OBSERVATIONS ON THE PRE-NATAL DEVELOPMENT OF THE INTERVERTEBRAL DISC IN MAN

A. PEACOCK

Anatomy Department, London Hospital Medical College

INTRODUCTION

This paper is concerned primarily with the pre-natal development of the intervertebral discs, but a series of discs at various ages after birth has been examined also for comparison. The development of the discs is intimately associated with that of the vertebral bodies and of the notochord. In the studies on the development of the vertebral column in man by Bardeen & Lewis (1901), Bardeen (1905, 1910), Müller (1906), Ask (1941), Reiter (1942), Wyburn (1944) and Sensenig (1949), and in the ox by Froriep (1886), in the white rat by Weiss (1901), in the mouse by Dawes (1930) and in the deer-mouse by Sensenig (1943), it is the vertebrae rather than the intervertebral discs that are chiefly dealt with.

The notochord has been studied as an independent structure in considerable detail by Schaffer (1930), and Prader (1945) has studied this structure in human embryos, while Williams (1908) studied its later development in mammals and included two references to human embryos.

The structure of the intervertebral disc at certain isolated pre-natal stages is referred to by Smith (1931), Keyes & Compère (1932) and Töndury (1947). Prader (1947*b*) gives a detailed account of the histogenesis of the peri-notochordal tissues in man, Luschka (1858) describes some embryonic stages of the human disc, while Carlier (1890) gives a detailed account of the development of the intervertebral disc in the sheep. Detailed studies of the human adult disc have been made by Fick (1904), Petersen (1930), Beadle (1931) and Coventry, Ghormley & Kernohan (1945*a*, *b*). The vascularization of the human disc has been studied by Übermuth (1929) and Böhmig (1930).

An examination of the literature just cited shows that there is no contribution dealing particularly with the development of the intervertebral disc, and apart from Prader's work (1947*b*), only references to pre-natal stages are scattered throughout the literature.

The present investigation was undertaken to determine, by the examination of a range of human embryos, the various stages in the histogenesis of the components of the disc, to ascertain the part played by the notochord in the formation of the nucleus pulposus, to study the relationship of the cartilage plates to the components of the disc and to make some observations on the vascularization of the developing disc.

MATERIALS

A closely graded series of thirty-eight human embryos and foetuses ranging from 3 mm. to full-term, and cut in coronal, horizontal, or sagittal planes, has been studied.

DESCRIPTION OF SPECIMENS

The specimens described are selected as showing well-marked stages of differentiation of the disc tissue.

8 *mm. embryo cut in the coronal plane* (Pl. 1, fig. 1)

This embryo shows the presence of mesodermal somites, bounded by intersegmental vessels. The myotomes are composed of large, heavily staining cells, a myocele is present, and the medial part of the somite is occupied by smaller cells, which are seen migrating towards the notochord. The cells are densely packed in the sclerotome, but are looser in the region of the notochord. An intrasclerotomic fissure of v. Ebner (1888) divides the sclerotome into anterior and posterior parts, but there is as yet no difference in cell density in these.

Although not seen in the photograph, the notochord is clearly defined and is composed of polygonal cells. No definite notochordal sheath is present, but there is a mesodermal sheath of several layers of cells.

7·5 *mm. embryo cut in the horizontal plane* (Pl. 1, fig. 2)

A marked distinction is seen in this embryo between the loosely and densely arranged cells of the sclerotomes, the two being disposed cranially and caudally respectively of the intrasclerotomic fissure. The notochord is well defined. The developing vertebral column is still in the blastemal stage.

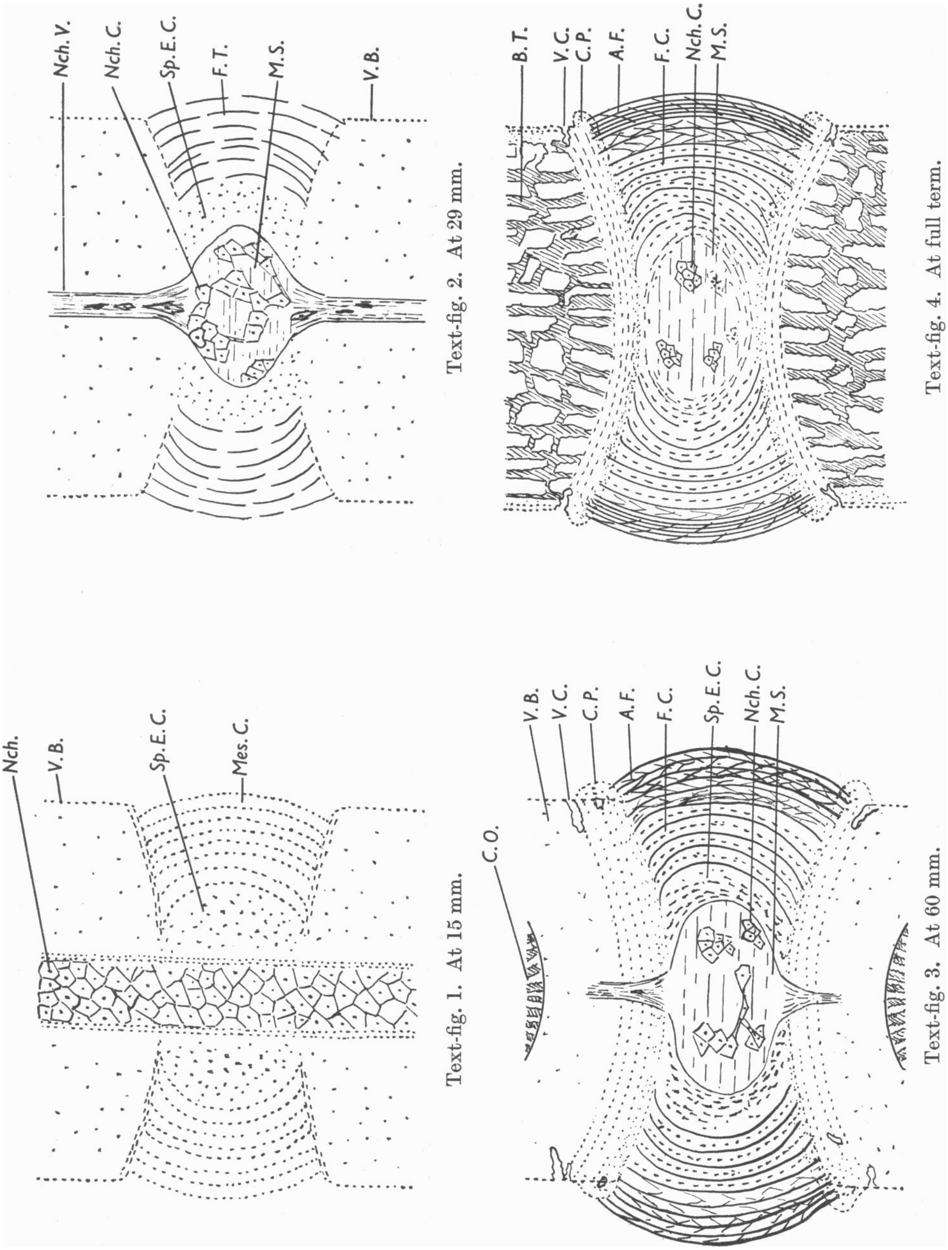
10 *mm. embryo cut in the coronal plane* (Pl. 1, fig. 3)

Chondrification is present in the vertebral bodies in this embryo. The notochord is of uniform diameter throughout and is situated somewhat ventral to the central axis of the developing vertebral column. The notochordal cells are numerous, closely aggregated and clearly defined. There is a peri-notochordal thickening of several layers of mesodermal cells.

The area of the future disc shows dense mesodermal tissue. The cells are long oval and are arranged in concentric lamellae. In the coronal plane, the intrasclerotomic fissure may still be recognized; the tissue of the disc is related to the fissure so that one-third is cranial to it and two-thirds caudal. In the thoracic region, in horizontal sections, at the ventral edge of the disc, several rows of closely aggregated cells are seen which pass laterally to merge with the mesodermal head of the corresponding rib. This cell aggregation represents the hypochordal bow. Similar conditions are found in the 13 and 14 mm. embryos.

15 *mm. embryo cut in the sagittal plane* (Pl. 2, figs. 4, 5; Text-fig. 1)

Significant changes are present in this embryo. The notochord can be traced from basis cranii to coccyx. The developing vertebral bodies are formed of embryonic cartilage. The discs are slightly thicker at the circumference than at the centre. As seen in sagittal section (Pl. 2, fig. 5) the densely aggregated circumferential mesodermal cells run in fairly parallel rows between one vertebra and the next. The cells of the disc become more rounded as they are traced towards the centre and are irregularly arranged round the notochord. They have more intercellular substance between them than in the case of the vertebral bodies. This tissue towards the centre of the disc



Text-fig. 1. At 15 mm.

Text-fig. 2. At 29 mm.

Text-fig. 3. At 60 mm.

Text-fig. 4. At full term.

Text-fig. 1–4. Diagrammatic representation of differentiation of the tissues of the disc.

resembles cartilage, indeed indications of actual cartilage capsules are seen at various places, and it will be referred to as 'specialized embryonic cartilage' (Text-figs. 1–3).

The above features are seen throughout the vertebral column. No vascularization of the developing vertebral bodies or of the discs is seen. Conditions in the 16 and 17 mm. embryo are similar.

21 *mm. embryo cut in the sagittal plane* (Pl. 2, figs. 6. 7)

In this embryo further changes are present, especially in the notochord. The vertebrae are formed of embryonic cartilage. The notochord can be followed from the basis cranii to the coccyx, and it shows slight expansions in the intervertebral regions and constrictions in the vertebral bodies, in some of which only a tract of homogeneous, acellular material marks its site. Furthermore, the whole notochord follows a slightly undulating course, with slight dorsal convexities in the intervertebral regions and ventral convexities in the vertebral bodies. At various points in the lumbar region, small processes of notochordal tissue project from the main structure and pass dorsally in the vertebral bodies.

The intervertebral discs show similar characteristics throughout the embryo. They are biconcave, and are composed, from the circumference to the centre, of mesodermal tissue, 'specialized embryonic cartilage' and notochord.

In paramedian sagittal sections of the circumferential area of the intervertebral disc, three zones are visible (Pl. 2, fig. 7*a–c*). The middle zone of dense mesodermal tissue (*b*) is the disc and the zones *a* and *c*, the cartilage plates.

No vascularization of vertebral bodies or discs is present. Similar features are seen in embryos of 22–25 mm.

26 *mm. embryo cut in the coronal plane* (Pl. 2, fig. 8)

In this embryo the disc shows, from without inwards, mesodermal cells, 'specialized embryonic cartilage', in which cell capsules can be seen, and the notochord.

29 *mm. embryo cut in the sagittal plane* (Pl. 2, fig. 9; Text-fig. 2)

In this embryo pronounced changes are present in the tissue of the notochord. The notochordal expansions and constrictions are somewhat more defined, the sheath being thickened in the intravertebral areas. In the notochord itself, spaces have appeared between the cells, and these spaces contain a homogeneous, slightly basophil substance. The separation of some groups of cells and compression of others gives the appearance of a network-like tissue, referred to as the 'chorda-reticulum'.

At the circumference of the disc definite fibres are now present, and this part of the disc may now be truly termed the annulus fibrosus. These fibres, running in parallel rows, cross the intervertebral space and their terminations are lost in the adjacent vertebrae. The innermost fibres are only half as long as the outermost; some of the fibres are seen to run obliquely and the disc as a whole is biconcave. The specialized peri-notochordal cartilage is well seen. Enlargement of intravertebral peri-notochordal cartilage cells indicates the preliminary stages of ossification. The cartilage at the ends of the vertebral bodies into which the fibres pass, stains more lightly with haematoxylin than that of the bodies themselves, and along the boundaries of the intervertebral spaces the cartilage cells are flattened and arranged in horizontal rows. These areas are the cartilage plates which serve to anchor the fibres of the disc, and which by proliferation of cells, are responsible for the growth of the vertebrae in height. No vascularization of vertebral bodies or discs is present. In a specimen of 30 mm. well-developed obliquely running fibres are also present in the annulus fibrosus.

47 mm. embryo cut in the horizontal plane (Pl. 3, figs. 10, 11)

The notochord has expanded in a transverse direction. The peri-notochordal cartilage, dorsal to the notochord, shows a looser arrangement of its cells and more intercellular substance than similar tissue ventral to the notochord. This loosening of tissue appears to precede a dorsal expansion of the notochord. Well-defined fibres are present in the annulus.

60 mm. embryo cut in the sagittal plane (Pl. 3, fig. 12; Text-fig. 3)

Centres of ossification are well defined in the vertebral bodies. The notochord has expanded in a dorsal direction and remnants only of the notochordal sheath are seen, near the upper and lower surfaces of the intervertebral discs. The notochordal cells are polygonal and vesicular, with large, heavily staining nuclei, the cytoplasm staining lightly with Biebrich's Scarlet. Spaces containing a lightly staining, amorphous, basophil substance are present between the cell groups, and in some regions a chorda-reticulum is present. More peripherally in the notochordal area, rows of cartilage cells are seen in an abundant matrix, those nearest the notochord encircle it and then pass to mingle with the cartilage of the vertebral bodies. A little further peripherally, the matrix is abundant and the cells run in parallel rows, with an outward convexity like that of the fibres of the annulus, seen still more peripherally. In tracing the tissues from the notochordal area to the circumference, there is a transition from the peri-notochordal cartilage to fibrocartilage and finally to the fibres of the annulus.

This succeeding tissue differentiation suggests that the peri-notochordal specialized embryonic cartilage is forming the future fibrocartilaginous component of the disc, and may contribute to the inner area of the annulus fibrosus. The fibres of the annulus are again seen to terminate in the cartilage plate. As regards vascularization of the vertebrae, vascular channels are present peripherally at the level of a plane passing between the vertebral body and the cartilage plate, while dorsally in the vertebral body a depression containing blood vessels is seen at the site of the definitive foramina for the basivertebral veins. No vascularization of the notochordal area or of the annulus fibrosus is present.

99 mm. embryo cut in the horizontal plane (Pl. 3, fig. 13)

In this embryo the notochordal area is seen expanded, with a chorda-reticulum and intercellular spaces containing a homogeneous substance, while more peripherally is the fibrocartilage zone, and beyond this the concentric fibres of the annulus fibrosus. Ventrally, at the circumference of the annulus, a dense fibre concentration is present, and ventral to this again there are fibres of the anterior longitudinal ligament. The annulus shows splitting and joining of the fibres of different lamellae and an interlocking of the various lamellae.

Among the peripheral fibres of the annulus a few small blood vessels are present in the dorsolateral areas of the disc, but there is no vascularization of the inner part of the disc nor of the notochordal area.

150 *mm. embryo cut in the sagittal plane* (Pl. 3, fig. 14)

In paramedian sagittal sections of this specimen the complicated architecture of the fibre system of the annulus fibrosus is particularly well seen.

210 *mm. embryo cut in the sagittal plane* (Pl. 3, fig. 15)

In this embryo the principal change is in the notochordal area. This has enlarged, and in a median sagittal section is elongated ventro-dorsally to occupy half the length of the intervertebral region. It contains a faintly basophil, structureless substance, in which groups of notochordal cells are present. These are much reduced in number and some show heavily staining, rounded nuclei, while in others the nuclei are pyknotic. The remains of a chorda reticulum are present. Passing from the notochordal area to the circumference, we see the peri-notochordal cartilage with its cells arranged in rows, forming a capsule for the notochord, then the fibro-cartilage and finally the fibres of the annulus.

The vascularization is as seen in the 99 mm. specimen.

The full-term foetus cut in the sagittal plane (Pl. 4, fig. 16; Text-fig. 4)

In this specimen, centres of ossification are present in the vertebral bodies; bony trabeculae are developed, and marrow occupies the intertrabecular spaces. The vertebral bodies are capped above and below with cartilage, which in the inter-vertebral area receives the fibres of the annulus and the fibrocartilaginous component. No vestige of notochord is present in the vertebral bodies.

In a median sagittal section the notochordal area is extensive, somewhat biconvex, and occupied by a faintly basophil, homogeneous substance, in which the remains of a chorda reticulum are present. Here and there are small groups of recognizable notochordal cells. At the circumference of the notochordal area collagenous fibres and cartilage cells are to be seen, embedded in the homogeneous, mucoid substance. These appear to be derived from liquefaction in the inner part of the fibrocartilaginous zone which surrounds the notochordal area. External to this zone is the annulus fibrosus. Vascular canals are present, as in the previous specimen, but no vessels are seen to enter the notochordal area. A few small vessels run between the lamellae of the annulus but are confined to the dorsolateral areas.

The ventral part of a disc of a full-term foetus, seen in horizontal section (Pl. 4, fig. 17), shows the architecture of the fibre system. To the right of the figure are seen the fibres of the anterior longitudinal ligament, deep to which are several very dense lamellae representing the contribution to the disc from the hypochordal bow. The intricate splitting and interlocking of the various lamellae are evident, and the whole structure of the annulus fibrosus resembles that of the adult.

Examination of a series of post-natal human intervertebral discs, ranging in decades from birth to 80 years of age, shows a progressive invasion of the notochordal area by collagenous fibres and cartilage cells, ultimately resulting in the complete transformation of this area to fibrocartilage. These elements are derived from the fibrocartilaginous zone of the disc, which in turn is derived from the peri-notochordal specialized embryonic cartilage. It may be noted that until transformation of this latter tissue occurs, the vertebral bodies are in cartilaginous continuity. Müller (1906) refers to this but does not describe the specialized character of the connecting cartilage.

The term nucleus pulposus is employed to designate the macroscopically gelatinous, apparently structureless, semi-fluid mass contained within the annulus fibrosus of the pre- and post-natal disc. The structure of the nucleus pulposus before birth is mainly notochordal and after birth, modified as described above. Thus, one term is employed to designate areas having similar sites but different histological structure. The difficulty could be overcome by the use of the terms 'pre-natal' and 'post-natal' nucleus pulposus.

REVIEW OF OBSERVATIONS AND DISCUSSION

(1) *Preliminary developmental changes*

The developmental changes of the human vertebral column are referred to by Bardeen (1905) as blastemal, chondrogenous and osseogenous, and though overlapping of these periods occurs, this classification adequately summarizes the main developmental phases.

In early stages the sclerotome is divided by the fissure of v. Ebner (1888) into a cranial and a caudal half with a loose cell aggregation in the former and a dense cell aggregation in the latter.

From the observations made in the present investigation, and by Remane (1936), Reiter (1942), Prader (1947*a*) and Sensenig (1949), the densely aggregated tissue is found after the 6 mm. stage both cranial and caudal to the fissure of v. Ebner, occupying the caudal third of the cranial half-sclerotome and the cranial two-thirds of the caudal half-sclerotome (see Pl. 1, fig. 3). This condensed tissue forms the *anlage* of the intervertebral disc, which therefore receives contributions from both cranial and caudal half-sclerotome. Bardeen (1905) refers to the 'primitive disc' as being strengthened anteriorly by a condensation of tissue bounding the fissure of v. Ebner, while Prader (1947*a*) considers that the condensed tissue, at first limited to the caudal half-sclerotome, 'migrates headwards' and forms the *analage* of the primitive intervertebral disc. From this it may be assumed that while the disc is formed by contributions from both half-sclerotomes, the major contribution is from the posterior half-sclerotome.

(2) *The annulus fibrosus*

This is developed from the dense tissue described above. At first the mesodermal cells are rounded and do not show any specific arrangement, but by the 10 mm. stage the cells have become elongated, and in transverse sections of the disc show evidence of concentric arrangement. From this time onwards there is a thickened band consisting of several layers of cells, which connects the costal elements of both sides across the front of the disc. This band can be identified at all subsequent stages and evidently represents the hypochordal bow of Froriep (1886) which is subsequently added to, and forms a component of, the intervertebral disc. Further elongation of the mesodermal cells follows, and by the 29 mm. stage fibres are present and concentric lamellae are well defined. By 38 mm. oblique fibres are well developed. These fibres run a spiral course from one vertebra across the intervertebral space to the next. Crossing of different sets of fibres, in some instances, occurs at an angle of almost 90°.

The annulus fibres bound an area of peri-notochordal specialized embryonic cartilage. As histogenesis proceeds, it may be observed that the most peripheral part of the disc is composed of closely aggregated fibres, while the inner part shows a more open tissue. It has been suggested by Prader (1947*b*) that the peri-notochordal cartilaginous area contributes to the inner part of the annulus. From 60 mm. onwards, fibrocartilage makes its appearance between the fibrous annulus and the narrow area of cartilage that surrounds the notochord and persists almost to the time of birth. In the full-term foetus, this cartilage has differentiated into fibrocartilage, and so far as the annulus is concerned, the definitive condition exists.

The attachment of the disc to the cartilage plate is effected by the termination of the disc fibres among the cartilage cells of the adjacent vertebrae previously referred to. The fibre constitution of the disc is denser ventrally than dorsally, and the connexion of the annulus to the anterior longitudinal ligament is more intimate than to the posterior longitudinal ligament.

Some reference may be made to the thickness of the disc *anlage*. In the somite stage as seen in sections in the coronal and sagittal planes, the dense tissue has the same thickness as the loose tissue. When chondrification of the vertebrae occurs, the disc becomes thinner, but the upper and lower surfaces are flat. By the 15 mm. stage viewed in median sagittal section, the disc is biconcave and this condition persists till birth.

The annulus fibrosus is the first component of the disc to show a definite cellular arrangement, and it achieves its highly complex architecture long before movement or any stress occurs in the vertebral column. It is fully differentiated at birth. Examination of adult discs shows that the structure of the annulus fibrosus remains unchanged for many years.

(3) *The notochord*

In the 3 mm. embryo, the notochord in the cranial region of the blastemal vertebral column is circular in outline and presents the suggestion of a canal in its lumen. His (1880) records a distinct lumen in an embryo of 2·4 mm. No definite lumen is seen in the notochord of other embryos in this series. In the caudal region, the notochord in the early stages is somewhat flattened and approaches the developing neural tube. Bremer (1906) describes similar features in a 4 mm. embryo and states that not far from the end of the tail, 'the notochord is lost by merging with the spinal cord'. Sensenig (1949) describes contact of the notochord with the neural tube in embryos up to 3·7 mm. This feature is not seen in the present series of embryos.

At the 10 mm. stage the notochord has a uniform diameter throughout, but by the 21 mm. stage, it shows an intravertebral narrowing and slight intervertebral fusiform expansion. These two parts of the notochord are referred to by Schaffer (1910) as 'Chordascheidenstrang' and 'Chordasegment' respectively. In the 26 and 29 mm. specimens, the intervertebral expansion is more pronounced. At 47 mm. the intervertebral notochord has passed from the spindle-like form of the 21 mm. stage, to that of an oval structure about as broad as it is long, while in the intravertebral region, a narrow tract of homogeneous, acellular substance representing the notochordal sheath is seen. At 60 mm. the notochord has expanded dorsally, as is also seen in the 93, 99 and 156 mm. stages, and by full term the notochordal area occupies a considerable proportion of the total area of the whole disc. In the 99 mm. embryo, in following serial sections through the disc from above downwards, at first a circular notochord is seen, then the dorsal expansion appears, while the rounded ventral part of the notochord is still visible, the whole area being key-hole shaped. At the same time the notochord expands laterally.

Böhmig (1930) considers the forms of intervertebral notochord as so characteristic that he designates them as 'Rhombusform', 'Pilzform', 'Stabform', 'Dachform' and 'V-form' and figures all types in his 86 mm. embryo. No such defined forms are seen in the series here investigated.

Schaffer (1910) and Prader (1945) consider the alterations in the form of the notochord to be due to cranial and caudal pressure which is responsible for the broadening and shortening, while the dorsal convexity of the embryo permits dorsal extension.

The position of the notochord relative to the central axis of the vertebral column demands consideration. In the early stages, it runs approximately centrally through the developing column (except as noted in the caudal extremity), but at 10 mm. it is slightly more ventrally placed and it retains this position during foetal life. When the cartilage cells at the centre of the developing vertebral body enlarge as a preliminary to ossification, the notochord passes through the ventral part of this area. When ossification occurs, the notochord maintains its position, and is represented for a time by the notochordal sheath until this disappears in later stages.

In the adult, the nucleus pulposus is situated in the dorsal part of the disc. This is accounted for by the fact that the disc and vertebral body do not increase in size concentrically. The peri-notochordal component of the disc increases more in a ventral than in a dorsal direction, and growth of the vertebral body occurs by accretion at the ventral surface, as has been shown by the radiological studies of Knutsson (1948).

The intervertebral expansion of the notochord begins at 21 mm. and thereafter is progressive. The cells in the intervertebral area increase in number, while those in the intravertebral area decrease. The question arises, as to whether there is degeneration of the intravertebral cells and proliferation of the intervertebral cells, or whether mere passive displacement of the cells occurs. Schaffer (1910) considers the mechanism to be one of passive displacement, a view previously held by Kölliker (1879). Estimation of the total number of cells shows that this remains the same. Mitoses are recorded by Prader (1945) up to the 3·5 mm. stage, but not later. Schaffer (1910) isolated notochordal cells in the fresh state, and found them to be vesicular, pressure-resisting and capable of displacement. Hence, the production of notochordal expansions may be due to pressure exerted on the notochord by the increasing chondrification of the vertebral bodies, resulting in the displacement of the notochordal cells to the intervertebral region.

Remains of notochordal cells, or elongated cells, are to be found occasionally in the notochordal sheath near the intervertebral region, where tissues are more yielding. Rarely, notochordal tissue persists in the intravertebral region, into adult life, as recorded by Musgrove (1891) and Schmorl (1928).

Another feature is the occurrence of segmental notochordal flexures. These have been described in the human embryo by Minot (1907), Schaffer (1910), Böhmig (1930), Prader (1945), and Sensenig (1949), and in the rabbit by Kölliker (1879) and Löwe (1879). The only comment on any part played by the flexures in relation to the disc is made by Carlier (1890) in reference to the sheep. He describes, in the lumbar region of an embryo of 1·25 in., a ventral intervertebral bending of the notochord, in the median sagittal plane; the curvature thus approaching the ventral surface of the column. In specimens examined just after birth, only the most ventral part of the intervertebral notochordal curvature persists to form the nucleus pulposus.

In the present series of embryos, segmental flexures of the notochord are seen in the lumbar region, in median and paramedian sagittal sections. At 15 and 21 mm. the curvatures are directed dorsally in the intervertebral region and ventrally in the intravertebral region. At 60 mm. there is evidence of a dorsally directed curvature in the intravertebral notochordal vestige, while the intervertebral notochord is so expanded that it cannot be related to any curvature.

Similar segmental flexures are illustrated by Böhmig (1930). The causation is obscure. Dursy (1869) suggests that they are due to excessive growth in length of the notochord, while Schaffer (1910) ascribes them to mechanical factors and the influence of the presence of ossification.

The sheath of the notochord in man is less complex than in lower vertebrates. Bardeen (1910) states that a sheath is present in the human embryo at the fourth week of intrauterine life (at approximately the 2·5 mm. stage). Linck (1911) does not describe a sheath till the 20 mm. stage, and Reiter (1942) describes a sheath in an embryo of 3·6 mm. Prader (1945) states that no sheath is present in his 3·5 mm. embryo but that a thin sheath is present from the 5 mm. stage onwards. Sensenig (1949) describes a thin homogeneous sheath in his specimens of 3–7·5 mm.

In the series of embryos investigated, a thin, amorphous sheath is first seen at 5 mm. and with the onset of chondrification of the column and the development of the notochordal expansions and constrictions, the sheath becomes progressively thinner intervertebrally and thicker intravertebrally. The sheath stains lightly with basic stains and though acellular shows a longitudinal striation and gives the impression of a fibrillar structure. Its appearance is very like that of the matrix of hyaline cartilage. At the 99 mm. stage a notochordal sheath seems to re-appear in the intervertebral region, and at the 210 mm. stage the notochordal cavity appears to be lined with a substance resembling the earlier sheath. At later stages it cannot be distinguished as a separate entity.

The part played by the notochord in the formation of the nucleus pulposus has been a matter of controversy. Certain authors (Gegenbaur, 1878; Hertwig, 1898; Williams, 1908) state that the nucleus pulposus is formed by the persistence of the notochord or increase of its cells, while others (Heiberg, 1880) consider that the notochord plays no part in its formation. The nucleus pulposus has been derived 'from a central growth of cartilage' (Virchow, 1857), or regarded as a secondary formation that develops by degeneration of the cartilage of the vertebral body in the intervertebral region (Weiss, 1901). Other authors merely record the presence of notochordal cells in the newborn (Löwe (1879) in the rabbit; Schaffer (1910) in the human foetus). Wiedersheim (1897) states that in mammals the notochord persists longer intervertebrally than intravertebrally, but disappears entirely by the time the adult condition is reached. Luschka (1858) concludes that the nucleus pulposus is formed partly by notochordal changes and partly by liquefaction of the innermost layers of the matrix of the surrounding tissue, while Keyes & Compère (1932) consider that up till birth, the notochord forms the chief source of the nucleus pulposus. Linck (1911) concludes that the structural characteristics of notochordal cells indicate that they are not secreting cells, that the mucoid substance is intercellular, and is produced by mucoid degeneration of these cells.

The present investigation shows that the nucleus pulposus at birth is formed by notochordal tissue (Text-fig. 4), modified as described previously.

(4) *The early vascularization of the disc*

Böhmig (1930), from a study of human pre- and post-natal specimens ranging from 60 mm. to 30 years of adult life, states that all discs up to 25 years of age are supplied from six principal vessels, two dorsal, ventral and axial vessels. He states that these not only supply the 'intervertebral cartilage' of embryos, but also the cartilage plates of juveniles, and the annulus fibrosus and nucleus pulposus of later stages. He figures these vessels in his Plate 11. On examination of this Plate, the vessels can be seen, but they appear to be running in the cartilage plates and do not enter the nucleus pulposus. The Plates are all of microscopic sections, with a maximum magnification of 35·0 and hence a general view only is obtained.

Übermuth (1929) describes peripheral vessels in the cartilage plates only, while Smith (1931) reports the presence of 'nutritive channels' in the nucleus pulposus and in the annulus, in post-natal stages only.

In the present series, small vessels certainly run in the cartilage plates, and small vessels are found from 93 mm. onward, running in the peripheral lamellae of the annulus fibrosus only, and confined to the dorsal regions of this. These vessels are well seen at 150 mm. (Pl. 4, fig. 18). No vessels are seen to enter the nucleus pulposus, which remains avascular during foetal life.

SUMMARY

1. Descriptions are given of the development of the intervertebral disc in a series of pre-natal human specimens ranging from 3 mm. to full term. The points particularly noted are the histogenesis of the annulus fibrosus, the notochordal changes in relation to the formation of the nucleus pulposus, the peri-notochordal tissue, the relationship of the cartilage plates to the disc, and the vascularization of the disc.

2. The intervertebral disc develops from the densely aggregated mesoderm, early differentiated in the somite. This tissue is found at early stages on both sides of the fissure of v. Ebner and hence the disc receives contributions from both cranial and caudal half-sclerotomes.

3. At early stages the peri-notochordal tissue is formed by a 'specialized embryonic cartilage' which, for a time, connects the vertebrae so as to form a continuous cartilaginous column. This specialized cartilage later differentiates to form the fibro-cartilaginous component of the disc, and is a potential source of additions for the growth of the nucleus pulposus of post-natal life.

4. In foetal life, the nucleus pulposus is produced by a modification of the notochord, characterized by the mucoid degeneration of its cells, resulting in the progressive disappearance of notochordal cells and increase of mucoid substance. At birth a diminished number of notochordal cells is present. The notochord continually changes in structure, and after birth fibres and cartilage cells are added to the notochordal area, producing the post-natal nucleus pulposus. The use of the terms 'pre-natal' and 'post-natal' nucleus pulposus is suggested to indicate the change in structure described.

The alteration in position of the site of the foetal and adult nucleus pulposus within the disc may be due to the growth in girth of the discs and vertebrae being greater at the ventral surface.

5. The annulus fibrosus is differentiated very early in development, the mesodermal *anlage* showing differentiation at 13 mm. The intricate fibre system develops long before the vertebral column is subject to external mechanical influences. Well-defined fibres are present at 29 mm.

6. The annulus fibrosus is anchored, from its beginning, to the cartilage plates. The cartilage plates are developed by extension of chondrification from the vertebral body.

7. The vertebrae are freely vascularized during foetal life, and some vessels enter the cartilage plates.

8. The nucleus pulposus is avascular during foetal life, while the annulus fibrosus is vascularized only in its outer lamellae dorsally, and by very small vessels.

I wish to thank Prof. J. D. Boyd and Prof. A. J. E. Cave for advice and assistance. I wish also to express my indebtedness for permission to study the embryological collections at the following Anatomy departments: London Hospital (embryos 10, 13, 14, 15·5, 16, 17, 21, 24, 26, 30, 35, 47, 55, 60, 76, 93, 94, 99 mm.), St Thomas's Hospital (23, 49 mm.), Middlesex Hospital (21 mm.), Royal Free Hospital (3, 5, 60 mm.).

I have also to thank Prof. A. N. Burkitt and Prof. C. W. Stump of the University of Sydney for departmental facilities and material (150, 285 mm. and post-natal specimens).

REFERENCES

Ask, O. (1941). Studien über die embryologische Entwicklung des Rückgrats und seines Inhaltes unter normalen Verhältnissen und bei gewissen Formen von Spina bifida. *Uppsala LäkFören Förh.* **46**, 243–348.

Bardeen, C. R. (1905). The development of the thoracic vertebrae in man. *Amer. J. Anat.* **4**, 163–174.

Bardeen, C. R. (1910). Development of the skeleton and the connective tissues. (In Keibel & Mall, *Manual of Human Embryology*, **1**, 292–453. Philadelphia: J. B. Lippincott Co.)

Bardeen, C. R. & Lewis, W. H. (1901). The development of the limbs, body-wall and back in man. *Amer. J. Anat.* **1**, 1–35.

Beadle, O. A. (1931). The intervertebral discs. Observations on their normal and morbid anatomy in relation to certain spinal deformities. *Spec. Rep. Ser. med. Res. Counc., Lond.*, no. 161, 1–79. H.M. Stationery Office.

Böhmig, R. (1930). Die Blutgefässversorgung der Wirbelbandscheiben, das Verhalten des intervertebralen Chordasegmentes und die Bedeutung der beider für die Bandscheibendegeneration. *Arch. klin. Chir.* **158**, 374–424.

Bremer, J. L. (1906). Description of a 4 mm. human embryo. *Amer. J. Anat.* **5**, 459–479.

CARLIER, E. W. (1890). The fate of the notochord and development of the intervertebral disc in the sheep with observations on the adult disc in these animals. *J. Anat., Lond.*, **24**, 573–583.

COVENTRY, M. B., GHORMLEY, R. K. & KERNOHAN, J. W. (1945*a*). The intervertebral disc. Its microscopic anatomy and pathology. Part 1. Anatomy, development and physiology. *J. Bone Jt Surg.* **27**, 105–112.

COVENTRY, M. B., GHORMLEY, R. K. & KERNOHAN, J. W. (1945*b*). The intervertebral disc. Its microscopic anatomy and pathology. Part 2. Change in the intervertebral disc concomitant with age. *J. Bone Jt Surg.* **28**, 233–247.

DAWES, B. (1930). The development of the vertebral column in mammals as illustrated by its development in *Mus musculus*. *Philos. Trans.* **218**, 115–170.

DURSY, E. (1869). *Zur Entwicklungsgeschichte des Kopfes des Menschen und der höheren Wirbelthiere.* Tübingen: Laupp.

EBNER, V. VON (1888). Urwirbel und Neugliederung der Wirbelsäule. *S.B. Akad. Wiss. Wien* (Abt. III), **97**, 195–206.

FICK, R. (1904). Handbuch der Anatomie und Mechanik der Gelenke, unter Berücksichtigung der bewegenden Muskeln. Erster Teil: Anatomie der Gelenke. In von Bardeleben's *Handbuch der Anatomie des Menschen.* Jena: Gustav Fischer.

FRORIEP, R. (1886). Zur Entwicklungsgeschichte der Wirbelsäule insbesondere des Atlas und Epistropheus und der Occipitalregion. II. Beobachtungen an Säugethierembryonen. *Arch. Anat. Physiol., Lpz.*, 69–150.

GEGENBAUR, C. (1878). *Elements of Comparative Anatomy.* London: Macmillan and Co.

HEIBERG, J. (1880). Ueber die Zwischenwirbelgelenke und Knochenkerne der Wirbelsäule bei den Neugeborenen und ihre Verhältniss zur Chorda dorsalis. *Mitt. embryol. Inst. Univ. Wien,* Bd. 1, 119–129.

HERTWIG, O. (1898). *Lehrbuch der Entwicklungsgeschichte des Menschen und der Wirbelthiere.* Jena: G. Fischer.

HIS, W. (1880). *Anatomie menschlichen Embryonen. I. Embryonen des ersten Monats*, 1–184. Leipzig: F. C. W. Vögel.

KEYES, D. C & COMPÈRE, E. L. (1932). The normal and pathological physiology of the nucleus pulposus of the intervertebral disc. *J. Bone Jt Surg.* **14**, 879–935.

KNUTSSON, F. (1948). Observations on the growth of the vertebral body in Scheuermann's disease. *Acta radiol.* **30**, Fasc. I–II, no. 173–174, 97–104.

KÖLLIKER, A. (1879). *Entwicklungsgeschichte des Menschen und der höheren Tiere.* Leipzig: Wilhelm Engelmann.

LINCK, A. (1911). Beitrag zur Kentnisse der menschlichen Chorda dorsalis im Hals und Kopfskelets, ihrer Entwicklung in der ersten Hälfte des Fötallebens und ihrer Beziehungen zur Anatomie des Nazenrachenraumes und zur Geschwulstbildung an der Schädelbasis. Ein entwicklungsgeschichtliche Studien. *Anat. Heft.* 1. *Arb. anat. Inst. Wiesbaden*, **42**, 605–736.

LÖWE, L. (1879). Zur Kentnisse der Säugetierchorda. *Arch. mikr. Anat.* **16**, 597–612.

LUSCHKA, H. (1858). *Die Halbgelenke des menschlichen Körpers*, pp. 1–144. Berlin: G. Reimer.

MINOT, C. S. (1907). The segmental flexures of the notochord. *Anat. Rec.* **1**, 42–50.

MÜLLER, Ch. (1906). Zur Entwicklung des menschlichen Brustkörbes. *Gegenbaurs Jb.* **35**, 591–696.

MUSGROVE, J. (1891). Persistence of the notochord in the human subject. *J. Anat., Lond.*, **5**, 386–389.

PETERSEN, H. (1930). In v. Möllendorff's *Handbuch der mikroskopischen Anatomie des Menschen.* Berlin: Springer.

PRADER, A. (1945). Beitrag zur Kenntnis der Entwicklung der Chorda dorsalis beim Menschen. Inaugural Dissertation. Zürich. Geneva: Albert Kundig.

PRADER, A. (1947*a*). Die Frühembryonale Entwicklung der menschlichen Zwischenwirbelscheibe. *Acta anat.* **3**, 68–83.

PRADER, A. (1947*b*). Die Entwicklung der Zwischenwirbelscheibe beim menschlichen Keimling. *Acta anat.* **3**, 115–152.

REITER, A. (1942). Die Frühentwicklung der menschlichen Wirbelsäule. 1. Die Frühentwicklung der Brustwirbelsäule. *Z. ges. Anat.* 1. *Z. Anat. EntwGesch.*, **112**, 185–220.

REMANE, A. (1936). Wirbelsäule und ihre Abkömmlinge. In *Handbuch der vergleichenden Anatomie der Wirbeltiere*, by L. Bolk, E. Göppert, E. Kallius and W. Lubosch, vol. 4, 1–144. Berlin and Vienna: Urban und Schwarzenberg.

SCHAFFER, J. (1910). Die Rückenseite der Säugetiere nach der Geburt nebst Bemerkungen über den Bau und die Verknöcherung der Wirbel. *S.B. Akad. Wiss. Wien* (Abt. III), **119**, 409–465.

SCHAFFER, J. (1930). In von Möllendorff's *Handbuch der mikroskopischen Anatomie des Menschen*, **2**, 31–44. Berlin: Springer.

SCHMORL, G. (1928). Über Chordareste in den Wirbelkörpern. *Zbl. Chir.* **37**, 2305–2310.

SENSENIG, C. (1943). The origin of the vertebral column in the deer-mouse, *Peromyscus maniculatus rufus*. *Anat. Rec.* **86**, 123–146.

SENSENIG, C. (1949). The early development of the human vertebral column. *Contr. Embryol. Carneg. Instn* **33**, 23–41.

SMITH, N. R. (1931). The intervertebral discs. *Brit. J. Surg.* **18**, 358–375.

TÖNDURY, G. (1947). Zur Entwicklung funktioneller Strukturen im Bereiche der Zwischenwirbelscheiben. *Schweiz. med. Wschr.* **24**, 643–645.

ÜBERMUTH, H. (1929). Über die Altersveränderungen der menschlichen Zwischenwirbelscheibe und ihre Beziehung zu den chronischen Gelenkleiden der Wirbelsäule. *Ber. sächs. Ges. Akad. Wiss.* **81**, 111–170.

VIRCHOW, R. (1857). *Untersuchungen über die Entwicklung des Schadelgrundes im gesunden und krankhaften Zustande und über den Einfluss derselben auf Schadelform, Gesichtsbildung und Gehirnbau.* Berlin: Reimer.

WEISS, A. (1901). Die Entwicklung der Wirbelsäule der weissen Ratte, besonders der vordersten Halswirbel. *Z. wiss. Zool.* **69**, 492–533.

WIEDERSHEIM, R. (1897). *Comparative anatomy of Vertebrates*, 2nd ed. London: Macmillan and Co.

WILLIAMS, L. W. (1908). The later development of the notochord in mammals. *Amer. J. Anat.* **8**, 251–284.

WYBURN, G. M. (1944). Observations on the development of the human vertebral column. *J. Anat. Lond.*, **78**, 94–102.

List of abbreviations for the text-figure

A.F.	Annulus fibrosus	*M.S.*	Mucoid substance
B.T.	Bone trabeculae	*Nch.*	Notochord
C.O.	Centre of ossification	*Nch.C.*	Notochordal cells
C.P.	Cartilage Plate	*Nch.V.*	Notochordal vestige
F.C.	Fibrocartilage	*Sp.E.C.*	Specialized embryonic cartilage
F.T.	Fibrous tissue	*V.B.*	Vertebral body
Mes.C.	Mesodermal cells	*V.C.*	Vascular canal

EXPLANATION OF PLATES

PLATE 1

Fig. 1. 3 mm. (C.R.). Human embryo. Coronal section, showing myotome, sclerotome, intrasclerotomic fissure. Haematoxylin and Biebrich's Scarlet. ×1950.

Fig. 2. 7·5 mm. (C.R.). Human embryo. Horizontal section, region of basis cranii, showing notochord, loosely and densely arranged mesoderm of half-sclerotomes, intersegmental vessels. Haematoxylin and eosin. ×68.

Fig. 3. 10 mm. (C.R.). Human embryo. Coronal section, lumbar region, showing notochord, loosely and densely arranged mesoderm of half-sclerotomes, intrasclerotomic fissure. Haematoxylin and eosin. ×415.

PLATE 2

Fig. 4. 15 mm. (C.R.). Human embryo. Median sagittal section, lumbar region, showing notochord, *anlagen* of vertebral bodies and intervertebral discs. Haematoxylin and eosin. ×75.

Fig. 5. 15 mm. (C.R.). Human embryo. Median sagittal section, lumbar region, showing notochord, 'specialized embryonic cartilage', mesoderm cells. Haematoxylin and eosin. ×300.

Fig. 6. 21 mm. (C.R.). Human embryo. Median sagittal section, lumbar region, showing intervertebral notochordal expansions and intravertebral constrictions, *anlage* of intervertebral disc, showing 'specialized embryonic cartilage' and peripheral mesodermal cells of developing annulus. Haematoxylin and eosin. ×60.

Fig. 7. 21 mm. (C.R.). Human embryo. Paramedian sagittal section, lumbar region, showing *anlagen* of vertebral bodies, and intervertebral disc (*b*) and *anlagen* of the cartilage plates (*a*, *c*). Haematoxylin and eosin. ×60.

Fig. 8. 26 mm. (C.R.). Human embryo. Coronal section, lumbar region, showing notochordal cells, 'specialized embryonic cartilage' and peripheral annulus mesodermal cells. Haematoxylin and eosin. ×500.

Fig. 9. 29 mm. (C.R.). Human embryo. Median sagittal section, lumbar region, showing notochordal reticulum, intercellular spaces in notochord, 'specialized embryonic cartilage' and fibres now present in the annulus. Haematoxylin and eosin. ×75.

PLATE 3

Fig. 10. 47 mm. (C.R.). Human embryo. Horizontal section, lumbar region, showing notochordal expansion, intercellular spaces in notochord, perichordal cartilage, fibres of annulus and loose texture of cartilage dorsal to notochord. Masson's Trichrome. ×125.

Fig. 11. 47 mm. (C.R.). Human embryo. Horizontal section, lumbar region, showing notochord (*a*) and perichordal cartilage (*b*). Masson's Trichrome. ×300.

Fig. 12. 60 mm. (C.R.). Human embryo. Median sagittal section, lumbar region, showing at the lower part of the figure, part of the notochordal cavity, above this the perichordal cartilage, succeeded by fibrocartilage and fibres of the annulus. Cartilage plates are shown receiving terminations of annulus fibres. Haematoxylin and Biebrich's Scarlet. ×100.

Fig. 13. 99 mm. (C.R.). Human embryo. Horizontal section, lumbar region, showing notochordal expansion, perichordal cartilage, fibrocartilage and fibres of the annulus. Masson's Trichrome. ×20.

Fig. 14. 150 mm. (C.R.). Human embryo. Paramedian sagittal section of annulus fibrosus from lumbar region, showing fibre architecture. Masson's Trichrome. ×100.

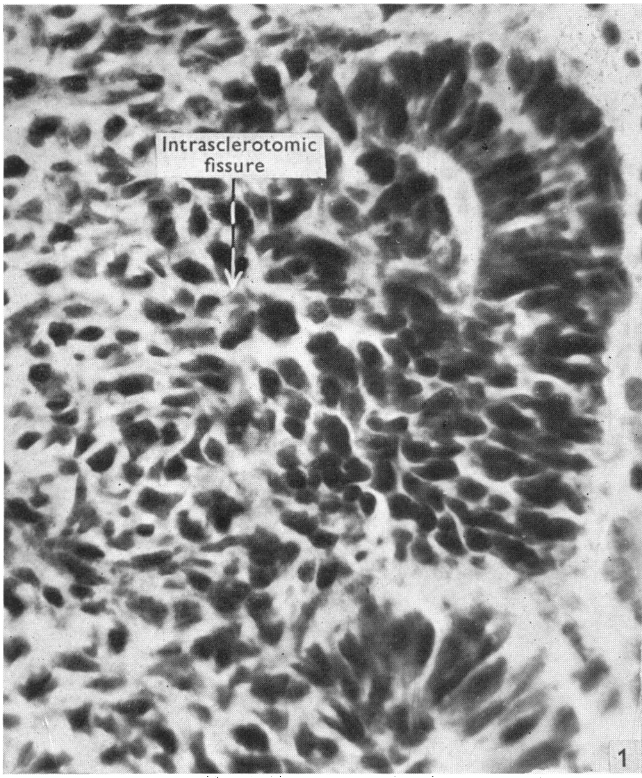
Fig. 15. 210 mm. (C.R.). Human embryo. Median sagittal section, lumbar region, showing notochordal cavity, containing few notochordal cells and abundant mucoid substance. Haematoxylin and eosin. ×50.

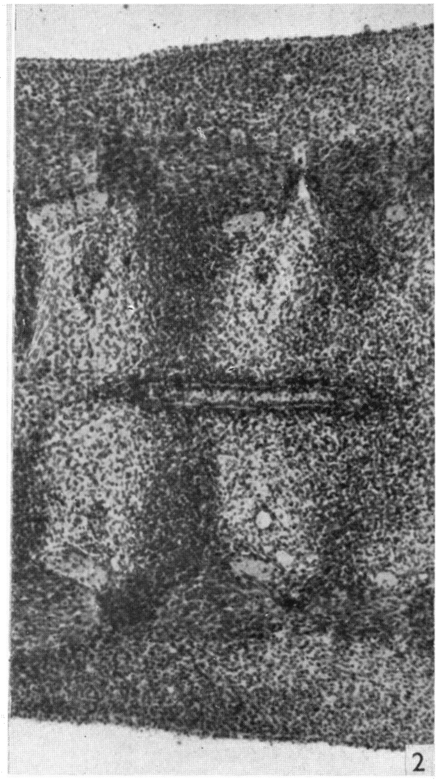
PLATE 4

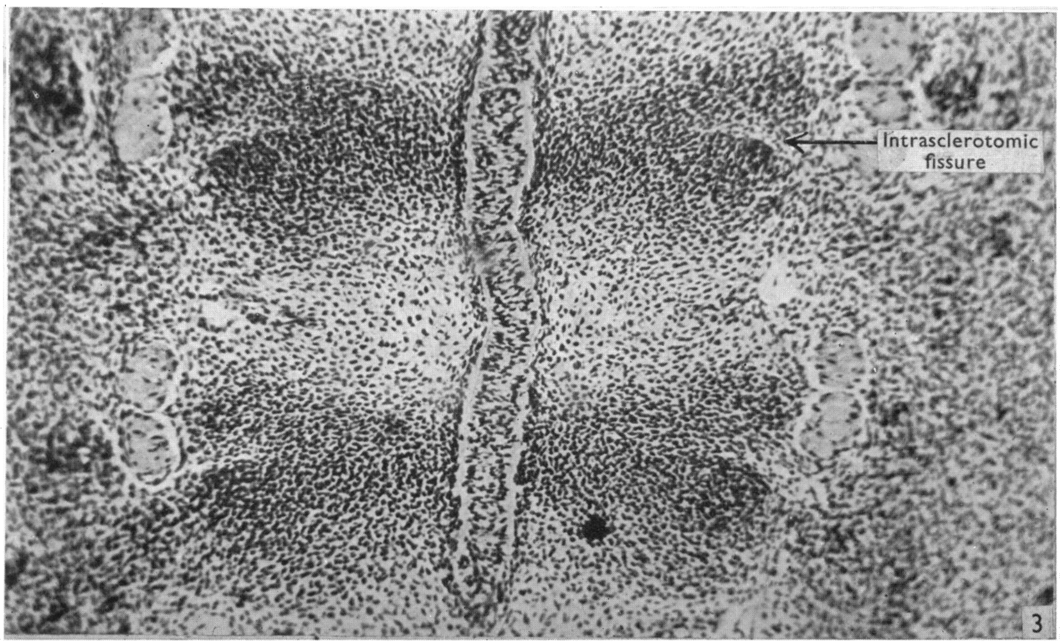
Fig. 16. Full-term foetus. Median sagittal section, lumbar region, showing intervertebral area, notochordal cavity containing few notochordal cells and abundant mucoid material. Vertebral bodies and vascular canals are shown. Haematoxylin and eosin. ×16.

Fig. 17. Full-term intervertebral disc. Horizontal section, lumbar region, showing architecture of annulus fibrosus. The dense fibre concentration to the right of the figure is the hypochordal bow component. Haematoxylin and eosin. ×200.

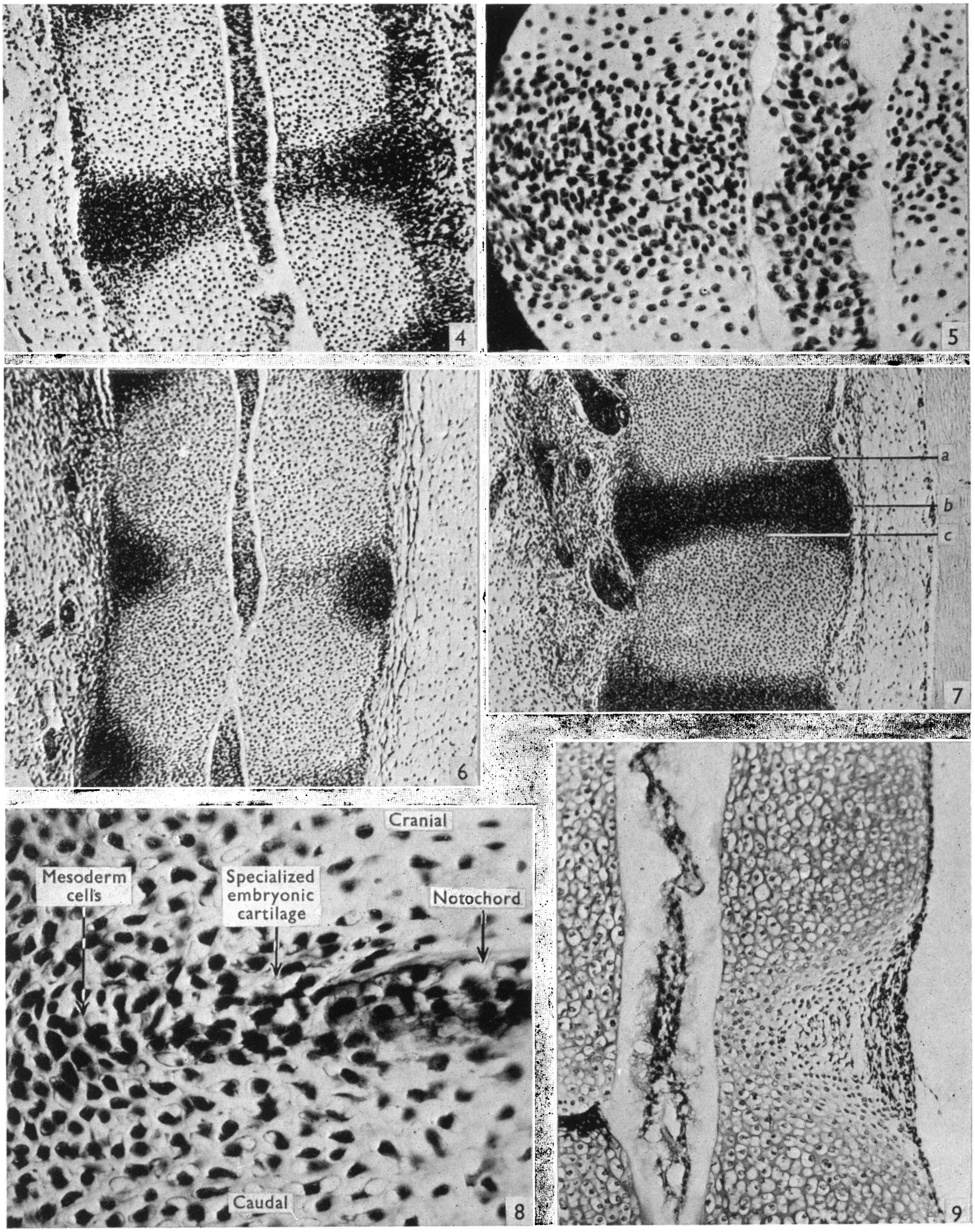
Fig. 18. 150 mm. (C.R.). Human embryo. Parasagittal section, lumbar region, showing vessels in the dorso-lateral aspect of the periphery of the annulus fibrosus. Masson's Trichrome. ×100.



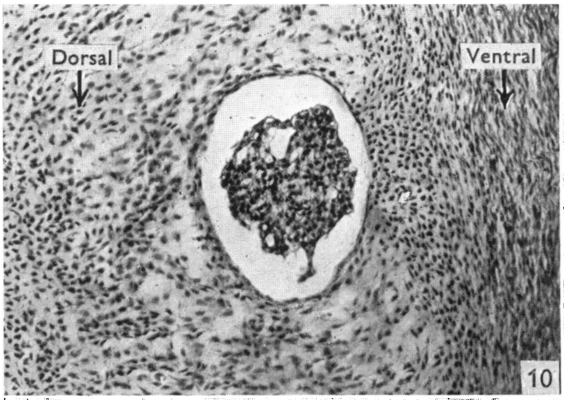


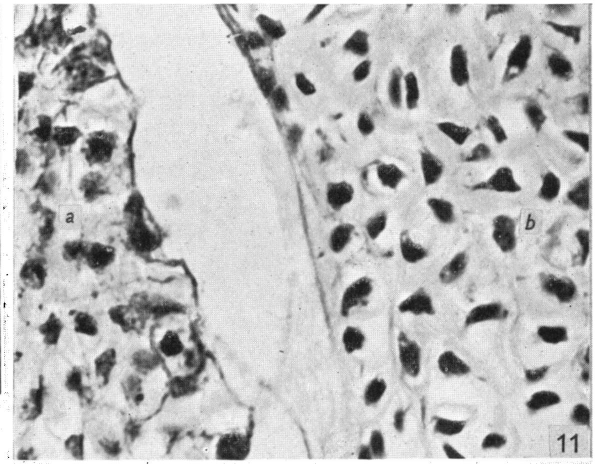


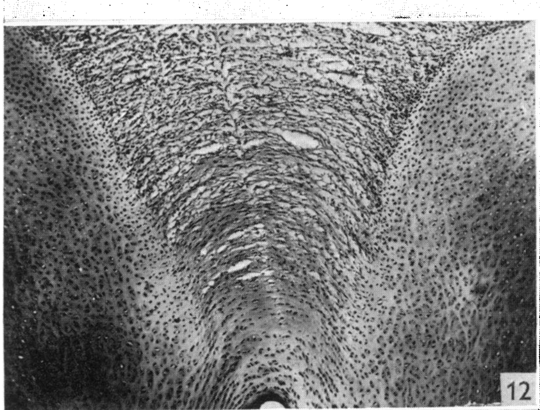
PEACOCK—PRE-NATAL DEVELOPMENT OF THE INTERVERTEBRAL DISC IN MAN

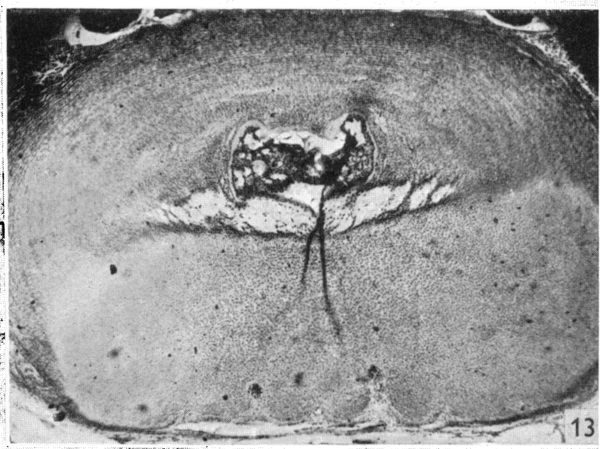


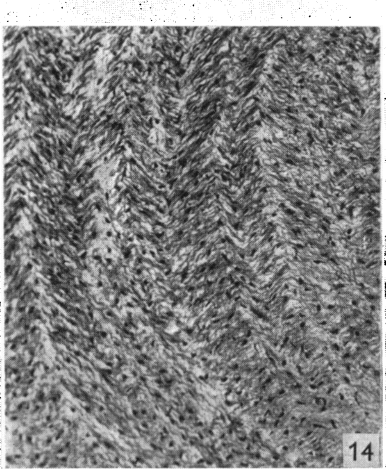
PEACOCK—Pre-natal development of the intervertebral disc in man

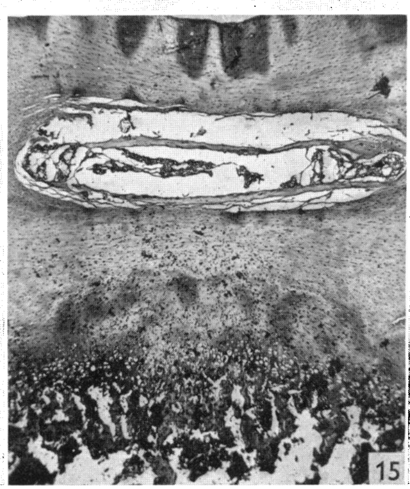

Dorsal
Ventral
10

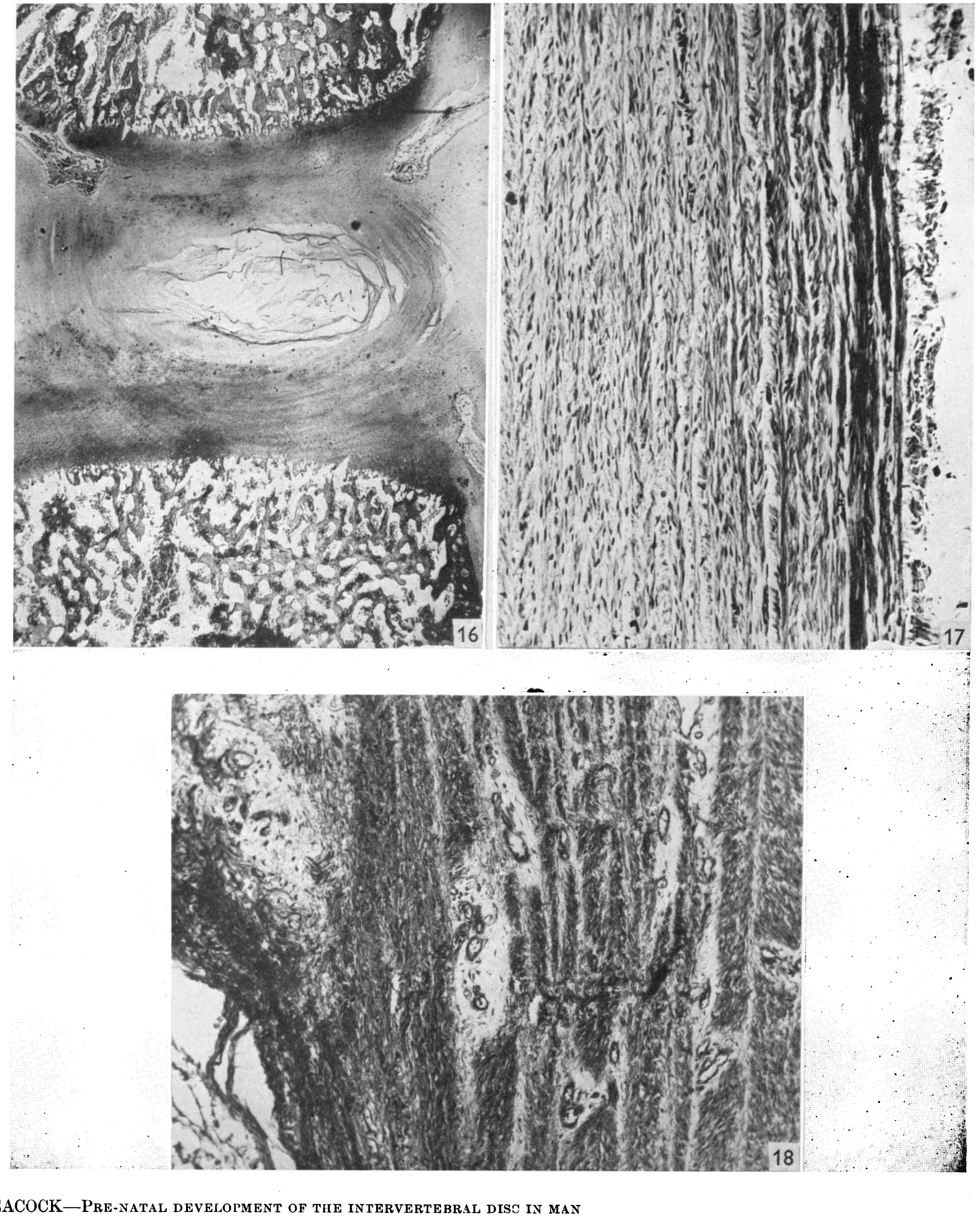

a
b
11


12


13


14


15



PEACOCK—PRE-NATAL DEVELOPMENT OF THE INTERVERTEBRAL DISC IN MAN