PAPERS AND ORIGINALS

Sudden Death in Infancy: A Study of Cardiac Specialized Tissue

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Summary

The hearts from 15 cot death patients have been compared with those of 15 controls. In one of the cot death patients an accessory atrioventricular connexion known to be capable of producing ventricular pre-excitation and sudden death was identified. In all hearts examined additional segments of specialized tissue were found in relation to the atrioventricular orifices which may have been significant in producing pre-excitation. Haemorrhagic lesions were present in the atrial myocardium and conducting tissues of hearts from both groups, but no evidence was found of cellular degeneration in the atrioventricular bundle. There is a need for further studies of conducting tissues in sudden death syndromes.

Introduction

A wide variety of aetiological factors have been implicated in sudden death in infancy for which there is no obvious cause (Bergman *et al.*, 1970; Camps and Carpenter, 1972). Pathological changes in the cardiac specialized tissue may account for some of these deaths. James (1968) described evidence of cell death and remoulding of the atrioventricular bundle and also haemorrhages in the autonomic cardiac ganglia. Ferris (1973) found haemorrhagic lesions in 13 out of 50 hearts from cot death patients, and suggested that they were consistent with hypoxia which in turn may have contributed to the sudden death. Another possible cardiac cause of sudden death is the ventricular pre-excitation syndrome, which is believed to function through accessory atrioventricular connexions (Ferrer, 1970), but to the best of our knowledge such connexions have not been sought in hearts from cot death patients. We have therefore examined such hearts for abnormalities of the atrioventricular bundle, haemorrhagic lesions, and accessory atrioventricular connexions. We have also examined as controls a number of hearts from infants dying of known, non-cardiac disease.

Materials and Methods

The hearts of 15 infants were obtained from the mortuary of Alder Hey Children's Hospital, Liverpool. Cot death was considered to have occurred when a previously well infant was discovered dead and no cause of death was established at necropsy. The ages of the infants ranged from 11 days to 2 years. We also studied hearts from 15 infants from the same age group who died at Alder Hey from non-cardiac illness during the period of study (table), together with the heart from an infant who died from cardiac arrest during thoracic surgery. The hearts from both groups were studied in identical fashion. Care was taken not to damage either the tricuspid orifice or the internodal atrial myocardium. Thus the right ventricle was examined through an oblique incision over its outflow tract, while the right atrium was examined after amputation of the right auricle. The left side of the heart was examined by bisecting the mitral valve ring in the plane of the interatrial septum, and removing the parietal wall of the left atrium and ventricle.

When cardiac anomalies had been excluded a block of tissue was prepared for histological examination. This comprised the entire atrial tissues and the proximal 1 cm of the remaining ventricular myocardium. The blocks were embedded in paraffin wax and serially sectioned at 10 micron thickness in one of three planes at mutual right angles. Three hearts from the control group were cut in transverse and three in sagittal planes relative to the posterior interventricular septum, and nine hearts were sectioned in the frontal plane. Since the frontal plane gave best visualization of specialized tissue all hearts in the cot death group were cut in this plane. At first one section in 50 was mounted and stained using Masson's trichrome technique. The

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Details of 15 Cot Death Cases and 15 Controls

Cot Deaths								Controls							
Case No.	Age	Haemorrhage: Posterior Ganglion	Haemorrhage: Nodal Approaches: Posterior	Haemorrhage: Nodal Approaches: Middle	Haemorrhage: Nodal Approaches: Anterior	Atrial Septum	Further Remarks	Case No.	Age	Haemorrhage: Posterior Ganglion	Haemorrhage: Nodal Approaches: Posterior	Haemorrhage: Nodal Approaches: Middle	Haemorrhage: Nodal Approaches: Anterior	Atrial Septum	Further Remarks
1	18 months						Accessory connexion	16	9 hours	+		+	+	+	
2	5 months	+				+		17	5 hours	+	+	+		+	
3	2 months	+	+		+		Ring tissue	18	9 months	+	+				Ring tissue
4	1 month	+	+	+	+	+		19	2 days	+	+	+	+	+	
5	4½ months		+			+		20	4 days		+		+	+	
6	16 months							21	11 months						
7	2½ months	+					Fibrous ring deficient	22	1 month	+					Ring tissue
8	3½ months							23	8½ months						Fibrous ring deficient
9	16 days							24	15 months						
10	2 months						Ring tissue	25	4 days				+	+	
11	11 days		+	+		+	Ring tissue	26	1 day	+	+			+	
12	2½ months	+			+		Fibrous ring deficient	27	4 months						Leukaemic deposits
13	4 months			+	+		Ring tissue	28	14 hours		+	+	+	+	Ring tissue
14	2 years							29	5 weeks					+	
15	2 months	+	+	+			Ring tissue, fibrous ring deficient	30	2½ months			+	+		Ring tissue

intermediate sections were stored and subsequently examined as deemed necessary.

Results

Atrioventricular Bundle.—The morphology of the bundle was identical in both groups. It usually pierced the fibrous atrioventricular skeleton as a discrete bundle of cells whose diameter was smaller than those of adjacent myocardium (fig. 1). In most hearts small fascicles ran from the left side of the penetrating bundle into the central fibrous body, but we were unable to see any evidence of pathological change occurring in relation to these fascicles.

Haemorrhages.—In most hearts the smaller venous channels and capillaries were engorged with blood cells, but we considered haemorrhage to be present only when red cells were seen in the intercellular spaces. In some situations the blood cells were widely dispersed over an area of myocardium (fig. 2), in others discrete clumps of cells were present enclosing several myocardial fibres (fig. 3). Both types of haemorrhage were seen in most of the hearts—most often among the thin, attenuated, atrial cells in the atrioventricular nodal area (fig. 4). The nodal morphology was such that the atrioventricular bundle was traced into the substance of the interatrial septum as a tract of cells that lay adjacent to the fibrous ring. This tract could be termed the lower nodal tract. The main body of the node lay above this tract, the two portions being enclosed by overlying

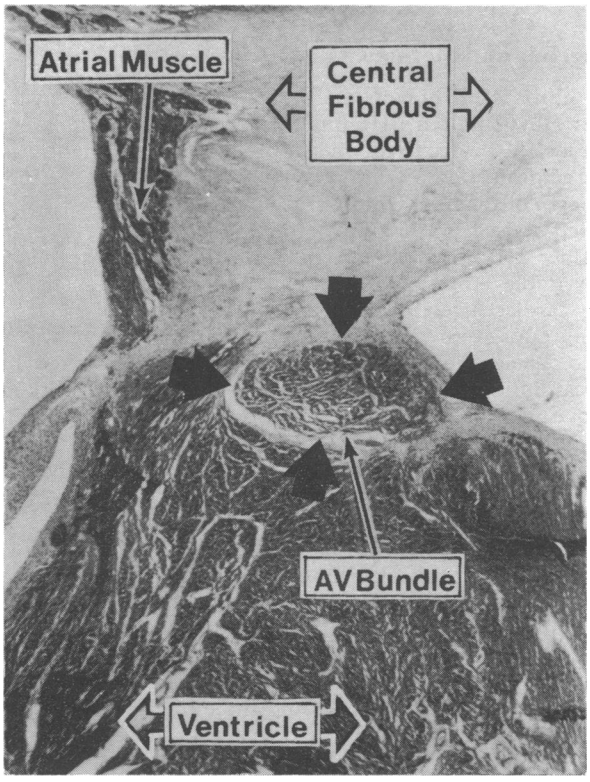

FIG. 1—Section of perforating atrioventricular bundle in heart of cot death patient. Bundle is dicrete (borders indicated by arrows). No evidence of cell death or similar pathological changes were seen in any heart examined.

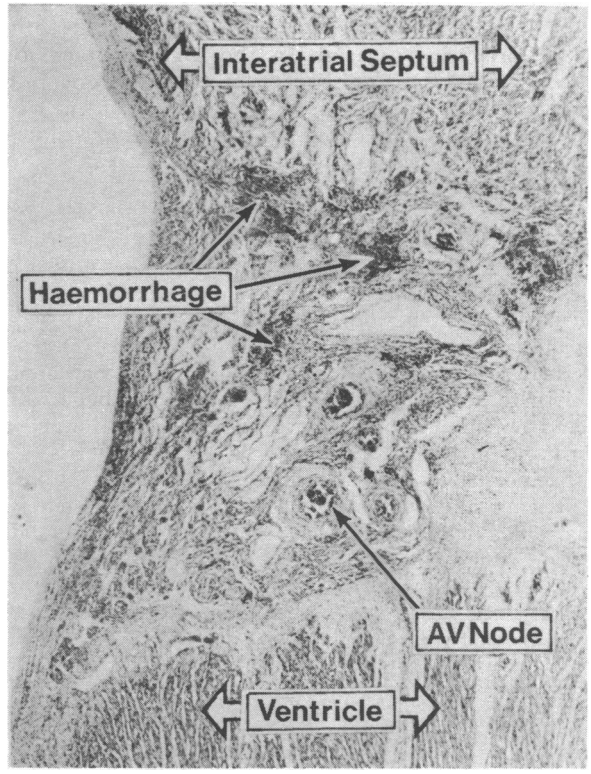

FIG. 2—Section of atrioventricular node from heart of patient who had cardiac arrest and open cardiac massage. Blood cells are dispersed in several clumps over wide area of transitional cells. Similar haemorrhage was also seen in atrioventricular bundle of heart.

atrial fibres orientated at right angles to the lower nodal tract. The atrial fibres in intimate contact with the node were slender and attenuated, were separated from each other by fibrous tissue septa, and made contact with the nodal cells. These fibres can therefore be termed transitional fibres and were organized into three groups. These connected the node to the myocardium of the anterior septum, sinus septum, and that beneath the coronary sinus. It was in these transitional cells that the haemorrhages were most often seen (table). When traced proximally into the atrial septum the cells lost their characteristic histological arrangement and were indistinguishable from other atrial myocardium. In this region of atrial myocardium haemorrhages were less common, and only this "working" type of myocardium was seen between the attenuated atrial, or transitional, cells and the sinuatrial node. Haemorrhages were also rare in the sinuatrial node, which was normally formed in all the hearts. Haemorrhagic lesions were seen, however, in the autonomic ganglia related to the posterior atrial wall and the sinuatrial node, but were again present in both groups (fig. 5, table). The findings in the heart which suffered cardiac arrest were particularly interesting. There was gross haemorrhage in the anterior transitional cells (fig. 2), and this was the only heart in which haemorrhage was also present in the atrioventricular bundle.

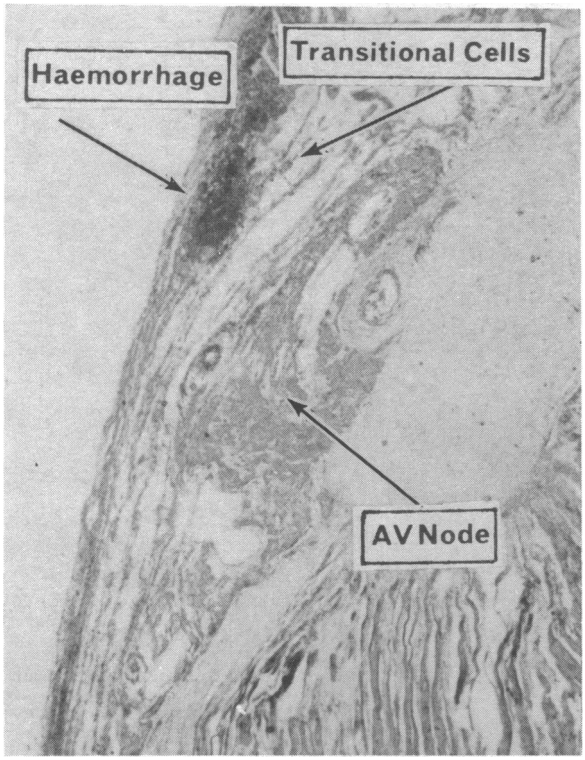

FIG. 3—Discrete haemorrhage in middle transitional cells of heart of cot death patient (case 13).

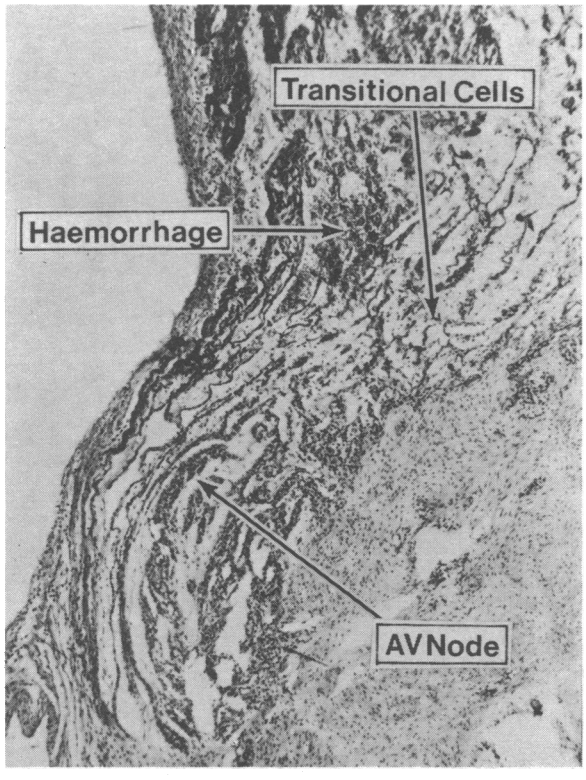

FIG. 4—Discrete haemorrhagic lesion similar to that seen in fig. 3 in posterior transitional cells of heart of control patient (case 20).

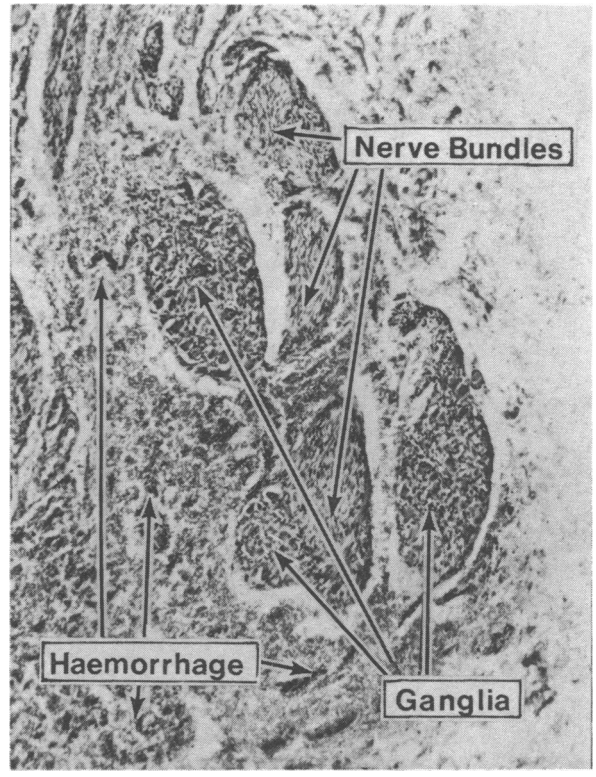

FIG. 5—Widespread haemorrhage surrounding group of autonomic ganglia from posterior atrial wall of heart of cot death patient (case 3). Similar haemorrhages were observed in hearts of control patients.

Accessory Atrioventricular Connexions.—In one heart in the cot death group a discrete accessory atrioventricular bundle was identified (fig. 6). This structure represented an elongation of the anterior transitional cells across the lower nodal tract. These cells usually terminate below the tract in the tricuspid valve base, but in this case they expanded below the tract into a thick bundle which pierced the tricuspid valve ring to contact the interventricular septum (fig. 7). The lower nodal tract continued anteriorly to the accessory bundle to form the normal penetrating atrioventricular bundle which gave rise to normal bundle branches. Though the entire tricuspid and the anterior and posterior margins of the mitral rings were examined in all hearts this was the only definite accessory connexion identified.

Nevertheless, in both groups additional segments of specialized tissue were identified in the distal margins of the atrial myocardium. In several cases these segments were well-formed

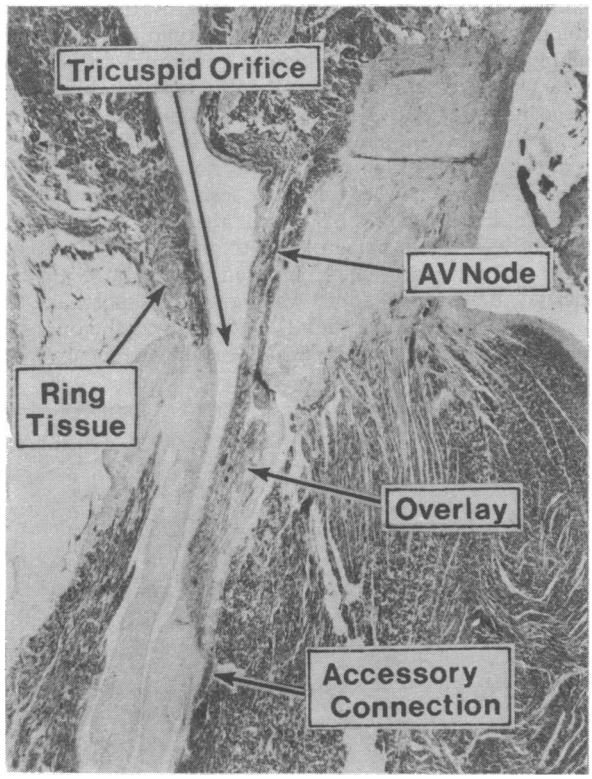

FIG. 6—Discrete accessory connexion from case 1. Anterior transitional fibres pass over hypoplastic node, expand in tricuspid valve base, and enter ventricular myocardium.

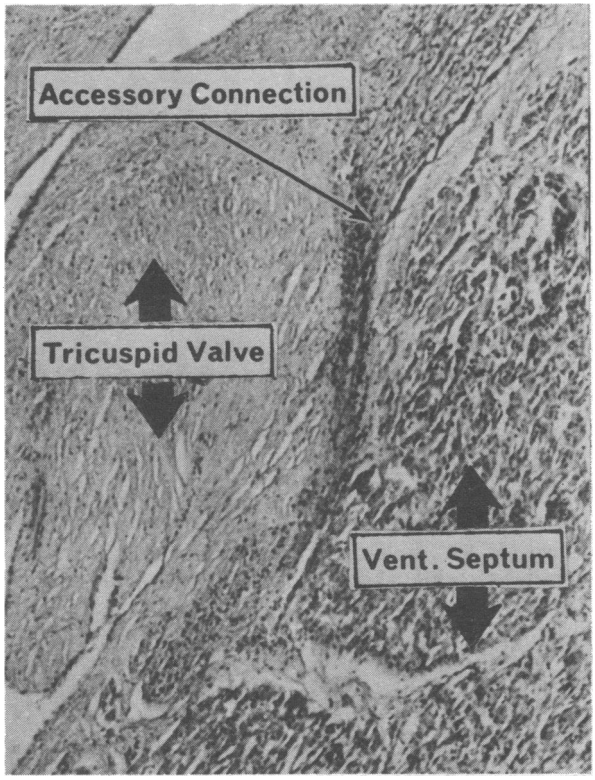

FIG. 7—Higher-power view of bundle entering ventricular myocardium (see fig. 6).

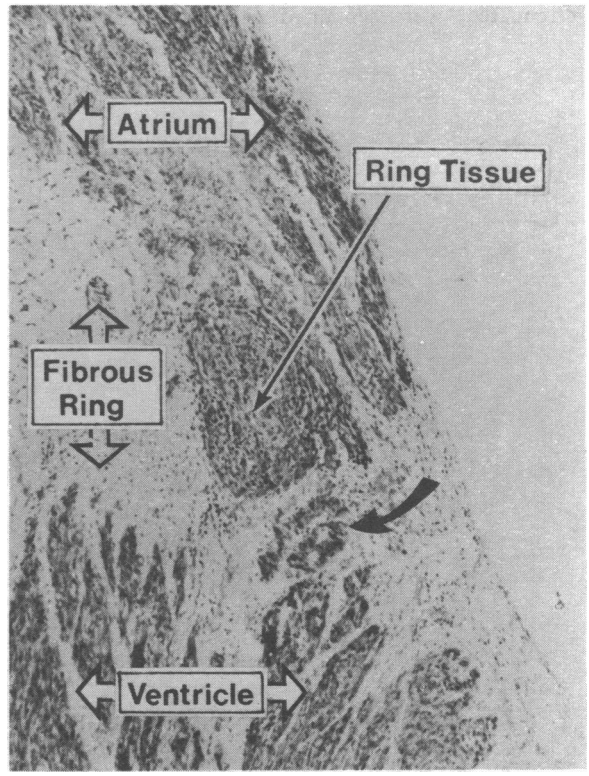

FIG. 8—Well-formed segment of ring tissue from heart of cot death patient (case 10). Note also segment of myocardium between ring tissue and ventricular myocardium (arrowed). Though direct contact was not made they came into close apposition.

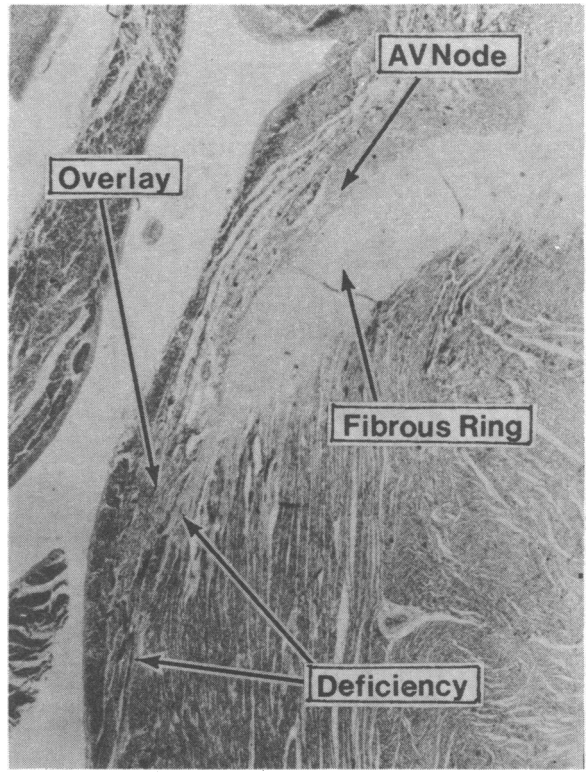

FIG. 9—Deficiency in fibrous ring beneath atrioventricular node in heart of cot death patient (case 12). Though thin fibrous septum was still present in area between arrows overlying segment of atrial tissue was again in close apposition to ventricular myocardium. Note close similarity to overlying segment illustrated in fig. 6, which actually made an accessory connexion.

(fig. 8), and evidence of such tissue, though less well-formed, was present in all hearts studied. In all cases, however, the tissue was separated from ventricular myocardium by the fibrous rings, though these were often attenuated in this situation. In several of the hearts the fibrous ring was also deficient beneath the posterior extent of the atrioventricular node, but though actual accessory connexions were not seen they often possessed features similar to those found in the heart with the connexion (fig. 9).

Discussion

It is difficult to implicate a single agent as the cause of death in cot death syndrome since, as Ferris (1973) pointed out, the associated pathological changes are minimal in the extreme. James (1968) first implicated the conducting tissue of the heart in sudden death in infancy syndrome when he described evidence of remoulding of the atrioventricular bundle. He also pointed out, however, that the pathological changes seen in these hearts were also universally present in controls. He rightly indicated that if the changes were implicated as the cause of cot death they must also be a possible final cause of death in infants dying from non-cardiac disease. We were unable to find the pathological changes described by James (1968) in any of the hearts we studied. We saw the fascicles he described, which run from the bundle into the central fibrous body, but were unable to detect any evidence of cell death or remoulding changes in these fragments. Nevertheless, like James (1968), we did see haemorrhagic lesions in relation to autonomic ganglia, but again these were present in both groups so therefore cannot be implicated as an unequivocal cause of cot death.

Ferris (1973) described petechial haemorrhages considered to be consistent with hypoxic changes in 13 hearts out of 50 studied. Some of the remaining hearts showed evidence of acute bronchiolitis, but he did not describe any studies on control hearts. He quoted much evidence to support the view that such changes could produce dysrhythmic episodes and lead to sudden death. Nevertheless, in order to relate some of the haemorrhagic lesions to conducting tissue he described them as occurring in the internodal tracts (James, 1963) without indicating which tracts were involved. Not all workers are convinced of the histological specialization of such tracts (Truex and Smythe, 1964) and in this investigation we were unable to find histologically-distinct fibres running through the internodal atrial myocardium. We saw petechial and other haemorrhages in a greater proportion of our cot death series than did Ferris (1973). Nevertheless, such lesions were also present in most patients in whom a non-cardiac cause of death was established. In our opinion, therefore, it is difficult to reconcile these changes as a likely cause of death in the cot death syndrome. They may well contribute in producing death, and this is supported by the finding of severe nodal haemorrhage in the heart from the infant in our series who died from cardiac arrest. It must also be pointed out, however, that this heart underwent open massage, and though haemorrhage was confined to the conducting tissue it may have been produced by post-mortem trauma. Similarly, the petechial changes present in both groups may well reflect hypoxic changes associated with impending death rather than vice versa.

Clearly the evidence of pathological changes in conducting tissue in the present group of cot death hearts is both circumstantial and equivocal. While the evidence relating to accessory connexions is also circumstantial a discrete anatomical connexion was, nevertheless, identified only in the cot death series, albeit in only one heart. It is therefore reasonable to suggest that in this heart a mechanism existed for producing supraventricular tachycardia, ventricular fibrillation, and hence sudden death. Nevertheless, segments of specialized tissue were seen around the atrioventricular orifices in all hearts studied, being better developed in some than others. Some writers believe that this tissue represents remnants of a complete ring of specialized tissue present in the human fetus (Anderson and Taylor, 1972; Anderson and Ashley, 1974) and there is evidence that some of these remnants persist in adult life (Davies and Anderson, 1973). Since the exact significance of these remnants to pre-excitation is not yet established it is presumptuous to suggest they may play a part in producing sudden death in infancy, but it is certainly a possibility that pre-excitation could exist through such pathways.

Clearly unequivocal changes in conducting tissue directly related to cot death have still not been established. To a certain extent our investigation was negative in that we were unable to confirm previous findings with regard to conducting tissue in these hearts, or else we found similar lesions in other hearts. Nevertheless, we did find possible substrates for ventricular pre-excitation and this indicates that conducting tissue may be implicated in some sudden deaths in infancy. If examination of the conducting tissues in such hearts became a more routine procedure possibly the significance of lesions in this tissue would be further elucidated.

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