POST-NATAL FATE OF THE ABDOMINAL PARA-AORTIC BODIES IN MAN

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INTRODUCTION

It is now generally accepted that the chromaffin cells of the human foetus or young child are to be found both inside the adrenal gland and in the retroperitoneal tissues closely associated with the prevertebral sympathetic plexuses. The extra-adrenal collections are known as sympathetic paraganglia or para-aortic bodies.

Both intra-adrenal and extra-adrenal chromaffin cells are developed from cells of the primitive sympathetic anlage (Kohn, 1903; Iwanow, 1930, 1932; Coupland, 1952), but whilst it is generally recognized that the adrenal medulla persists throughout life, the subsequent fate of the para-aortic bodies is less well understood. In earlier investigations attention has invariably been focused primarily on the largest individual collection of chromaffin cells which are to be found close to the origin of the inferior mesenteric artery—the organs of Zuckerkandl. In the present work the writer has attempted to follow the fate of the extra-adrenal chromaffin tissue as a whole, from birth to adult life.

HISTORICAL

Relatively little work has been done on the post-natal fate of the para-aortic bodies.

Bonnamour & Pinatelle (1902) observed an apparently normal body in a 6-year-old child, but failed to find extra-adrenal chromaffin cells in the adult. Zuckerkandl (1912) reported hyaline degeneration of these structures in a 2-year-old child and a 15-year-old youth; in specimens obtained from subjects aged 19 and 39 years, microscopic collections of chromaffin cells were observed 'in regions formerly occupied by them'; the actual site was not indicated.

Lucas Keene & Hewer (1927) reported fibrous degeneration in the bodies of a new born child, but did not continue the investigation into older post-natal specimens.

The most extensive investigations into the post-natal fate of the para-aortic bodies were undertaken by Ivanoff (1925) and Iwanow (1930); these authors concentrated primarily on the organs of Zuckerkandl, and concluded that maximum development was reached at about 2 years of age with subsequent degeneration. Degenerative changes described included hyperaemia, lymphoid infiltration, nuclear pyknosis and irregularity, vacuolation and hyalinization of cytoplasm. The final stage was said to be one of fibrosis. Iwanow (1930) found that the degenerative changes were associated with a gradual diminution in the size of the organs of Zuckerkandl. An extensive review of the pre- and post-natal human adrenal gland and extra-adrenal chromaffin tissue was published by Iwanow (1932); this included

a discussion on the physiology and pathology of these structures. On the subject of the post-natal fate of the para-aortic bodies no new facts were added to his previously published observations.

MATERIAL AND METHODS

Material used included two infants aged 5 months and 18 months; other specimens were aged 3, 5, 6, 7, 14, 22, 41 and 49 years. Tissues were obtained as soon as possible after death (2–12 hr.). The abdominal aorta and surrounding tissues were removed *en masse* and fixed by immersion in formol-dichromate (neutral formaldehyde 5 %, potassium dichromate 3 %) for 24 hr.; in the older specimens fixation was completed by immersing in 5 % formaldehyde for a further 2 days. One specimen (3 years) was fixed by immersing in formol-potassium iodate. Specimens were cut into suitable portions, dehydrated and embedded in paraffin wax, serial sections were made and 1 in 4 to 1 in 10 (depending upon the size of the specimen) mounted. Alternate slides were stained routinely by Ehrlich's haematoxylin and Giemsa, the Giemsa being differentiated in an acid medium (Coupland, 1954). A few slides were stained with haematoxylin and eosin and iron haematoxylin. Graphic reconstructions were made.

RESULTS

5-month-old infant

Death resulted from broncho-pneumonia.

Para-aortic bodies are numerous (Text-fig. 1) and are associated with the pre-vertebral sympathetic plexuses. Chromaffin cells are arranged in cords alongside capillary blood vessels, the whole being surrounded by a fibrous capsule (Pl. 1, fig. 2). Nerve fibres are observed traversing sections of the larger bodies. The general appearance is similar to that of the older foetus (Pl. 1, fig. 1). Mitotic figures are not observed. One small body is seen in apposition with a lymph node but the capsule is intact and there is no evidence of lymphoid infiltration.

The organs of Zuckerkandl have a maximum length of 9 mm. and are not united by an isthmus.

18 *months*

Death resulted from pneumonia which complicated diabetes mellitus.

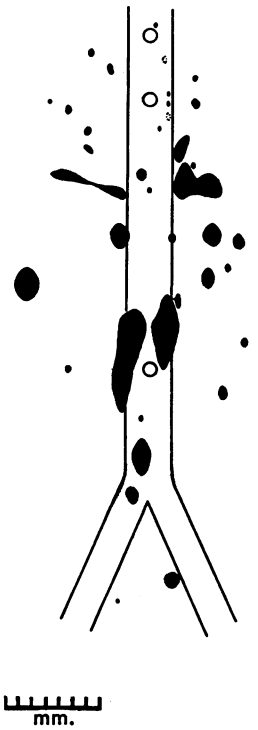
When received, this specimen had less peri-aortic tissue than the previous one, a fact which probably accounts for the apparent reduction in the number of bodies as compared with the previous specimen (Text-fig. 2). The para-aortic bodies are again scattered throughout the pre-vertebral sympathetic plexuses and have a late foetal appearance. There is no evidence of degeneration or cellular infiltration. The organs of Zuckerkandl have a maximum length of 12 mm. and are not united by an isthmus. Mitotic figures are not observed.

3 *years*

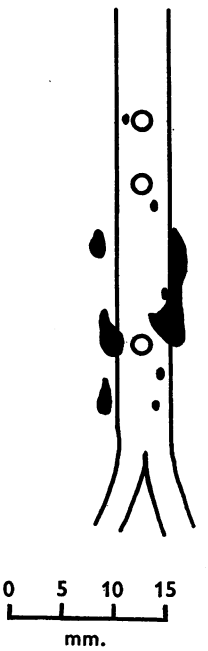
Death followed operation for congenital heart disease (Fallot's tetralogy).

Para-aortic bodies are numerous (Text-fig. 3) and resemble those of earlier specimens (Pl. 1, fig. 3). The organs of Zuckerkandl are larger than those of any earlier specimen and have a maximum length of 20 mm. A process extends across the midline from the left body but the two are not structurally continuous.

The chromaffin cells of the adrenal medulla and para-aortic bodies appear identical after staining with Ehrlich's haematoxylin, iron haematoxylin and Giemsa. The nuclei are rounded with a diameter of 6–9μ and contain scattered chromatin granules. The cytoplasm is faintly granular but the chromaffin reaction is poor as formol-iodate was used as a fixative; formol-iodate is much inferior to formol-dichromate in producing adrenochrome (Coupland, 1954). No degenerative



Text-fig. 1.



Text-fig. 2.

Text-fig. 1. Reconstruction of the abdominal aorta and surrounding tissues of a 5-month-old child. The sites of origin of the coeliac, superior mesenteric and inferior mesenteric arteries are indicated. Para-aortic bodies black.

Text-fig. 2. Reconstruction of an 18-month-old child. Para-aortic bodies black.

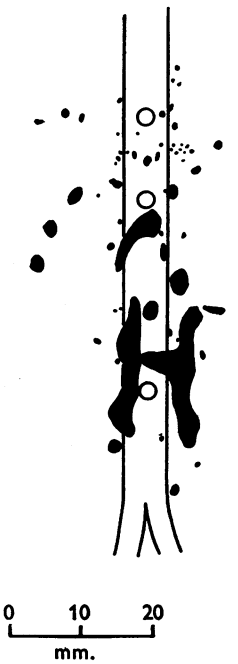
changes are present, nor is there evidence of cellular infiltration or of an obvious increase in connective tissue stroma. In the region between the superior and inferior mesenteric arteries a small body is observed lying in the centre of a lymph-node; it has an intact capsule and there is no evidence of lymphoid infiltration (Pl. 1, fig. 4).

5 years

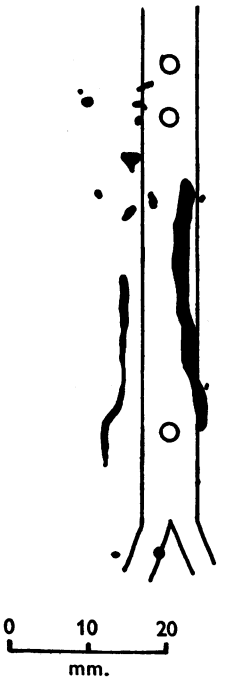
Cause of death was miliary tuberculosis.

When received, the rostral part of the specimen was relatively denuded of peri-aortic tissue; this fact probably accounts for the small number of para-aortic bodies in the region of the superior mesenteric artery and coeliac axis (Text-fig. 4).

The organs of Zuckerkandl are now longer than in any previous specimen but, when compared with the organs of the younger child and foetus, have a definitely abnormal appearance. The most striking feature is an increase in the amount of connective tissue stroma and in peri-arterial fibrous tissue (Pl. 2, fig. 5); these changes affect all bodies. Blood vessels of nearby lymph-nodes also show a similar peri-



Text-fig. 3. Reconstruction of a 3-year-old child. Para-aortic bodies black.



Text-fig. 4. Reconstruction of a 5-year-old child. Para-aortic bodies black.

arterial increase in fibrous tissue, and it is likely that this is a general change and not one confined to the para-aortic bodies. There is no evidence of endarteritis. In the specimen many of the chromaffin cells are vacuolated, as are many of the nearby sympathetic neurones, and it is concluded that this is either a toxic or post-mortem change. Lymphoid infiltration is not observed.

6 *years*

Death resulted from a cerebral tumour.

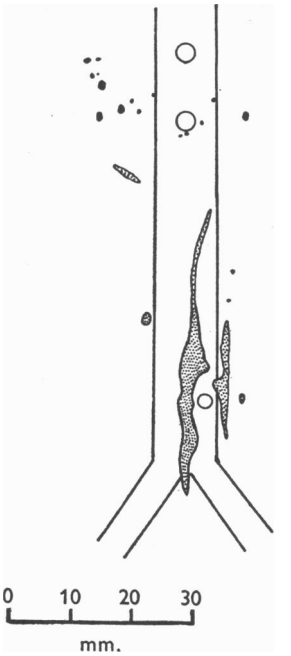
All the para-aortic bodies show some increase in connective tissue stroma and peri-arterial fibrous tissue, but again the latter change can be observed in nearby blood vessels which are not connected with the para-aortic bodies. There is no evidence of endarteritis. Apart from these changes the para-aortic bodies in relation to the upper part of the aorta have a normal appearance. The organs of Zuckerkandl have undergone further changes and are now virtually unrecognizable as definite structures; instead small groups of chromaffin cells associated with nerve fibres and

vascular connective tissue (capillaries being numerous) extend down in association with the pre-aortic plexus on each side of the inferior mesenteric arteries. There is no evidence of lymphoid infiltration.

7 years

Death was due to a cerebral abscess.

As in the previous specimen, the organs of Zuckerkandl no longer exist as distinct entities, and instead small collections of chromaffin cells associated with vascular connective tissues and nerve fibres of the pre-aortic plexus extend down on each side of the inferior mesenteric artery (Pl. 2, fig. 6). In comparison with earlier specimens there has been a definite reduction in the number of chromaffin cells present in any one transverse section of the region formerly occupied by the organs of Zuckerkandl. Chromaffin cells extend further in a cranio-caudal direction (Text-fig. 5): a finding which suggests distraction of the organs. Collections of chromaffin cells in the vicinity of the superior mesenteric and coeliac arteries (Pl. 2, fig. 7) resemble more closely the bodies of the earlier post-natal specimens, but differ in having a more abundant stroma; the larger bodies are also more irregular and in this respect resemble the remains of the organs of Zuckerkandl. There is no evidence of lymphoid infiltration.



Text-fig. 5. Reconstruction of a 7-year-old child. Encapsulated para-aortic bodies black; the positions of the scattered collections of chromaffin cells are indicated by stippling.

14, 22, 41 *and* **49** *years*

Deaths were due respectively to appendicitis (post-operative), subarachnoid haemorrhage, mitral heart disease and coronary thrombosis.

In each case the findings are similar to those reported for the 7-year-old specimen (Text-fig. 5).

In the neighbourhood of the superior mesenteric artery two to four discrete para-aortic bodies have been found in all specimens; these usually differ from the late foetal bodies in that the connective tissue stroma is more abundant and that they are less regular in shape (Pl. 2, fig. 8). However, one rostral body of the 41-year-old subject has a close resemblance to those of the young child (Pl. 2, fig. 9). In the 14-year-old specimen the bodies are engorged with blood, a condition which probably resulted from the disease process. A few fat cells are associated with one of the larger bodies (diameter 1·6 mm.) found in the 49-year-old specimen. Lymphoid infiltration is not observed. In the caudal part of the specimens discrete bodies are not found but a few scattered chromaffin cells are associated with pre-aortic sympathetic nerve fibres and extend down on each side of the inferior mesenteric artery; they are usually associated with vascular connective tissue. The findings are very similar to those reported for the 7-year-old specimen; the discrete rostral bodies have a similar position and differ structurally only in the further increase in stroma, which may

include fat cells, whilst in the caudal part of the specimen scattered chromaffin cells are found in the area indicated in Text-fig. 5. The large size of the adult specimens and scattering of cells makes difficult a quantitative estimation and subsequent comparison with the young child. The writer is, however, of the opinion that in the period between 7 years and adult life there is a considerable reduction in the number of chromaffin cells in the caudal half of the pre-aortic region. The reduction in chromaffin tissue in the rostral portion of the specimens, if any, is much less marked. In a preliminary communication on this subject (Coupland, 1953*b*), the writer stated that extra-adrenal chromaffin cells had not been observed in a 49-year-old specimen. It is now apparent that this failure to find the cells was due to the examination of an insufficient amount of peri-aortic tissue, and the further examination of other parts of the same specimen has revealed the presence of discrete collections of chromaffin cells. It is necessary to section all the retroperitoneal tissues which lie anterior and immediately lateral to the aorta, plus the aorta itself if the bodies are to be found.

DISCUSSION

The results of the present investigation differ from those of previous works in showing that a considerable number of extra-adrenal chromaffin cells is present in the adult. Earlier workers either failed to find extra-adrenal cells in the adult (Bonnamour & Pinatelle, 1902) or found only isolated small collections (Zuckerkandl, 1912; Ivanoff, 1925; Iwanow, 1930, 1932). The failure of these earlier workers to find greater numbers of extra-adrenal cells is probably due to the fact that their attention was focused mainly on the organs of Zuckerkandl, which, as distinct entities, disappear during childhood.

The organs of Zuckerkandl undergo very marked changes during early post-natal life (Pls. 1 and 2, figs. 1–6) which have in the past always been referred to as degenerative: a term which, for the want of a better alternative, has been retained in this work. According to Ivanoff (1925), the change takes place in three stages, the first being one of hyperaemia, the second lymphoid infiltration and the third fibrosis; these changes were said to be associated with a concomitant change in the chromaffin cells, nuclear pyknosis or irregularity, and vacuolation or hyalinization of the cytoplasm.

During the present investigation, an increase in stroma has been observed in all para-aortic bodies obtained from specimens of and above 5 years of age; this increase is often most obvious in the perivascular region, but is in fact a diffuse change affecting the whole structure. In specimens aged 6 and 14 years, some of the bodies were engorged with blood, a condition described by Ivanoff (1925) as 'hyperaemia' and regarded by him as being a sign of degeneration. In the present series this engorgement has been an inconsistent finding and is most probably due either to the disease process present before death or to agonal changes. In at least one of the cases in which Ivanoff (1925) observed lymphoid infiltration, death resulted from caseous pneumonia (possibly tuberculosis), and it is conceivable that the infiltration was a pathological change. In the present series lymphoid infiltration has never been observed. When post-mortem material is used the cellular changes of the type described by Ivanoff (1925) and Iwanow (1930, 1932) are without significance

because nuclear pyknosis, vacuolation, hyalinization or 'cloudy swelling' of the cytoplasm is commonly present in greater or lesser degree not only in chromaffin cells but in other glandular organs and even in the sympathetic neurones; the changes being due to a combination of ante-mortem toxaemia and post-mortem degeneration. In the present work only the more permanent changes in the structure of the para-aortic bodies, viz. an increase in connective tissue stroma and gross irregularity of shape have been used as criteria for assessing degeneration. In spite of the difference in methods of assessing degeneration in the present investigation and in the works of Ivanoff (1925) and Iwanow (1930), there is a close correspondence in the estimation of the time at which the extra-adrenal chromaffin tissue reaches maximal development, i.e. 3 and 2 years respectively. Degenerative changes then supervene.

Iwanow (1930) considered that the isthmus form was typical of the fully developed organ of Zuckerkandl, and that absence of an isthmus in a child over the age of 2 years was a sign of early degeneration. As reported previously (Coupland, 1952), the writer considers the isthmus form to be an accidental occurrence and in no way specific. The findings during the present work support this view.

The para-aortic bodies increase in size throughout foetal life (Coupland, 1952), and continue to grow up to the age of 3 years. Nerve fibres are always closely associated with the bodies and may be observed passing through them. As the para-aortic bodies undergo a gradual change in structure throughout foetal and post-natal life, it is impossible to say at which stage they have a 'normal' appearance. In early foetal life the bodies contain primitive sympathetic cells as well as chromaffin cells and stroma; in late foetal life only chromaffin cells and supporting tissues are present; in post-natal life there is a gradual increase in the stroma which becomes very obvious after 3 years. At 5 years all these bodies show a marked increase in their fibrous tissue content; an increase in perivascular connective tissue is also observed but is not confined to the para-aortic bodies as it affects small arteries in all parts of the specimen, and it is not considered to be a factor specifically associated with the break up of the organs of Zuckerkandl. In the same specimen the organs of Zuckerkandl are becoming elongated and there is a definite reduction in the number of chromaffin cells present in any one section of these organs (as compared with earlier specimens). At 7 years and in all older specimens the more rostral bodies are still recognizable as distinct encapsulated units, but differ from earlier specimens in the greater amount of stroma, and, in some cases, the irregularity of shape. The chromaffin cells of the organs of Zuckerkandl no longer form circumscribed units but, instead, form small groups scattered along fibres of the pre-aortic sympathetic plexus.

It is difficult to estimate the total bulk of the extra-adrenal chromaffin tissue in the adult, but present findings indicate that in the rostral part of the specimen it approximates to that present in the young child, whilst in the lower pre-aortic region there is a definite reduction after the age of 7 years. The reduction may either be true—the result of cell death—or apparent—the result of the movement of chromaffin cells from the immediate vicinity of the aorta into the offshoots of the pre-aortic plexus. Examination of the proximal $1\frac{1}{2}$ in. of the inferior mesenteric plexus and the upper part of the hypogastric plexus in adult specimens failed to

reveal the presence of chromaffin cells, and it would appear that a true reduction is involved.

During pre-natal life the extra-adrenal chromaffin tissue is precocious in development; present work indicates that it is at a maximum at 3 years of age. The early cessation of growth in chromaffin tissue is not confined to man, as Elliott & Tuckett (1906) found little increase in the size of the rabbit's adrenal medulla after the animal had reached 900 g. weight, and that the medulla of the 15-day-old guinea-pig had already attained adult proportions.

The fact that the elongated organs of Zuckerkandl are more markedly involved in the so-called degenerative changes which result in a subsequent disintegration of these structures, whilst the more circumscribed rostral bodies are less affected, suggests that the change is due to some local rather than a systemic influence. In the 3-year-old child the length of the abdominal aorta from coeliac axis to bifurcation in the formalin-fixed preparation is 5 cm., at 5 years this length has increased to 6 cm., at 7 years to $6\frac{1}{2}$ cm., and in the adult is approximately 12 cm. As the aorta increases in length the pre-aortic nerve fibres are increasing in girth and length, and it is likely that the differential growth rate between the fully developed organs of Zuckerkandl and these nerve fibres results in the break up of the bodies and dispersal of chromaffin cells. Encapsulated collections of chromaffin cells can be observed in the 46 mm. human foetus (Coupland, 1952) and gradually increases in size up to the age of 3 years. Since the chromaffin cells of the human foetus and post-natal specimens appear identical after Bouin or formol-dichromate fixation and staining with haematoxylin or Giemsa or iron haematoxylin, and because extracts of foetal and neo-natal para-aortic bodies contain a pressor principle (West, Shepherd & Hunter, 1951; Coupland, 1953*a*), it appears reasonable to suppose that the chromaffin cells are mature and functionally active during this period. Goormaghtigh (1935) reported the post-natal migration of chromaffin cells in the mouse. It is, however, unlikely that in man a true migration of apparently mature and functionally active chromaffin cells occurs at this late stage. The fact that the major effect of differential growth is confined to the bodies in the pre-aortic region is explained by the close association between nerve fibres and the long axis of the bodies, whereas the small more circumscribed bodies found around the coeliac and superior mesenteric arteries, which have a maximum diameter of 3 mm. and are usually smaller, are less commonly traversed by obvious nerve fibres. Endarteritis has not been observed. Microscopic extra-adrenal collections of chromaffin cells have been observed in the adult by Zuckerkandl (1912), Ivanoff (1925) and Iwanow (1930, 1932), but these authors do not state the frequency with which such collections are found. In the present series extra-adrenal chromaffin cells have been found in all the adult specimens examined and appear to be a constant feature.

The general disposition of the extra-adrenal chromaffin tissue in the child and adult can be correlated with the site of formation of phaeochromocytomata. MacKeith (1944), reviewing the literature on this type of tumour, found that in 165 cases, 152 had involved the adrenal medulla whilst 13 had arisen in the retroperitoneal tissues between the kidneys.

The close association between lymphoid tissue and chromaffin tissue previously reported in the foetus (Coupland, 1952) has again been noted in post-natal specimens.

This either takes the form of side-to-side apposition of lymph node and para-aortic body or, less commonly, a small body may be seen lying in the centre of a lymph node; in both cases the capsule of the bodies is intact and there is no evidence of lymphoid infiltration. Lymphoid infiltration has not been observed in any para-aortic bodies. It is, therefore, concluded that the relation is fortuitous; this conclusion is supported by the relatively frequent finding of sympathetic nerve fibres in close apposition to or actually running through the centre of lymph-nodes.

SUMMARY

The abdominal para-aortic bodies increase in size up to the age of 3 years. Between 3 and 5 years so-called degenerative changes supervene in all bodies and are at first characterized by an increase in stroma. The changes are most marked in the organs of Zuckerkandl, which become elongated and eventually disintegrate. This process of disintegration can be observed in the child of 6–7 years of age and is complete by 14 years.

In the older child and adult the rostral bodies show an increase in stroma and in some cases irregularity, but disintegration is not usually observed.

In the adult discrete para-aortic bodies exist in the vicinity of the coeliac and superior mesenteric arteries, whilst only small microscopic collections of chromaffin cells are associated with the lower pre-aortic plexus.

Degenerative changes are not associated with lymphoid infiltration and the occasional juxtaposition of chromaffin and lymphoid tissue appears to be fortuitous.

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EXPLANATION OF PLATES

PLATE 1

Fig. 1. Encapsulated para-aortic body from the lower pre-aortic region of a 3 lb. 10 oz. premature infant. Haematoxylin and eosin. (× 50.)

Fig. 2. Section through an organ of Zuckerkandl of a 5-month-old infant. *A* = aorta. Haematoxylin and eosin. (× 38.)

Fig. 3. Para-aortic body from the lower pre-aortic region of a 3-year-old child. Haematoxylin and eosin. (× 62.)

Fig. 4. 3-year-old child. An encapsulated collection of chromaffin cells is lying inside a lymph node. Haematoxylin and eosin. (× 122.)

PLATE 2

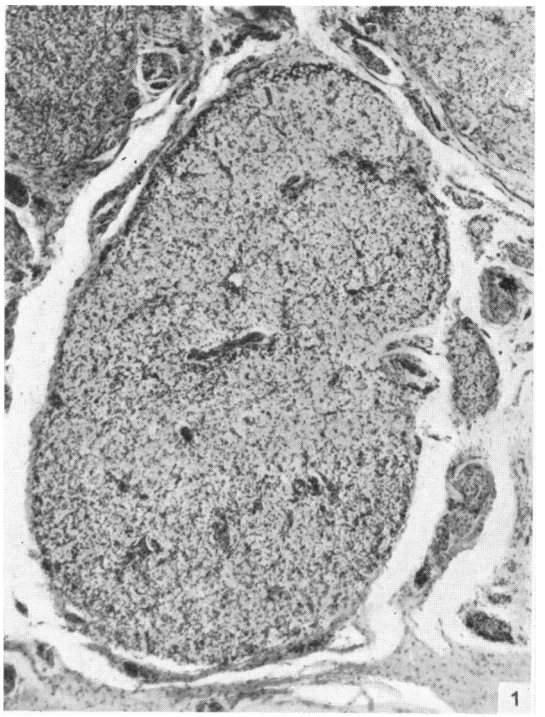
Fig. 5. Section of an organ of Zuckerkandl of a 5-year-old child. There is a marked increase in perivascular connective tissue. Iron haematoxylin. (× 80.)

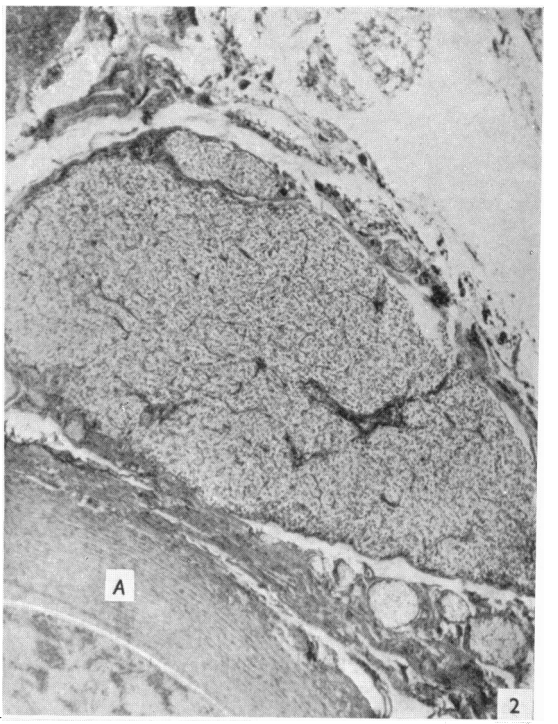
Fig. 6. Section through an organ of Zuckerkandl of a 7-year-old child. Chromaffin cells (*C*) no longer form circumscribed bodies but are dispersed amongst nerve fibres (*N*) and connective tissue (*T*). Giemsa. (× 86.)

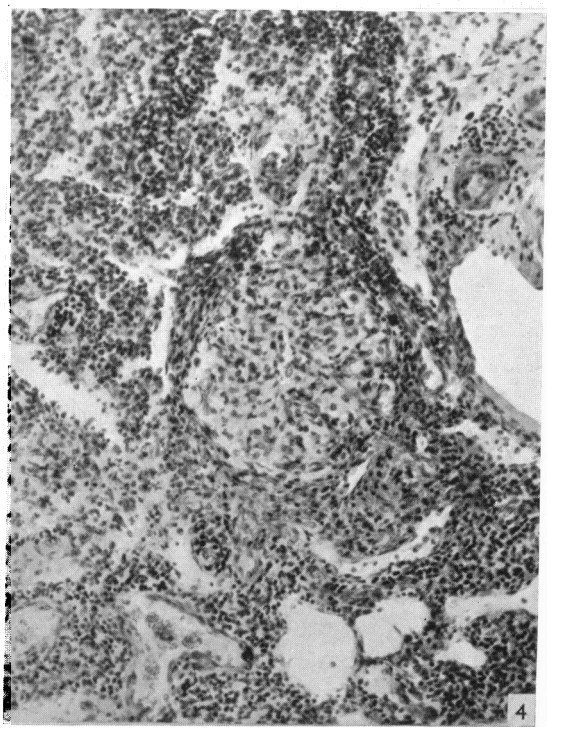
Fig. 7. Para-aortic body from the coeliac plexus of a 7-year-old child (left) in contact with a lymph node (right). Haematoxylin. (× 110.)

Fig. 8. A somewhat distorted but intact para-aortic body from the vicinity of the coeliac artery of a 41-year-old adult. Haematoxylin. (× 80.)

Fig. 9. Para-aortic body from the region of the superior mesenteric artery of a 41-year-old adult. This closely resembles the bodies of the young child. Haematoxylin. (× 90.)







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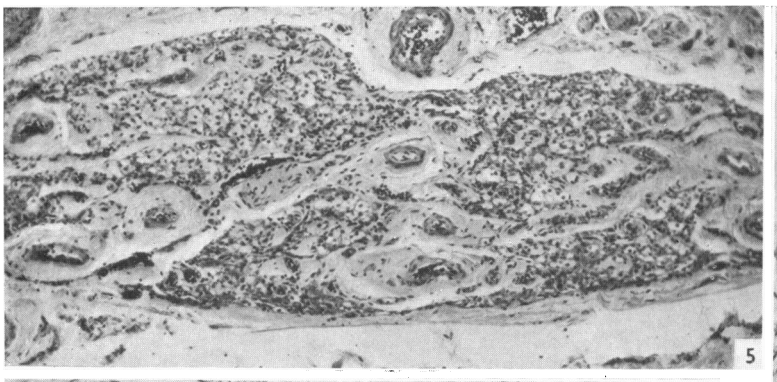
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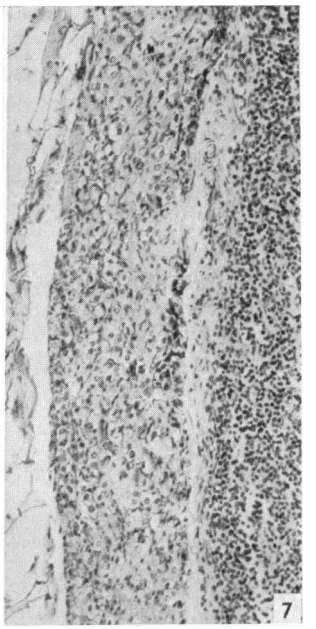
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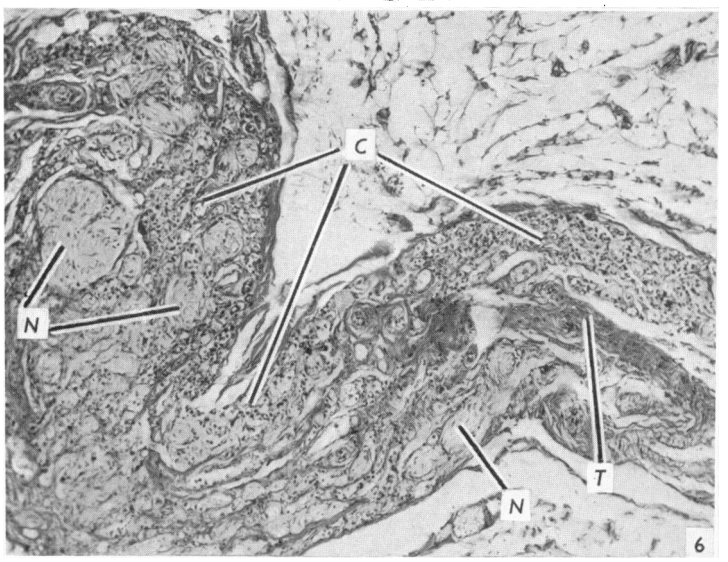
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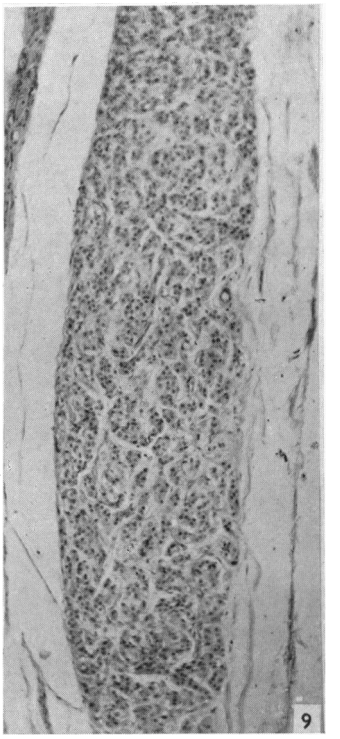
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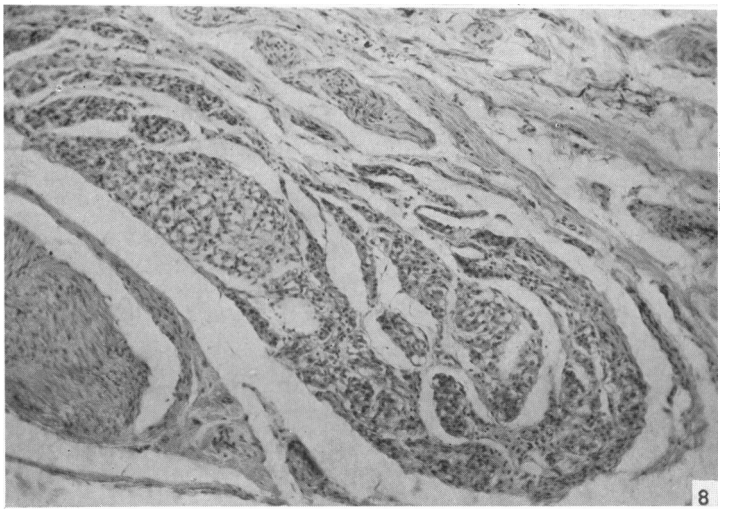
8