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Occipitocervical segmentation in staged human embryos

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ABSTRACT

Serial sections of 108 human embryos from stage 11 to stage 23 were investigated, and 33 reconstructions were prepared. The existence of 4 occipital somites was confirmed. The important developmental distinction between axial (central) and lateral components obtains in the occipital as well as in the vertebral region. The lateral occipital components begin to show dense areas as the cervical region is approached. The lateral occipital and vertebral components arise in registration with the initial sclerotomes. In both the occipital and the vertebral region the related nerves and intersegmental arteries traverse the loose areas of the sclerotomes. The axial occipital region is not segmented, whereas the cervical components develop from perinotochordal loose areas. Three complete centra (known as XYZ) develop in the atlanto-axial region, although they are related to only 2½ sclerotomes and only 2 neural arches. The height of the XYZ complex equals that of 3 centra elsewhere, and not 2½, as previously maintained. The experimental findings in the occipitocervical region of the chick embryo show both similarities to, as well as differences from, the data for the human embryo. A scheme showing the early development of the entire vertebral column is included.

Key words: Sclerotomes; occipitocervical somites; vertebrae.

INTRODUCTION

A revival of interest in problems of segmentation has been stimulated by the detection of Hox genes, as well as by the continuing use of such techniques as autoradiography and chick–quail transplantation. The somites are important examples of segmental structures, not only in the development of vertebrae and muscles, but also because of their inductive function, as illustrated in the segmentation of the nervous system (Keynes & Stern, 1984).

Several authors (e.g. Dalgleish, 1985; Christ & Wilting, 1992) have rightly stressed the importance of distinguishing developmental events in the lateral regions from those in the central column. The sclerotomes are concerned with the former, whereas the perinotochordal cellular sheath is crucial to the latter. The central portion of the axis, however, presents a special problem. Its 3 components have been designated XYZ by O'Rahilly et al. (1983, see figs 1B and 5C, D) in order to avoid prior commitment to any one view of their interpretation. X corresponds to what has often been termed the proatlas (Cave, 1938; Reiter, 1944; Sensenig, 1957; Frame, 1969), and its independent ossification results in the os odontoideum. Y has frequently been considered to represent the centrum of the atlas (Cave, 1938; Kladetzky, 1955; Sensenig, 1957), and Z is the centrum of the axis.

It needs to be stressed that the main parts of a developing vertebra are the centrum and the neural arch, the latter being formed by fusion of the bilateral neural processes. The junction of the 2 parts becomes the temporary neurocentral joint on each side, and hence the 2 developmental subdivisions do not correspond exactly with the body and the vertebral arch, which are purely topographical terms. The term body has been used incorrectly for centrum, however, by many authors (e.g. Dalgleish, 1985; Strasmann, 1987; Christ et al. 1988; Christ & Wilting, 1992).

MATERIALS AND METHODS

Serial sections of 108 human embryos from stage 11 (~ 3 mm GL and ~ 4 postovulatory weeks) to stage 23 (27–31 mm GL and 8 postovulatory weeks) were

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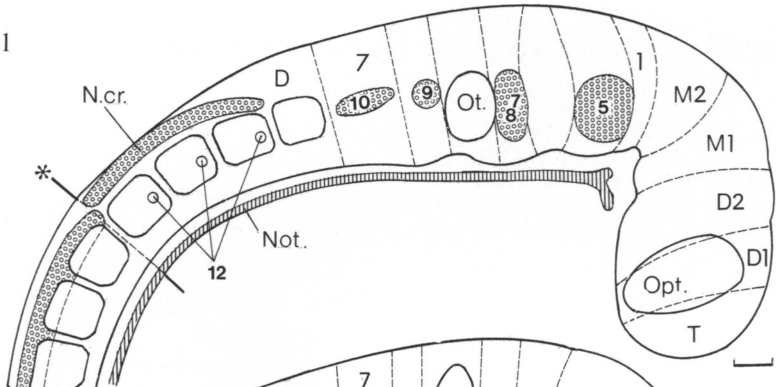

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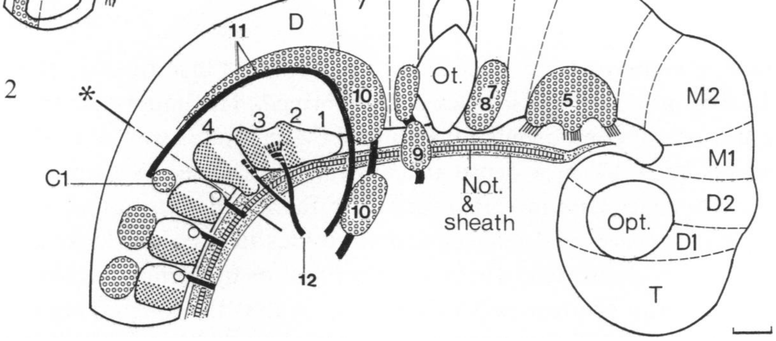

Fig. 1. Graphic reconstruction, right lateral view, at stage 12 (no. 7852), showing the occipital somites innervated by hypoglossal fibres (small circles). Three cervical somites are included, as are the various neuromeres (from T to D). The neural crest associated with the occipital somites is hypoglossal and perhaps accessory, that related to the cervical somites is still undivided. The asterisks in Figures 1, 2 and 5 indicate the junction between the occipital and cervical regions, between somites 4 and 5, i.e. between the territories of hypoglossal and spinal innervation. D, rhombomere D; D1 and D2, diencephalon; M1 and M2, mesencephalon; N.cr., neural crest; Not., notochord; Opt., optic vesicle; Ot., otic vesicle; T, telencephalon; 1 and 7, rhombomeres 1 and 7; 5, 7/8, 9, 10, ganglia of cranial nerves; 12, hypoglossal roots. Bar, 0.1 mm.

Fig. 2. Graphic reconstruction, right lateral view, at stage 14 (no. 1280 and no. 4245 combined), showing the ventral displacement of the somitic material and its transformation into sclerotomes (lateral vertebral primordia), in which loose and dense areas are indicated. Hypoglossal fibres and cervical ventral rami emerge in relation to the loose zones. Sclerotome 4 lies immediately rostral to the occipitocervical junction (asterisk). The occipital neural crest is now seen to be mostly accessory, and the cervical crest has become subdivided into spinal ganglia. The perinotochordal sheath (medial vertebral primordium) extends rostrally as far as the termination of the notochord. Abbreviations as in previous figure, and also: C1, spinal ganglion 1; 1–4, occipital sclerotomes; 11, accessory crest and nerve; 12, hypoglossal nerve. Bar, 0.2 mm.

studied: stage 11 (5 embryos), 12 (22), 13 (22), 14 (22), 15 (7), 16 (8), 17 (7), 18 (2), 19 (3), 22 (1), and 23 (9). Most of the embryos were from the Carnegie Collection, and 22 of the 108 were impregnated with silver. Coronal, sagittal, and horizontal planes were available. The fixative was generally formalin, and double-embedding in celloidin and paraffin was usual. The sections were 5–20 µm in thinness and the most frequent stains were haematoxylin and eosin, alum cochineal, and 'azan.' 33 graphic reconstructions (at least 1 at each stage) were prepared according to the point-plotting method. Every 4th section was projected, usually at a magnification of 50. For the details of the hypoglossal and upper cervical nerves, however, every section was used. The registration was controlled from photographs of the embryos at the same magnification: the brain and the easily defined notochord were plotted first, and then the smaller structures were added. The outlines of the somites are generally sharp, especially in silver preparations. For the sclerotomes, sagittal and coronal sections are needed in the cervical region, sagittal and horizontal in the occipital region. The notochordal sheath is clearly limited peripherally. Dense and light sclerotomic areas become well defined at stages 14 (in the lateral region) and 15 (in the central region). Photomicrographs as well as sections were found useful in preparing the reconstructions. In stages 13 to 17, some of the reconstructions were made from negative photographic prints onto which the sections had been projected directly. By this method, varying densities in mesenchymal areas could be distinguished more clearly. Further study of precise graphic reconstructions of the whole chondrocranium at stages 22 (Müller & O'Rahilly, 1991) and 23 (Müller & O'Rahilly, 1980) permitted better insight into the transitional region between skull and vertebral column. In addition, in order to measure the central components of the first 3 cervical vertebrae, median or almost median sections of 15 fetuses (32.2–78.5 mm in length) in the Carnegie Collection were examined. The ratio between the height of the XYZ complex and that of the 3rd cervical vertebra was obtained from measurements taken from photomicrographs of median sections.

In assigning numbers to the somites, the problem posed by the 1st somite was taken into consideration. In early stages, where the 1st somite was small in size, it was nevertheless present and was included in counting. Two such embryos, which were investigated in detail by reconstruction, had also been studied by Arey (1938), who agreed that the 1st somite was still discernible.

RESULTS

The lateral occipital region

Stage 12 is illustrated in Figure 1, which includes the brain and the neuromeres: 3 prosencephalic (T, D1, D2), 2 mesencephalic (M1, M2), and 8 rhombencephalic, the 8th being known as rhombomere D. The rhombencephalic ganglia of the future cranial nerves are present and they are related to specific rhombomeres. At this stage, a distinction can be made for the first time between the occipital and the cervical region. Somites 1–4 are interpreted as hypoglossal, because intramural hypoglossal nerve fibres related to somites 2–4 have appeared. The neural crest in the occipital region is mostly hypoglossal and perhaps also accessory. Froriep's ganglion (O'Rahilly & Müller, 1984, p. 252), which should be at the level of somite 4, was not found (in agreement with Pearson, 1939). The proximity of the vagal ganglion to somite 1 is maintained in the following stages.

At stage 14 (Fig. 2), 4 occipital sclerotomes are visible, and the 3rd and 4th are the most distinct. The 4th is separated from the first 3, which are now fused. Laterally in the fused region, 2 dense areas can be seen. No ganglia are present in the occipital region.

The occipitocervical, craniovertebral, and cerebrospinal junction is determined as follows: (1) at stage 12 (when silver impregnation is generally necessary) all nerve fibres are hypoglossal and intramural, and the most caudal somite to be innervated is the last (4th) occipital; (2) at stages 14 (Fig. 2) and 15 (Figs 3–5) the junction is situated between the hypoglossal rootlets and the 1st spinal ganglion.

Two representative sagittal sections at stage 15 are illustrated in Figures 3 and 4, and a key drawing to both is provided in Figure 5. The plane of section is indicated in Figure 6.

Rostral to the occipitocervical junction a segmental pattern can be recognised, and 3 dense areas, those of occipital sclerotomes 2 to 4, are clearly visible. The loose area of sclerotome 4 is becoming occupied by several hypoglossal rootlets and by the hypoglossal artery, only a small sprout of which is visible in the section (A in Fig. 5).

In a section closer to the median plane (Fig. 4), 3 lateral dense areas are identifiable in the occipital region. The 1st group of hypoglossal rootlets, accompanied by the hypoglossal artery, passes through the loose portion of sclerotome 4; the 2nd group of rootlets converges towards the loose portion of sclerotome 3, which contains an intersegmental artery.

That a segmental pattern is present in the occipital region can be seen in Figure 5, which shows in addition that the first 4 sclerotomes are now fused. The hypoglossal nerve, from its first indication at stage 12, does not, however, show a clearly segmental pattern. Somite 1 appears to be devoid of innervation in most embryos of stages 12 and 13. The single fibres present up to stage 13 begin to form rootlets: as many as 7 in stage 14, and as many as 12 at stages 15 and 16. The 2 groups of rootlets unite to form 2 hypoglossal stems during stage 14 (Fig. 2). It is clear already that the later-appearing hypoglossal canal has to extend over 2 sclerotomes: the main component contains the rootlets in the loose area of sclerotome 4, whereas the rostral portion contains rootlets in the loose area of sclerotome 3 (Fig. 5). The dense area between the 2 loose areas with rootlets is retained in some embryos, whereas in others it disappears shortly after stage 15. Major changes in the occipital region, other than growth, are not evident from stage 17 to stage 23.

Figure 6, which is based on stages 16–19, summarises a number of the results. The alternating pattern of loose and dense areas is shown schematically in A. As can be seen in B, the dense area of sclerotome 4, which is at first present only bilaterally, reaches the median plane at stages 16–17. The dense areas of sclerotomes 2 and 3 are present only laterally, where they separate the 2 stems of the hypoglossal nerve. The lateral portion, or exoccipital, develops from only lateral components, which correspond to the cervical neural arches. The basioccipital, however, develops at least mainly from the median primordium and hence is comparable to the cervical centra. Careful examination suggests that the occipital condyle (Figs 6, 7) may develop from the 1st cervical somite (as has been found in the chick embryo by Couly et al. 1993).

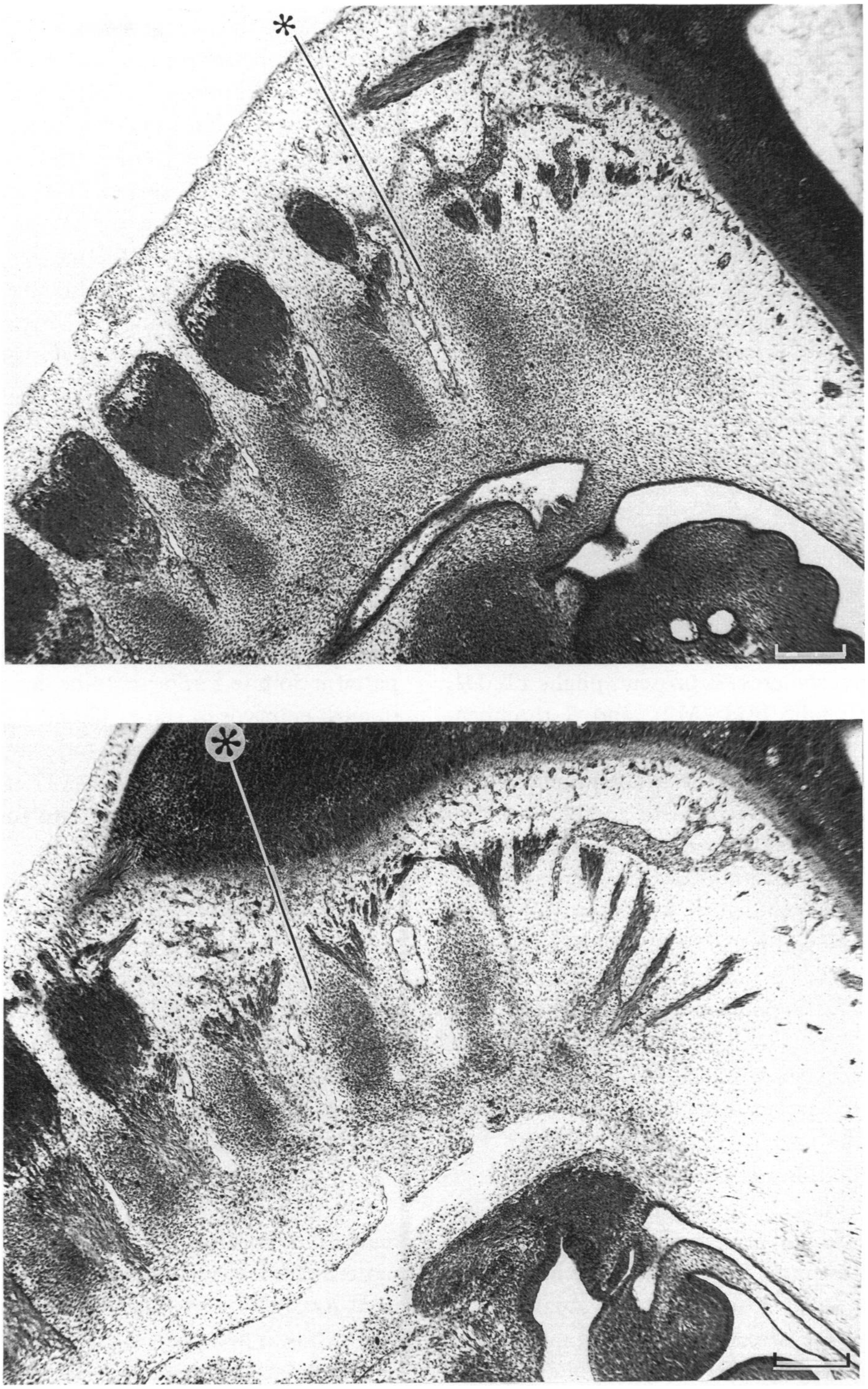

Fig. 4. Sagittal section a little more medial than the previous figure. A key is provided in Figure 5. This embryo was also studied by Sensenig (1957). Bar, 0.17 mm.

The lateral cervical region

The development of the cervical region, particularly with regard to nerves, takes place a little later than in the occipital region. At stage 12, the cervical neural crest is not yet organised into ganglia (Fig. 1). At stage 13, ventral nerve roots begin to develop, and a small 1st cervical ganglion is distinguishable in some embryos. At stage 14, the 1st cervical ganglion is still small, whereas the following ganglia are extensive and each occupies a whole segment (Figs 2–5). The cervical ventral rami are well developed. Loose rostral areas and dense caudal areas become visible in the sclerotomes (Fig. 2). At stage 15, the sclerotomes are situated more ventrally than in stages 12–14. The loose area of the 1st cervical sclerotome (5 in Fig. 5)

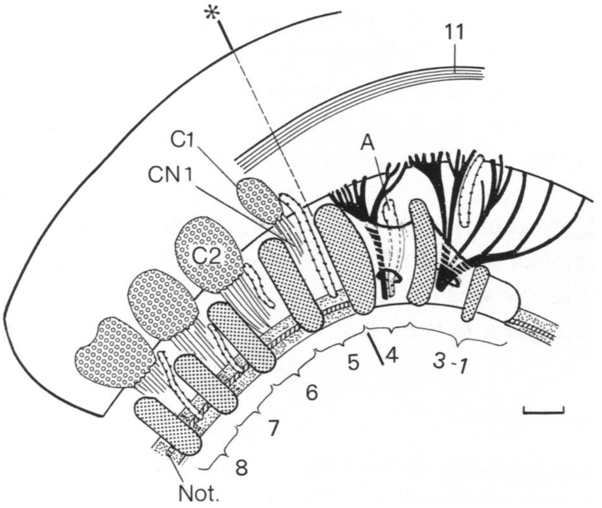

Fig. 5. Key to Figures 3 and 4, showing the dense areas of sclerotomes 1–8 at stage 15. Intersegmental arteries are visible in the loose areas of the sclerotomes. An asterisk indicates the occipitocervical junction, which passes between sclerotomes 4 and 5. All the nerve fibres emerging between the dense areas of occipital sclerotomes are hypoglossal. Two hypoglossal foramina are shown. Four spinal ganglia and some spinal nerve fibres are included. The notochord and its sheath have been added. A, hypoglossal artery; CN1, cervical nerve 1; C1, C2, spinal ganglia 1 and 2; Not., notochord; 1–8 sclerotomes; 11, accessory nerve. Bar, 0.18 mm.

is occupied by an intersegmental artery and branches of the 1st cervical nerve. Spinal ganglion C2 occupies almost the whole extent of a sclerotome, as do also the following ganglia.

At stage 17, the dense area of sclerotome 5 on each side gives rise to the corresponding neural process of the atlas, and the 2 neural processes are in line with X (Fig. 6). The neural arches begin to chondrify at about stage 18.

The central occipital region

The somites of the occipitocervical region at stage 12 are shown in Figure 1. The paraxial mesenchyme has not yet become condensed to form the perinotochordal sheath. At stage 13, however, a sheath of sclerotomic origin can be discerned in the occipital region. The appearance at stage 14 is shown in Figure 2. Central (or axial) as well as sclerotomic components can now be distinguished, and the axial mesenchyme extends as far as the rostral tip of the notochord. No dense areas are present in the axial part of the occipital region, however, and even those in the cervical region are ill defined.

The central cervical region

At stage 14, dense areas are not clearly distinguishable in the axial mesenchyme, but they become defined at stage 15, when vertebrae can be said to be developing.

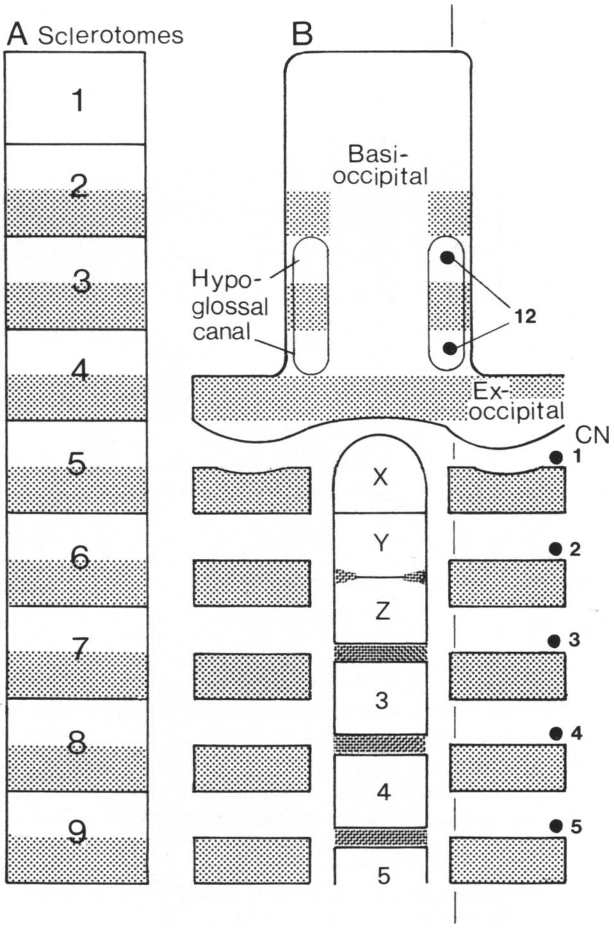

Fig. 6. Scheme of the early development of the human craniovertebral region. A is a view of one of the bilateral sclerotome columns. Sclerotomes 1–4 are occipital. B is a dorsal view of the occipitocervical region. The sclerotome derivatives are shown bilaterally (shaded in grey). The central column of the axis consists of 3 parts, labelled XYZ. The interrupted vertical line indicates the approximate plane of section of Figures 3 and 4. CN, cervical nerve; 12, hypoglossal nerve.

Dorsal rami of the cervical nerves have also become visible. At stage 16, axial dense areas can be seen very distinctly in sagittal and in coronal sections, and they are situated between the future centra, beginning with Z and proceeding caudally (dark grey in Fig. 6*B*) but they are absent between X and Y, and between Y and Z.

As shown in Figure 6*B*, X is on the level of sclerotome 5, whereas Y and Z are in line with sclerotome 6 and also with the loose area of sclerotome 7. Thus the XYZ unit is in register with $2\frac{1}{2}$ segments, and any apparent lack of registration between these components and the sclerotomes is negligible or absent. The typical shift in registration begins with Z, the centrum of which is clearly in line with 2 sclerotomes, namely 7 and 8.

To study the precise number of centra incorporated in the XYZ unit, the height of the 3 components

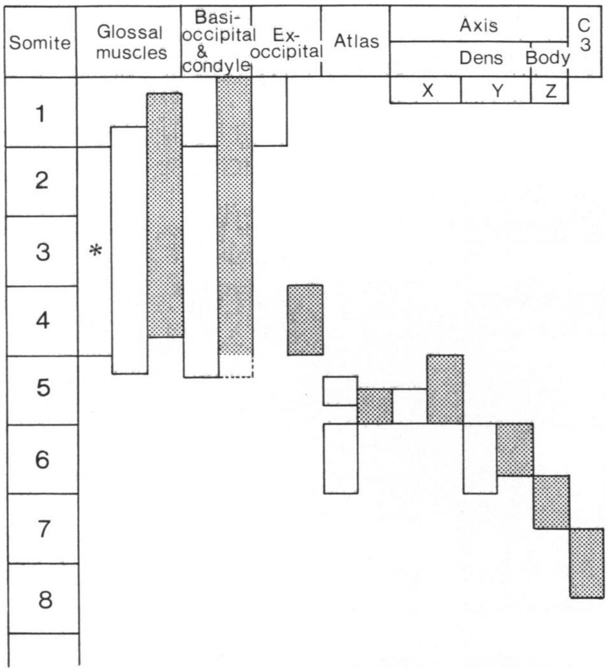

Fig. 7. Graph to show the somitic (sclerotomic) origin of the craniovertebral region in human (stippled) and in avian (unshaded) embryos. The first avian column (asterisk) is based on Noden (1983), the remaining avian columns on Couly et al. (1993). The human data are those of the present authors. The basioccipital, exoccipital, atlas, and dens are in registration with the somites.

Table. *Determination of the number of segments in the XYZ complex during the first trimester* (*details in text*)

Stage	No	XYZ:C3	GL	No	XYZ:C3
18	408	3.7	32.2	5017	3.0
	144	3.3	33	145	2.8
19	390	3.5	36	449	3.0
	1390	3.1	36	878	2.6
20	431	3.2	37	972	3.2
21	1008	3.0	39	362	3.0
	148	3.0	40	6658	2.95
	632	3.0	46	95	3.0
23	75	3.1	46	1686	3.2
	5422	2.95	50	184	3.25
	9226	2.9	50	1537	3.0
			52	448	2.7
			60	907	3.3
			67	1656	3.5
			78.5	1455	2.9

GL, greatest length of embryo or fetus in mm; No, Carnegie number of embryo or fetus; XYZ:C3, ratio of height of XYZ complex to that of cervical vetebra 3.

during the 1st trimester was measured and compared with that of the centrum of cervical vertebra 3, exclusive of the intervertebral disc. When the height of C3 is considered to be unity, the proportion XYZ to C3 varied from 2.6 to 3.7, and was commonly of the order of 3:1, as can be seen from the Table. Hence, contrary to a commonly held view, the XYZ complex, at least during the 1st trimester, consistently remains composed of 3 full segments.

During stage 17, a temporary intervertebral disc appears peripherally between Y and Z, but generally begins to disappear at stage 21, although remains can be found in the adult. No disc develops between X and Y. Also during stage 17, chondrification begins in the cervical centra. The anterior arch of the atlas, the origin of which is unclear, can be discerned at least by stage 19 and is evident at stages 21–23.

DISCUSSION

The following points have already been established in human development. The notochord completes its development during stages 11 and 12, except for the most caudal portion. The perinotochordal cellular sheath is present in the entire occipital region at stage 13, and extends even further rostrally at stage 14 (O'Rahilly & Müller, 1986). The axis incorporates 3 centra and is related to 3 cervical nerves (O'Rahilly et al. 1980, 1983). Somites are first encountered at stage 9. Their core cells, together with their ventromedial component, constitute sclerotomes at stage 11. Four occipital somites and 4 occipital myotomes are present at stage 12 (O'Rahilly & Müller, 1984). The occipital somites are associated with rhombomere D in the terminology of Müller & O'Rahilly (1983). Reiter's (1944) claim that 5 occipital segments exist in the human embryo was based on an erroneous identification of hypoglossal ganglia, and was already criticised by Sensenig (1957). Kunitomo (1918), on the other hand, acknowledged only 3 occipital segments and hence numbered the somites incorrectly. Laterally situated dense areas in the occipital and cervical sclerotomes participate in the formation of the chondrocranium and of the neural arches of the vertebrae (O'Rahilly & Müller, 1984). Sclerotomes 1–3 form the rostral part of the basioccipital. Occipital sclerotome 4 forms (1) an incomplete centrum axially, and (2) exoccipital elements laterally (O'Rahilly & Müller, 1984).

During the present study it became clear that the developmental distinction between axial and lateral components is valid in both the vertebral and the occipital regions. The lateral components in the vertebral region, i.e. the neural processes, arise in situ from the dense areas of the sclerotomes. In the occipital region, however, the lateral portion resembles the cervical, at least in part, in that dense areas are observed in parts of sclerotomes 2–4. Those of sclerotomes 2 and 3 are restricted and become associated with the hypoglossal canal (Figs 5, 6*B*),

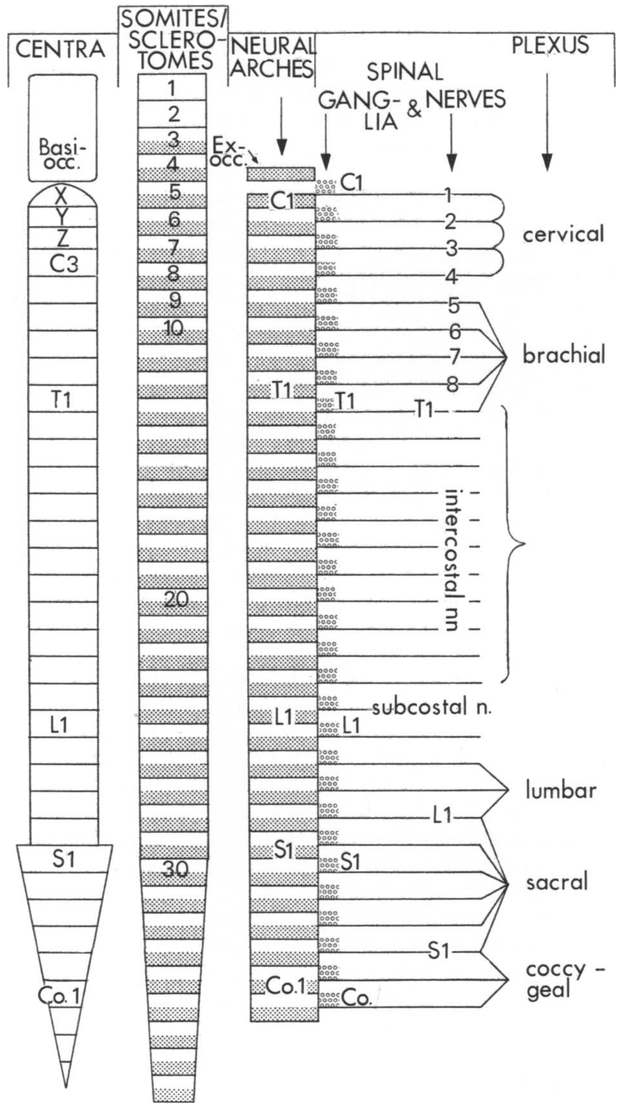

Fig. 8. Scheme of the early development of the vertebral column and related nerves. This figure replaces a highly simplified scheme of somitic-vertebral correlation published previously (Müller & O'Rahilly, 1986, fig. 2) purely as an aid in assessing the developmental descent of organs.

which may be divided even in the adult. The dense areas of sclerotome 4 are more extensive and form the exoccipital, which is sufficiently distinctive to be regarded as corresponding to the neural arches. The axial components in the vertebral region are formed from the perinotochordal territory. In an important autoradiographic study of the thoracic vertebrae of the mouse, Dalgleish (1985) concluded that the mammalian centra 'do not originate from sclerotome halves but rather from chondrific centers originating in unsegmented somite-derived tissue surrounding the notochord, the perichordal tube.' (He also confirmed that 'resegmentation during vertebral formation is no longer valid' in mammals.) In the axial portion of the occipital region the perinotochordal material does not show dense areas, i.e. segmentation is absent. The perinotochordal cells rostral to the level of sclerotome 1 seem to become incorporated in the basioccipital while the latter grows rostrally. In other words, more than the original perinotochordal sheath would seem to be involved in the formation of the basioccipital. In the occipitocervical transitional region no change in registration occurs. The definitive elements arise in phase with the initial sclerotomes (Fig. 6).

One neural arch develops for the atlas and another for the axis. Each of the neural processes that are the precursors of the posterior arch of the atlas arises from the dense area of sclerotome 5, and is at the level of X. The anterior arch of the atlas is also at the level of X or is, in some instances, between X and Y (O'Rahilly et al. 1983, fig. 5*C*, *D*). Each of the neural processes for the arch of the axis arises from the dense area of sclerotome 6, and is at the level of Y and Z, particularly the latter. Three centra develop for the atlas and axis, although they are related to only $2\frac{1}{2}$ sclerotomes. X is at the level of sclerotome 5 (the first cervical sclerotome), and Y and Z together are at the level of sclerotome 6 and the rostral half of sclerotome 7. The XYZ complex belongs ontogenetically to the axis, so that the atlas does not appear to incorporate a part of the central column. The typical lack of registration between centra and sclerotomes begins with part Z and continues caudally. Although $2\frac{1}{2}$ segments have also been proposed by other authors (e.g. Reiter, 1944; Sensenig, 1957; Christ et al. 1987, 1988), these authors incorrectly allowed only half a segment for component X. It is clear from the Table, however, that the height of XYZ equals 3 times that of the centrum of cervical vertebra 3, and hence that a half segment is not involved (Fig. 6*B*). Additional confirmation of the 3:1 ratio was obtained by measuring the vertical height of each component of XYZ and of the succeeding cervical vertebrae in the detailed reconstruction at stage 16 by Strasmann (1987, fig. 6), whose general interpretation, however, is not supported here. According to some preliminary observations, it seems that this ratio still holds at birth.

At stage 12, a considerable gap is present between the rostral end of somite 1 and the rostral end of the notochord, which is close to the hypophysis. This still holds at stages 14 and 15 (Figs 1–5). At the end of the embryonic period, the rostral portion of the notochord is no longer 'naked' but is included in the basioccipital, which seems to have grown rostrally. The tip of the notochord is approximately at the spheno-occipital junction, i.e. it is still near the hypophysis.

In both the occipital and the cervical regions the nerves traverse the loose areas of the sclerotomes. In the vertebral region, nerve fibres and intersegmental arteries grow through the loose areas of the sclerotomes. In the occipital region, in those stages (14 and 15) when occipital sclerotomes show loose and dense areas, the 2 stems of the hypoglossal nerve traverse the loose areas of sclerotomes 3 and 4. They are accompanied by the 2 occipital intersegmental arteries, the more caudal of which is the temporary hypoglossal artery. In a study of lectin binding, however, it has been found that 'human PNA receptors in contrast to those of the chick embryo, are in all probability not involved in the control or regulation of axonal outgrowth and neural crest migration' (Götz et al. 1993).

With regard to other species, the most complete experimental results are in avian species, which are summarised in Figure 7, based largely on the valuable data of Couly et al. (1993). A number of features show a fairly close resemblance, but differences are also evident. Further comparative studies may help in assessing the significance of the dissimilarities.

The data given by Christ et al. (1988) and by Christ & Wilting (1992) for the occipitocervical region of the human embryo are not included in the absence of documentation: material, stages, methods, reconstructions, relationship to nerves and vessels, etc. These authors made the unsupported claim that 'the boundary between head and neck corresponds to the boundary between the 5th and the 6th somite... for the chick as well as for the human embryo'. This error for the human embryo was apparently based on accepting Reiter's (1944) incorrect view, which had already been criticised by Sensenig (1957), who is not cited by the above authors.

In conclusion, some developmental features of the entire vertebral column are summarised in Figure 8. It can be seen that the somites and sclerotomes are in registration with the neural arches and with the spinal ganglia, whereas the centra (shown separately on the left) are out of phase. Somite 31, which is in line with sacral neural arch 2, is at the level of the final closure of the caudal neuropore (O'Rahilly & Müller, 1994).

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