Virchows Arch [Pathol Anat] (1983) 400:119–142

Virchows Archiv A

The hemangioendothelioma of the thyroid

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Summary. 65 cases of hemangioendothelioma (HE) of the thyroid were accepted as such after control of slides of surgical or autopsy specimen or both. In a few of the more recent cases material could be examined by electron microscope and in some the search for factor VIII-related antigen (FVIIIRAG) was carried out.

The demonstration of Weibel-Palade bodies in tumour cells in two cases and the evidence of FVIIIRAG in tumour cells of at least two cases, including primary tumour and distant metastasis, finally show, that the hemangioendothelioma of the thyroid is not simply an anaplastic carcinoma with some peculiar features; at least some of these tumours are true endotheliomas.

The proposal that the term hemangioendothelioma be eliminated from the classification of thyroid tumours is therefore unfounded.

Key words: Thyroid neoplasms – Hemangioendothelioma – Electron microscopy – Factor VIII-related antigen (FVIIIRAG) – Tumour classification

Limacher (1898) of the Institute of Pathology of Berne was the first to describe the hemangioendothelioma (HE) of the thyroid under the heading: "Blutgefässendotheliom der Struma". Hedinger (1909) of the same Bernese Institute published the fundamental paper on this tumour. In 1926 this tumour was clearly described by Wegelin (1926) in the Handbuch of Henke-Lubarsch, and until recently the HE has been fully accepted as an entity in the German as well as in the Italian literature. Contrary to this, the HE is almost unknown in the English and American relevant literature. Willis (1953) and Ackerman and Del Regato (1954) do not even mention it; it is also missing in the Tumor Atlas of the Armed Forces Institute of Pathology by Warren and Meissner (1953), while there is a short comment on it in the second series of the Atlas by Meissner and Warren (1969). These authors feel, that these tumours usually represent undifferentiated carcinomas.

Many authors, who do not accept the theory, that the HE is a tumour of vascular origin, agree, that it has certain features distinguishing it from

other thyroid tumours, especially the undifferentiated carcinoma, thus permitting a classification of these cases as a relatively distinct entity.

A large collection of relevant cases at my disposal prompted me to review our material. I shall discuss the pathological-anatomical picture of the tumour on the basis of our own biopsy and autopsy specimens, including metastases, the electron microscopic picture of the tumour, the results of the investigation of the presence of factor VIII-related antigen (FVIIIRAG) in tumour cells, and the clinical picture.

Material and methods

Autopsy and biopsy material from the Winterthur Cantonal Hospital's Institute of Pathology, from the Institute of Pathology of the University Hospital, and from the former Institute of Histopathology of the University of Zürich, was at my disposal.

Only filed cases with complete personal data and slides for reexamination were beeing considered. In 11 cases the pertinent slides were missing or insufficient. In two cases there was no tumour but only hemorrhage in various stages of organization. Seven cases had to be reclassified as undifferentiated carcinomas. Therefore, only 65 of the 85 filed cases fulfilled all criteria, including the histological criteria of Hedinger (1909).

In the following table, source, years of observation, kind of material, sex and patient age are summarized (Table 1).

From four patients with a HE of the thyroid we received biopsy material for rapid frozen section which we could therefore examine by means of the electron microscope.

Small tissue fragments were processed for electron microscopy immediately after tissue for frozen section had been separated. For this purpose, tissue was cut into blocks of about 1 mm^3, fixed in 2,5% phosphate buffered glutaraldehyde for two hours and postfixed in 2% buffered osmium tetroxide. Dehydration and embedding in epon. Thick and thin sections were cut with a LKB or a Reichert OM-U3 microtome. Thick sections were stained with methylene blue and toluidin for light microscopic examination and area selection. Thin sections were stained with both uranyl acetate and lead citrate for study with a Zeiss EM 9 S-2 electron microscope.

Factor VIII-related antigen (FVIIIRAG) is an established marker for vascular endothelial cells. It has been identified with immunofluorescence techniques. Recently, the presence of this marker has also been demonstrated with immunoperoxydase techniques in formalin-fixed paraffin-embedded (Burgdorf et al. 1981; Sehested and Hou-Jensen 1981) normal and neoplastic vascular tissues, and has become commercially available.

Table 1. Source of our cases of HE of the thyroid

	Cases dated	Biopsy	Autopsy	Both b. & a.	Sex		Mean age
					m	f	
Institute of Pathology Cantonal Hospital Winterthur	1959–1981	7	8	10	13	12	70.7
Department of Pathology University of Zurich	1948–1970	28	5	7	27	13	65.1
		35	13	17	40	25	67.3

Our most recent cases, including those that had been examined by electron microscopy, were therefore studied with this marker. Paraffin sections were processed according to Mukai et al. (1980), with the only exception, that swine and swine antirabbit serum was used instead of sheep serum.

Cotimmun – AHG – ass. protein lot: 105712 Behring, provided by Hoechst, and Swine immunoglobulin of the rabbit code Nr. Z 196 and PAP of the rabbit code Nr. Z 113, both provided by Dako were applied. For control purposes the slides were treated with rabbit serum instead of specific immunoserum using the same dilutions. In a second series an Immulok factor VIII histoset was applied to the slides of the same blocks as used before. The results of these two studies proved to be virutally identical.

Results

Light microscopy

a) Primary tumour

Macroscopic and microscopic appearance of the HE have been described in detail by Hedinger (1909) and by Wegelin (1926). Since these descriptions have been the criteria of my classification, I shall summarize them and give some illustrations from some of my cases. The descriptions by Hedinger (1909) and by Wegelin (1926) interpret the HE as a tumour of vascular (endothelial) origin.

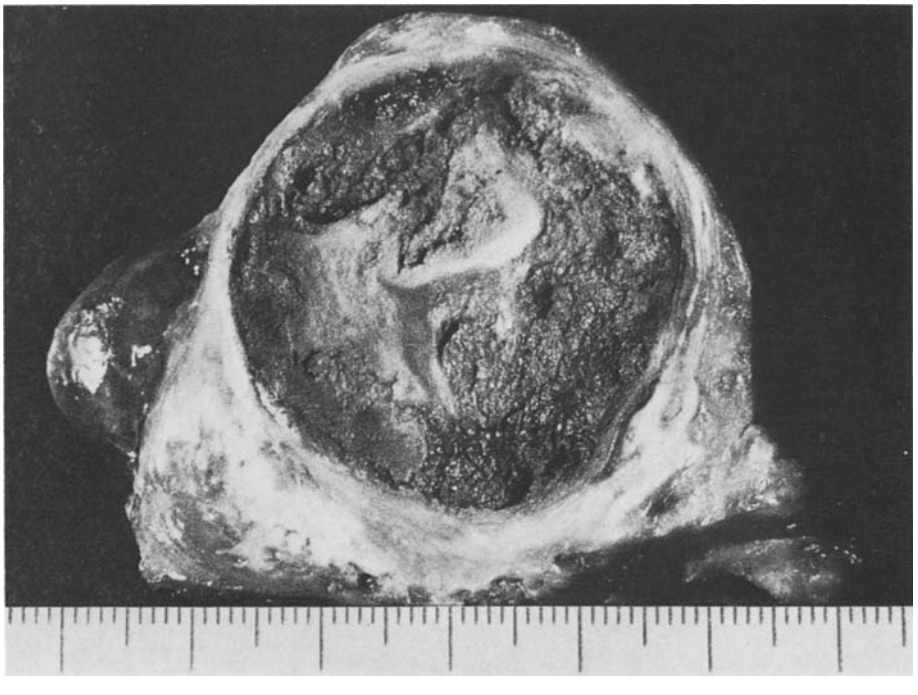


Fig. 1. Hemithyroidectomy specimen. Node with friable hemorrhagic material. Capsule and surrounding thyroid tissue invaded by whitish tumour tissue. BW 9217/73

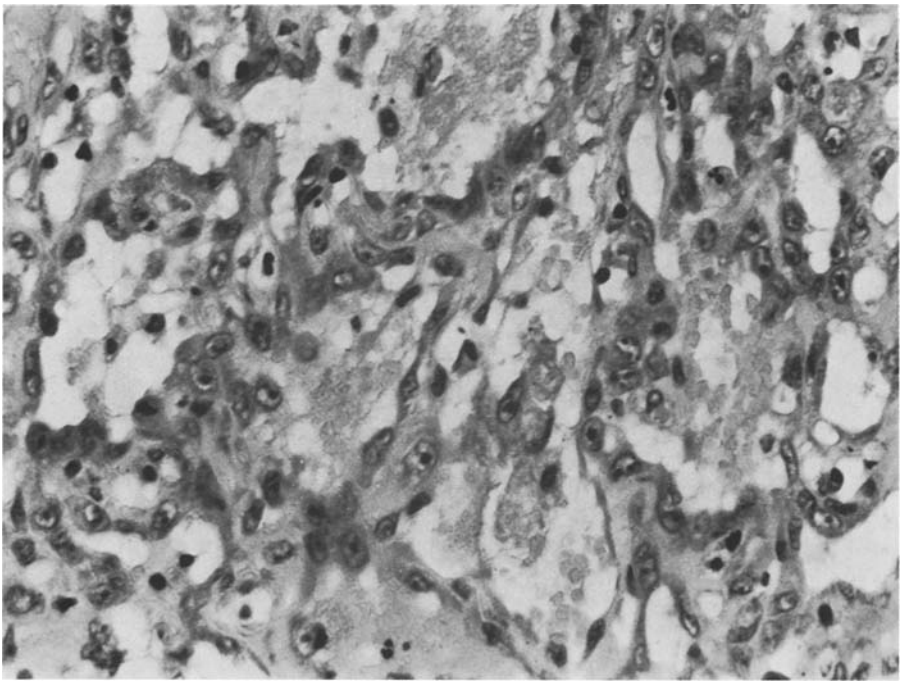


Fig. 2. Teleangiectasia-like pattern of only slightly enlarged cells with prominent nucleoli. BW 5284/76, H & E, ×300

Macroscopic features. The HE can very often be recognised macroscopically. The tumours form nodes which contain a central hole filled with coagulated or fluid blood. This hole is bordered by a layer of "rubber-hyalin" surrounding the blood and blending on the outside with grayish tumour tissue. The tumour tissue contains areas of hemorrhage and necrosis and is ill defined. It may penetrate into the surrounding soft tissues or the trachea. In most cases, there is only one tumour node. It very often lies within an adenomatous goitre (Fig. 1).

Microscopic features. The microscopic appearance of the HE is extremely variegated. According to Hedinger (1909), the first stage of tumour development is a multiplication and widening of the capillaries similar to teleangiectasia (Fig. 2).

However the endothelium already shows certain irregularities, since some cells are protruding into the lumen and have larger nuclei. Starting with such capillaries one may observe a gradually increasing proliferation of the endothelium (Fig. 3). The polymorphic endothelial cells may form several layers or may be very losely arranged, and mixed with red and white blood cells. Sometimes, tumour cells with a cytoplasm stuffed with globoid inclusions may be encountered. These inclusions have been interpreted as phagozytized red blood cells.

If the tumour cells in the lumen keep growing, expanding into larger spaces, a picture closely resembling a carcinoma is formed (Figs. 4 and 5).

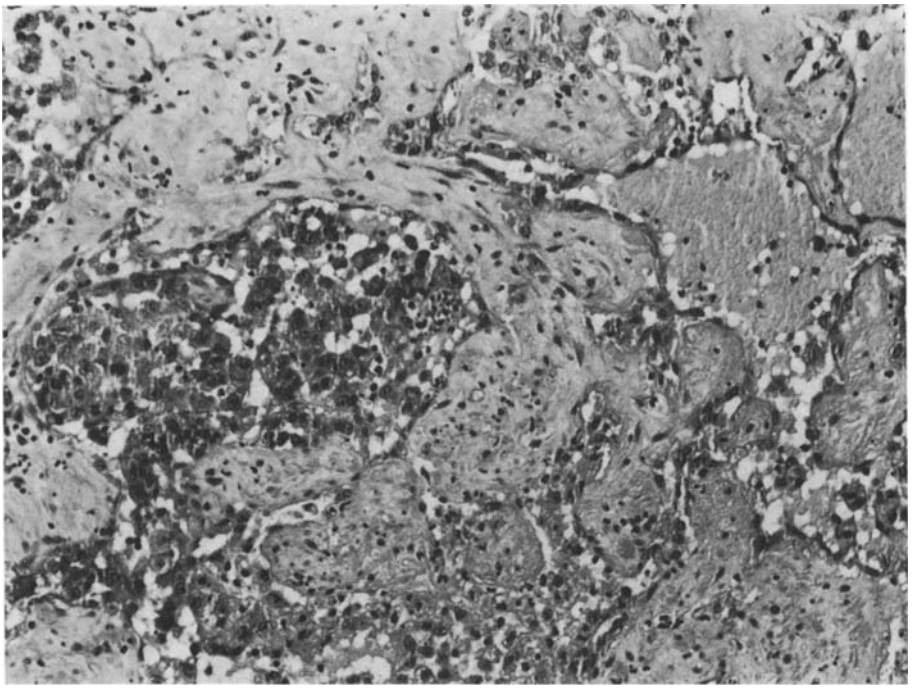


Fig. 3. Clusters of proliferating tumour cells within lumina of "vessels". BW 1191/77, H & E, ×125

While some areas have therefore the aspect of a carcinoma, others have that of an angiosarcoma. Polymorphic or spindle shaped tumour cells lie as single cells or small groups in a fibrous tissue (Fig. 6).

Necrosis is often seen and may be due to clogging of vessels. Hemorrhages are frequent and may be the source of hemosiderin formation. In some cases, the formation of irregularly shaped and ramifying cavernous cavities is a prominent feature, but here too, the endothelial cells are abnormally large and irregular (Fig. 7). At numerous places a cord-like invasion of the stroma occurs.

The propagation of the tumour tissue into the bordering thyroid or thyroid adenoma tissue follows the interstitium. Thereby, single or groups of tumour cells may appear between the thyroid follicles (Fig. 7).

Metastases

Metastases of HE of the thyroid are frequent. On autopsy 22 of the 30 patients who died of HE were found to have distant metastases, most often occuring in the lung and in the pleura. Some metastases of the HE were identified in very uncommon sites (see Table 2).

Furthermore some surgical specimens contained lymph node metastases.

The investigation of metastases may sometimes produce a clue as to the character of the primary tumour. Therefore, the examination of metastases seems important in a tumour of disputed origin.

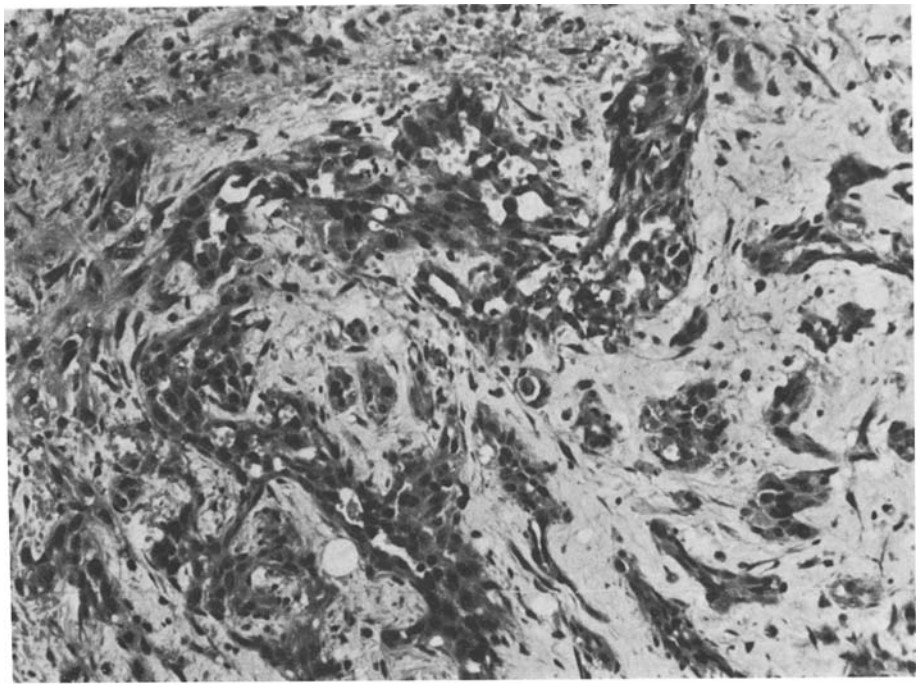


Fig. 4. Carcinoma-like tumour area with solid and cleft strands of tumour cells. BW 9193/73, H & E, ×125

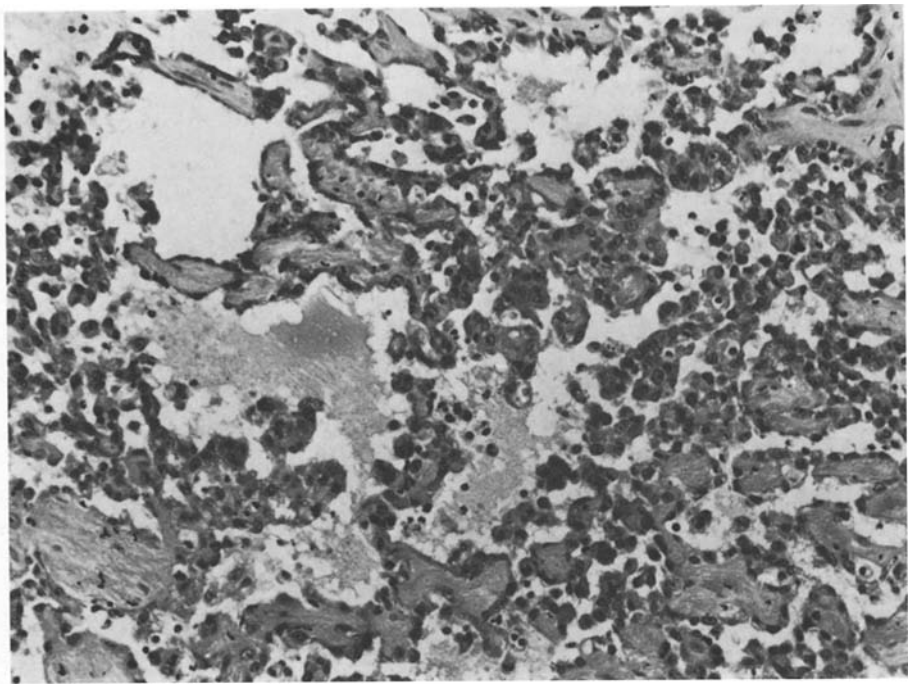


Fig. 5. Cavernous spaces with papillary projections. BW 1191/77, H & E, ×125

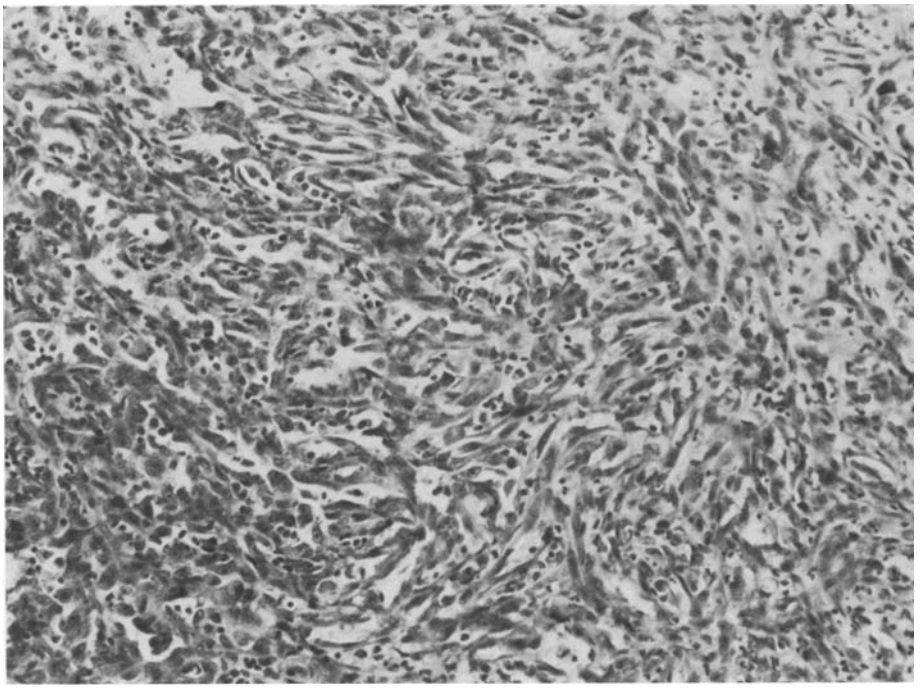


Fig. 6. Undifferentiated carcinoma-like, spindle cell type area of HE. BW 5268/76, H & E, ×125

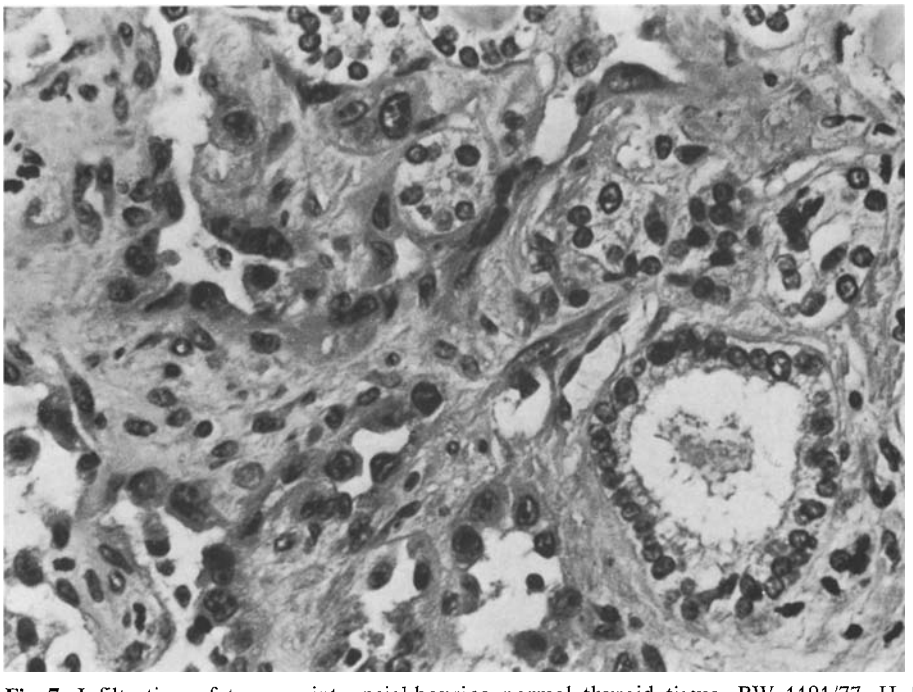


Fig. 7. Infiltration of tumour into neighbouring normal thyroid tissue. BW 1191/77, H & E, ×300

Table 2. Location of metastases (histologically proven)

Lung	18	Skeleton	4
Pleura	11	Gums	3
Lymph nodes	10	Pericardium	1
Adrenals	6	Endocardium	1
Intestine	4	Tongue and Pharynx	2
Stomach	3		

Histologically, the angiomatous pattern of the tumour is often much more prominent in metastases than in the primary tumour. Sometimes this may even help in establishing the diagnosis of a HE in a case, in which the primary tumour can not be classified with certainty as a HE because it contains areas similar in appearance to undifferentiated carcinoma.

Metastases of the HE are practically always hemorrhagic and it is not unusual that they give rise to obscure hemorrhages in the gastro-intestinal tract, pleural effusions or intracerebral hemorrhages.

Electron microscopy

The wide variation in the light microscopy picture of the HE is confirmed in electron microscopy: tumour cells show a wide variation of form, size and arrangement. In some areas, the tumour cells are sparse and separated by cell debris, inflammatory cells, erythrocytes, fibroblasts, granular and fibrillar substance as well as by collagen fibres. In other areas, the tumour cells are arranged in cords or rows or in small solid clusters (Figs. 8 and 9). Finally the tumour cells may surround a central lumen, often filled up with erythrocytes, thus giving the impression of a vascular structure (Fig. 10). In some sections, remnants of thyroid follicles are recognizable and clearly distinguishable from the tumour cells (Fig. 11). These follicles are surrounded by basement membrane substance, show a central lumen, sometimes filled with colloid, and are composed of thyroid cells with microvilli, intercellular junctions, and typical organellae and are therefore easily recognizable as such.

Most tumour cells are frankly atypical with large, very irregular nuclei. These are round or elongated and often show deep cytoplasmic identations and inclusions. The chromatin is unevenly distributed and plump nucleoli may be found.

The content of cytoplasmic organellae in the tumour cells is variable. There are relatively dark looking cells with a cytoplasm containing osmiophilic bodies, some mitochondria and a well developed rough endoplasmatic reticulum (Fig. 8). On the other hand, there are a few pale looking cells, with a cytoplasm containing only a few tubular structures coated with granules (Fig. 12), very few mitochondria and droplets and a high content of free ribosomes. These pale cells probably represent a low state of differentiation but can be found immediately next to dark cells, or even forming an epithelium or an endothelium-like row with other cells.

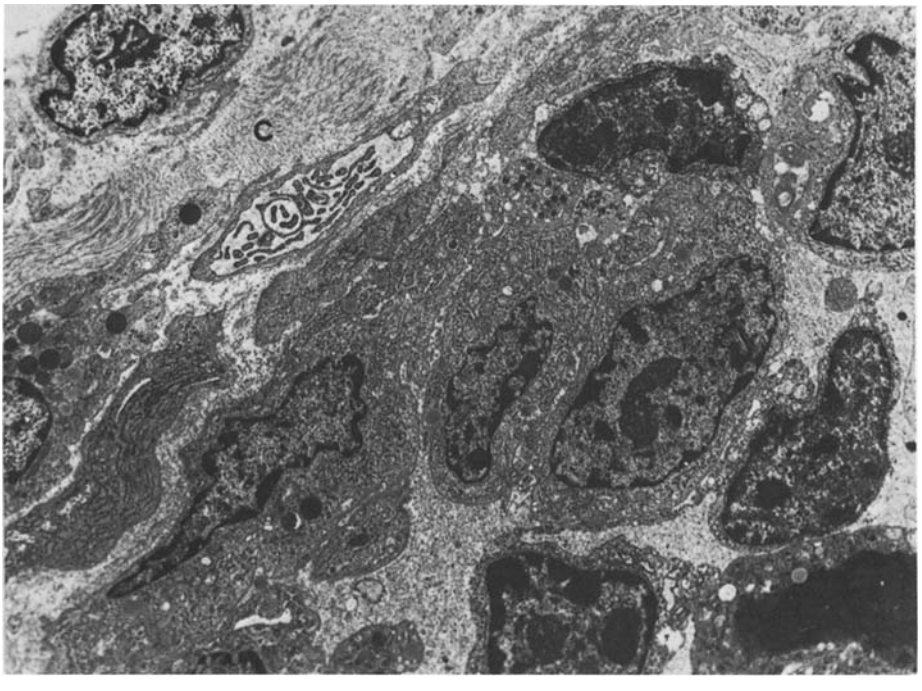


Fig. 8. Loosely arranged dark tumour cells, collagen fibres (*C*), a fibroblast, granular intercellular substance. BW 9193/73, ×3,600

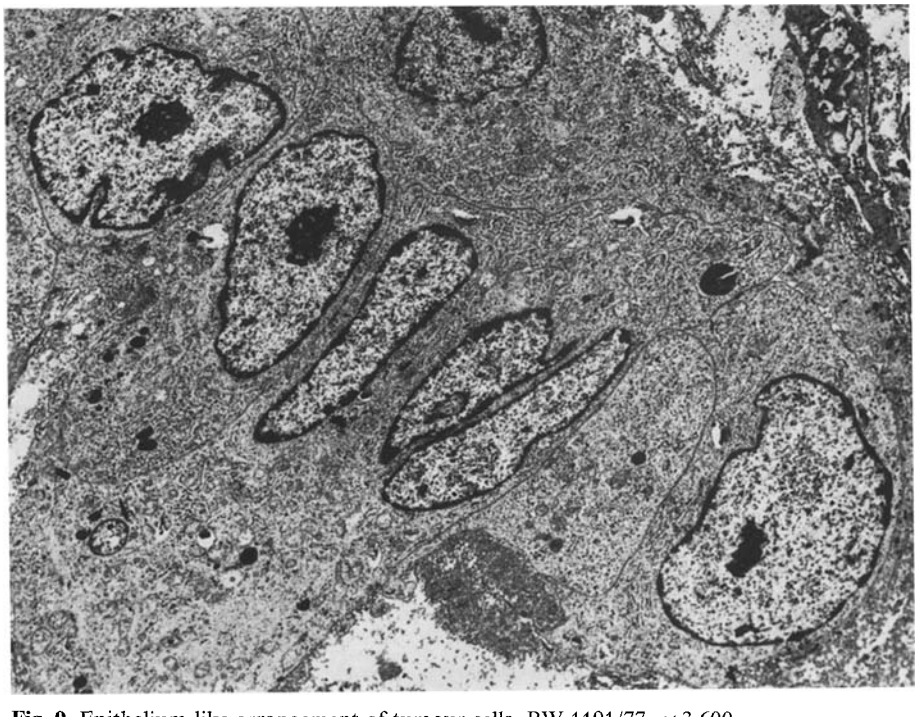


Fig. 9. Epithelium-like arrangement of tumour cells. BW 1191/77, ×3,600

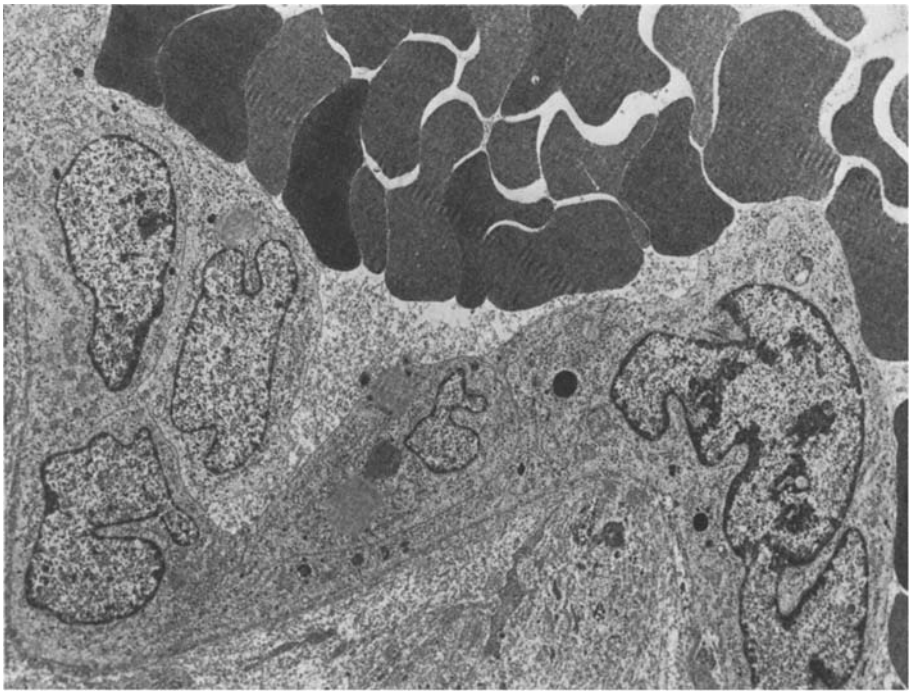


Fig. 10. Tumour cells arranged in an endothelium-like manner, surrounding an erythrocyte filled lumen. BW 5268/76, ×3,600

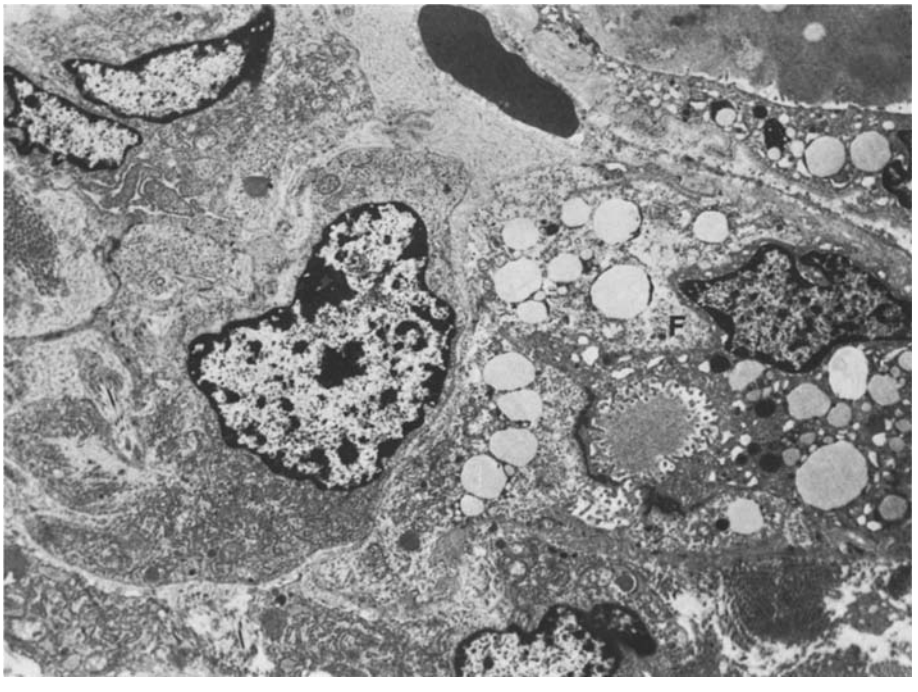


Fig. 11. Tumour cells between remnants of thyroid follicles (*F*), with colloid filled central lumen. BW 9213/73, ×3,600

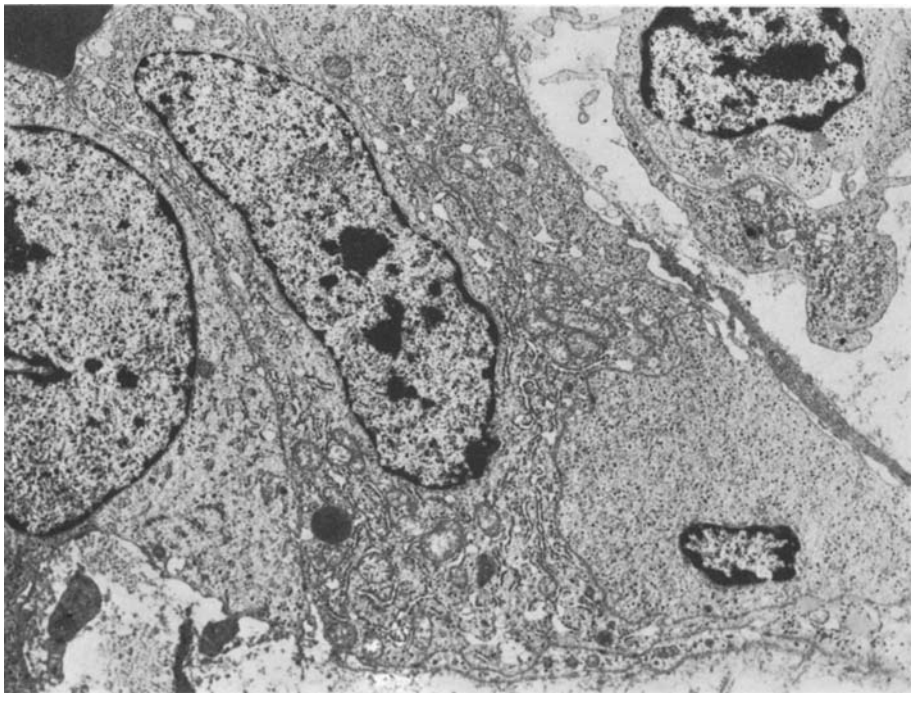


Fig. 12. Light tumour cells. Small number of organelles. BW 9217/73, × 3,600

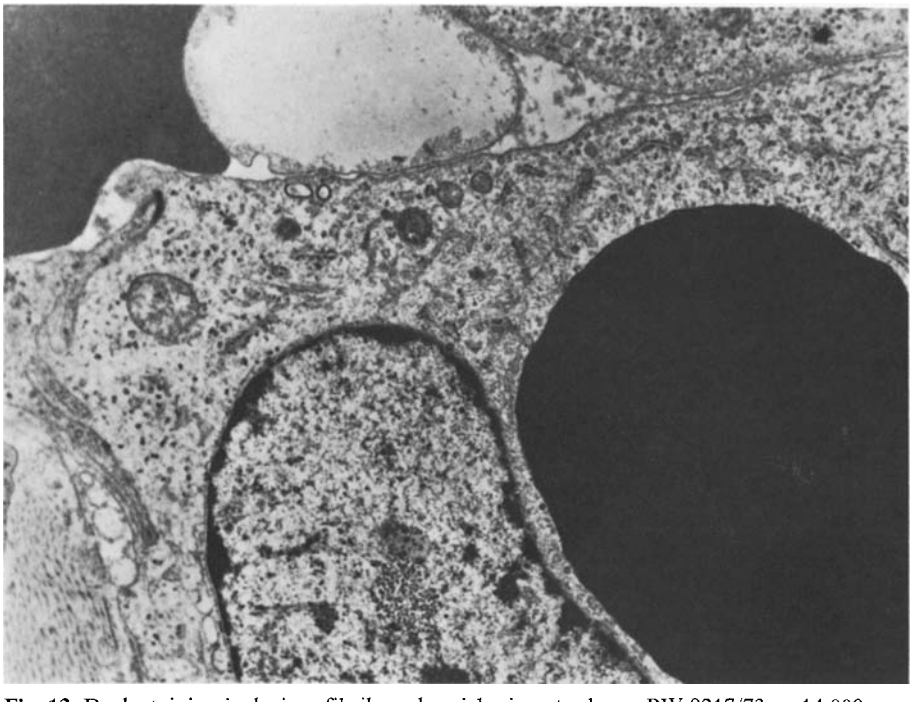


Fig. 13. Dark staining inclusion, fibrils and vesicles in cytoplasm. BW 9217/73, × 14,000

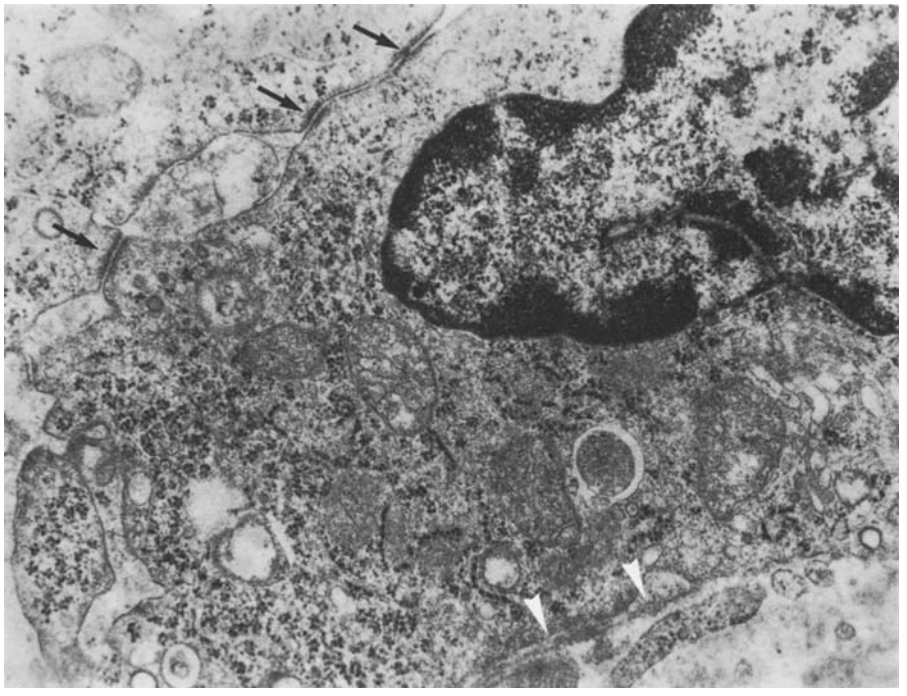


Fig. 14. Intercellular junctions (*black arrows*), possible fragments of basal lamina (*white arrows*). BW 9193/73, ×1,900

Occasionally, smaller and larger inclusions of high electron density, suggesting phagozytized erythrocytes, may be found. Some of these inclusions are probably lipid droplets but some consist of erythrocyte substance (Fig. 13). Some of these inclusions are fully incorporated in the cytoplasm of tumour cells, others show globules that are only partially surrounded by cytoplasmic fingerlike protrusions, suggesting erythrophagia.

Junctions between individual tumour cells are absent in areas with loosely arranged tumour cells. In areas with tumour cells arranged in cords or rows, some intercellular junctions may be found, exceptionally even a tight junction (Fig. 14).

The demonstration of basement membrane substance is not often possible (Fig. 14). Even in areas with otherwise epithelium or endothelium-like cell arrangement, basement membrane substance may be absent.

Small areas with abundant intraplasmatic fibrils and some pinocytic vesicles can be demonstrated in all cases submitted to electron microscopy. In two cases where a more prominent vascular component of the tumour also appears in light microscopy, rod-shaped organelles with tubular structures may be seen in some tumour cells. These organelles measure arround 0,1–0,15 μ in diameter and show tubular structures in longitudinal as well cross-sections. In another case, only very few of these organelles may be

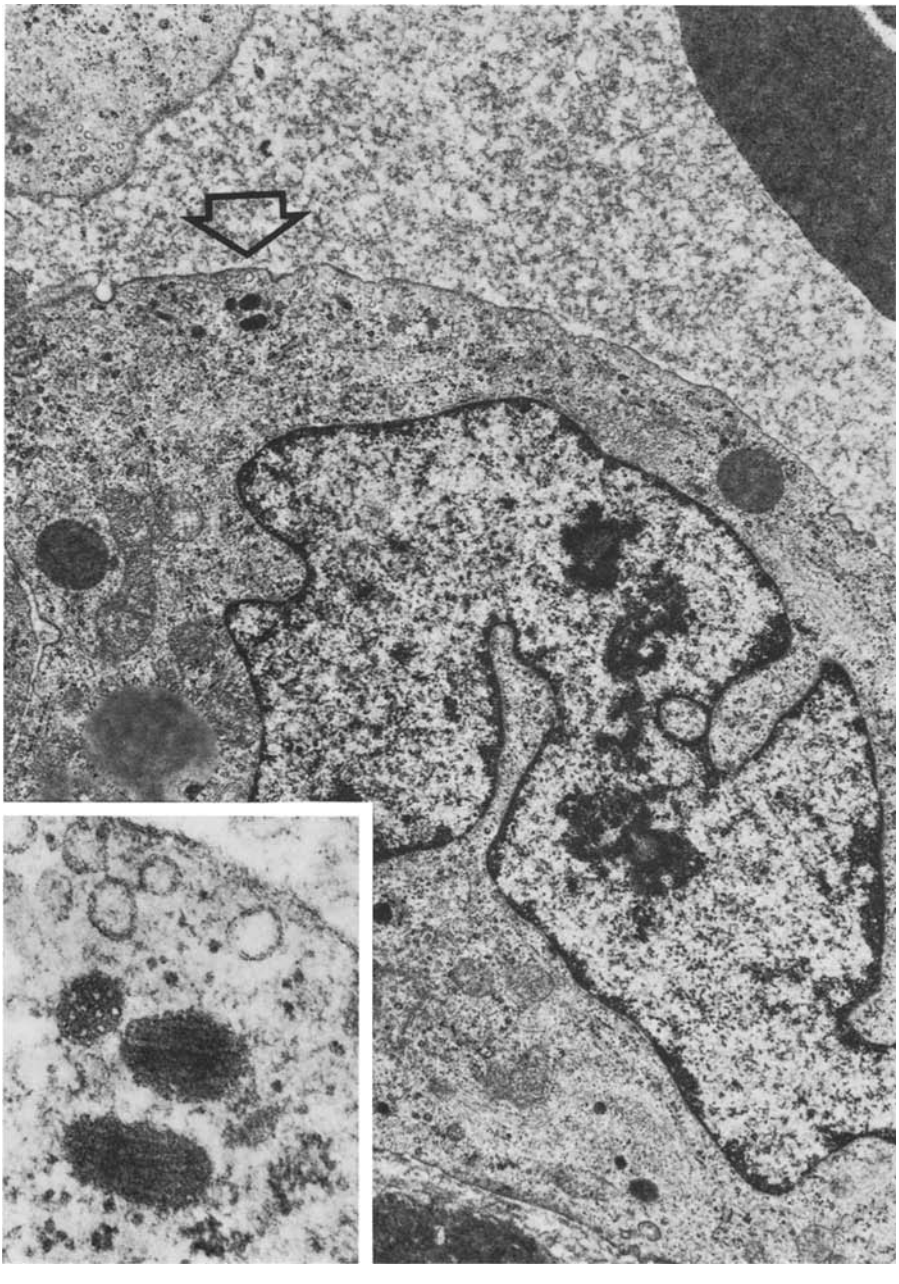


Fig. 15. Tumour cell with rod-shaped tubulated bodies and pinocytic vesicles (*arrow*). BW 5268/76, ×11,500, *Inset* ×70,000

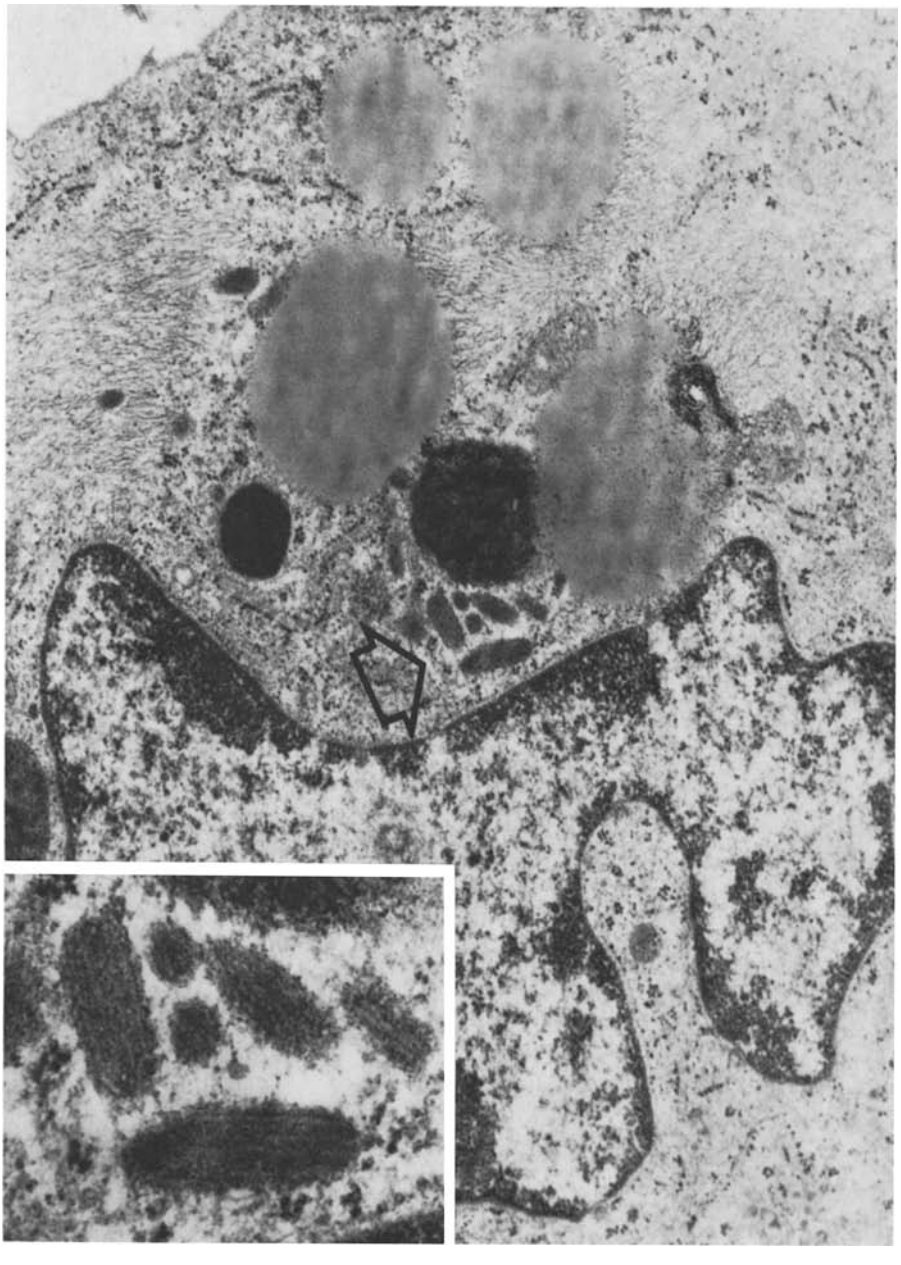
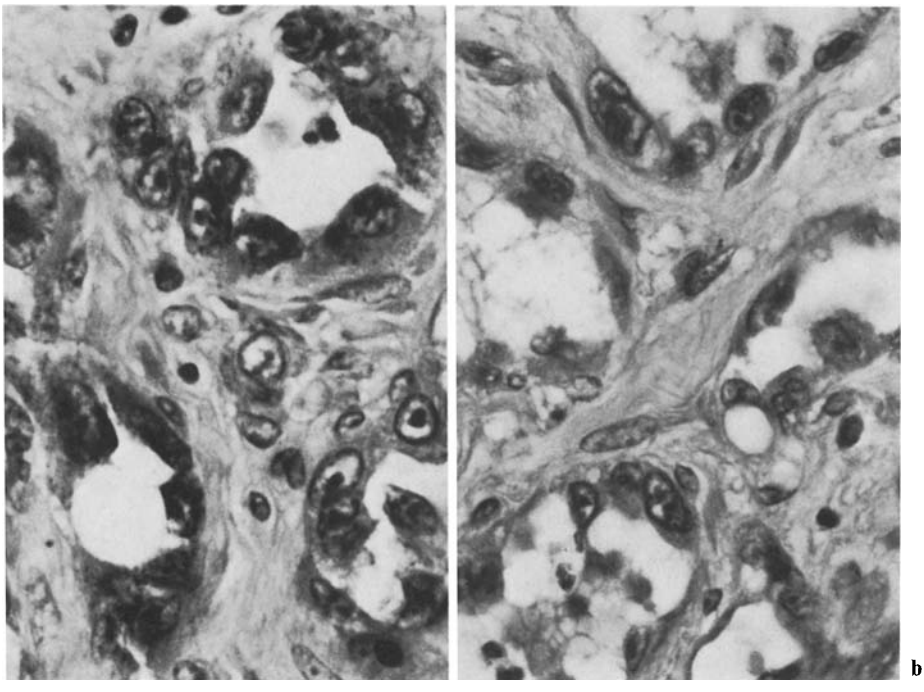


Fig. 16. Tumour cell with rod-shaped tubulated bodies (*arrows*), intraplasmic fibrils and dark and light staining droplets. BW 5268/76, ×24,000, *Inset* 70,000



a b

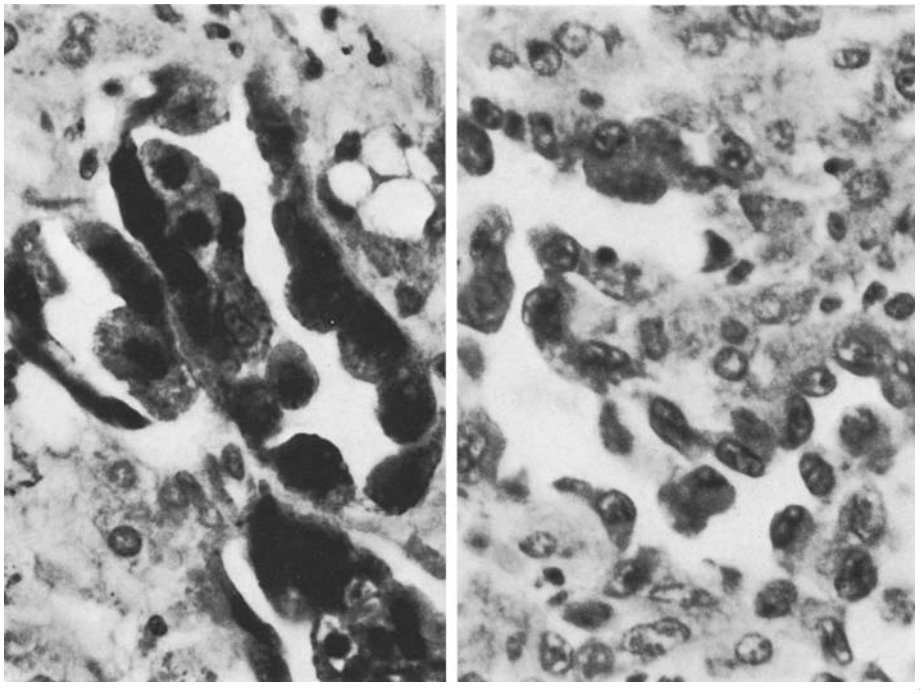
Fig. 17a, b. *Left:* Immunohistochemical localization of FVIIIRAG in tumour cells of a HE of the thyroid BW 1191/77, PAP, ×500. *Right:* Adjacent control-section of the same tissue without specific antibody. BW 1191/77, PAP, ×500

found being less well preserved, so that it is less convincing, that these organelles represent Weibel-Palade bodies (1964) (Figs. 15 and 16).

In still another case, no rod-shaped tubulated organelles may be detected.

Factor VIII-related antigen (FVIIIRAG)

Only the most recent cases were checked for the presence of FVIIIRAG. A more systematic examination of our material will be reported later. The PAP staining reaction was totally negative in one case (BW 7647/79), only faintly positive in two cases (BW 5284/76 and BW 2736/78) and distinctly positive in one autopsy and two biopsy cases (BW 5286/76, BW 1191/77 and AW 198/77). In some slides only a few tumour-cells showed a distinct, sometimes diffuse, sometimes more granular, brown coloration. In other slides there were groups or rows of positive staining cells, and finally in case AW 198/77 almost all tumor cells in the adrenal metastasis gave a positive reaction, which was regularly supressed in the control sections, treated in the same manner, but without anti-human-factor VIII-associated protein (Figs. 17a, b, and 18a, b).



a b

Fig. 18a, b. Adrenal gland metastasis of a HE of the thyroid. Slides from autopsy of same patient as preceeding figures. *Left:* Specific staining for FVIIIRAG. *Right:* Control without specific antibody. AW 198/77, PAP, ×500

Discussion

1. Electron microscopy findings

As far as I know, there is no description of electron microscopy findings of a HE of the thyroid in the literature. Even such descriptions of HE of other sites are infrequent. In 1977 Waldo et al. (1977) reviewed published ultrastructural observations of vascular tumours and presented additional findings from their laboratory. It seems evident that in well-differentiated lesions such as hemangiomas and lymphangiomas, the resemblance of tumour-vessels to normal vascular structures is apparent. Major differentiating problems are associated with angiosarcomas containing large undifferentiated areas. Ultrastructural characteristics of endothelial cells, e.g. pinocytic vesicles and Weibel-Palade bodies, are not found in epithelial cells. If these features can be identified, even in scanty number, the vascular nature of this lesion is established.

The findings of Waldo et al. (1977) are summarized in the following table (Table 3).

There are also relatively few papers on electron microscopy of undifferentiated thyroid neoplasms. The features of the tumour cells of an undiffer-

Table 3. Ultrastructural features of vascular tumours (Waldo et al. 1977)

	Endothelial cell	Periendothelial basal lamina	Pericyte
Hemangioma	1. forms single layer 2. may be fenestrated 3. tight junctions 4. villouslike luminal and basal clublike projections	continuous (may be multilayered)	usually interrupted layer
Hemangiopericytoma	1. forms single layer often atypical	may be discontinuous, multilayered or absent	1. surrounding basal lamina may be discontinuous or absent 2. pseudolumina formation 3. periendothelial cell processes
Kaposi's sarcoma	1. forms single layer 2. junctions of variable kinds 3. cytoplasmic filaments 4. increased number of cytoplasmic organelles 5. abundant hemosiderin 6. erythrophagocytosis	may be discontinuous or multilayered	1. interrupted layer 2. erythrophagocytosis
Angiosarcoma	1. forms single layer or occurs as nests 2. may be fenestrated 3. junctions of variable kinds 4. cytoplasmic vacuoles	may be discontinuous or absent	may be present
Hemangioendothelial sarcoma of bone	1. forms single layer 2. junctions of variable kinds 3. increased number of cytoplasmic organelles 4. phagocytic	may be discontinuous	interrupted layer

entiated carcinoma are still similar to those of the normal thyroid (Fisher et al. 1974; Graham and Daniel 1974). Gaal et al. (1975) describe two cases of anaplastic giant cell carcinomas. They found pleomorphic tumour cells with large bizarre-shaped nuclei and relatively little cytoplasm rich in rough ER. Various intercellular junctions could be detected. Jao and Gould (1975) studied three cases of anaplastic spindle and giant cell carcinomas. In two of the cases, foci of recognizable follicular carcinoma were present.

In these foci the tumour cells displayed prominent mitochondria and rough ER. Desmosomes and complex cellular interdigitations were evident. Basal laminae were present, with conspicuous reduplication in the well-

Table 4. Comparison of electron microscopy findings in thyroid tumors[a]

	Follicular carcinoma	Epithelial undifferentiated	Sarcoma	Hemangioendothelioma
architecture	follicles	± microfollicles	–	single cells, rows, solid clusters and capillary-like formations
basal membrane	present	± loss of BM	absent	sometimes present
junctions	typical	only few and sometimes atypical	absent	± sometimes atypical
cytoplasm organelles	osmiophilic granules (dense bodies, lysosomes, cytosomes) secretory granules some ER	± free ribosomes decreased and atypical mitochondria ± dilated ER	abundant ER cytoplasmic inclusions of lipid and glycogen	intraplasmatic and intercellular erythrocytes ± organelles
special features	microvilli occasional pinocytic vesicles	dark and bright cytoplasm bizarre nuclei, increased microfibrils and tubuli		dark and bright cytoplasm, fibrils, sometimes abundant ± pinocytic vesicles ± Weibel-Palade bodies bizarre nuclei
intercellular substance	little	increased (fibrils, collagen)	abundant	abundant

[a] Summarized from Cameron et al. (1975); Fischer et al. (1974); Gaal et al. (1975); Graham and Daniel (1974); Jao and Gould (1975); Johannessen et al. (1978); Saito and Sharma (1976); Valenta and Michel-Béchet (1977) and authors findings

differentiated foci. The pleomorphic spindle and giant cells showed cytoplasmic and nuclear characteristics similar to the better differentiated carcinomatous follicular elements, but contained only occasional desmosomes and no basal lamina. The authors believe that the basic ultrastructural similarity between follicular and anaplastic tumour cells confirms their common epithelial origin, though the anaplastic cells lose their capacity to synthesize basal lamina and to develop complex cellular attachments.

In Table 4 the findings of these authors are summarized and compared with our findings of the HE of the thyroid. The most striking difference between the electron microscopic features of the HE and the undifferentiated carcinomas is the presence of pinocytic vesicles, intraplasmatic fibrils and especially the presence of Weibel-Palade bodies in some of the tumour cells of the HE. Tumour cells forming microfollicles are absent in the HE. These findings are a strong argument for the theory, that the HE of the thyroid is a tumour of vascular origin.

2. Factor VIII-related antigen (FVIIIRAG)

Recently, results of examination of tumours of allegedly vascular nature by means of FVIIIRAG have been published [Mukai et al. (1980); Burgdorf et al. (1981); Sehested and Hou-Jensen (1981); Weldon-Linne et al. (1981)]. These authors agree that benign tumours such as hemangiomas show positive reactions of almost all endothelial cells. Reactive endothelial proliferations in pyogenic granulomas show a lesser positivity. Malignant tumours give less uniform results. There are hemangio-endotheliosarcomas with only a few positive tumour cells, other tumours show a positive reaction of 90% of the tumour cells (Sehested and Hou-Jensen 1981). The amount of positive cells seems to decrease as the nuclear pleomorphism of the tumour cells increases. Burgdorf et al. (1981) found only occasional positively reacting tumour cells in an angiosarcoma. They conclude that this might be a result of tumour dedifferentiation, leakage of FVIIIRAG through a defective cell membrans, or increased turnover rate.

Our own results are extremely variable, ranging from total negativity in some cases of HE, to almost total positivity in others. These findings are compatible with those observed in other authors' studies of undifferentiated angiosarcoma. Our positive results therefore are another good argument, that the HE of the thyroid is a tumour of endothelial origin.

3. Clinical datas

a) Incidence. Among the cases of HE, collected from different institutes, an exact incidence could not be established. In his paper "Thyroid malignancies in the autopsy and biopsy material of Zürich from 1900 to 1964" (histologically not controlled) Kind (1966) found 69 HE in 416 autopsy cases and 97 HE in 964 biopsy cases of thyroid malignancies, giving an incidence of 16,5% and of 10% respectively. In Berne, Thalmann (1954) found an incidence of 22%, while Stühlinger (1940) in Innsbruck reported a percentage of 9,9. In more recent papers, the incidence of HE in Switzerland is much lower. Bubenhofer and Hedinger (1977) diagnosed 7,1% of all thyroid malignancies from 1925 to 1941 at the University of Zürich as HE (histologically controlled). Neracher and Hedinger (1975) found in the same collection between the years 1962 to 1973 only 4,3% HE.

Morever, in the large collection of 1181 cases of thyroid malignancies of Woolner et al. (1968), the HE does not appear at all.

b) Age and sex. Of 65 patients with known histories 40 were men and 25 women with an average age of 65.2 years for men and of 68.1 years for women at the time of the first examination. Therefore, in our material, the HE is a tumour of old age. The youngest male patient was 49, the youngest female patient 30 years old. Somewhat exceptional for a thyroid tumour is our sex distribution of 40:25 in favour of men, though some other authors also mention a strikingly higher incidence of men. In the files of the Institute of Pathology of Berne, there are 22 cases of HE in the years between 1947 and 1963 (Cottier 1966, personal communication).

The distribution of sex is 15:7 (male:female), i.e. essentially the same as in our material. In contrast to these findings, the distribution in cases collected from the literature is about 1:1.

c) Symptoms and signs. A goitre, present and having had the same size for years, suddenly starting to grow, sometimes with pain in the neck radiating into the head or into the arms, is a frequent finding in our cases.

Difficulty swallowing, and dyspnea are mentioned too. Sometimes, an increasing emaciation is the only sign.

When the trachea is invaded, one may find bloodtinged sputum or massive hemoptysis. Sometimes, the initial presentation is rather unusual: Blum (1936) was the first to report a hemothorax, originally of unknown origin. Further reports came from Stühlinger (1940) and from Sapinski (1941). Our material too contains similar cases.

Bacher (1953) was the first to describe in detail a case in which fever was a prominent sign. Other reports came from Hedinger (1909), Rausch (1935/36), and Bretscher (1955). We too find occasional cases with fever. Initially therefore, the neoplasia is often diagnosed and treated as thyroiditis. Sometimes, even a melena may be the first sign of a HE (Ferber (1962); our own case).

Hemorrhage of the gums following a metastasis in the gingiva has been described by Matti (1935). Since then, this sign though it is rare (three cases in our collection), is thought to be especially characteristic.

d) Course. The course of the disease depends mainly on the stage at which the patient first receives treatment. Too often, the tumour cannot be radically removed at the initial operation, because either it has already invaded the trachea or the esophagus, or the tumour is ill defined against the surrounding tissues. In these cases, in spite of intensive therapy, there are local recurrences after a very short time.

For our 18 patients with both surgical and autopsy material, the mean interval between operation and death was 3,2 months. The course of the disease is sometimes so rapid, that metastases are manifest before the primary tumour is detected, or that the primary tumour can be found only at the post-mortem examination after death due to a tumour of unknown origin.

4. Geographical distribution of the HE

Up to the end of 1981, 143 detailed cases could be found in the literature. Many of these were reported before 1940.

79 cases are described in papers from Switzerland, 40 cases in papers from Austria (plus 74 cases without details) and seven more cases from France.

Therefore, it may be inferred, that the HE is a tumour which is described essentially in Central Europe and especially in countries of which the Alps constitute a major part. Outside this geographic area, the tumour has been described only sporadically. From this observation, two conclusions could be drawn:

1. The HE of the thyroid is a tumour occuring almost exclusively in the Alps area, which is also an area of endemic goitre. Although there are areas of endemic goitre outside the Alps, where the HE is unknown, the HE is also found in the goitre area of the Andes in South America [Cubilla (1974) personal communication; Cuello (1968) personal communication]. Other still unknown factors could be the cause of this peculiar distribution.

2. The interpretation of this tumour varies from country to country. This assumption could very well explain the difference in incidence of this tumour between the German and the English language literature.

Conclusions

The HE of the thyroid is a distinct tumour with a characteristic clinical picture and course and a peculiar geographic distribution.

The light microscopic appearance is very variable, ranging from a picture similar to an anaplastic carcinoma to one resembling an angiosarcoma. This has been the reason for much controversy concerning the nature of this tumour culminating in the statement, that all these tumours in reality are undifferentiated carcinomas, simulating vascular structures because of shrinking artifacts.

In our electron microscopic study of some of these tumours we could demonstrate in two cases certain, and in another case equivocal presence of Weibel-Palade bodies within tumours cells.

Together with the presence of intracytoplasmic filaments and pinocytotic vesicles, these components prove the endothelial origin of the cells, in which they were found.

The presence of FVIIIRAG also confirms the endothelial character of these cells. The fact, that this factor was demonstrated in two cases, and especially that it was found in metastatic tumour cells, supports the opinion in these cases of HE of the thyroid, that the tumour cells have an endothelial origin.

Some cases were classified light microscopically as HE in which neither Weibel-Palade bodies nor the presence of FVIIIRAG could be detected. This could be explained by the dedifferentiation of tumour cells in many cases of HE. This explanation is also given by other authors for negative findings of FVIIIRAG in angiosarcomas.

This may also signify, that the HE of the thyroid is a heterogenic group of tumours of endothelial and epithelial origin.

The proven endothelial origin of the tumour cells of at least some of the HE of the thyroid justifies the continuance of the HE as a tumour class in the classification of thyroid tumours.

Acknowledgements. The author wishes to express his gratitude to:

Proff. Chr. Hedinger, Zürich, and J.R. Rüttner, Zürich, for their kind permission to use the material of the Department of Pathology and the former Institute of Histopathology of the University of Zürich, as well as far their general support.

Proff. H. Cottier, Berne, F. Gloor, St. Gallen, Th. Hardmeier, Münsterlingen, J.P. Mühlethaler, Aarau, and R. Siebenmann, Zürich, for sending pertinent material.

To Mrs Sarem, Zürich, for doing the FVIIIRAG examination; to Dr. Schlatter, Winterthur, for her assistance with the English manuscript; and to Mrs. Ehrensperger, Winterthur, for her bibliographic support.

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Accepted March 21, 1983