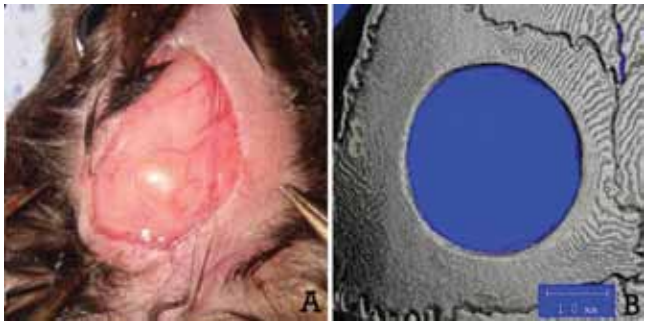

Fig. 1. Mice calvarial defect model. **A:** A 3-mm-diameter round dental bur was used to create a 3-mm (noncritical) calvarial defect on the left parietal bone in a wild-type mouse. The underlying dura mater was kept intact. **B:** A 3D micro-CT scan of a calvarial defect immediately following wound creation, showing the perfect bone defect.

The first studies of critical-size cranial defects were conducted in 1899 by Berezowsky,[8] who reported that the presence of the dura mater in rabbits is required for calvarial bony healing to occur. In rabbits, the critical-size defect is a bony deficit greater than or equal to 15 mm.[28,29] Other larger animals have been described in the literature as models for studying critical-size defects. Dogs, for example, have been frequently used to study calvarial defects.[31,97,115] Canine critical-size calvarial defects are 20 mm in diameter.[19] More recently, sheep have been used to study critical-size defects (22 mm)[116] as have other nonhuman primates such as monkeys (15 mm).[43] Clearly, many different animals have been used as model systems for studying critical-size defects of the cranial skeleton. The animal chosen by a research team must suit their needs and be both ethically acceptable and economically feasible to purchase and maintain.

Materials Used for Defect Repair

Ever since critical-size defects were first described and the limitations of endogenous healing were understood, physicians have come to the conclusion that novel strategies should be developed to enhance bony healing. Hence, scaffolds have been one of the main targets of ongoing research. The idea has been that a biocompatible and biodegradable matrix inserted into a cranial defect will support, guide, and enhance bone healing. After the failed use of empty scaffolds,[94] people have been trying to improve the efficacy of the scaffold by using it as a delivery system or a carrier for cells and/or growth factors. To facilitate the delivery of cells, drugs, and extracellular matrix material to a localized bony defect, an appropriate carrier device is often required, and several different materials have been proposed (Table 2). The ideal scaffold will have to be biocompatible and osteocompatible and allow for osteogenesis, osteoinduction, and osteoconduction (Fig. 2). In addition, the scaffold must demonstrate mechanical strength and resilience, and its degradation products must not trigger any inflammatory reaction.

Many new polymers and synthetic materials have been developed in recent years and are being tested as scaffolds. However, all current scaffolds have in common the properties of being both biocompatible and resorbable.[111] In addition to the multitude of new compounds and polymers currently developed, for many years people have been using calcium phosphate– or calcium carbonate–based scaffolds because of their similar composition to bone.

Calcium Phosphate Scaffolds

Beta-Tricalcium Phosphate. Beta-tricalcium phosphate is one of the earliest compounds to be used as a scaffold for osseous regeneration.[81] It has a compressive and tensile strength that is nearly equivalent to cancellous bone,[49] and this makes it an attractive compound for use as a scaffold material. As early as 1920, there were reports that β-TCP, when injected into the gap of a segmental bony defect, increased bone union.[5] In research models, β-TCP has been used as an empty scaffold to promote bone healing in rats[40] and has also been shown to promote bone regeneration in cranial defects of canines when the scaffold is seeded with bone marrow–derived stromal cells.[114] Additionally, investigators have used a composite scaffold composed of β-TCP, collagen, and autologous bone fragments fixated with fibrin glue to correct cranial defects in canines.[60] Although β-TCP is replaced by bone in vivo, replacement does not occur in a predictable 1:1 ratio. In other words, as β-TCP is resorbed, less new bone is laid down than β-TCP is resorbed.[42] This has limited its clinical applicability up to this point.

Hydroxyapatite. Intuitively, the ideal biomaterial should be a biomimetic reproduction of the matrix of native bone. The inorganic element of the natural bone matrix consists of mainly crystalline mineral salts in the form of HA. In addition to providing the raw materials for mineralized matrix formation, HA has a nanoscale topography that promotes cellular adhesion, differentiation, growth, and proliferation. For these reasons, many groups have advocated the use of HA scaffolds in regenerating bone both in vivo and in vitro. To prevent ischemia and allow for vascularization of the scaffold and proper seed-

TABLE 2: Characteristics of preferred scaffolds for bone-tissue engineering purposes

Scaffold	Composition	Pros	Cons	Resorption Rate	Release Minerals	Stiff or Moldable
HA	$Ca_{10}(PO_4)_6(OH)_2$	native inorganic bone matrix	brittle & resorbs slowly	very slow (takes yrs)	yes	stiff
β-TCP	$Ca_3(PO_4)_2$	native bone calcification minerals	significantly less bone laid down than β-TCP resorbed	very slow (>3 yrs)	yes	stiff
BCP	variable	combination of native bone matrix & minerals	must vary amount of HA & β-TCP to generate useful scaffold	rapid (wks)	yes	stiff
calcium sulfate	$CaSO_4 \cdot 2H_2O$	highly moldable & easily shaped	not native bone material	rapid (4–12 wks)	yes	moldable
OCP	$Ca_8H_2(PO_4)6.5H_2O$	composed of native bone minerals, osteoinductive	not as much known about material as traditional calcium phosphate	slow (6 mos to over 1 yr)	yes	stiff
advanced nanomaterials	variable	customizable & can be generated w/ desired characteristics	new & underdeveloped technology	variable	no	moldable

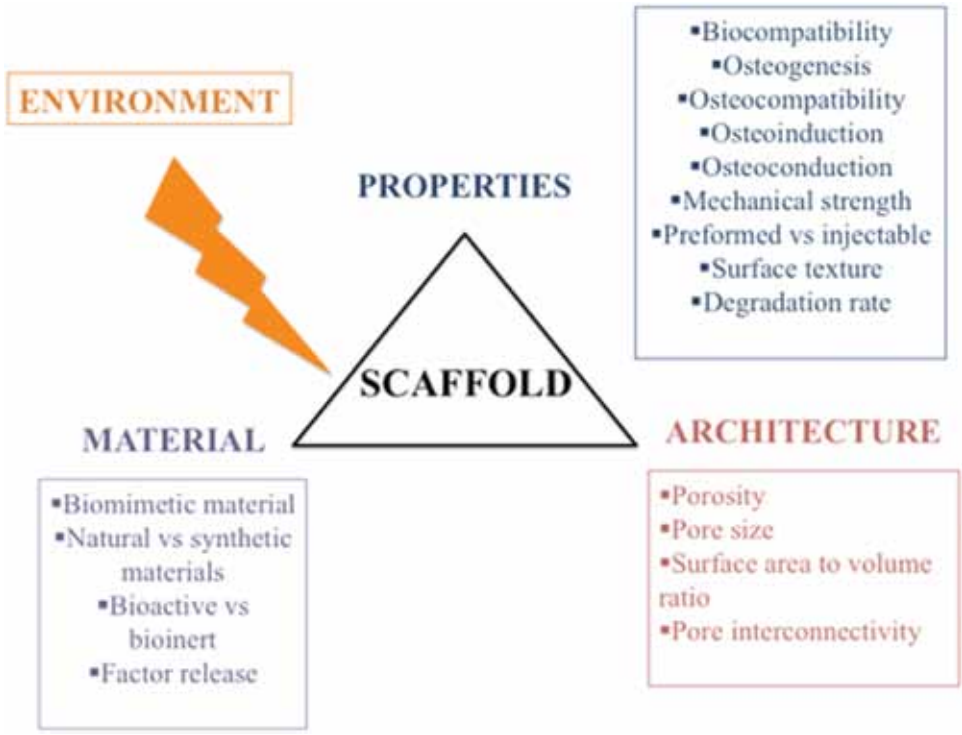

Fig. 2. Bone-tissue engineering: properties and characteristics to consider for the design of a scaffold. The ideal scaffold will have to be biocompatible and osteocompatible (to be inserted into a cranial defect to support, guide, and enhance bone healing) and allow for osteogenesis, osteoinduction, and osteoconduction. In addition, the scaffold must demonstrate mechanical strength and resilience and its degradation products must not trigger an inflammatory reaction. The surrounding environment and the seeding of cells onto the scaffold play a major role for bone growth as well.

ing of cells within it, the scaffold needs to have pores that have a relative diameter of about 100–150 μm.[46] The geometry and porosity of HA scaffolds have also been shown to be important in the capacity of these scaffolds to heal cranial defects in rabbits.[25] One downside to this scaffold material is that it tends to be brittle, not easily molded, and its resorption rate is also very slow. To enhance its usability as a scaffold material, people have added polymers such as Pluronic F-127 to HA to increase its moldability.[15,125] In 1997, Lew et al.[69] demonstrated that empty HA scaffolds could promote osteoconductive bone healing in canine calvarial defects. Additionally, by coating a zirconium porous scaffold with an outer layer of highly porous HA, calvarial defects in rabbits have been demonstrated to exhibit up to 50% new bone formation at 12 weeks.[58]

Biphasic Calcium Phosphates. Biphasic calcium phosphates are mixtures of β-TCP and HA of varying amounts.[95] As a BCP scaffold is resorbed in vivo, it releases calcium and phosphate ions into the microenvironment of the implant, and these ions can then be used to build bone de novo.[104] Although there have not been much published data on using BCP scaffolds to heal critical-size cranial defects, the scaffolds have been used to successfully aid in bone regeneration in mandibular defects in canines[48,105] and iliac wing defects in goats.[64] Additionally, a BCP scaffold (60% HA plus 40% β-TCP) seeded with rhBMP-2 was used to demonstrate complete spinal fusion in a nonhuman primate model.[101] In our laboratory, we can fabricate HA and TCP scaffolds using a custom-designed 3D microprinting process (Fig. 3). We have demonstrated that these BCP scaffolds, when implanted into a critical-size alveolar defect in rats either empty or seeded with rhBMP-2, are capable of inducing new bone formation.[84] Further experiments using HA-TCP scaffolds are being pursued in our laboratory.

Octacalcium Phosphate. Octacalcium phosphate is a biological precursor of apatite crystals[11] and has been shown to promote differentiation and maturation of osteoblasts in vitro.[6,72,108] Studies have also shown that OCP, compared with HA or β-TCP, has the capacity to increase attachment of osteoblasts to the scaffold.[32] Furthermore, OCP/collagen scaffolds have been demonstrated to direct improved bone regeneration in rat calvarial defects compared with HA or β-TCP alone or HA/collagen or β-TCP/collagen scaffolds.[54] An additional benefit of OCP scaffolds is that they are osteoinductive, which is not an attribute of HA or β-TCP.[37,42]

Calcium Sulfate Scaffolds

Calcium sulfate, also known as plaster of Paris, is thought to act as an osteoconductive substrate for the invasion of blood vessels and associated osteogenic cells; for this to occur, it is imperative that the calcium sulfate scaffold be in intimate contact with viable endosteum or periosteum.[16] Additionally, calcium sulfate scaffolds serve as an excellent site of adherence for osteoblasts[106] and cause no appreciable inflammation on implantation.[93]

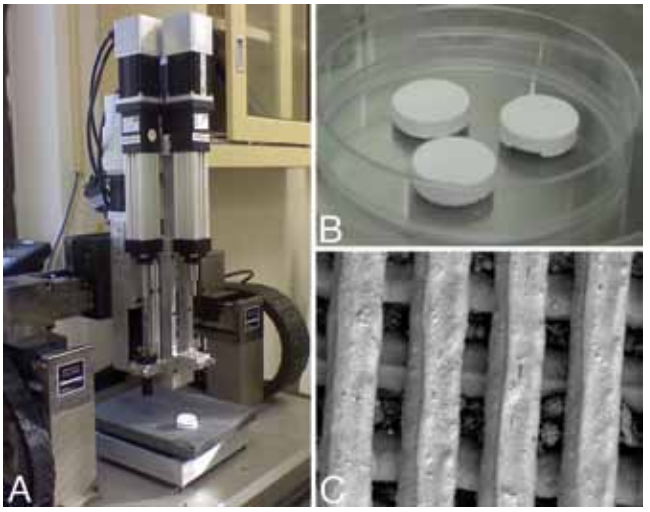

Fig. 3. Scaffold printing system. The 3D microprinting process is fully customized (diameter, pore size, strut size, and porosity) and can produce novel scaffolds in less than 3 hours. **A:** The 3D microprinting processor. **B:** Several HA-TCP sample scaffolds. **C:** The microarchitecture of a customized scaffold.

In vivo studies have been conducted in rat calvarial defect models and demonstrate that calcium sulfate, when combined with allogeneic bone matrix, promotes bone formation.[98] For more information about calcium sulfate scaffolds please see review article by Pietrzak and Ronk.[96]

Advanced Scaffold Materials

The recent advent of nanotechnology and advances in polymer chemistry have led to the development of many novel and ingenious scaffold materials. Osathanon et al. recently described the use of a nanofibrous fibrin scaffold for bony regeneration in a mouse calvarial defect model.[89] This scaffold served to immobilize enzymatically active alkaline phosphatase, which promoted bone formation by increasing the amount of biologically available inorganic phosphate. In another recently published article the authors used PuraMatrix (a self-assembling peptide nanomaterial) seeded with either mesenchymal stem cells or platelet-rich plasma to aid in bone regeneration.[123] This scaffold has the added benefit of being easily molded and readily shaped to conform to any bony defect.[61] Electrospun silk fibrin scaffolds can also be used for bone regeneration because the nanofibers of the scaffold function like the native bone extracellular matrix.[70,120] This electrospun silk fibrin scaffold promotes osteoblast proliferation and increases osteoblastic alkaline phosphatase activity.[90] Many scaffold materials have been used as well: polyethylene glycol,[53,78,111] nano-HA membranes,[124] poly β-amino esters,[10] injectable chitosan gel, minimally invasive tissue-engineered bone,[107] and others. An exhaustive evaluation of current and future scaffold materials is available in the literature and is beyond the scope of this article.

Materials for Pediatric Use

Importantly, titanium implants, alloplastic, and inorganic scaffold materials such as those mentioned above are not the most appropriate options for the pediatric or adolescent patient.[51] Because these patients require further ossification of the cranial vault, autogenous and allogeneic banked bone are better options because of their capacity for osteointegration and growth with the pediatric skull. Despite this general consensus among neurosurgeons, plastic surgeons, and maxillofacial surgeons, successful treatment of pediatric patients using hybrid alloplastic materials has been achieved.[7]

Cell-Based Strategies

In addition to a proper scaffold for recruitment of cells that promote bone growth, it may be necessary to deliver cells to a bony defect to achieve proper regeneration. While tremendous progress has been made in the design, engineering, and manufacturing of construct technology, scientists are still struggling to find appropriate cell sources. Those cell-based strategies that use a scaffold material may come in 2 varieties: 1) scaffolds preseeded with cells and then implanted or 2) acellular scaffolds that require in vivo recruitment of autologous cells.[122] Acellular scaffolds may also be designed to recruit cells from nearby or distant sources.[39] Moreover cells may be used in bony regeneration without the use of a scaffold.

Many different cell types may be used. In this section we will discuss the variety of cell sources as well as their current use and success in generating neovascularized craniofacial constructs.

Bone Marrow–Derived Mesenchymal Stem Cells

Bone marrow–derived mesenchymal stem cells are multipotent cells that have the capacity to differentiate into many mesodermally derived cell types.[21] They can be easily differentiated in vitro into osteoblasts. Bone marrow–derived mesenchymal stem cells have mainly been used in 2 different ways: either seeded on a scaffold after in vitro osteogenic differentiation or seeded directly as uninduced BMMSCs on a scaffold. In the latter case, to make BMMSCs more potent promoters of bone growth, they may be coadministered with osteogenic cytokines such as BMP-2 and FGF-2.[76] Treatment of BMMSCs with BMPs has been demonstrated to help heal critical-size defects in the rat[44,45] (77.45% healed in 8 weeks)[21] as well as in the rabbit[14] ("near complete repair" at 3 months). Furthermore, when treating cranial defects in rats, naive BMMSCs are more potent inducers of osteogenesis than platelet-rich plasma.[57] One of the limitations of using BMMSCs to promote bone growth is that they have a limited life span. Nakahara et al. demonstrated that bone repair is enhanced by delivering BMMSCs to the defect that has been transfected with human telomerase reverse transcriptase, thus immortalizing the BMMSC cell population.[83] That being said, BMMSC populations are of limited quantity, and therefore it would be beneficial to have a source of adult stem cells that is more extensive. The recent discovery of ADMSCs provides a promising contender.

Adipose-Derived Mesenchymal Stem Cells

Adipose-derived mesenchymal stem cells are multipo-

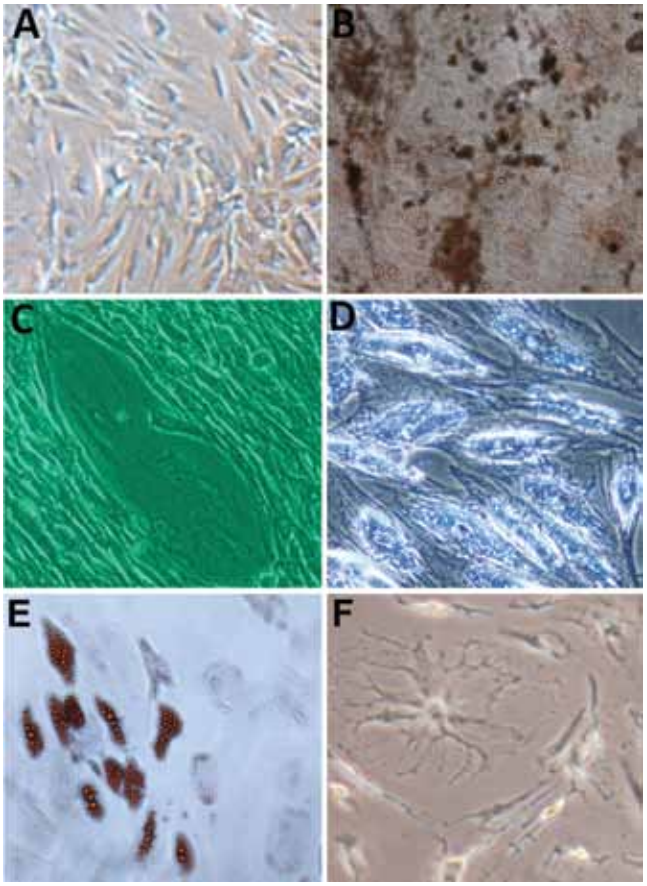

Fig. 4. Photomicrographs showing human mesenchymal stem cell multilineage differentiation. Under the appropriate stimuli, mesenchymal stem cells can differentiate into various cell types: undifferentiated (**A**; alkaline phosphatase, original magnification × 400), bone nodule (**B**; von Kossa, original magnification × 400), endothelial tubule (**C**; fluorescent GFAP, original magnification × 200), cartilage (**D**; Alcian blue, original magnification × 400), adipocyte (**E**; Oil Red O, original magnification × 200), neuron (**F**; GFAP, original magnification × 400).

tent cells that can differentiate into numerous cell types including osteogenic cell types[19] (Fig. 4); the apparent availability of these cells makes them a potent cell source for bone-tissue engineering. This cell type, with its multipotent differentiating capacity, was characterized in 2001 by Zuk et al.,[126] and the use of ADMSCs to treat calvarial defects was first studied by Cowan et al.[18] 3 years later. Cowan et al. showed that implanted poly(lactic-coglycolic acid) scaffolds seeded with ADMSCs promoted complete bone bridging in 12 weeks in a rat model of calvarial defects and also that the ADMSCs contributed 84–99% of the newly formed bone as determined by chromosomal detection. Although naive ADMSCs may have some therapeutic benefit when transplanted into a bony defect,[50] preimplantation osteoinduction seems to provide more benefit.[22,24,123] When critical-size cranial defects were made in canines, Liu et al.[71] demonstrated that osteoinduced ADMSCs successfully repaired the defect when seeded on coral scaffolds, and Cui et al.[19] confirmed that this reossification remains present at 6 months postimplantation.[57] Osteoinduced ADMSCs have also been shown to repair critical-size defects in rabbits when seeded on polylactic acid scaffolds.[50] Future research into the applicability of ADMSCs for regeneration of osseous structures will undoubtedly yield important clinical insights.

Chondrocytes

Most of the bony skeleton forms by endochondral ossification. Briefly, this involves the proliferation and hypertrophy of chondrocytes followed by apoptosis and replacement with osteoblasts. Although calvarial bone is formed by intramembranous bone formation that is independent of chondrocytes, it appears that chondrocytes may actually be able to help heal critical-size defects of the calvaria.[23,52,79,87,88] Just this year, Doan et al.[23] demonstrated that chondrocytes, when implanted directly into a critical-size cranial defect in mice, heal the defect by 6 weeks postimplantation. Montufar-Solis et al.[79] had first made this observation about chondrocytes in healing mouse cranial defects 6 years earlier.

Recombinant Protein–Based Strategies

Recombinant protein–based strategies for improving bone healing are based on the premise that augmenting endogenously produced cytokines will enhance bone regeneration.[27] Although the use of many different recombinant proteins such as fibroblast growth factor, activin, BMP, and VEGF for improved healing of bony defects in vivo has been demonstrated,[55,56,100,118,121] we will focus on the osteogenic BMPs and angiogenic VEGF. These 2 morphogens can be delivered to a calvarial defect by preseeding one of the previously discussed scaffolds with the recombinant protein. This allows for concentrated local delivery of the protein and avoids systemic administration.

Bone Morphogenetic Proteins. Bone morphogenetic proteins come in many different isoforms that play many dynamic roles in patterning of the embryo, bone growth and formation, and other processes (Table 3). Endogenous BMPs are typically found in the human body at a concentration of 2 mg/kg of cortical bone.[109] Thanks to the isolation and cloning of the BMPs in 1981,[99] recombinant human proteins can be made in high yield by transfecting Escherichia coli cells with human genes and utilizing the bacterial cellular machinery to produce the protein of interest in large quantities.[66] Bone morphogenetic protein–2, –4, and –7 have all been shown to induce bone formation in vivo, and Hyun et al.[47] have demonstrated this in a model of rat calvarial defects. Bone morphogenetic proteins have been shown to be strongly osteoinductive and can be delivered to a wound bed in numberous ways. Murine stromal cells were transfected by a retrovirus carrying a BMP-4 transgene, and these cells were then embedded in a gelatinous matrix and placed into a critical-size defect in a rat model;[36] this treatment completely healed the defect by 4 weeks. Additionally, a chitosan gel matrix loaded with BMP-2 and placed into a rat cranial defect was shown to promote bone regeneration.[13] Finally, rats with critical-size calvarial defects have been completely healed by utilizing collagen or β-TCP scaffolds embedded with rhBMP-4.[3] It is important to note that the use of BMPs in bone regeneration has been demonstrated in noncranial spinal defects

TABLE 3: Bone morphogenetic proteins grouped by amino acid sequence homology*

Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
BMP-2†	BMP-5	GDF-5	BMP-9	GDF-10 (BMP-3b)	BMP-15
BMP-4†	BMP-6	GDF-6 (BMP-13)	BMP-10	BMP-3	
	BMP-7† (OP-1)	GDF-7 (BMP-12)			
	BMP-8 (OP-2)				

* The human genome codes for more then 20 BMPs and with the exception of BMP-1, which was mistakenly classified as a BMP, these low-molecular-weight glycoproteins belong to the transforming growth factor–beta family. The BMP family has been grouped into subsets based on amino acid sequence homology. Abbreviations: GDF = growth differentiation factor; OP = osteogenic protein.
† BMP-2, BMP-4, and BMP-7 have all been shown to induce bone formation in vivo.

in humans. Two studies have demonstrated that bilateral treatment of the posterolateral spine with rhBMP-2 resulted in complete spinal fusion in 100% of patients receiving the treatment.[9,73] The action of BMPs in vivo can even be enhanced by coadministration of NELL-1,[2] COX-2 inhibitors,[65] treatment with simvastatin,[86] or a combination of simvastatin and α-TCP.[85] Last, it is important to clarify that in Europe, rhBMP-2 is commercially available for the treatment of acute open tibial fractures (InductOS implant kit, Medtronic Sofamor Danek and Wyeth Pharmaceuticals) as a lyophilized powder, dissolved in sterile water, and applied to an absorbable collagen matrix made of Type 1 bovine collagen. A similar kit (InFuse bone graft, Medtronic Sofamor Danek) is available in Europe and in the US for the treatment of degenerative lumbar disc disease.[110]

Neovascularization Strategies

Numerous groups have shown that the combination of artificial scaffolds and osteoprogenitor cells can lead to the formation of new bone,[12,33,75] but the clinical applicability of this technique is still questionable. The limited clinical success may be explained by a lack of vascularization. Vascularization is vital for the survival of the implanted cells on a carrier material after implantation, and apart from that, vascularization is a critical process during bone growth and repair. Studies have shown that fracture healing and ectopic bone formation can be blocked by the administration of angiogenesis inhibitors.[38,82] Other investigators have demonstrated that new bone formation in porous scaffolds was significantly increased by the insertion of a vascular pedicle in the scaffold[4,59] and that endothelial cells form vascular structures in vitro,[20,34,102] which can anastomose to the vasculature of the host after implantation.[68,112]

Thus, promoting vasculogenesis is an important aspect of promoting bone growth when attempting to correct calvarial defects. Briefly, this can be accomplished in 1 of 3 ways: 1) impregnating a scaffold with VEGF or another angiogenesis-promoting substance as previously discussed, 2) seeding endothelial cells or other vasculogenic cells onto a scaffold, or 3) implanting scaffolds into highly vascular tissues, waiting for vessel ingrowth to occur, and then transplanting the vascularized scaffold to the bony defect. Vascular endothelial growth factor is a very potent angiogenic morphogen.[122] Incorporation of VEGF into a scaffold material has been shown to induce angiogenesis and promote bone formation.[62] In mice, this is especially true when the VEGF is released slowly over time through the use of a calcium phosphate scaffold (in one study, bone healing occurred at a rate 1.56 times as fast[119]). Additionally, a combination therapy of VEGF and BMPs seems to have a synergistic effect on bone formation during the first few weeks of treatment: critical-size defects made in rat calvaria have been rescued by coadministration of VEGF/BMP-2 embedded in a gelatinous matrix. The 2 compounds acted synergistically to promote bone formation at 4 weeks postimplantation but exhibited little more effect than BMP-2 alone at 12 weeks.[92] As for the implantation of a scaffold into a highly vascularized tissue, a site of choice may be the abdominal mesentery[117] or any tissue with a rich arterial supply and venous drainage.[74] Briefly, this technique involves implantation of a scaffold into a highly vascularized tissue, waiting for the scaffold to become vascularized, removing the scaffold, and replanting the scaffold into the cranial defect. Future research into promoting neovascularization in bony defects will yield important methods by which we can improve osteogenesis and bone regeneration.

Discussion

After many years of research on bone-tissue engineering and after numerous attempts to develop an ideal scaffold including the appropriate combination of bone growth factors, we have yet to find the answer. A major limitation is the current availability of cranial defect models. While large models may seem more intuitive, technically, economically, and even ethically, smaller models such as the mouse or the rat are currently more feasible and are thus used more commonly. Nevertheless, there will always be a translational issue concerning the application of results seen in an animal model to the human body.

There is widespread agreement that the ideal solution would be to find a way to enhance endogenous bone healing in a patient without the use of an external device like a scaffold. Because our technology has not gotten to that point yet, however, scientists have focused their research on developing biocompatible and osteocompatible scaffolds capable of osteoinduction and osteoconduction. These scaffolds have ranged broadly in their composition from synthetic to natural, and all of them have had different properties, benefits, and flaws. Because its structure is

so close to actual bone, HA-TCP has been one of the most frequently investigated materials. It has undeniable advantages such as its composition and its capacity to be both osteoconductive and osteoinductive when in the presence of osteogenic cells (www.surgeryencyclopedia.com);[77] however, it is rarely osteoinductive when implanted on its own.[91] The major downside to using HA-TCP scaffolds is that they are quite brittle and resorb rather slowly. As previously mentioned, OCP scaffolds are being generated as a potential scaffold with similar characteristics to HA-TCP, but they have the added benefits of being both osteoconductive and osteoinductive. It seems that OCP scaffolds are superior to HA-TCP in their capacity to serve as an attachment site for osteoblasts and their ability to help direct bone formation in vivo. Octacalcium phosphate scaffolds may have a bright future in bone regeneration.

Due to the progress of cell-based therapy, the idea of bringing osteogenic cells to a defect has been actively investigated. Many cells types are being studied, and the ability of BMMSCs and ADMSCs to differentiate into osteoblasts and chondrocytes has led researchers to focus on them. Seeded on the appropriate scaffold and placed in the appropriate environment, these two cell types have shown their ability to create bone. However, a major issue has always been, and still remains, that the quantity of cells available is limited; this is especially true when considering mesenchymal stem cells.

Since their discovery in the 1960s, BMPs have been providing us great hope but disappointment as well. They were thought to be the missing link for ex vivo and in vivo bone growth stimulation but proved to be less successful than expected. That said, recent advances in rhBMP delivery vehicles, as well as the application of BMPs in orthopedic surgery, have renewed expectations in their capacity to regenerate bone in humans.

Research led to the observation that vascularization may be a key missing factor for bone-tissue engineering. Every single tissue needs a patent blood supply to survive and bone is no exception to the rule. Thus, the use of vasculogenic factors and cells became obvious. Both have shown great results, enhancing bone formation and bone healing.

The research on cranial bone defects is promising. There have been leaps and bounds in the past 2 decades, and certainly the next few decades will show even more progress. For those people born with craniomaxillofacial defects or those in whom they are acquired due to trauma, this research is an integral part of their future livelihood. It has been demonstrated that cranial bone defects can be healed in animal models, and this provides hope for applications in humans. It is only a matter of time before we are able to give patients with craniomaxillofacial defects a second chance.

Conclusions

This review highlights most of the current translational bone tissue–engineering strategies. Although numerous different materials and techniques have been and are under investigation all around the world, we have yet to find the perfect solution to bone reconstruction; that said, we have made tremendous progress. We are getting closer every day, and ultimately, we may find the gene-modified, cell-based, tissue-engineering strategies that will almost perfectly imitate nature and succeed today's reconstructive strategies.

Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author contributions to the study and manuscript preparation include the following. Analysis and interpretation of data: Barr. Drafting the article: Szpalski. Critically revising the article: Warren, Szpalski, Wetterau, Saadeh.

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