OXYCEPHALY AND ALLIED CONDITIONS IN MAN AND IN
THE RABBIT

BY HARRY S. N. GREENE, M.D.

(From the Laboratories of The Rockefeller Institute for Medical Research)

PLATES 60 AND 61

(Received for publication, March 10, 1933)

Despite the numerous studies which have been made on oxycephaly and allied abnormalities of the skull, there is still some uncertainty concerning the pathogenesis of these conditions. Some investigators attribute the deformities to primary abnormalities of the sphenoid bone, but the majority opinion is that premature sutural fusion in the calvarium is fundamental in their production.

Injuries in early life, diseases of the cranial bones, abnormalities of the brain, and inflammation of the meninges have been considered as possible causes of the premature bony union, and tuberculosis and syphilis have been emphasized in the theories supporting an inflammatory origin. At present it is, however, quite generally agreed that the sutural fusion arises either as a result of injuries during early embryonic life or actual changes in the germ plasm. Faber (1) suggests that injuries resulting from increased amnionic pressure on the extremely vulnerable differentiating blastema may play an important part. The theory advanced by Rieping (2) is of particular interest. He describes an oxycephalic skull showing ossification centers common for both frontals and parietals situated in the fused coronal sutures, and considers the deformity due to this abnormality in position.

Study of the literature concerning the inheritance of these conditions shows their occurrence in more than one generation of a family to be relatively uncommon, and although more frequent in members of the same generation, the majority of cases are found as isolated instances.

These conceptions are based entirely on studies of human material which is not subject to experimental test or control. A comparable series of synostotic variations has been found in the rabbit (3).
ability to breed animals showing the abnormalities and to follow their development through embryonic and postnatal life affords a new method of approach to such problems.

The present paper describes the deformities as they occur in the rabbit, compares them with those found in man, and summarizes briefly the results of studies on their pathogenesis.

Types of Synostosis

Examination of a large series of skulls of different ages shows that in the rabbit there are four distinct types of deformity based on premature sutural fusion and depending upon the suture or sutures affected. These are illustrated in Figs. 1 to 8 and may be designated as scaphocephaly, trigonocephaly, plagiocephaly, and oxycephaly.

In order to avoid confusion a definition of these terms is necessary. The normal skull of the rabbit is illustrated in Figs. 1 and 6. Scaphocephaly (Figs. 3 and 4) is used in reference to the deformity resulting from fusion of the sagittal suture, plagiocephaly (Fig. 8) to that resulting from fusion of a single segment of the coronal, left or right, trigonocephaly (Fig. 5) to fusion of both coronals, and oxycephaly (Figs. 2 and 7) to fusion of both coronals and the sagittal suture.

These various types are common in certain breeds of rabbits and apparently are in no way incompatible with healthy cage life. Casual observation would not distinguish affected animals from normal members of the same litter, and although close examination may separate a shortened or asymmetrical head, correct differentiation can only be made by careful palpation. In this respect the deformities differ from those occurring in man. In man they produce a striking physiognomy and an unsightliness which prompted Homer's use of oxycephaly in portraying Thersites as the ugliest of men who ever came to Ilium.

Associated Abnormalities

Syndactylism and other physical anomalies occasionally associated with craniosynostosis in man have not been found in the rabbit. It is of interest to note, however, that these cranial variations were first recognized in a line of closely inbred rabbits which showed, among other abnormalities, an extreme adiposity. In two other inbred lines cryptorchism is of frequent occurrence (hereditary). One of these
lines transmits hydrocephalus and the other a “cretinoid” condition of uncertain etiology. In view of the cases reported in man, in which cranial abnormalities were associated with hemorrhagic icterus, it is also of interest to note that in a litter from the mating of an F₁ doe to her trigonocephalic parent, there were two typical cases of hemorrhagic icterus. Other instances of this condition may have escaped notice. However, none of these conditions can be regarded as a necessary accompaniment of the cranial abnormality. The frequency of association is apparently accidental as synostotic variations have been found in other lines of animals which present none of these irregularities.

Signs of craniosynostosis, other than those present in the skull, are inconstant. A mild degree of exophthalmos is common in one adipose albino line, but no more pronounced in craniosynostotic than in normal members. Examination of the bony orbit shows no structural cause for this condition and its probable explanation lies in increased size of fatty pads. In other lines affected individuals show no exophthalmos, their eyes appearing rather more deeply placed than normal. In plagiocephaly it is usual to find that the eye of the normal side protrudes more than that of the synostosed side. Nystagmus is uncommon although in plagiocephaly a degree of squint occurs compensating for the asymmetrical orbits. Retinal examinations have not been made, but observation of the behavior of many animals gives the impression of deficient sight. In man, cases of coronal fusion ordinarily show considerable exophthalmos which is explained by the shallowness of bony orbits. The failure of this sign to develop in rabbits is accounted for by the absence of such an anatomical alteration.

The Adult Skull

Adult craniosynostotic skulls present structural alterations not generally pronounced at birth and will be described in detail. The normal contour of the calvarium is modified and the size, shape, and relations of individual bones are altered.

The Calvarium

Oxycephaly.—In oxycephaly (Figs. 2 and 7) a raised peak occupies the bregmatic region and sharp ridges indicate the sagittal and coronal sutures obliterated by the angular union of parietal bones and of
parietal with frontal bones. The frontal bones show an anteroposterior shortening, most evident between the bases of their supraorbital processes and the fused coronal sutures. The posterior wings of these processes present an increased and irregular lateral curvature with their thick extremities in contact with the anterior tips of pronounced temporal lines. Frontal eminences are absent and the slope of the bones unchanged from the frontonasal suture to the obliterated coronals. Parietal bones are markedly flattened, sometimes slightly concave, and form more posterior walls than roofs of the cranial cavity. Bosses are not present.

*Trigonocephaly.*—In trigonocephaly (Fig. 5) the bregmatic peak is absent and a transverse ridge marks the fused coronals. Frontal bones are similar to those described above and at their union with parietals the slope of the calvarium is reversed. Parietals articulate with each other at a slight angle to form a sagittal suture of normal appearance. The degree of parietal flattening makes two classes of this type of skull. In one class these bones are markedly flattened from birth and show small ill defined bosses lying close to the fused coronals. In the other class, the bones are more rounded with well marked bosses in their normal positions.

*Plagiocephaly.*—In plagiocephaly (Fig. 8) the disproportionate growth between the fused and normal sides causes a complete loss of symmetry with distortion of individual bones. The fused side presents all the characteristics of trigonocephaly, and here also the two different classes may be distinguished. The parietal and frontal bones are shorter and the nasal bones longer in anteroposterior extent on the affected side. The sagittal and frontal sutures, instead of forming a straight line between lambda and nasion, describe a curve convex toward the normal side. The nasal suture presents a slight curve in the reverse direction so that the combined midline sutures of the skull tend to resemble the letter S. The contour of the interparietal, a small oval bone lying between the two parietals and the supraoccipital, is markedly changed, the portion on the affected side being much larger than that on the normal side. The position of the bone is also altered, its plane facing posterolaterally rather than directly posterior as in the normal skull. Fusion of the sagittal suture may occur with this variation, increasing the distortion and accentuating the lateral curvature of the skull.
Scaphocephaly.—Fusion of the sagittal suture in scaphocephaly (Figs. 3 and 4) produces a ridged condition of the posterior calvarium in which flattened parietals unite at a considerable angle and the vertical distance between squamosal and sagittal sutures is increased. Parietal bosses are small but distinctly outlined and lie close to the fused sagittal suture. The coronal sutures and the anterior calvarium are not affected.

In all these deformities, sometimes called the peak, dome, unilateral dome, and ridge because of the calvarial modification, the affected suture may be obliterated throughout its extent and entirely replaced by bone. In most instances, however, true bony union occurs only in its middle portion, extremities being open although devoid of normal denticulations. Cross-section through a fused suture shows both inner and outer tables thickened and separated by an increased amount of diploe.

The Orbit

Orbital changes are present in oxycephaly, trigonocephaly, and on the fused side in plagiocephaly. In all these variations the circumference of the orbit is increased by greater curvature of the zygomatic arch. Its depth is not decreased, the more perpendicular plane of the frontal portion of the roof being compensated for by its greater extent. The posterior wall shows a more convex curvature both toward the orbit and the ventral surface of the skull, and the alisphenoid occupies a nearly transverse plane. The orbital foramina are not constantly altered but are often smaller than normal or constricted in one diameter.

Cranial Fossae

The cranial fossae are also altered in these deformities. In oxycephaly, the floors of the middle and posterior fossae are deepened and widened and their walls show convolutional markings and deep sinus grooves. The middle fossa is somewhat constricted by bulging of the posterior orbital walls. Similar but less marked changes occur in trigonocephaly, and the disporportions expected from the calvarial asymmetry are evident in plagiocephaly. Middle and posterior fossae are deeper and narrower in scaphocephaly than in the other deformities.
Changes in the sella turcica are not marked. The hypophyseal fossa shows no constant change although in oxycephaly and trigonocephaly the posterior clinoid processes are slightly longer and directed more laterally than normal.

Base of the Skull

The base of the skull in oxycephaly and trigonocephaly shows a varying degree of lordosis. In plagiocephaly, the occipital bone together with the tympanic bulbae is twisted toward the fused side. The portion anterior to the sphenoid-occipital synchondrosis shows a twist in the opposite direction. This distortion, by changing the plane of the cutting edge of the upper incisors, causes unequal wear and there results a gradual shortening of the teeth toward the fused side. Scaphocephalic skulls show no basilar changes. In none of these conditions do the basal foramina show either consistent enlargement or constriction.

A comparison of the different craniosynostotic types shows that the alterations resulting from coronal fusion are more deforming and probably of much greater functional importance than those resulting from sagittal fusion. This observation may have a practical bearing on the treatment of oxycephaly. In man, an operation has been advocated in which artificial coronal and sagittal sutures are made by the excision of strips of cranium, and if performed during early infancy, is said to prevent the usual deformity. In view of the above observation, it seems probable that a similar result would be obtained by limiting the operation to coronal excision alone and foregoing the more dangerous sagittal excision.

Changes in Other Organs

The brain in these variations is apparently not altered in size but is modified in shape to conform to the altered cranial cavity. The hypophysis presents no gross anatomical change and microscopic examination has not been made. Meninges show no indication of local or general inflammation. Hydrocephaly in any form has not been found associated with oxycephaly or trigonocephaly. Internal hydrocephaly is occasionally found in plagiocephaly in which condition the otherwise normal side is bombose and shows numerous scattered
areas of deficient calcification while the fused side shows nothing but its characteristic deformity. Although not commonly found in scaphocephalic animals, hydrocephaly is unusually frequent in the non-craniosynostotic litter mates of one line. Examination of other organs shows no consistent pathological changes and evidences of syphilis and tuberculosis are entirely absent.

Pathogenesis of Cranial Deformities

Examination of a series of craniosynostotic skulls beginning with the embryonic and continuing through succeeding age periods to the mature adult shows an increasing degree of deformity. Fusion of sutures has been found in feti of the 3rd week of embryonic development, and in such skulls the structural alteration characteristic of the adult is absent. The deformity is thus dependent upon skull expansion and results from inhibition of growth at fused sutures and compensatory increased growth in normal regions. It is noteworthy, in view of the theory that these deformities occur as a result of abnormalities in the sphenoid bone, that sutural fusion is present while the base of the skull is still cartilaginous and the sphenoid entirely normal for that period. Sutural fusion is thus a cause rather than a consequence of the deformity.

It is seen from the foregoing descriptions that certain changes in neighboring bones are constantly associated with sutural fusion. In coronal fusion, with frontal eminences absent, similar structures are found in the fused line and the normal, slightly rounded contour of the frontal bones is lost. In oxycephaly and scaphocephaly, parietal bosses are displaced from their normal positions to lie close to the fused sagittal and the parietal bones are flattened. Also, in a variety of trigonocephaly, parietal bosses are found close to the fused coronals and parietals show a more marked flattening than in the ordinary deformity. It is, therefore, characteristic of these skulls that primary ossification centers are displaced into or close to the sutural line. Accompanying this displacement, is an alteration in bone development resulting in modified contour. It is interesting that when these animals are subjected to an inadequate diet, areas of deficient calcification are found in the regions occupied in non-craniosynostotic rabbits by primary ossification centers.
The question arises, relative to coronal fusion, as to whether or not a true suture separating frontal and parietal bones is ever formed in synostotic skulls. From the evidence at hand, it seems probable that the suture is closed from the start, the displaced frontal center causing frontal and parietal union with earliest bone formation. A similar question applies to sagittal fusion with parietal bosses close to but not in the suture line. In scaphocephalic skulls, it has often been observed that fusion is limited to the sutural region between the bosses, the remainder of the suture, although devoid of denticulations, is unfused. The inference is, therefore, plausible that the closely approximated position of parietal bosses is in some way responsible for ossification in the suture line. A detailed study of embryonic development is necessary before satisfactory answers to the problems can be found, and such a study is now under way.

Inheritance of Craniosynostosis

Breeding experiments show that the craniosynostotic abnormalities which have been described are hereditary variations which may be transmitted unaltered from parents to offspring. It is definitely known that all these types are recessive to the normal but the exact number or combination of genetic factors that produces them is still uncertain. Every breed of rabbit so far tested has been found to carry factors concerned in their production. The widespread occurrence of these factors is illustrated by the appearance of a trigonocephalic animal in a litter resulting from the mating of a trigonocephalic buck with a doe imported from China and showing no visible or palpable skull deformity. The inability to find normal animals from which to obtain true F₁ progeny makes the study of inheritance of these variations extremely difficult. The usual methods of approach are blocked, and the only available means of study consists in a comparison of litters obtained from the same parent by different matings. This is necessarily long and complicated, and no attempt will be made in the present paper to analyze the results so far obtained.

The problem is further complicated by the occurrence of anatomically unrelated cranial variations in litters from craniosynostotic parents. Trigonocephalic and plagiocephalic rabbits do not always breed true and their litters, although largely made up of offspring showing the
parental deformity, also contain animals with normal skulls, accessory bones, and reversed sutures. Accessory bones are supernumerary bones in the bregmatic region produced by an accessory suture extending from the coronal to the sagittal suture. They have also been found to occur without relation to craniosynostosis, and in such condition their production seems to depend upon the action of a single pair of hereditary factors. Reversed suture is a condition in which the normal course of the coronal is altered at some distance from the bregma by a more or less abrupt posteromedial change in direction that continues to the sagittal which is thus intersected in its middle third. This condition is relatively rare and little is known of its genetics. It is possible that these variations together with the normal skulls found in such litters are produced by heterozygous combinations of the factors responsible for craniosynostosis. A sufficient number of offspring have as yet not been obtained from oxycephalic or scaphocephalic parents to show that true breeding occurs, but the existence of a genetic as well as a formal relationship between the various types is proved by the fact that all have been obtained by different matings from the same oxycephalic parent.

CONCLUSIONS

Craniosynostosis and the pathological complex with which it is associated in the rabbit are not identical with the abnormalities seen in man; but apparently the two sets of conditions have enough in common to warrant the conclusion that they probably have a common mode of origin. The evidence so far obtained shows that in the rabbit these conditions are hereditary. The factors for the production of the cranial abnormalities are widespread, but the occurrence of deformities is comparatively rare in a general animal population. In-breeding and selective matings, however, tend to increase their frequency and also the frequency of other abnormalities with which they may be associated, either by chance or by close genetic relationship in the germ plasm. In this way, a pathological complex is built up and perpetuated.

In so far as the cranial abnormalities are concerned, it seems now that oxycephaly and related conditions are variations resulting from a displacement or division of primary ossification centers controlled by hereditary factors.
REFERENCES


EXPLANATION OF PLATES

PLATE 60

FIG. 1. Lateral view of normal skull of the rabbit.

FIG. 2. Oxycephaly. Note the altered shape of the orbital foramen and contour of the whole orbit as compared with Fig. 1.

FIG. 3. Scaphocephaly. The anteroposterior arch shown by this skull is more marked than usually found in scaphocephaly and is due to conditions other than the sagittal fusion.

PLATE 61

FIG. 4. Calvarium in scaphocephaly showing absence of normal denticulations in the sagittal suture and fusion of the portion lying between parietal bosses (compare with Figs. 5, 6, 8).

FIG. 5. Calvarium in trigonocephaly. Fusion is limited to the mid-section of each coronal segment and these sutures are devoid of normal denticulations. Parietal flattening, frontal shortening, and the changed relationship between these bones is brought out by comparison with the normal skull shown in Fig. 6.

FIG. 6. Calvarium in normal skull.

FIG. 7. Calvarium in oxycephaly. The abnormalities found in Figs. 4 and 5 are combined.

FIG. 8. Calvarium in plagiocephaly showing fusion of the right coronal segment. The abnormalities characteristic of trigonocephaly are seen on the fused side and the deformity resulting from disproportionate growth is obvious. The asymmetrical interparietal bone is seen lying between the two parietals and the occipital bone.
(Greene: Oxycephaly in man and rabbit)
(Greene: Oxycephaly in man and rabbit)