Virchows Arch. A Path. Anat. and Histol. 370, 185—192 (1976)

Case Report

A Carcinoid Occurring in the Testis

K. Wurster, O. Brodner, J. A. Rossner, and D. Grube

Institute of Pathology and Pathologic Anatomy
(Director: Prof. Dr. W. Doerr), Institute of Anatomy,
University of Heidelberg

Received September 15, 1975

Summary. Carcinoids of the testis are rare tumours developing in three different ways: 1. It may differentiate within a teratoma, 2. it may be a metastasis of a "loco alieno" seated carcinoid and 3. it may represent a real primary carcinoid. The observation of a primary testicular carcinoid in a man aged 55 years afforded the opportunity to study such a tumor for the first time by electron microscopic and fluorescence microscopic methods. Thereby, it could be shown, that this testicular carcinoid corresponds to the carcinoids of the lower small gut. According to the specific ultrastructure of the intracytoplasmic granules it must derive histogenetically from an EC-cell. At the moment it cannot be decided whether the primary testicular carcinoid represents an autochthonous tumor of the male gonad or solely a teratoma with one-sided differentiation in the sense of a simplified teratoma.

Zusammenfassung. Carcinoide des Hodens sind selten. Für ihre Entstehung sind drei verschiedene Möglichkeiten gegeben: Erstens können sie Differenzierungsprodukte einer teratoiden Geschwulst darstellen; zweitens kann es sich um Metastasen loco alieno gelegener Carcinoide handeln und drittens können sie als echte primäre Carcinoide vorliegen. Die Beobachtung eines primären Carcinoids bei einem 55jährigen Mann gab uns die Gelegenheit, eine solche Geschwulst erstmals elektronenoptisch und fluorescenzoptisch zu untersuchen. Es zeigte sich, daß sie in ihrem Aufbau den Carcinoiden des unteren Dünndarms entspricht und histogenetisch von einer EC-Zelle abstammt. Eine endgültige Entscheidung darüber, ob das primäre testikuläre Carcinoid eine autochthone Geschwulst der männlichen Gonade oder einfach ein einseitig ausdifferenziertes Teratom im Sinne eines "simplified teratoma" darstellt, ist momentan jedoch noch nicht möglich.

The observation of an argentaffin testicular tumor was first mentioned by F. Feyrter (1951). A more detailed study was given by Simon et al. (1954). Since then 10 other cases have been reported, their pathogenic specialities are classified in 3 different groups (Table 1). Three cases developed in teratomas (Simon et al., 1954; Berkheiser, 1959; Sinnatamby et al., 1973), 3 cases corresponded to metastases of intestinal carcinoids (Collins and Pugh, 1964; Kemble, 1968; Dockerty and Scheifley, 1955) and only 5 cases which have been primary carcinoids (Collins and Pugh, 1964; Kemble, 1968; Kermarec and Duplay, 1968; Yalla et al., 1974). In all these cases the pathological diagnosis was made with the aid of conventional histological slides only.

The observation of another case gave us the opportunity to examine the tumor by electron microscopic and fluorescence microscopic methods under the view of its endocrinological activity, especially the synthesis of serotonin and also its histogenetical relation to the APUD-System.

Table 1. Cases of testicular carcinoids reported until now

Authors, age of patient	Size of tumors	Localization	Metastases	Argentaffinity	Carcinoid syndrome	Postoperative control
Group 1: carcinoids developing in teratomas						
Simon (1954) 58 y	teratoma diff. ⌀ 5 cm carcinoid ⌀ 8 mm	left-side	—	+	—	—
Berkheiser (1959) 54 y	teratoma 8 × 6, 5 × 5 cm, carcinoid disseminated	left-side	—	+	—	—
Sinnatamby (1973) 31 y	teratoma ⌀ 4 cm	left-side	—	+	—	6 months
Group 2: testicular metastases of an intestinal carcinoid						
Kemble (1968) 63 y	⌀ 5 mm	right-side	liver, mesenterial and portal lymph nodes	+	—	died several months later
Collins and Pugh (1964) —	—	—	mesentery, peritoneum	+	—	died several months later
Dockerty and Scheifley (1955) 35 y	⌀ 2,5 cm	right-side	mesenterial and retroperitoneal lymph nodes	no information	+	died 12 years later by pericarditis constrictiva
Group 3: primary carcinoids						
Collins and Pugh (1964) (two cases)	up to 3 cm	—	—	+	—	5 and 24 years
no age indicated		—	—	+	—	
Kemble (1968) 53 y	5 × 3 × 3,5 cm	right-side	—	+	—	3 years
Kermarec (1968) 59 y	8 × 4 × 3,5 cm	left-side	—	+	—	11 months
Yalla (1974) 45 y	ca. 6 cm	right-side	—	+	—	> 4 years
Wurster (1976) 55 y	7 × 8 × 6 cm	right-side	—	+	(+)	3 years

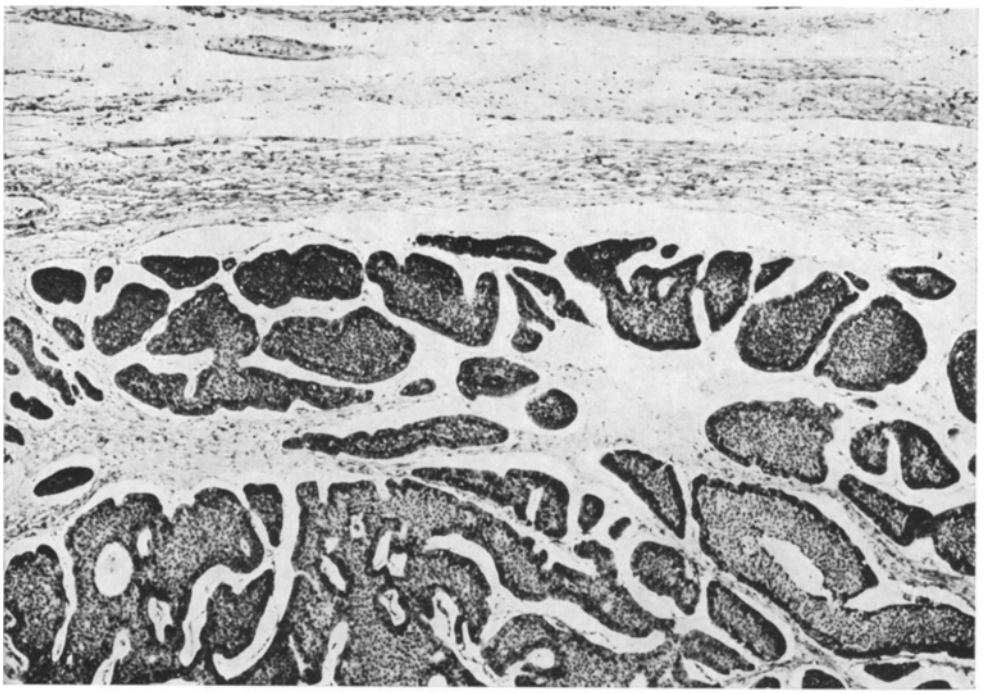

Fig. 1. Primary carcinoid of testis. Regressively changed and compressed testicular tubes are present in the upper part of the figure. G. S. 55 y., EH 35047/72, HE, ×80

Case

The 55 year old obese patient recognized a slowly increasing swelling of the right testicle which was symptomless in the beginning, but later he developed an increasing feeling of heaviness. Further he complained about diarrhoea and postprandial sweating. Suspicious of a testicular tumor, orchiectomy was done. Diarrhoea and postprandial sweating disappeared postoperatively. Four years later the steadily controlled patient is still symptomless.

From the patients' history it is noted a myocardial infarction in 1968 and he had excised twice adenomatous polyps of the large bowel.

Blood Chemistry. BSR 22/49 (Westergreen), total bilirubin 1.26 mg-%, total lipids 1.629 mg-%, neutral fat 420 mg-% (Hyperlipoproteinemia IIa).

Other blood, serum, plasma and urinary values within normal ranges.

Pathological Examination (EH 35047/72)

Macroscopy. The right testicle measures 7×8×6 cm, possessing a smooth and gleaming surface. The cutsurface shows a yellow partially necrotic tissue interspearsed with multiple small haemorrhagies. Intact testicular tissue is no longer to identify. Epididymis and funiculus spermaticus are not infiltrated.

Microscopy. (Staining methods: HE, v. Gieson, Bodian, Fontana-Masson) (Figs. 1 and 2).

The tumorous tissue presents the typical histomorphology of a small bowel's carcinoid showing distinct argyrophil and argentaffin behaviour. The eosinophilic and fine granulated tumorous cells, arranged in coarse strands and nests are predominantly round and polygonal shaped. But the surface of cell clusters are covered by columnar cells arranged in a single

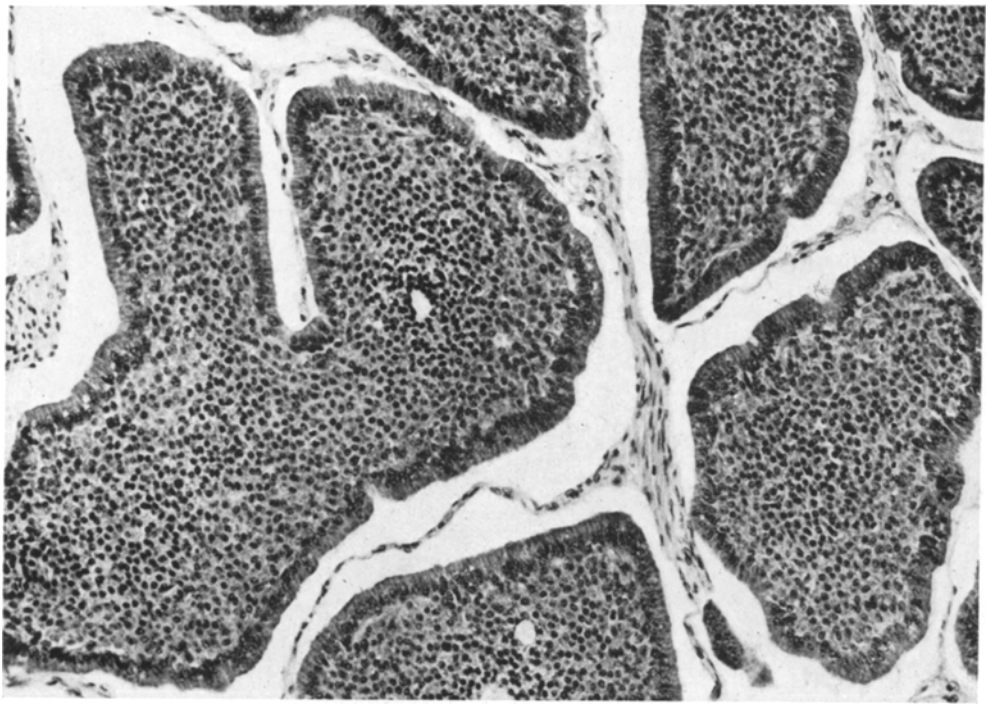

Fig. 2. Cell clusters of testicular carcinoid surrounded by columnar tumor cells. HE, ×220

layer and showing an increasing density of granulation along the cellular basis. Nuclear pycnosis are often present, but mitotic activity is only seen in a few cells. The loosely woven interstitial tissue is well capillarized. Implicating encapsulation the surface of the mass is covered by fibrous tissue which is in some parts infiltrated by the tumor. A small seam of compressed and regressively changed testicular tissue is still present between tunica albuginea testis and the tumor.

Electron Microscopic Examination

Originally fixed in 4% neutral formalin and embedded in paraffin the tissue was subsequently embedded in Araldit® for electron microscopic examination, using the KMU-technic of J. A. Rossner (1971). Inspite of extensive autolytic changes there could be found a multiplicity of pleomorphic granules in the extranuclear space of the cells, which are variable in size but equally osmiophilic. Measuring a hundred of them the diameter is 290 nm in average. The even recognizable prickly outline of the surface is to be interpreted as a shrinking effect (Fig. 3). The nuclear chromatin is clotted and the nuclear membranes are showing signs of disintegration.

Fluorescence Microscopic Examination (Method of Enerbäck, 1973)

After appropriate treatment the tissue shows an extensive yellow fluorescence under uv-light, which is specific for a high concentration of serotonin (Fig. 4). The fluorescence is more extensive in the peripher located columnar cells than in the central located cells of round and polygonal shape. By fixation of tissue specimen in aqueous formalin, serotonin diffuses into the interstitial tissue, which shows therefore a strong fluorescence too.

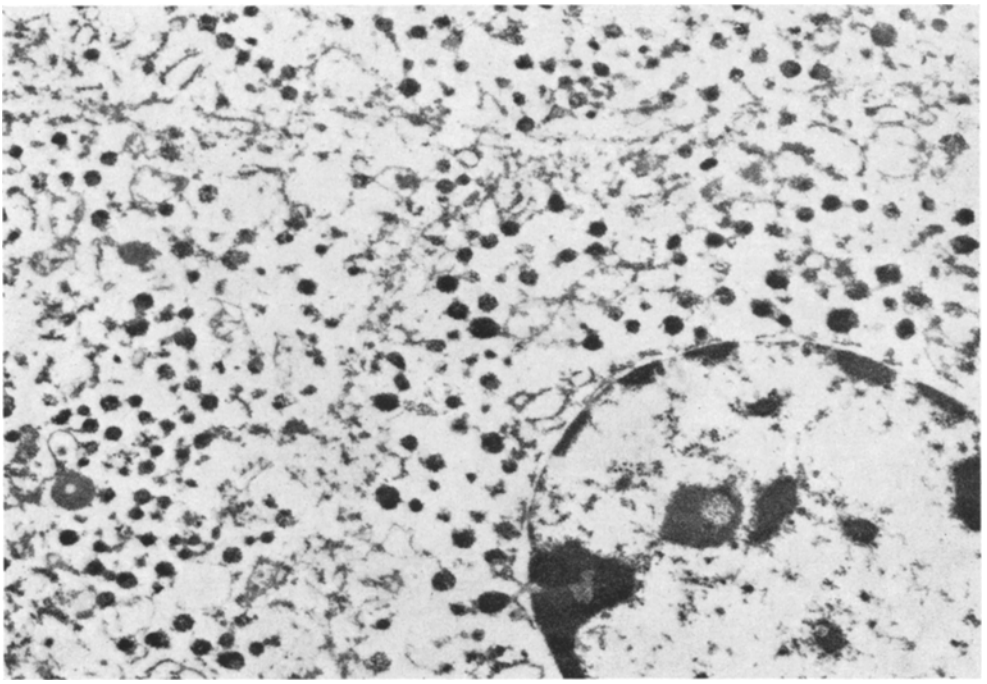

Fig. 3. Multiple pleomorphic and osmiophilic granules in the cytoplasm of tumor cells. ×19,380

Discussion

Carcinoids belong to the group of "apudomas", histogenetically deriving from the diffuse endocrine cell system, the socalled "APUD"-System of Pearse (1969), respectively the "Helle-Zellen"-System of Feyrter (1956, 1958). According to Pearse (1969) these cells emigrate the neural ridge during its ontogenesis, finding them spreading all over the body (Hamperl, 1952; De Muylder und Fayt, 1954; Feyrter, 1958).

The carcinoids are a heterogenic group of tumors. Examination of different intestinal carcinoids concerning the morphology of its granules have shown, that for their histochemic behaviour and its secretory quality, the tumorous cells look like those endocrine stemcells, which are normally present in these places (Black, 1968; William and Sandler, 1963). Pearse assumes at least 18 different cell types of his "APUD"-cell series (Pearse, 1969; Pearse and Welbourn, 1973). Enteral endocrine active cells are postulated, that they are to be characterized definitely by the shape of their secretory granules (Forssmann and Solcia, in Creutzfeldt (Ed.) 1970). Grube (1974) was able, relating to informations given in the international literature and to his own electron microscopic examinations, to differentiate 9 intestinal endocrine active cells. But only the EC-cells contain granules, which are simultaneously pleomorphic, variable in size and osmiophilic, like the granules of our tumor case. The fact, that in our case the diameter of granules, which are normally 350 nm, measured only 290 nm in average is to be

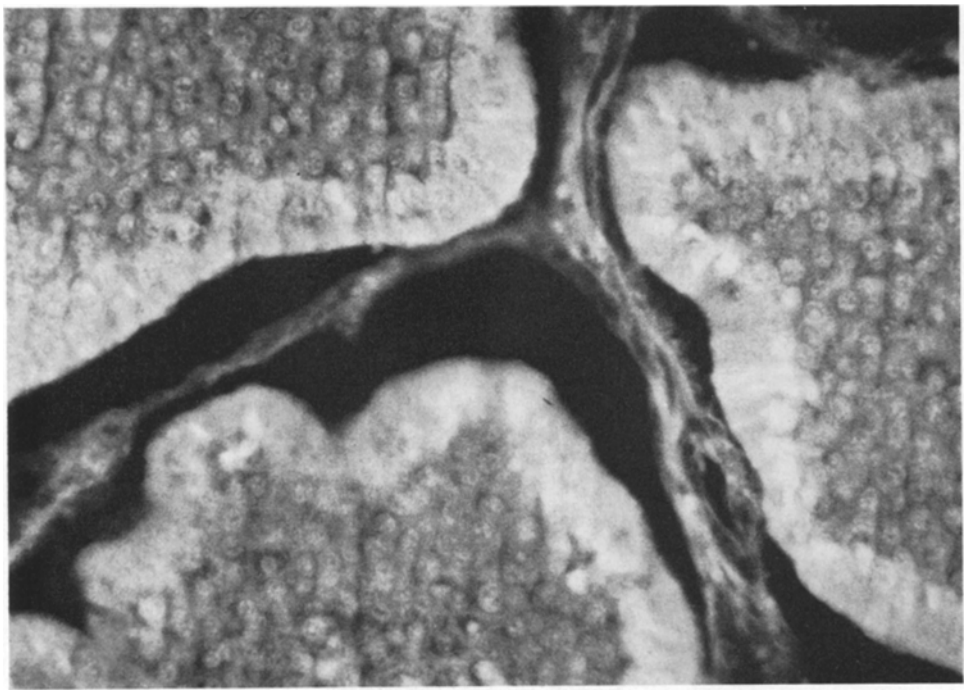

Fig. 4. Intensive yellow fluorescence of tumor tissue, specific for serotonin. ×650

interpreted as a consequence of fixation in formalin, which is inadequate for electron microscopic examination. Further only the EC-cell is in a position to synthesize Serotonin besides 5-HTP, Motilin and probably also VIP (Pearse et al., 1974; Grube, 1975). The characteristic histomorphology of the tumor tissue (Feyrter, 1934), its argentaffinity and its ability for synthesis of serotonin and also the typical electron microscopic shape of intracytoplasmic granules justifies the conclusion, that this testicular tumor derives from an EC-cell.

Table 1 shows the cases of testicular carcinoids, reported so far, behaving also as argentaffin except for one case not examinated. Carcinoids as parts of teratomas are relatively more often seen in the ovary (Qizilbash et al., 1974). Probably they develop from APUD-cells in gastrointestinal or respiratory epithelium of these tumors (Climie and Heath, 1968; Simon et al., 1954; Sinnatamby et al., 1973). Those cases, which represent testicular metastases of intestinal carcinoids, are easily understood. But finally the histogenesis for the cases of group 3 remains obscure. Following the concept of Pearse (1969) it seems possible, that APUD-cells reach also the gonadal anlage. But to the best of our knowledge, EC-cells haven't been discovered in the testis until now. On the other hand it is to be discussed, if these primary carcinoids represent monophyletic, one-sided differentiated, socalled "simplified" teratomas (Brown and Richart, 1969; Kermarec and Duplay, 1968). Argentaffin cells have been pointed out in the tunica mucosa of urinary bladder and urethra, in the prostate and Cowper's glands and recently

also in the epididymis (Feyrter, 1951; Grube, 1975). Therefore, it seems justifiable to postulate an EC-cell, originally present in the testis, as source of primary testicular carcinoids.

On average the patients with primary carcinoids whose ages reached from 45 to 59 years, given in 4 of 6 cases (Table 1) are older than the average age of patients with testicular germinal tumors (Wurster, 1973). Also relatively old are those patients with carcinoids developing in teratomas. The given sizes of tumors vary between "just visible" in the case of Berkheiser (1959) and $7 \times 8 \times 6$ cm in our case. Further it seems worth mentioning that carcinoids developing in teratomas are small compared with the sizes of primary carcinoids, a point also contradicting the concept of primary carcinoids as a "simplified teratoma", like the relatively old average age in patients with primary carcinoids.

Symptoms of a carcinoid syndrome, present in 50% of cases with ovarian carcinoids (Brown and Richart, 1969), developed only in 2 patients with testicular carcinoids (Dockerty and Scheifley, 1955, own case). Because of its exposed location, testicular carcinoids are earlier recognized and earlier operated than ovarian carcinoids. Our patient complained of diarrhoea and postprandial sweating only after having been asked directly about it.

The postoperative courses of the individual cases are reported in Table 1. Two patients of group 2 died as consequence of metastasizing, primary intestinal carcinoids. Concerning the cases of group 1 prognostic conclusions are not possible. Cases of group 3 are partially under control since a long time and it seems, that primary testicular carcinoids correspond to the carcinoids of the lower small bowel not only in its morphology, but also in its biologic behaviour (Feyrter, 1934).

References

Berkheiser, S. W.: Carcinoid tumor of the testis occurring in a cystic teratoma of the testis. J. Urol. (Baltimore) **82**, 352–355 (1959)

Black, W. C.: Enterochromaffin cell types and corresponding carcinoid tumors. Lab. Invest. **19**, 473–486 (1968)

Brown, P. A., Richart, R. M.: Functioning ovarian carcinoid tumors. Obstet. and Gynec. **34**, 390–395 (1969)

Climie, A. R. W., Heath, L. P.: Malignant degeneration of benign cystic teratomas of the ovary. Cancer (Philad.) **22**, 824–852 (1968)

Collins, D. H., Pugh, R. C. B.: The pathology of testicular tumours. Brit. J. Urol. **36**, Suppl., 75–76 (1964)

Creutzfeldt, W. (Ed.): Origin, chemistry, physiology and pathophysiology of the gastrointestinal hormones. Stuttgart-New York: Schattauer 1970

De Muylder, C. H., Fayt, P.: Au sujet de la nature réelle de certaines tumeurs primitives des bronches. Acta chir. belg. **53**, 716–721 (1954)

Dockerty, M. B., Scheifley, C. H.: Metastasizing carcinoid. Report of an unusual case with episodic cyanosis. Amer. J. clin. Path. **25**, 770–774 (1955)

Enerbäck, L.: Specific methods for detection of 5-Hydroxytryptamin in carcinoid tumors. Virchows Arch. Abt. A **358**, 35–43 (1973)

Feyrter, F.: Carcinoid und Carcinom. Ergebn. allg. Path. path. Anat. **29**, 305–489 (1934)

Feyrter, F.: Zur Pathologie des urogenitalen Helle-Zellen-Systems. Virchows Arch. path. Anat. **320**, 564–576 (1951)

Feyrter, F.: Zur Lehre von den peripheren endokrinen (parakrinen) Drüsen des Menschen, neue Erkenntnisse. Wien. med. Wschr. **106**, 515–516 (1956)

Feyrter, F.: Über die peripheren endokrinen (parakrinen) Drüsen des Menschen. Krebsarzt **13**, 169–180 (1958)
Grube, D.: Die endokrinen Zellen des Magen-Darmepithels und der Stoffwechsel der biogenen Amine im Magen-Darmtrakt. Habilitationsschrift, Heidelberg 1974
Grube, D.: Personal communication
Hamperl, H.: Über argyrophile Zellen, Virchows Arch. path. Anat. **321**, 482–507 (1952)
Kemble, J. V. H.: Argentaffin carcinomata of the testicle. Brit. J. Urol. **40**, 580–584 (1968)
Kermarec, J., Duplay, H.: Tumeur carcinoide apparemment primitive du testicule. Arch. Anat. Path. **16**, 56–58 (1968)
Pearse, A. G. E.: The cytochemistry and ultrastructure of polypeptide hormon-producing cells of the APUD-series and the embryologic, physiologic and pathologic implications of the concept. J. Histochem. Cytochem. **17**, 303–313 (1969)
Pearse, A. G. E., Polak, J. M., Heath, C. M.: Polypeptide hormone production by "carcinoid" apudomas and their relevant cytochemistry. Virchows Arch. Abt. B **16**, 95–109 (1974)
Pearse, A. G. E., Welbourn, R. B.: The Apudomas. Brit. J. Hosp. Med. 1973, 617–624
Quizilbash, A. H., Trebillock, R. G., Patterson, M. C., Lamint, K. G.: Functioning primary carcinoid tumor of the ovary. Amer. J. Clin. Path. **62**, 629–638 (1974)
Rossner, J. A.: Morphologische Untersuchungen im Licht- und Elektronenmikroskop mit der kontinuierlichen morphologischen Untersuchungstechnik (KMU-Technik). Verh. dtsch. Ges. Path. **55**, 824 (1971)
Simon, H. B., McDonald, J. R., Culp, O. S.: Argentaffin tumor (carcinoid) occurring in a benign cystic teratoma of the testicle. J. Urol. (Baltimore) **72**, 892–894 (1954)
Sinnatamby, C. S., Gordon, A. B., Griffiths, J. D.: Teratoma of the testis. Brit. J. Surg. **60**, 576–579 (1973)
Williams, E. D., Sandler, M.: The classification of carcinoid tumours. Lancet **1963I**, 238–239
Wurster, K.: Klassifizierung testikulärer Keimzellgeschwülste. Neue Gesichtspunkte auf Grund morphogenetischer Studien. Habilitationsschrift, Heidelberg 1973
Yalla, S. V., Yalla, S. S., Morgan, J. W., Eberhart, C. A., Olley, J. F.: Primary argentaffinoma on the testis: a case report and survey of the literature. J. Urol. (Baltimore) **111**, 50–52 (1974)

Priv. Doz. Dr. med. K. Wurster
Institute of Pathology and
Pathologic Anatomy, University
of Heidelberg
Im Neuenheimer Feld 220–221
D-6900 Heidelberg
Federal Republic of Germany