A CRITIQUE OF CURRENT VIEWS ON ACROCEPHALY AND RELATED CONDITIONS

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ACROCEPHALY

CERTAIN conditions associated with mental deficiency derive their name from some characteristic skeletal deformity. One of these is abnormal highheadedness or acrocephaly, a term often used interchangeably with oxycephaly, tower skull or turricephaly. To be sure, certain criteria have been recommended by some workers for confining each of the above terms to different sub-varieties of high-headedness and many alternative names have also been proposed (Günther 1941), but none of these have taken root. A distinction is made by many writers between acrocephaly and hypsocephaly or ordinary highheadedness: it is stated that the essential feature of acrocephaly is not highheadedness in itself but exaggerated upward pointing or angling of the head at some distance along its superior curvature so that, in theory, an acrocephalic head need not necessarily be hypsocephalic. However, it is doubtful if this distinction can always be sustained since many otherwise quite normal individuals have abnormal angling of the skull, while some recorded cases of acrocephaly presented a smooth and rounded profile of their upper cranial curvature in photographs and lateral skull X-rays.

Acrocephaly may be combined in recurrent patterns with other cranial and skeletal malformations to constitute acrocephalosyndactyly or Apert's syndrome and cranio-facial dysostosis or Crouzon's disease. These conditions are often discussed with other forms of cranial deformity (dysostosis), viz., hypertelorism, scaphocephaly, Franceschetti's syndrome or mandibulo-facial dysostosis, and the cleidocranial dysostosis of Marie and Sainton, although acrocephaly is an inconstant finding in these diseases.

A difficulty arises because some of the above terms are used in regard to people with no obvious disease but an anomaly of a particular physical measurement. Thus, it seems evident from the descriptions, and still more from the photographs, that the individuals with hypertelorism reported on by Günther (1934) and with Crouzon's syndrome (Günther, 1933) or the negro children with oddly shaped skulls described by Gordon (1958) as craniostenotic could hardly be regarded as examples of a pathological syndrome. On the other hand, the distinction between purely pathological syndromes and mere anthropological anomalies may be tenuous. It cannot be gainsaid, moreover, that the acrocephalic syndromes can manifest themselves incompletely.

This ambiguity weakens the generalizations of many authors and imperils simple comparison between different series. It will be pointed out below, for example, that it is still impossible to estimate even roughly the incidence of mental retardation among acrocephalic individuals. Precise information on certain crucial anatomical findings, such as patency or synostosis of some of the

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cranial sutures, and on clinical signs, natural history and so on is also lacking. Moreover there is a need for additional quantitative data. Measurements are difficult to obtain and interpret because the pathological picture in each affected individual is made up of an inconstant number of variable deviations from the norm, some of which are slight and elusive (Grewel, 1948-49).

Acrocephalosyndactyly was first described as a separate disease by Apert (1906), following earlier publication of similar cases by different authors. In a recent study, Blank (1959 and 1960) found 88 recorded instances of the full disease and 41 of what he termed atypical acrocephalosyndactyly. He was also able to collect 37 new cases of the full and 14 of the "atypical" disease.

The cranial and skeletal features are striking. The skull is high and short antero-posteriorly. The eyes are prominent and widely set, sloping downwards and outwards in a so-called "anti-mongolian" slant. The palate is high and sometimes cleft showing in some cases a shelf-like osseous projection at the alveolar margin. The upper teeth are crowded. While the obvious abnormality of the hands and feet is syndactyly, the underlying skeletal dysplasia, well described by Valentin (1938) and Blank (1959), is in reality much more complex. In addition to the failure of some of the developing digits to separate transversely, there is frequent absence of the terminal phalanges (failure of vertical separation) and of some metacarpal and metatarsal bones. (Although this is the probable explanation of the digital deformities, another less likely one is secondary fusion of the phalanges.) The distal phalanges of the hands are often joined to each other by bony arches and may have a single common nail; this is particularly so in the case of the 3 middle fingers which usually form a "mid-digital mass". Visceral malformations occur frequently in the more seriously affected infants dying at or shortly after birth (Blank, 1960). An interesting change which has tended to be overlooked in the literature occurs in older patients. The digital bones acquire outgrowths projecting from the main body and this lends the phalanges a stellate appearance in radiographs (Valentin, 1938). This is reflected in limitation of joint movements.

Examination of the skull after death reveals very characteristic abnormalities in the shape of the bones, cranial fossae and calvarium. The details have been fully described by many authors (Greig, 1926; Günther, 1931) and need not all be recapitulated here: certain features pertinent to the present critique will be referred to below.

It is clear that the obvious change in the appearance of the patients must be paralleled by a greater or lesser deformity in the shape or size of most of the cranial bones and different authors ascribed, rather inconclusively, decisive significance to one or other of these bones or regions: some stressed changes in the vault and others at the base. For example, according to the recent observations of Kissel, Dureux and Tridon (1959) the principal deformity in the cranial dysostoses is at the base of the skull: brachybasia, shortening and exaggerated elevation of the anterior fossa, flattening of the orbits leading to exophthalmos, and increased distance between the lesser wings of the sphenoid causing hypertelorism. They thus feel able to characterize the cranio-facial dysostoses as "hypoplasia of the spheno-ethmoidal region".

The mobility of some of the larger joints, e.g., shoulders and elbows, may be impaired by flattening of the articular surfaces, epiphyseal fragmentation or ankylosis. The bodies and arches of some vertebrae are frequently fused or show deformities and outgrowths, while sacralization of the lower lumbar vertebra is common. Attention has been drawn by Wigert (1932) to the fact that acrocephalosyndactyly is a widespread skeletal dysplasia, the deformity of the

skull, fingers and toes being only its most conspicuous manifestation, while, as mentioned already, even more widespread malformations also occur in the more severe cases.

Besides those already mentioned, other noteworthy contributions on acrocephalosyndactyly include those of Davis (1915), Ruh (1916), Rieping (1919), Park and Powers (1920), Davis (1925), Weech (1927), Bronfenbrenner (1932), Ferriman (1941), Sirkin (1943-1944), Cohn (1945), Zellweger and Muralt (1952) and Gross (1957).

Cranio-facial dysostosis or *Crouzon's syndrome* (Crouzon, 1912 and 1929) is characterized by cranial and facial deformity which is essentially similar to that of Apert's syndrome. It has been said by those who distinguish between the two conditions that in Crouzon's disease the nose is more beaked or "parrot-shaped", the superior maxilla smaller, exophthalmos more common, and the mandible more prominent. But those differences are probably not real (Buckley and Yakovlev, 1948; Ferriman, 1941; and Schönenberg, 1958). It was also once held that Crouzon's disease was, unlike Apert's, hereditary, but a number of familial cases of Apert's disease and atypical acrocephalosyndactyly have now been recorded (Chotzen, 1932-33; Weech, 1927; Blank, 1959). A true distinction between the two conditions is, of course, the absence of syndactyly in Crouzon's syndrome, but this may be regarded as a sign of incomplete or atypical manifestation of acrocephalosyndactyly. Atkinson (1930) reviewed 86 cases of Crouzon's disease and 121 recorded cases had accumulated by 1948 when Eshbaugh (1948) reported a further example.

Blank (1959) divides all cases of acrocephalosyndactyly into two groups: (1) Apert's syndrome, as originally described, and (2) Atypical acrocephalosyndactyly. He uses very strict criteria for distinguishing between the two groups, placing, for example, cases with partial syndactyly, i.e., union of digits by soft tissue only, with the atypical instances of the disease.

Related conditions are often considered with those above under some common generic title such as cranial, facial or mandibulo-facial dysostosis, while other authors, laying stress on the presumed primary importance of premature synostosis, refer to the conditions as craniosynostosis or even craniostenosis.

Hypertelorism is characterized by excessive width in the spacing of the eyes. The great wings of the sphenoid are disproportionately small, and the small wings—large. The palate is high and narrow. Hypertelorism is very common in acrocephalic individuals, but may occur on its own. The original case described by Greig (1924) was in fact acrocephalic (or hypsocephalic). It is worth mentioning that the impression of increased interorbital distance is often not borne out by accurate measurements. *Scaphocephaly* or marked antero-posterior elongation of the head is, in the view of some workers, the result of premature synostosis of the sagittal suture. As pointed out by Park and Powers (1920), malformations of the extremities may also occur in cases of scaphocephaly. In another condition, the *Franceschetti* syndrome or mandibulo-facial dysostosis (Franceschetti and Klein, 1949; Weyers, 1951; Hövels, 1953) there is an "antimongolian" slant of the eyes, hypoplasia of the zygomata and mandible, malformation of the outer and, less frequently, the middle and inner ears, colobomata in the outer parts of the lower eyelids, a big mouth with a high palate, misplacement of the teeth and a blind fistula between the ears and mouth. A rare disease occasionally mentioned in relation to this group of conditions is the *cleidocranial dysostosis* of Marie and Sainton (Stewart, 1928-29).

It has been stated by Jaensch (1952) that transitional forms occur between

all of the above conditions. Hypertelorism in particular is, according to him, very common to them. It can be almost regarded as a constituent element of most of the cranial dysostoses. The relation of hypertelorism with the other dysostoses has been also considered by Zunin (1955).

Aetiology

Nothing certain is known about the aetiology of any of the above conditions and all the theories advanced by earlier workers have had to be abandoned for lack of evidence. These theories, enumerated by Günther (1931), include syphilis, rickets, birth injury, glandular disturbance, compression of the prechordal mesoderm by excessive flexion of the foetal head, non-specific meningitis, and so on. Blank (1959) concluded that typical acrocephalosyndactyly may be caused by a single gene in a heterozygous form and that mutation to this allele is correlated with increasing paternal age. Atypical acrocephalosyndactyly is, according to him, a heterogeneous collection of disorders, some of genetic origin. It is of interest that syndactyly is one of the malformations produced in the offspring of rats kept on a diet deficient in Vitamin B during gestation (Grainger, O'Dell and Hogan, 1954).

General Incidence

For reasons already outlined it is difficult to assess the incidence of the acrocephalic syndromes. Blank (1959 and 1960) estimates it at 1:160,000 at birth for acrocephalosyndactyly and 1:2,000,000 in the general population. He could make no reliable estimate for the atypical condition, but states that atypical acrocephalosyndactyly is even less frequently reported in the literature and in medical practice.

Pathogenesis

Apart from their general interest, the acrocephalic syndromes are of some practical importance: it is often asserted that early surgical treatment can obviate the danger of mental retardation and blindness in some cases. The view is based on the following theory of pathogenesis.

It is held that the cranial deformity results from the premature fusion (synostosis) of some of the sutures, the coronal in the case of acrocephaly and the sagittal in scaphocephaly. Bony growth in the direction perpendicular to the fused suture stops and the growing brain thereupon expands in the direction of the still patent sutures. This leads to the characteristic cranial deformity. It is further stated that cerebral growth in these abnormal conditions is accompanied by a rise in intracranial tension and this, in its turn, endangers the brain and the optic nerves. Hence it is recommended that the fused bones be redivided surgically, thus allowing the brain to expand more freely.

One of the main originators of the above theory was Rudolf Virchow (1852) who also suggested that the cause of the premature synostosis was local inflammation. It seems useful therefore to consider, as a background to the present critique, the following features of Virchow's thinking.

The first is his opposition to the various non-materialist trends of thought which prevailed before him and were still current in his lifetime (Rather, 1958). These included many "schools" and "systems" based on little more than speculation and tradition. Perhaps the chief weakness of non-materialist medicine in Virchow's time was its reliance on the so-called "natural-philo-

sophical method" ("Naturphilosophie") stemming largely from the teaching of Kant, which sought the answer to all biological problems in abstract thought. Having brought the microscope to the study of pathological processes, Virchow was in a position to base his views on the demonstration of material changes in diseased cells and organs, formulating later his classical cellular theory of pathology. The emphasis on local demonstrable change which could become irreversible and endanger the patient's life was incorporated in due course as a basic principle of pathology, especially surgical pathology. It may be said that Virchow's concepts were *par excellence* the ideology of surgery and have, as such, contributed greatly to the remarkable progress of that science in the ensuing century. By the same token, however, Virchow's tendency to oversimplify and to attach undue significance to localized events and mechanical causes has detracted from the usefulness of his concepts in the study of more complex non-surgical conditions. His attitude to cranial deformities is a good illustration of this point. The concept of their causation by localized inflammatory change and the subsequent abnormal moulding of the skull by mechanical forces is characteristically Virchowian. If true, his views would have clarified once and for all the aetiology and treatment of these conditions—surgical treatment; but, if false or only partially true, they could not stimulate further progress.

Secondly, Virchow was a lifelong enemy of racialism. A new feature of the racialist ideas circulating in 19th century Germany was the vigorous support given to them by some persons of academic standing, who tried to put the doctrine of racial superiority (or inferiority) on a "scientific" basis. One of their assertions was that the elongated skull found more commonly among the Northern Europeans was superior to the more rounded skull of the Slavs and Mongols. As an argument they used the association of low intelligence with roundheadedness in such conditions as acrocephaly and mongolism, which was then mistakenly regarded as a form of cretinism. Virchow refuted this argument by demonstrating that these conditions were not the expression, however extreme, of racial physical or mental characters, but the result of purely pathological processes, not specific to any race or people. While the details of his argument are no longer fully tenable, his insistence on the pathological nature of the extreme forms of cranial deformity, such as acrocephaly, remains, of course, perfectly valid. Moreover, his foresight in realizing the need for opposing racialism was confirmed a century later by the disasters which overtook his country and the world. A sinister detail of the Nazi legislation was the listing of acrocephalic individuals among those affected by the law "Zur Verhütung erbkranken Nachwuchses" (On the Prevention of Descendants with Hereditary Diseases) which was published before the mass murders in German and Austrian mental hospitals and old people's homes (Jensch, 1941-1942).

The Cranial Sutures in Acrocephaly

It is often taken for granted that the cranial sutures are always obliterated in acrocephaly. Blank (1959) states, for example, that normal suture markings are absent in all but the youngest cases of Apert's syndrome. The lambdoid, sagittal, coronal, metopic and squamous sutures, usually easily distinguishable in the crania of children and young adults, cannot be seen. A patent coronal suture was said by Jensch (1941–42) to have never been observed in any of the 82 cases reviewed by him. But this has not always been so in the experience of other workers. For example, the coronal suture was patent, but abnormally

situated, in a girl aged 1 year and 11 months presented by Carpenter (1910). A table showing the state of the sutures in 11 infants under 18 months reviewed by Park and Powers (1920) lists 3 as closed, one as patent, one as probably patent and 6 as having no record. In another series (Schönenburg, 1958), the coronal suture could be visualized radiologically in 7 of the 15 acrocephalic cases. In addition to the already discussed terminological ambiguity, the discrepancy may, perhaps, be also partly accounted for by the length of the coronal suture. A very short rudimentary suture is apparently often present as an extension of the lateral angle of the patent anterior fontanelle in cases showing an otherwise complete union of frontal and parietal bones (Gross, 1957).

While admitting its frequency, some workers are not prepared to attach decisive importance to premature synostosis. Günther (1931) and Greig (1924) regarded, for example, hypoplasia of the base of the skull as the primary abnormality, premature synostosis of the sutures in the cranial vault following, in their view, secondarily. Symptoms, if they occurred, were caused, according to Günther, by the narrowing of the foramina at the base of the skull and the resulting venous congestion. However, his observations have not been confirmed by other workers and it is difficult to see why, in the absence of conclusive evidence, an anomaly at the base should be preferred to that in the vault as the leading link in a long chain of abnormal events. It seems better to share Schönenburg's (1958) view, who regards premature synostosis as only one of the signs of widespread cranial dysplasia without any special pathogenetic significance. This view seems particularly reasonable since it has long been known that premature obliteration of sutures may be unassociated with any cranial deformity (Bolk, 1914–1915). Virchow's contention that synostosis leads to arrest of bone growth in a direction perpendicular to the fused suture has also been challenged on the basis of experimental study and growth measurements by Thoma (1924).

Many workers have discussed the way the synostosis comes about. Virchow's suggestion of an inflammatory origin has had to be abandoned. In the view of Rieping (1919), premature synostosis is the result of undue proximity to each other and to the coronal suture of the ossification centres in the frontal and parietal bones. Greig (1926 and 1935) believed that cranial sutures are not formed at all in such cases: the ossifying edges of the adjacent bones simply fuse with each other as soon as they come in contact. Greig (1926) distinguishes "true oxycephaly" in which there is complete obliteration of all cranial and facial sutures from "delayed oxycephaly" which is not congenital in origin and is never accompanied by exaggerated deformity or somatic defect. In a third group, "pseudo-oxycephaly" the synostosis is, according to him, limited to a few or even only one cranial suture while the facial sutures are never involved and the base of the skull is not affected. According to Eshbaugh (1948) and to Gross (1957) the continuity of the bones is not always the result of fusion; the bones may ossify *ab initio* from one common centre. Gross explains that the position of the missing suture is indicated in such cases by a bony ridge projecting to the interior of the skull.

In such discussions it is usually assumed that cranial bones grow mainly at their margin near to the suture lines but, according to Clark (1954), this may not be so.

It would thus seem that, pending further study, opinion on the constancy of premature synostosis and its significance in acrocephalic individuals must be reserved. Although frequent, premature synostosis is not invariable and is probably not the leading event in the development of this group of conditions.

Intracranial Pressure

The danger of rising intracranial pressure seems to have been reiterated from paper to paper and book to book without serious verification. Benda (1952) states, for example: "The first symptom is an increase in intracranial pressure which may be as high as 500 mm. of water; if the discrepancy between brain thrust and bony resistance is too great, children die from brain pressure." In fact, however, the C.S.F. pressures appear to have been seldom measured. It is true that workers, particularly surgeons, have reported elevated pressures in some of their, presumably selected, cases (Laitinen and Sulamaa, 1954–55; Laitinen, 1956). In most other records, C.S.F. readings were, if mentioned, well within normal limits (Bussola, 1928; Wigert, 1932). It is moreover difficult to understand how pressures of the order mentioned by Benda (1952) can be compatible with prolonged survival and not result in a wide separation of the still patent sutures in the manner familiar in cases of obstructive hydrocephalus. It is also unlikely that excessive pressure could, if prolonged, fail to produce progressive mental and physical deterioration, the absence of which in acrocephalic individuals has already been noted.

"Digital" Impressions of the Skull

An interesting and very common accompaniment of acrocephaly is the occurrence of "digital marking" or "copper-beaten" appearance in skull radiographs. Post-mortem examination of the affected skulls shows corresponding areas of bone wasting or cranio-lacunation. In fact, some of these laminae contain no bone at all, consisting merely of soft tissue which disappears entirely if the skull is macerated after death (i.e., immersed in water until complete disintegration of the soft tissues occurs). The brain may even herniate through one of the holes, as in a case presented by Gross (1957), but it is not clear from his report whether the hernia was congenital or not.

The digital markings are usually taken as evidence of raised intracranial pressure; they are held to follow upon the excessive pressure or pulsation exerted by the contiguous cerebral convolutions. However, there have also been dissenting opinions. Digital impressions in infants, as contrasted with adults, may not always be caused by raised pressure according to Jensch (1941–42). Weigandt (1921) went so far as to deny that digital impressions corresponded to the pattern of cerebral convolutions, i.e., that they were gyral imprints. This particular objection appears to be unfounded. There are many statements in other reports testifying to correspondence between gyri and digital impressions. This was so in a case at the Fountain Hospital, also mentioned below, where the skull was removed at autopsy and macerated. Careful matching with the fixed brain of this case confirmed that the digital impressions and perforations (lacunae) were true imprints of the cerebral convolutions. It does not follow, however, that the digital impressions, even if true imprints of gyri, are necessarily produced by elevated pressure. It is noteworthy that no histological evidence of bone resorption, such as might be expected if the thinning of the bone were due to pressure erosion, was found by Candreviotis (1955) in cases of spina bifida—another condition often associated with digital impressions. In the histological examination of the bones in a case of oxycephaly (Howkins, Jefferiss and Handley, 1938) there was also no evidence of bone resorption. The authors consider that the pathological material indicated "disorganization in bone growth and joint formation". Schönenburg (1958) suggests that the impressions in acrocephaly are only one manifestation of a general dysplasia,

and this appears to be the most reasonable view in the present state of knowledge.

What has not been hitherto stressed in published reports is the obverse process—overgrowth or excessive relief of the bone upon the interior of the skull in at least some cases. This presents either as exaggeration of the normally present ridges and elevations or as new structures (Eshbaugh, 1948). It is difficult to conceive of this appearance as a result of simple intracranial hypertension; it certainly does not occur in established cases with high intracranial pressure, whether accompanied by a lacunation or not. (Greig (1926) states, however, that the inner table of the cranium is smooth in "true oxycephaly" in contrast to its roughness in "false oxycephaly".)

It should also be noted that digital impressions have been observed and recorded in some of the youngest acrocephalic infants. Thus, if produced by raised pressure, this must happen antenatally.

Optic Atrophy

Like the "digital impressions", optic atrophy is often cited as evidence of rising intracranial pressure. The finding of optic atrophy in acrocephalic individuals was being reported even before Apert's publication (Uhthoff, 1905) and early workers believed it to be very common (Dorfmann, 1908). According to Fletcher (1911) impairment of vision and optic atrophy were "almost invariable in this condition". These very high estimates have declined in the course of years: Jensch (1941–42), for example, put it at 12·2 per cent in his series of avowedly severe instances of acrocephaly, all in mental hospitals. Blank (1959) gives no estimate of optic atrophy, but he could find no instance of blindness among his cases. It is possible that the anomaly of the optic discs when observed in acrocephaly tended to be diagnosed as optic atrophy secondary to raised intracranial pressure because this is what was expected to happen.

Many acrocephalics are mentally defective and mental defectives often have encephalopathies associated with smallness and other anomalies of the optic nerve; these are relatively seldom caused by raised intracranial pressure, being usually a manifestation of widespread neural dysplasia. This may well be so in acrocephaly. Blank (1959) quotes a number of cases of acrocephalosyndactyly in whom the C.S.F. pressure was quite normal in spite of an existing disc anomaly. He does not think raised intracranial pressure is responsible for the "optic atrophy". This is in accord with the views of Kissel, Dureux and Tridon (1959) who are also dissatisfied with the mechanical explanation of the ocular anomalies in the cranio-facial dysostoses and draw attention to the fact that many of the reported ocular anomalies were in fact true malformations.

In considering possible causes of optic nerve changes and failing vision, it is necessary to bear in mind the exophthalmos due to the flattened orbits. This may lead in severe cases to dislocation, corneal ulceration and other damage to the eyeball (Sherne, 1938). The failing vision in a case reported recently by Kahn and Fulmer (1955) may have also been caused in this way, since the patient had exophthalmos, bilateral keratotonus and rupture of one cornea.

Following upon an earlier, rather casual, suggestion of Greig (1926), another mechanical explanation of "optic atrophy" has been recently offered by Gross (1957). He suggests that the foreshortening of the skull and its upward distortion lead to an exaggeration of the usual upward convexity and basal concavity of the cerebral hemisphere—"cerebral kyphosis". As a result, the diencephalic structures are lifted off the base of the skull, the basal cisterns are

deepened and the structures traversing them are displaced upward at their cranial attachment. The optic nerves are thereby stretched and abnormally angled as they emerge from the optic canals. It is this stretching and rubbing of the nerves against the bony rims of the canals which are, in his opinion, responsible for the atrophy.

Acrocephaly and Mental Retardation

Most of the recorded cases of acrocephaly were either very young infants or mentally retarded children. It is difficult to assess the incidence of mental retardation in the group as a whole. According to Günther (1931) 20 per cent. of acrocephalic individuals in his series showed slight mental retardation, but this could be an underestimate for the pathological syndromes under discussion here since, as mentioned already, a single abnormality of one physical measurement was sufficient to place the individuals concerned in Günther's acrocephalic group. Similar considerations apply to the group of 37 African children showing "cranistenosis" with oxycephaly and scaphocephaly studied by Gordon (1959); none of his cases presented any neurological or mental abnormality.

There seems to be no doubt that a number of individuals exhibiting the whole, or a considerable part of any of the acrocephalic syndromes are mentally retarded and, sometimes, severely so. Five of Blank's (1959) 37 cases were, for example, patients in mental deficiency hospitals but examples were specially sought in such hospitals. Three of these were rated as feebleminded, one imbecile and one an idiot. However, some of the cases may be of average or even, albeit rarely, above average intelligence (Kahn and Fulmer, 1955). One of Blank's (1959) cases had an I.Q. of 120 (personal communication). He states, however, that some mental impairment was judged to be present in every one of his cases of Apert's syndrome (Blank, 1960). On the other hand, it is noteworthy that, in spite of many pronouncements in the literature as to the danger of developing mental deterioration in cases of acrocephaly with an initially normal intelligence, there is no published evidence that this is really so. On reading the very lengthy case reports, one is struck on the contrary by the non-progressive nature of the conditions described.

As could be foretold from the general rarity of the acrocephalic syndromes, affected individuals are also in a small minority among other mental defectives. Thus, in a series of some 2,000 admissions at the Fountain Hospital, only 11 were classified as acrocephalic and 14 as having hypertelorism. Most of these cases had only a minor degree of the deformity; one had full acrocephalosyndactyly.

Other Symptoms

Raised intracranial pressure has been also held responsible for other symptoms in acrocephaly: anosmia, headaches, paralysis and epilepsy. Other symptoms include ophthalmoplegia (Kreindler and Schachter, 1934), nystagmus and vestibular disturbance, while progressive middle ear deafness has been described by Heuyer, Lebovici and Homualk (1950) and attributed to ankylosis of the ossicles. It is difficult to estimate the frequency of these signs but they are certainly uncommon in typical cases. Thus the 3 cases of acrocephalosyndactyly recorded by Gross (1957) showed no "neurological" symptoms and disc changes, in spite of well marked "digital impressions" in the skull. Case 4 in his series, without syndactyly and complicated by cerebral hernia, presented, on the other hand, both epilepsy and paralysis.

It is necessary to restate the argument used already in relation to "optic atrophy": mentally defective individuals are often the victims of epilepsy and paralysis, but these are by no means always the result of high intracranial pressure and there is, in fact, no certain evidence linking such symptoms specifically with raised pressure in acrocephaly.

Surgical Treatment

All the procedures recommended for the relief of the cranio-dysostoses, i.e., in the main acrocephaly and scaphocephaly, aim at securing greater freedom for the expansion of the growing brain by artificially dividing the cranial bones and thus re-establishing, for a time, flexibility and elasticity in the already hardened skull (Bennett, Keegan and Hunt, 1936; King, 1938; Dandy, 1943; Mount, 1947; Ingraham, Alexander and Matson, 1948; McLaurin and Matson, 1952; Laitinen and Sulamaa, 1954–55; Mullan, 1960). The procedures include linear craniectomy, morcellation, subtemporal decompression, and cranioplasty and duraplasty. If valid, the claims for the success of such treatment could be interpreted as evidence in support of the theory of restriction of bone growth by "craniostenosis".

However, many of the reported cases appear to have shown no abnormality other than highheadedness or scaphocephaly, having no mental retardation or other cranial or skeletal features of acrocephalosyndactyly. The C.S.F. pressure has not been often recorded and, indeed, most authors have advocated and resorted to surgical intervention before the anticipated rise in intracranial pressure. In other cases, the operation appears to have been undertaken chiefly for cosmetic reasons. Neither descriptions nor photographs of the patients before and after treatment entirely convince the reader that similar or better general results could not have been had without operation.

Since mental or physical progressive deterioration is probably infrequent in the acrocephalic syndromes, some degree of progress can be expected simply from growing up, and it is therefore difficult to accept the claims made for surgery. Nevertheless, there is perhaps some reason to believe that the patient's appearance may be improved in certain selected cases (Mullan, 1960).

This is not to deny that raised intracranial pressure, amenable to surgical measures, may develop for incidental reasons in some acrocephalic individuals. It is, moreover, possible that cases of widespread cranial and cerebral deformity, such as acrocephaly, might be (Dussik, 1949) more than normally prone to such a complication, but this is still far from proven.

Pathological Data

It remains now to consider the recorded pathological findings. Unfortunately, save for some meticulously thorough descriptions of the cranial and skeletal changes, pathological data are exceedingly scanty. Thus, Eshbaugh (1948) found only 25 references to the state of the brain in the literature, and observed that in 15 of these the brain was merely described as normal. Even the weights of the brains were only recorded in a few cases, and these were within normal limits. The fullest summaries of the pathology are contained in the reports of Günther (1931), Valentin (1938), Gross (1957) and Blank (1959).

The shape of the brain conforms to the contours of the skull: it is abnormally high, shortened antero-posteriorly with the temporal lobes orientated more vertically than usually. Allowing for the general change in orientation, the pattern of gyri is usually normal, although some may be situated below the

level of the neighbouring convolutions. The meninges have been mostly normal except in the cases of Eshbaugh and Case 4 of Gross (1957), which showed localized thickening. Vascular abnormality has only been reported in the above-mentioned Case 4 of Gross, which also had unilateral stenosis of the jugular foramen and absence of the sigmoid sinus as well as cerebral herniation.

Flattening of the convolutions with pressure-coning of the brain-stem has been only described in Cases 4 and 5 of Gross (1957), although an early report by Wheaton (1894) referred to "bulging" of the brain when the dura was incised. Park and Powers (1920) mentioned "convolutional atrophy" without specifying this any further.

Ventricular dilatation, mild or moderate, has been mentioned by Eshbaugh (1948), Valantin (1938), Ripeing (1919) and by Martischnig and Thalhammer (1952) and Böök and Hesselvik (1953). Blank (1959) found 6 instances of ventricular dilatation in the literature, including some of those referred to already. The dilatation was recognized either radiologically or at post-mortem. Three of his own cases showed evidence of ventricular dilatation during life and four at autopsy. Hydrocephalus was also present in a case recorded by Jacobsen (1930). It is likely that, in this instance, ventricular dilatation was non-obstructive in origin since the skull was plagiocephalic and one of the cerebral hemispheres markedly atrophic. Compensatory ventricular dilatation following underdevelopment of the neighbouring neural tissue may also be the true explanation of the hydrocephalus in most of the other cases.

By contrast, Case 5 of Gross (1957), a girl aged 4 months, showed changes which could be more clearly attributed to raised intracranial pressure. The ventricles were considerably dilated, the convolutions were flattened and the corpus callosum and septum pellucidum had undergone atrophy. The white matter was thinned and showed moderate gliosis on histological examination. It is noteworthy, however, that in spite of these indications of raised intracranial pressure and the presence of marked digital impressions, the fundi were normal.

Other recorded pathological data include a single example, certainly incidental, of inflammatory meningeal and cerebral change. A few brains have shown evidence of gross cerebral dysplasia. The corpus callosum was absent in two cases: in one of Valentin's (Case 6) and in another of Swanzy (1898). The above case of Valentin showed also a marked polygyric deformity with enlargement of parts of both cerebral hemispheres. Hypoplasia of the corpus callosum was present in one of Gross' cases, and absence of the septum pellucidum, diagnosed only by radiology, in a case reported by Zellweger and Muralt (1952). Visceral changes had been wholly unspecific. In one of Valentin's (1938) cases all endocrine glands were examined, showing no histological abnormality. The association of the cranio-facial dysostosis with spina bifida, syringomyelia and hydrocephalus has been reviewed by Kissel, Dureux and Tridon (1959). They stress that the cranio-facial dysostoses are often associated with indubitable malformation of the eyes and central nervous sytem.

I am able to add to the above the following summary of a further case, which it is hoped to publish more fully elsewhere.

This girl, S. T. (Fig. 1), born with all the features of acrocephalosyndactyly, comes from a family free from other congenital disease. An X-ray report at 2 months stated that "most of the sutures of the vault appear to be fused except for the sagittal suture and the fontanelles. Posteriorly there is a moderate degree of craniolacunation. The anterior fossa is short and the middle fossa and sella lie almost in a vertical plane." She had a marked high palate. No clinical evidence of raised intracranial pressure was noted at any time. An operation

was performed at 4 months, strips of bone "including the coronal and lambdoid suture" being removed and tantalum foil inserted over the bone edges. It was recorded at operation that the two halves of the coronal suture were firmly fused and the suture itself presented as a small white ridge. The right half of the lambdoid suture was completely united, as was the lower half of the left one, but the upper half of the left one was described as still patent. The sagittal suture was widely open.

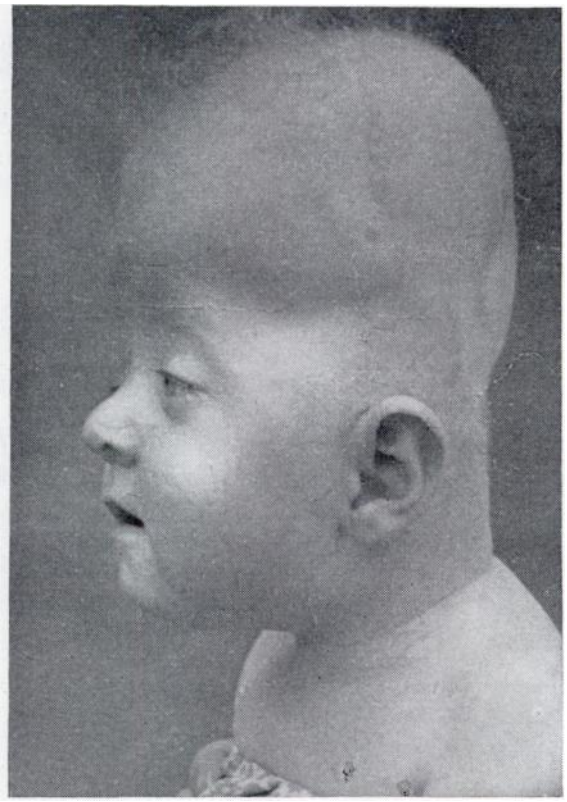

FIG. 1.—Patient, aged 14 months.

The patient's mental development was abnormally slow and at one year her mental level was assessed at 4 months on the Vineland Social Maturity Scale. Nevertheless, in the end she learned to walk and tried hard to talk, although her speech remained very indistinct. Optic atrophy did not develop. She had slight swelling of the nipples and enlargement of the clitoris. The patient succumbed rather suddenly to respiratory infection at 5 years.

At autopsy, the typically acrocephalic skull showed protruding fragments of tantalum foil on its surface, while most of the foil had been incorporated into the fully fused bones in the areas corresponding to the coronal and lambdoid sutures. Many lacunae became evident after macerating the skull. They were particularly conspicuous near or at the otherwise fully united bones at the

site of the operation. The interior of the skull showed the usual deformities associated with acrocephaly, notably, digital impressions and exaggerated relief markings (Fig. 2).

The brain was normal in weight (1,345 g.), its shape corresponding to the malformed cranium. As mentioned already, the gyri fitted closely into the grooves and lacunae of the skull. Allowing, however, for the anomalous form of the brain, the pattern of gyri appeared normal. There was no evidence of

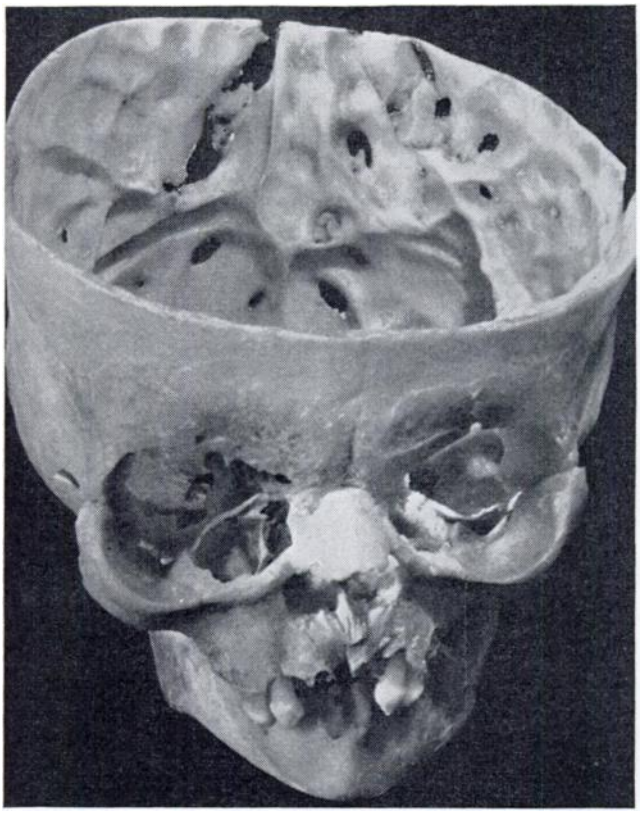

FIG. 2.—Oblique photograph of the skull to show exaggeration of relief markings and the perforations.

past or present rise in intracranial pressure either on naked-eye or histological examination. In appropriately-stained sections, the cerebral cortex showed some blurring of lamination and neuronal scarcity, most marked at the bottom of the sulci. Moderate neuronal deficiency was also present in the Sommer sector of the hippocampus. Glial cells and fibres were slightly increased around the 3rd and 4th ventricles. A small nodule of ectopic cortex was seen in the cerebellar white matter, and a few very small foci (200–300μ) of softening with microglial replacement were present in the descending root of the 5th nerve of the medulla and in the anterior column of the spinal cord. The optic nerves and tracts were normal.

All somatic organs were also examined, the only noteworthy changes being found in the salivary glands, which showed chronic non-specific inflammation, and in the lungs, which presented multifocal collapse and bronchiolar infection.

It may thus be concluded upon the available, rather unsatisfactory, pathological information that there has been either no evidence, or no certain evidence, of raised intracranial pressure in the great majority of cases. This is particularly significant since most of the pathological reports referred to infants and young children, and fatal cases, being usually the frailest and most handicapped of the group, may be expected to exhibit greater pathological changes than survivors.

Some of the equivocal changes such as ventricular dilatation can be more reasonably interpreted as evidence of congenital cerebral dysplasia, of which there were also other manifestations, such as absence of hypoplasia of the corpus callosum and septum pellucidum.

Conclusions

It would seem to follow from the above review that mechanical factors have been overstressed in considering the pathogenesis of acrocephaly. The theory formulated by Virchow (1852) rests upon untenable premises. Whilst present knowledge is still insufficient for the formulation of an alternative theory, certain facts may be significant.

There is, *firstly*, the association of the cranial with other evidence of skeletal and general dysplasia. This must mean that the area of embryonic dysosteogenesis can be either wide or narrow, and any explanation must account for both the general disturbance and localizing factors. These processes are associated, *secondly*, with cerebral dysplasia which may, in its turn, be either gross, as in the cases showing absence of the corpus callosum, or less obvious and even not apparent or entirely absent. *Thirdly*, the digital impressions of the skull are true imprints of the cerebral convolutions. The latter do not normally begin to assume their definitive shape till the seventh month of intrauterine life. Taken together with other evidence of much earlier dysosteogenesis, viz., failure of separation of the digital bones in the limb buds and anomalies in the situation of the centres of ossification in the cranial bones, the evidence indicates no finite event but a lasting process. This is further supported by the curious phalangeal outgrowths in older individuals. *Fourthly*, since, as seems likely, the cranial impressions are not the result of raised intracranial pressure, the appearances point to an altered responsiveness of the bones to normal pressure, traction or other inductive factors in contiguous structures, including other bones. That this is so is even clearer from the exaggerated relief markings on the inner surface of the skull, the failure of separation of the cranial and digital bones, and the occasional changes in some of the joints.

As a hypothesis, it may be permissible to translate these circumstances into terms of possible biochemical events by postulating a disturbance in the nature and/or synergistic action of interdependent enzymes and possibly other biochemical factors concerned chiefly in osteogenesis. This disturbance may reach out, temporally or spatially, to neighbouring systems such as those involved in cerebral morphogenesis. The underlying biochemical abnormality, which may be genetic in origin, begins to manifest itself in early embryonic life producing the maximum amount of deformity at the time of the greatest growth and differentiation and thereafter becoming less apparent. Nevertheless, the facts suggesting that the underlying disturbance persists, if only in a modified or latent form, hold out the promise of a profitable biochemical search in patients of every age.

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