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The cellular architecture of the human atrioventricular node, with a note on its morphology in the presence of a left superior vena cava

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INTRODUCTION

The atrioventricular node as delineated by morphologists (Tawara, 1906; Copenhaver & Truex 1952, and others) is smaller than the area detected as nodal by electrophysiological techniques (Hoffman & Cranefield, 1960). The electrophysiologists have worked mainly with the rabbit, and recently ultrastructural and light microscopic evidence has been presented to support their findings on the extent of the node in this animal (Defelice & Challice, 1969; Anderson, 1971). The present paper reports the results of an investigation on the human atrioventricular nodal region. The opportunity of studying this area was afforded us during earlier work on the course of the atrioventricular bundle in hearts containing interventricular septal defects (Latham & Anderson, 1971). We have examined the history of the atrioventricular nodal area and compared our findings with the previous reports of both electrophysiologists and morphologists working with rabbit tissues. In addition the morphology of the node in a number of hearts having a persistent left superior vena cava has been compared with that in hearts possessing a more normal venous drainage.

MATERIALS AND METHODS

The hearts studied were taken from the collection of the Royal Liverpool Children's Hospital. Twelve specimens were examined (Table 1): ten presented interventricular septal defects, one exhibited an interatrial septal defect, and the remaining heart had an intact septum. Four of the hearts possessed a left superior vena cava.

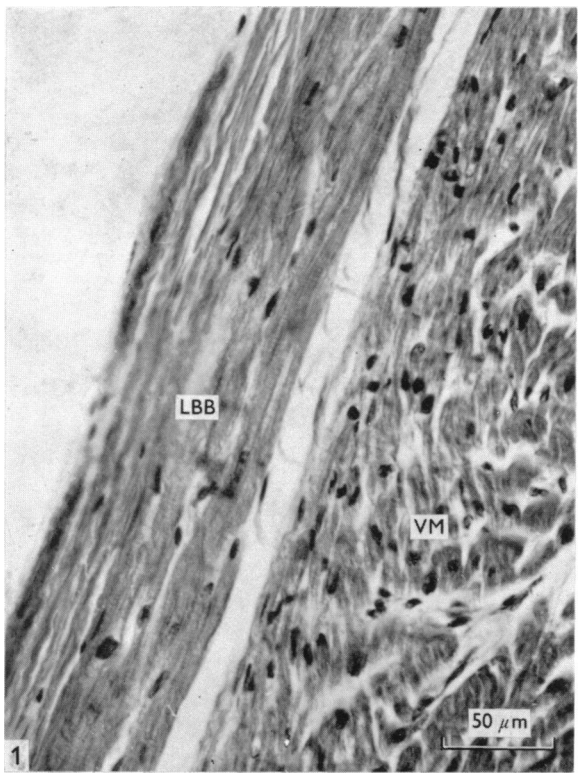
From each heart studied a block of tissue was removed which contained the coronary sinus, the posterior portions of the outflow tracts, and segments of the interatrial and interventricular septa. These blocks were photographed to facilitate subsequent microscopic examination, and then dehydrated and embedded in paraffin wax. The blocks were sectioned at 10 μm in a plane at right angles to the atrioventricular septum. One section in each fifty cut was mounted and stained using Masson's trichrome technique. The intervening sections were stored, and when the nodal region was subsequently identified additional sections were mounted and stained as required.

In addition some sections were mounted and processed to demonstrate the presence of glycogen, using the periodic acid–Schiff technique. Following oxidation, the

sections were immersed in 5 % Dimedone to block all carbohydrates but glycogen (Bulmer, 1959) and the sections were developed using the cold Schiff reagent of Lillie (1954).

RESULTS

Although by no means easy, it was possible to recognize the specialized cells by their histological appearances. They were well demarcated in the atrioventricular bundle and its branches, and in this situation were slightly larger than ventricular



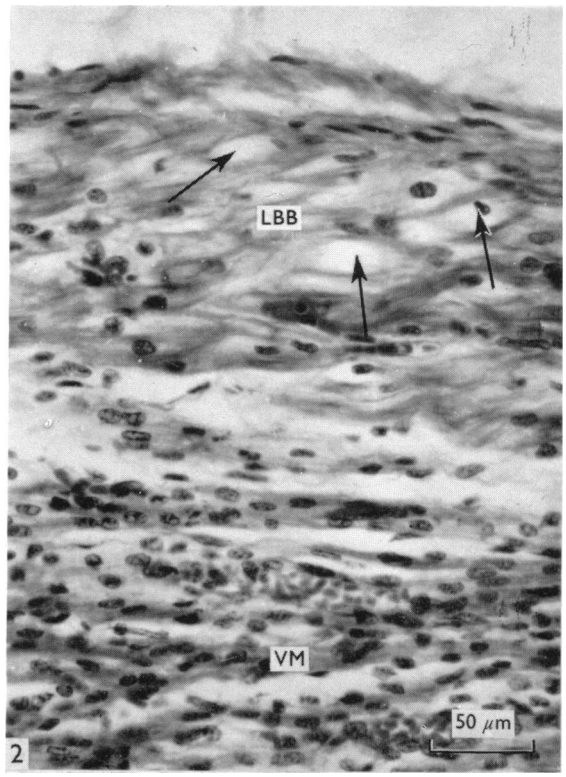


Fig. 1. Typical constituent cells of the left bundle branch (LBB). Note that the cells are marginally larger than the cells of the ventricular myocardium (VM).

Fig. 2. Cells of left bundle branch (LBB) from a poorly fixed specimen. Note fixation artefacts (arrowed) giving the cells 'Purkinje' characteristics.

myocardial cells (Fig. 1). However, they bore little resemblance to the 'Purkinje' cells described in artiodactyla by many other workers. Only in poorly fixed tissues were cells approximating to this type identified (Fig. 2).

The area occupied by nodal specialized cells extended between the coronary sinus and the point at which the atrioventricular bundle pierced the right fibrous trigone (Fig. 3*a*). The specialized cells formed a half-oval, the base of which was formed by the right fibrous trigone. In most of the hearts studied the trigone was found to be horizontal, or nearly so, when viewed in the coronal plane. Sheets of atrial myo-

cardial fibres overlaid the half-oval of specialized cells on the right and left sides, separating it from the endocardium of the atria (Fig. 3*b*). The right-hand sheet was much thinner than the left, but neither sheet made contact with ventricular myocardial cells. The cells of the right sheet were traceable towards the ventricle but were always inserted into the tricuspid valve base.

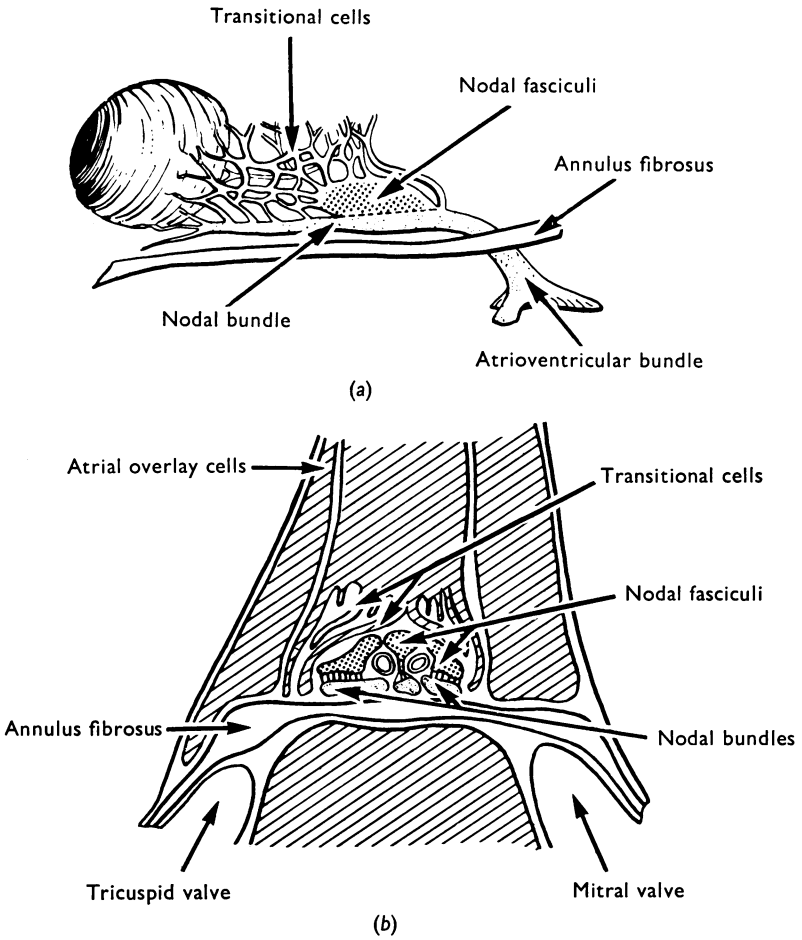
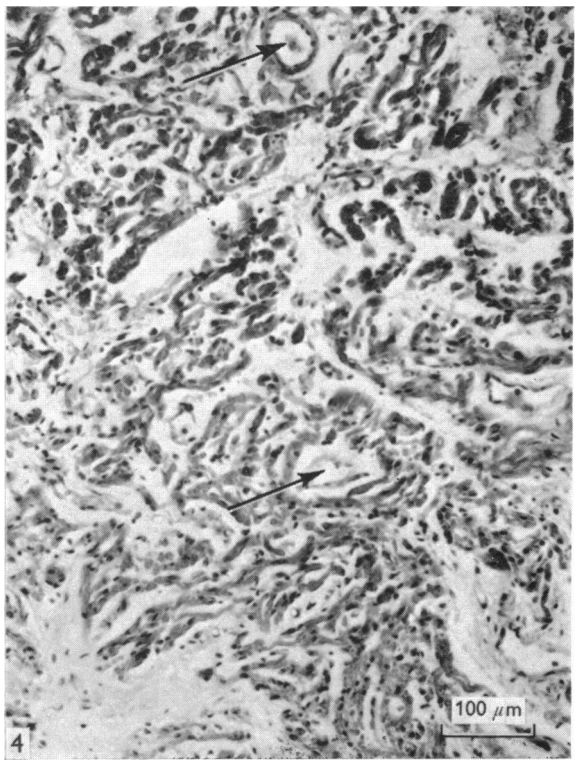


Fig. 3 (*a*). Diagram showing area occupied by the node and its constituent cells. (*b*) Diagram showing section through node in coronal plane. The hatching of cell types is as in (*a*). Note the layers of atrial overlay muscle distinct from the circumferential transitional cells.

Although half-oval in the coronal plane, the node was elongated in the sagittal plane, extending posteriorly towards and beneath the ostium of the coronary sinus (Fig. 3*a*). The specialized cells forming the nodal tissue were not of uniform morphology. At the periphery of the node lay cells which were transitional between atrial myocardium and the cells of the inner node. They originated predominantly from the middle cells of the interatrial septum in front of and beneath the coronary sinus, and made few contacts with the overlying subendocardial cells. The posterior region

of the node was composed mainly of these transitional cells, which were orientated in an antero-posterior direction. They were smaller than atrial cells, and formed complex interconnecting networks with each other as they merged together at their



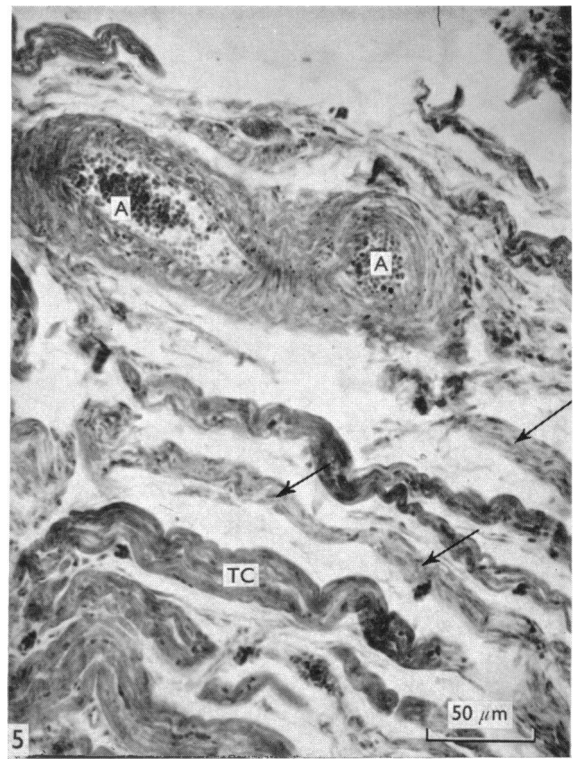


Fig. 4. Transitional cells in region of septum anterior to coronary sinus. Notice cells interweaving in complex patterns and terminal branches of nodal arteries (arrowed).

Fig. 5. Transitional cells (TC) from the posterior extent of the node with intervening nerve bundles (arrowed). Note also the large artery (A).

anterior ends (Fig. 4). The individual transitional cells were separated by connective tissue containing many nerve bundles (Fig. 5), but no ganglion cells were identified.

At their anterior ends the transitional cells merged to form large fasciculi which aggregated to form a more compact unit of specialized cells (Figs. 6, 12) which were smaller and shorter and possessed few cross-striations. The fasciculi were densely packed, with little intervening connective tissue (Fig. 7), but they did not occupy the whole of this compact area of the node. Running against the fibrous trigone were bundles of specialized cells which were larger than those of the fasciculi, individually arranged, more vacuolated, and more obviously cross-striated (Fig. 8). The cells were identical with those of the atrioventricular bundle (Fig. 9), and when traced anteriorly were continuous with them. The nodal bundle cells were not confined to the compact node, where they merged with the nodal fasciculi (Fig. 10), but extended posteriorly beneath the coronary sinus. This backward extension was not clearly identified in all

hearts, but when seen its cells were morphologically identical with those of the atrioventricular bundle (Fig. 11). The cells of the backward extension made contact with transitional cells in this region, and through them merged with atrial myocardium, disappearing beneath the coronary sinus.

In the region of the compact node transitional cells were identified (Figs. 12, 13); these were similar in morphology to those identified in the posterior node, and made contact mostly with underlying nodal fasciculi (Fig. 14). In some cases they formed

Table 1. *Defects present in specimens studied*

Age of infant	Defects present	Left sup. vena cava	Position of A-V node
19 weeks	Intraventricular septal defect	Yes	Vertical
5 days	Interatrial septal defect. Cleft M.V.	No	Horizontal
22 days	Interventricular septal defect	No	Horizontal
27 days	Interventricular septal defect	Yes	Vertical
1½ years	Interventricular septal defect	No	Horizontal
12 weeks	Interventricular septal defect	No	Horizontal
5½ years	I-V S.D. Double outflow R.V.	Large coronary sinus	Oblique
3 weeks	None	Yes	Vertical
4 months	Interventricular septal defect	No	Horizontal
10 weeks	Interventricular septal defect	No	Horizontal
2 years, 8 months	Interatrial and interventricular S.D.S	Yes	Vertical
2 years, 1 month	Interventricular septal defect	Large coronary sinus	Oblique

junctions with the nodal cells resembling those of the atrioventricular bundle, and also occasionally made contact with the overlying atrial cells. However, for the most part they were distinctly separated from the latter (Fig. 15). It was difficult to be sure of the direction in which these cells were running, but they appeared in the main to pass circumferentially around the half-oval of noded cells, giving the node its compact form.

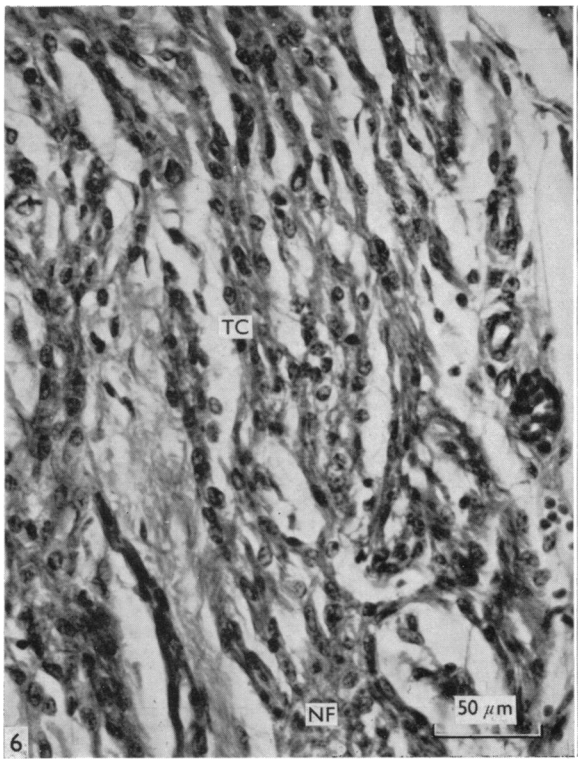
One or two arteries were usually identified within the confines of the compact node (Fig. 12). They originated within the atrial tissue, and were not present in the atrioventricular bundle. They could be traced posteriorly beyond the compact node into the transitional cells around the coronary sinus, branching amongst these cells. In serial sections they were not traceable posterior to the coronary sinus.

In all the hearts studied the transitional cells at the margins of the node merged with atrial myocardium after passing short distances. Tracts of specialized cells

coursing towards the sinuatrial node could not be identified in any specimen. All transitional cells were of small calibre, and no 'Purkinje' cells were identified in the A-V node.

The possession by a heart of a left superior vena cava (LSVC) did not affect the arrangement or presence of cell types within the atrioventricular node. However, hearts containing a LSVC did differ in the arrangement of the right fibrous trigone.

In hearts possessing a small coronary sinus the trigone lay horizontally, the tricuspid and mitral valves were at the same horizontal level in the coronal plane, and the half-oval of nodal specialized cells was similarly horizontal (Fig. 16). In hearts



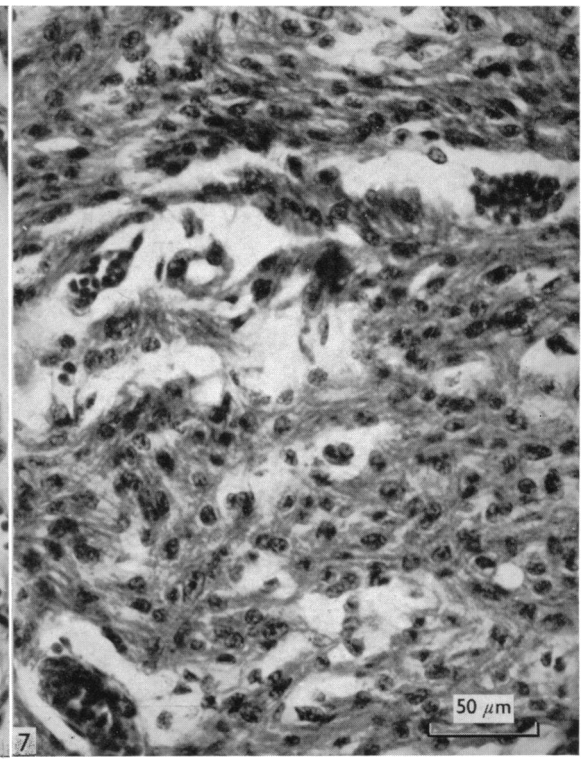


Fig. 6. Transitional cells (TC) forming a complex interweaving network, and merging to form nodal fasciculi (NF).

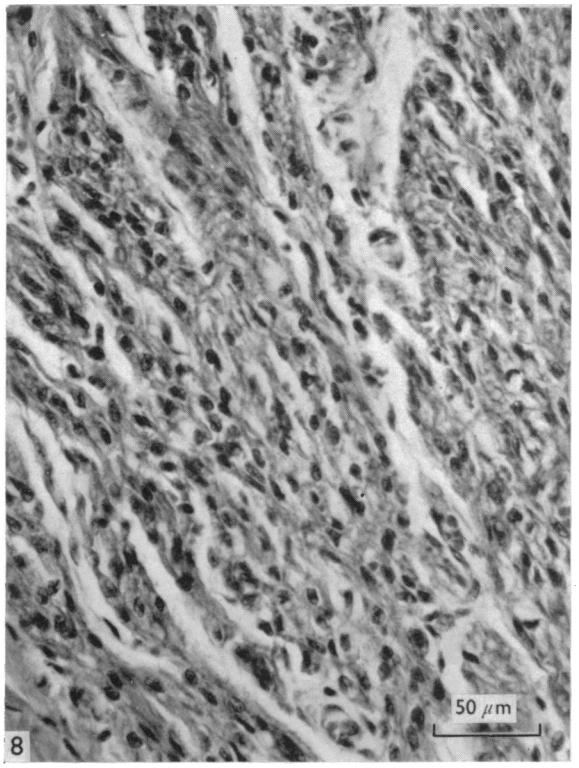
Fig. 7. Nodal fasciculi of compact node. Note how the fasciculi (arrowed) are made up of multiple aggregated small cells.

Fig. 8. Typical cells of atrioventricular bundle.

Fig. 9. Cells of the atrioventricular nodal bundles lying inferiorly to nodal fasciculi of the compact node. Note similarity to Fig. 7.

Fig. 10. Junctional region between cells of nodal fasciculi (NF) and nodal bundles (B) within compact node.

Fig. 11. Section taken from level of coronary sinus showing backward extension of nodal bundle (B). Note similarity to cells of A-V bundle (Fig. 8).


50 μm
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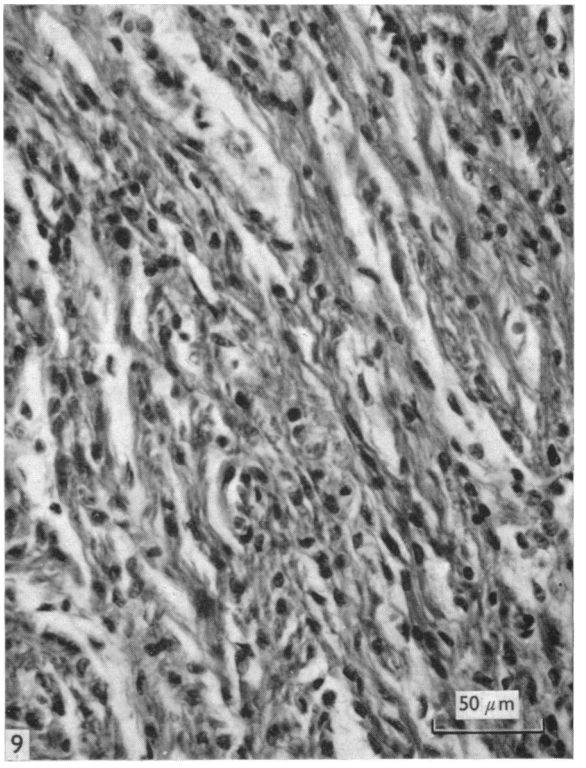
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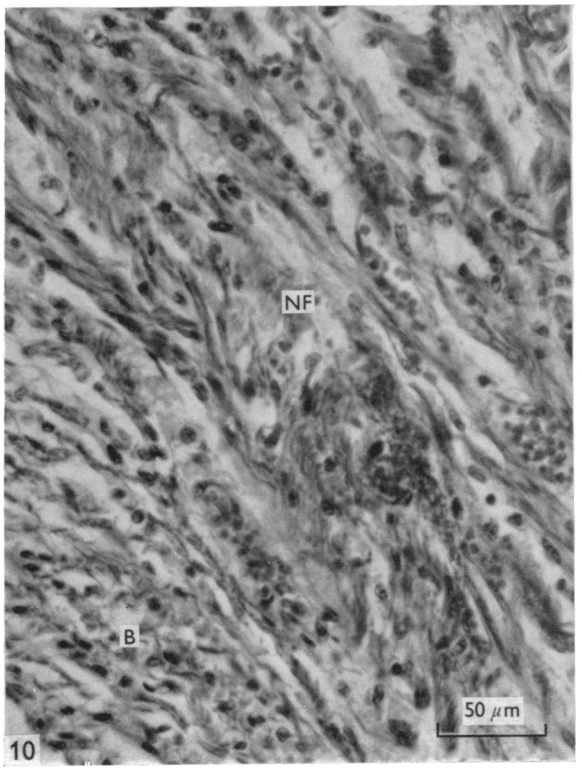
NF
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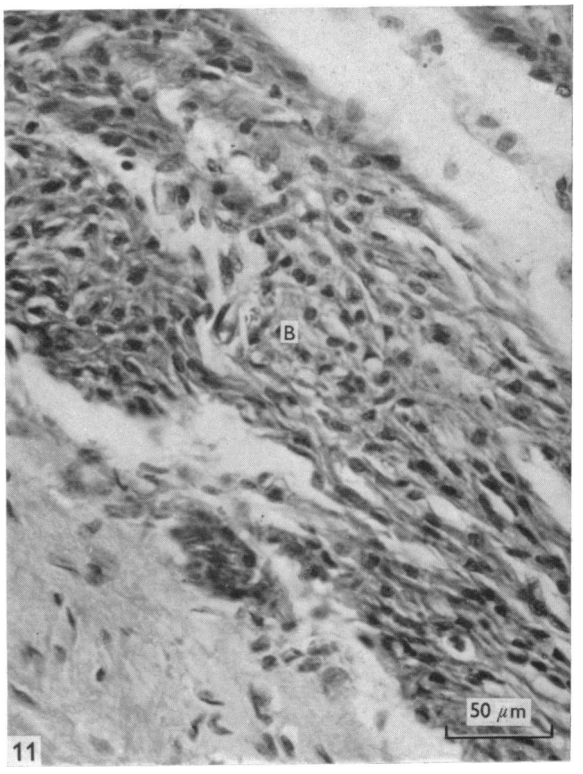
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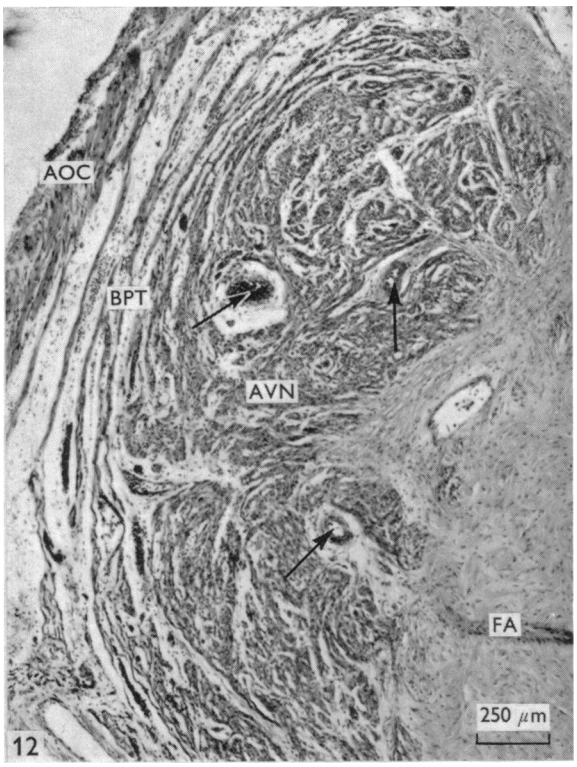
AOC
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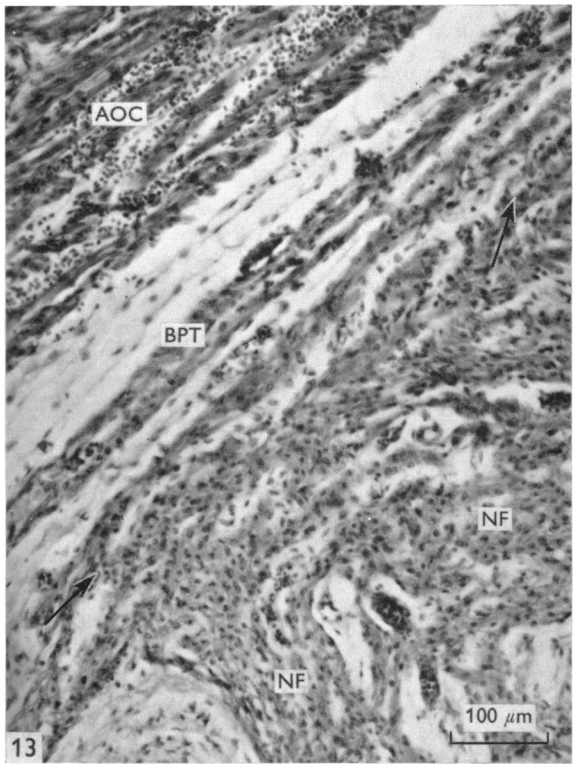
12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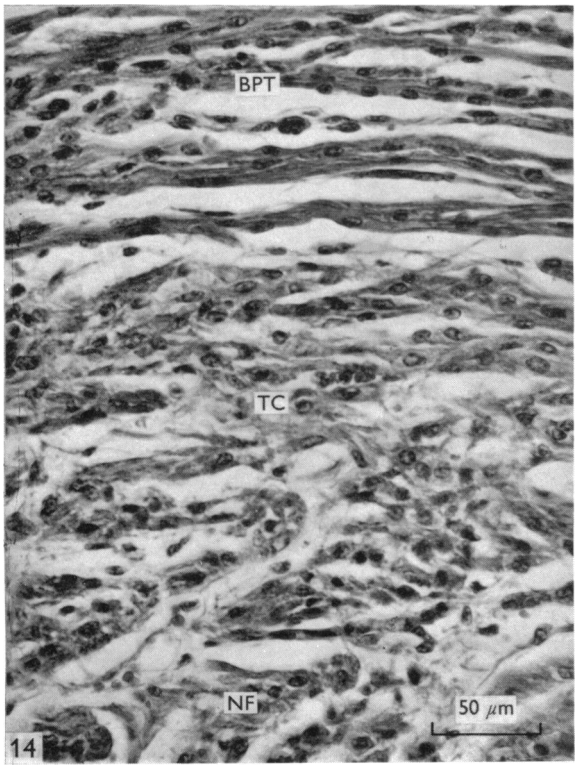
BPT
NF
NF
100 μm
13


BPT
TC
NF
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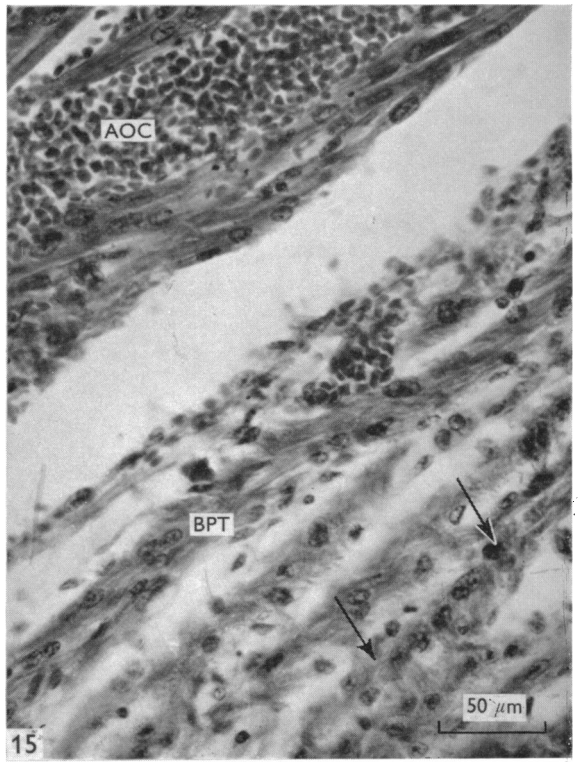
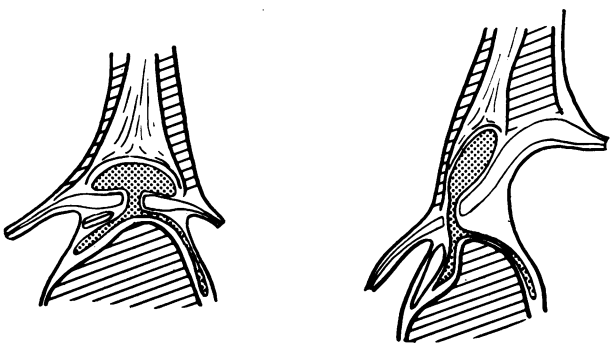
14


AOC
BPT
50 μm
15

with a LSVC the fibrous trigone lay obliquely, so that the base of the tricuspid valve was appreciably lower than that of the mitral valve. In these hearts the half-oval of specialized cells was apposed to the trigone in a more vertical plane (Fig. 16). The atrioventricular bundle pierced the annulus very superficially in such hearts, whereas in the horizontally arranged hearts it pierced the trigone more deeply in the interatrial septum.

Several hearts had a large coronary sinus whilst not possessing a left superior vena cava. The fibrous trigone was less oblique than in hearts with a LSVC, and the inclination of the atrioventricular node was intermediate between the types described. The atrioventricular bundle in these hearts was found to pierce the trigone in a relatively superficial position.



(a) Horizontal node (*b*) Vertical node

Fig. 16. Drawing showing the different positions of the fibrous annulus and nodal half-oval in hearts (*a*) with normal venous drainage, (*b*) with a left superior vena cava.

DISCUSSION

The general morphology of the atrioventricular node was identical in all the hearts studied in the present investigation despite the presence of various congenital abnormalities. It also corresponded closely with the arrangement reported by previous workers (Tawara, 1906; Copenhaver & Truex, 1952; James, 1961; Titus, Daugherty & Edwards, 1963; Truex & Smythe, 1967). It is extremely unlikely, therefore, that the present findings are in any way a consequence of the congenital malformations present in the hearts. In all the hearts examined the nodal area was well defined histologically, and we are unable to support the contention of Todd (1932), Glomsett &

Fig. 12. Compact atrioventricular node (AVN). Note the half-oval of specialized cells with the base on the fibrous trigone (FA). The circumferential transitional cells (BPT) at the periphery of the node are distinct from the overlying atrial cells (AOC). Arrows indicate nodal arteries.

Fig. 13. Higher power of by-pass tracts (BPT) and overlay cells (AOC). Note communications (arrowed) with nodal fasciculi (NF).

Fig. 14. Cells of by-pass tract (BPT) distinct from transitional cells (TC) and nodal fasciculi (NF).

Fig. 15. Section showing the morphological differences between the overlay cells (AOC) and the by-pass tracts (BPT). Note communications with underlying node (arrowed).

Glomsett (1940) and Glomsett & Birge (1945) that the node is merely a segment of myocardium.

The present report, however, diverges from earlier accounts in several important aspects. The atrioventricular node previously described in the literature appears to correspond only to the compact node delineated in this investigation. Hoffman & Cranefield (1960) pointed out that the anatomically defined atrioventricular node (our compact node) was much smaller than the area producing action potential recordings typical of specialized cells. If the area which we have described as occupied by transitional cells is included as part of the anatomical atrioventricular node, then the limit corresponds closely to that demonstrated by electrophysiological techniques. Acceptance of these transitional cells as part of the atrioventricular node would lead to a correspondence of terminology, at present lacking, between morphologists and electrophysiologists. Whilst it could be argued that the so-called 'transitional' cells represent the point of entry of internodal tracts (James, 1961) it must be stressed that we found no morphological evidence of such tracts. In all cases the transitional cells were smaller than atrial myocardial cells, and merged with atrial myocardium above the node. No 'Purkinje' cells, as described by James, were identified.

Previous reports (Kistin, 1949; Copenhaver & Truex, 1952; James, 1961; Titus *et al.* 1963) indicated that the nodal cells were of uniform morphology, merging at their anterior limits with the cells of the atrioventricular bundle. James (1961) found that this junction was due to a parallel orientation of the nodal fibres, a view confirmed by Titus *et al.* (1963), who were unable to define a sharp boundary. In the present investigation the cells of the atrioventricular bundle were found to pass posteriorly in bundles through the inferior part of the compact node, and to extend backwards towards the coronary sinus, where they merge, through short transitional cells, with atrial myocardium.

These cells within the node are identical with the cells of the atrioventricular bundle, but form an integral part of the node throughout its length. They bear no resemblance to the inferior by-pass tract described by James (1961), but are similar in morphology to the nodal cells illustrated by him. However, neither James (1961) nor Kistin (1949) described the nodal fasciculi, above this nodal bundle, which we consider to be made up of bundles of multiple small cells, rather than interweaving single cells, and which merge with the nodal bundle cells at their apposing surfaces. Titus *et al.* (1963) commented that the nodal cells were arranged in bundles with many nuclei, whilst Lev, Widran & Erickson (1951) thought that the multinucleate appearance was due to the presence of an endothelium-lined sheath around the conduction system. In our sections interweaving single cells were seen only at the transitional-nodal cell junctions, then merging to form the aggregated small cells of the nodal fasciculi. Thus the present investigation indicates that the human atrioventricular node is made up of three morphologically identifiable cell layers. These communicate at their adjacent surfaces, and the lower layer is continuous with the atrioventricular bundle.

These findings are in close agreement with the electrophysiological plan of the node constructed by Paes de Carvalho (1961). This worker used rabbit tissues, and morphological evidence to support his findings has been produced by Defelice & Challice (1969), and by Anderson (1971*a*, *b*). Our results closely parallel the latter's findings in

the rabbit, but are confined to histological studies of wax-embedded specimens, whereas the findings in the rabbit were confirmed by histochemical studies on fresh tissues. Our description of the cellular arrangement of the node also parallels closely the cellular model constructed by Hoffman & Cranefield (1961) to explain the mechanism of nodal delay. This delay apparently occurs at the atrionodal (transitional cell–nodal cell) junction, and can result from impulses reaching the same point leading to cancellation (Moe, Preston & Burlington, 1956). The multiple cellular connexions which we have described at the transitional nodal cell junction would provide a morphological mechanism in the correct position to produce such nodal delay.

James (1961) postulated that dual conduction pathways capable of producing cancellation also existed outside the node in the form of by-pass tracts, which, he believed, could produce nodal delay by the dual-conduction theory. He also suggested that they might be responsible for producing ventricular pre-excitation (Wolff–Parkinson–White syndrome, 1930) in the absence of accessory atrioventricular bundles (Kent, 1914; Lev & Lerner, 1955). The circumferential transitional cells described by us occupy the same position as James's by-pass tracts, but consist of small cells, whereas the distinguishing feature of these tracts was said by James to be the presence of 'Purkinje' cells. The presence of such cells in hearts other than artiodactyl hearts has long been a subject for argument. In the present investigation no such cells were distinguished in the tissues studied, supporting previous findings in man by Davies (1942) and Copenhaver & Truex (1952). The latter workers considered that 'Purkinje' cells in animals other than ungulates might well be artefacts, since segments of atrial cells on occasion were found to possess 'Purkinje' features. This belief was reiterated by Truex (1961) and is endorsed by the present report. The question of 'Purkinje' cells apart, the tracts we have described closely correspond to the by-pass tracts of James. They are quite separate from the atrial overlay fibres which terminate in the tricuspid valve base. Whether they contribute to delay or ventricular pre-excitation is a matter of conjecture, and, as pointed out by James, any effect produced is likely to be intermittent. Truex & Smythe (1967) suggested that even if present the tracts would be unlikely to contribute to pre-excitation since they are longer than was suggested by James. It would appear, however, that they by-pass the multi-junctional region of the node responsible for nodal delay, and would thus be capable of producing pre-excitation irrespective of length. We have described a further tract of cells capable of by-passing the 'delay region' of the node. This is the backward extension of the nodal bundle, merging posteriorly with transitional and atrial cells and directly continuous anteriorly with the atrioventricular bundle. This tract could produce either ventricular pre-excitation or delay by the dual-conduction theory. The bundle may well correspond to the atrioventricular ring bundle described by Paes de Carvalho (1961) or the 'coronary sinus node' of Scherf & Cohen (1964).

The morphology of the atrioventricular node in the presence of a left superior vena cava has been previously commented on by Lev (1959), who found the node deviated in a horizontal plane. This is the opposite of our findings, in which the node was upright in four hearts possessing an LSVC. In hearts with a small coronary sinus there is more muscular tissue in the nodal area, and this would allow the node to be horizontal, whereas the larger sinus may have the effect of deviating the node to the

upright position. However, it may well be that a horizontal node is found only in early life, since James (1961), in the majority of 78 adult hearts, found the right fibrous trigone and the node to be oblique, and in several of his illustrations the node is almost vertical.

Another significant point with regard to the presence of a LSVC is that it does not alter the cellular morphology of the node. This is of interest in view of the suggestion by James (1967) that the structure of the node in the rabbit is primitive due to failure of absorption of the LSVC, which is normally present in this animal. Anderson (1970) did not consider the node primitive, and indeed its morphology is very similar to that of the human node, as described above. In view of the unchanged morphology in a human heart with a LSVC the explanation offered by James with regard to the rabbit seems unlikely.

SUMMARY

1. The morphology of the atrioventricular node is described in twelve human hearts, four of which possessed a left superior vena cava.

2. The node is composed of cells of three types: transitional cells, nodal cells proper, and cells identical with those of the atrioventricular bundle.

3. The nodal cells proper are confined to the compact node, which corresponds to the accepted anatomical definition. If the transitional cells are included, the node corresponds to the area delineated by electrophysiological techniques.

4. The cells identical with those of the atrioventricular bundle form a tract extending posteriorly to the coronary sinus, where they merge with atrial myocardial cells.

5. No 'Purkinje' cells were identified in the atrioventricular node, but by-pass tracts of transitional cells were identified passing circumferentially around the compact node.

6. The presence of a left superior vena cava deviated the atrioventricular node from a horizontal to a vertical position without altering the cellular morphology of the node.

7. The findings are discussed with particular reference to previous electrophysiological findings and the mechanisms of nodal delay and ventricular pre-excitation.

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