Virchows Arch. A Path. Anat. and Histol. 370, 207—224 (1976)

Cyto- and Histomorphogenesis of the Prostate Carcinoma*

A Comparative Light- and Electron-Microscopic Study

H. Kastendieck and E. Altenähr

Institute of Pathology (Head: Prof. Dr. G. Seifert) of the University of Hamburg

Received December 18, 1975

Summary. The fundamental histologic proliferation patterns of the prostate carcinoma are presented by the glandular and solid and/or cribriform structures. These were ultrastructurally analyzed from 28 carcinomas based on the cell forms in prostate carcinomas, which were already defined by electron microscope. These are characterized by their different cytoplasmic differentiation, whereby the singular cell types each represent a different functional state of a common tumor cell. The results indicate that the prostatic carcinoma develops morphologically in phases. The well-known growth patterns of the tumor are equivalent to its different states of development. In the first phase, a pattern develops out of a tumor stem cell (perhaps "primary atypical reserve cell"), which is either glandular or solid/cribriform, whereas this depends on the trend of the tumor cells to differentiate. The glandular structure possesses centrifugally proliferated glandular, often functionally deranged tumor cells, and shows signs of early stromal infiltration. The solid/cribriform pattern consists of centripetal proliferated, often less-differentiated tumor cells with or without lumen formation, and a peripheral layer of basal cells, whereby the idiopathic stroma architecture remains as it is. In the successive phase, stroma infiltration and destruction is distinctly marked during tumor growth. Histologically, one often sees at this stage an "anaplastic" pattern; however, ultrastructurally its origin can be recognized as being glandular or solid/cribriform. The advanced stages of the tumor are furthermore characterized by a mixed cell pattern with all states of differentiation and by progressing tumor cell degeneration.

Introduction

The morphologic classifications of the prostate carcinoma are numerous (Edwards et al., 1953; Gleason, 1966; Utz and Farrow, 1969; Mostofi, 1969; Mostofi and Price, 1973; Dhom, 1974). They are based on the histologic growth patterns of the tumors and/or cellular atypia. The aspired result is a histologic or cytologic grading, which allows a prognostic statement to be made about the tumor behavior or its susceptibility to therapy (Wiederanders et al., 1963; Gleason, 1966; Mellinger et al., 1967; Esposti, 1971; Gleason et al., 1974). Unfortunately, until now one has not been able to agree upon a uniform and generally recognized classification of the prostate carcinoma. The reason for this is caused by the variable appearance of each prostatic carcinoma in itself. Furthermore, the difficulties for a proper prognosis result because different structures are often found side by side in one histologic slide (Mostofi, 1969; Mostofi and Price, 1973).

The former investigations on the ultrastructure of prostatic carcinoma were primarily concerned with describing the cytomorphologic features of the carcinoma cells; secondly, with finding an electron-microscopic correlation to well- or poorly differentiated prostate carcinomas (Takayasu and Yamaguchi, 1962; Brandes

* Supported by the foundation: "Hamburger Stiftung zur Förderung der Krebsbekämpfung"

et al., 1964; Fisher and Jeffrey, 1965; Mao et al., 1966; Kudo, 1967; Kirchheim and Bacon, 1968; Fisher and Sieracki, 1970; Sinha and Blackard, 1973). The essential result of these investigations shows that ultrastructurally high- and poor-differentiated tumor cells are to be found in histologically high-differentiated as well as in anaplastic prostate carcinomas (Mao et al., 1966).

In the present study the histologic proliferation patterns of the prostate carcinoma is analyzed ultrastructurally. Hereby we try to find a correlation between the fundamental histologic structures — glandular and solid and/or cribriform — and the cell forms in the prostate carcinoma, which we have already described electron microscopically (Kastendieck et al., 1973).

These investigations show on the one hand striking similarities with the singular histologic differentiation types and their ultrastructure (Murad and Scarpelli, 1967; Goldenberg et al., 1969; Murad, 1971; Ozzello, 1971, 1974; Slemmer, 1974; Gould et al., 1975), and on the other hand new aspects of formal pathogenesis of prostatic carcinoma.

Material and Method

Twenty-eight histologically proven, clinically mostly advanced prostate carcinomas were studied by light and electron microscope. The tumor classification was based upon their histologic proliferation patterns and divided into three groups: (1) mainly glandular, (2) mainly solid and/or cribriform, and (3) different patterns with anaplastic areas. Two carcinomas with papillary architecture were not considered for this study. In semithin sections the specific structure patterns were located and then ultrastructurally analyzed. This investigation was based on the existing electron microscopically defined cell forms in the prostate carcinoma (Kastendieck et al., 1973). The preparation of the tumor material, which was obtained by transrectal punch biopsy, was identical to the method described in the preliminary studies (Kastendieck et al., 1973, 1974, 1975). Equipments: ultramicrotome Om U/2 Reichert; electron microscopes: Zeiss EM 9A, Siemens Elmiskop I.

Results

Morphology of the Prostatic Carcinoma

The prostate carcinoma represents itself fundamentally in three different light-microscopic structure forms:

1. Glandular pattern (Fig. 1).
2. Solid and/or cribriform pattern (Fig. 5).
3. Anaplastic pattern (Fig. 9).

Five different tumor cell types are found ultrastructurally:

1. Undifferentiated, embryonic tumor cell (Type I; Fig. 6).
2. Immature tumor cell with a beginning glandular differentiation (Transition form, Type II; Fig. 2, 7).
3. Highly differentiated glandular tumor cell (Type III; Fig. 2).
4. Functionally deranged glandular tumor cell with cytoplasm overloaded by organelles (Type IV; Fig. 3, 4).
5. Degenerative tumor cell (Type V; Fig. 11).

Furthermore, one may find typical basal cells in some carcinomatous structures (Fig. 5).

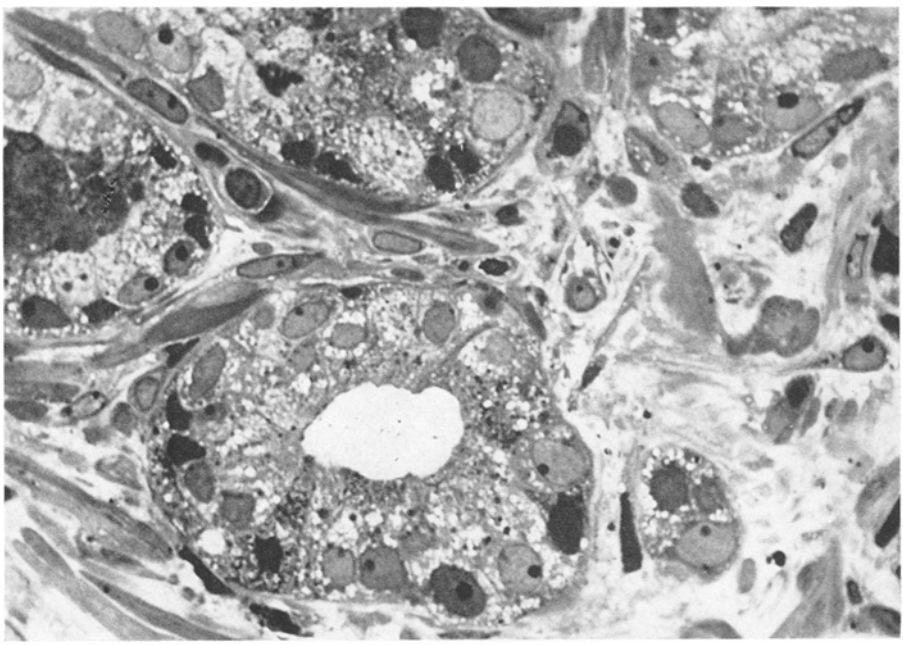

Fig. 1. Histology of glandular pattern: small acinus with central lumen and one layer of cylindric tumor cells. Mixed cell picture; distinct cellular atypia with polymorphous, light and dark nuclei. Toluidine blue. × 800

1. Glandular Pattern. Here one sees with the light microscope microacinar complexes of tumor cells, where cuboid and cylindric cells are grouped around a small lumen usually in one single layer (Fig. 1). Although the polar structure of the tumor cells is often intact, the cellular atypia is distinctly marked. The nuclear and cytoplasmic density of the tumor cells varies strongly, the cellular pattern becomes mixed. Electron microscopically the cytoplasm of the tumor cells is differently formed because of its variable content of organelles, whereby different stages of tumor cell maturation may be found next to each other (Fig. 2). Hereby carcinomatous glandular cells can be developed so highly that no morphologic sign for a potential malignancy exists (Type III). The functionally deranged glandular tumor cells (Type IV; Fig. 3) are, however, mostly represented in the glandular pattern. Its nucleus is usually heterochromatic, the cytoplasm seems dark and has a great number of organelles which are capable of secretion. The disproportional increase of organelles, their irregular distribution (e.g., polytope Golgi complexes), and the progressive dilatation of the rough endoplasmic reticulum are noticeable features of these tumor cell types. Additionally one finds a disturbed surface differentiation with partially branching, bulky, and very long microvilli (Fig. 3). Near the surface the tumor cells are connected by chainlike desmosomes. Typical matured secretory vacuoles are seldom found in the cytoplasm and almost never in the lumen of the tumor glands.

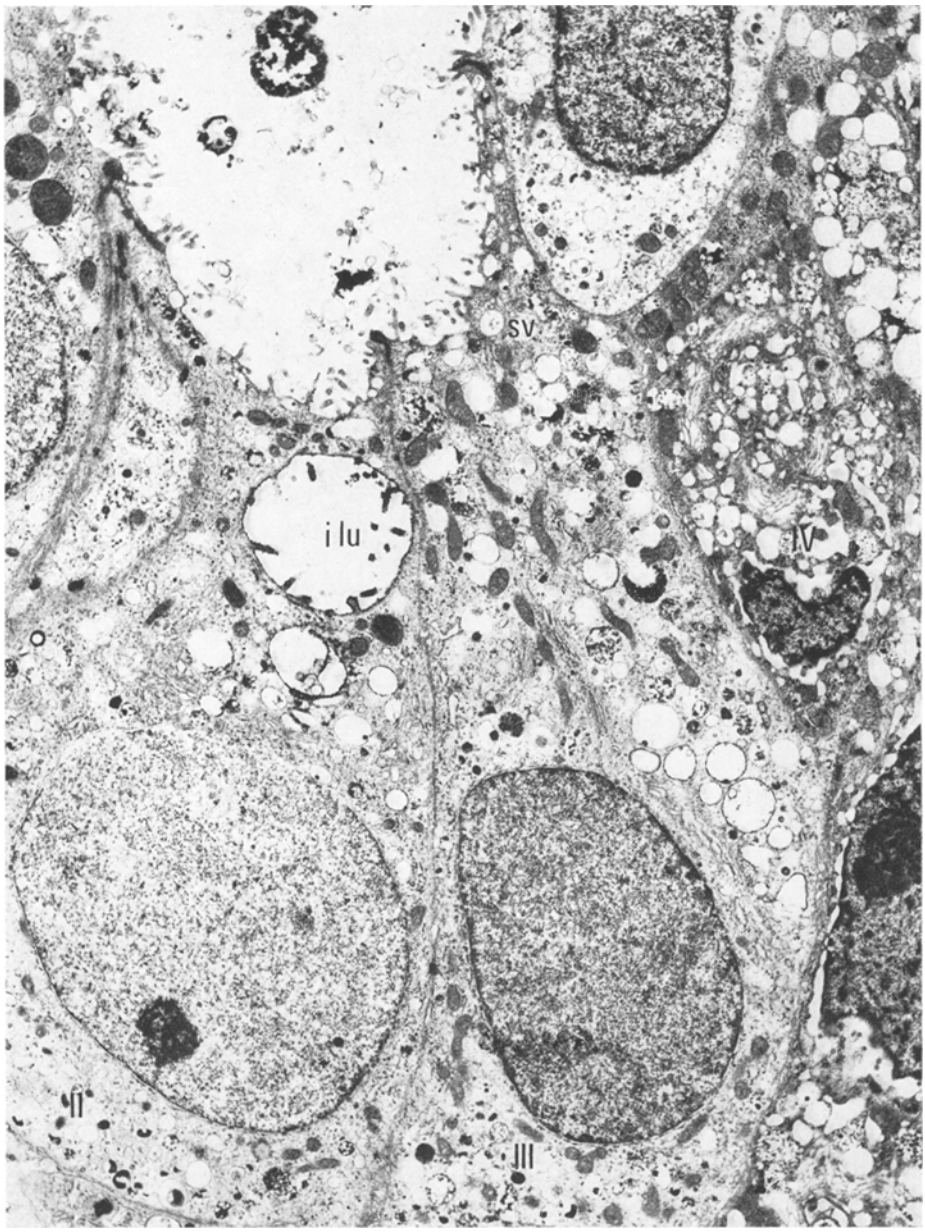

Fig. 2. Ultrastructure of glandular pattern: glandular tumor cells at different stages of development. Left: tumor cell with beginning maturation of cytoplasm and euchromatic nucleus (Type II); middle: highly differentiated tumor cell with polar architecture and signs of functional activity (Type III); right: part of functionally deranged tumor cell with dark cytoplasm, rich in organelles (Type IV). *ilu* intracytoplasmic lumen, *sv* secretory vacuoles. × 7,000

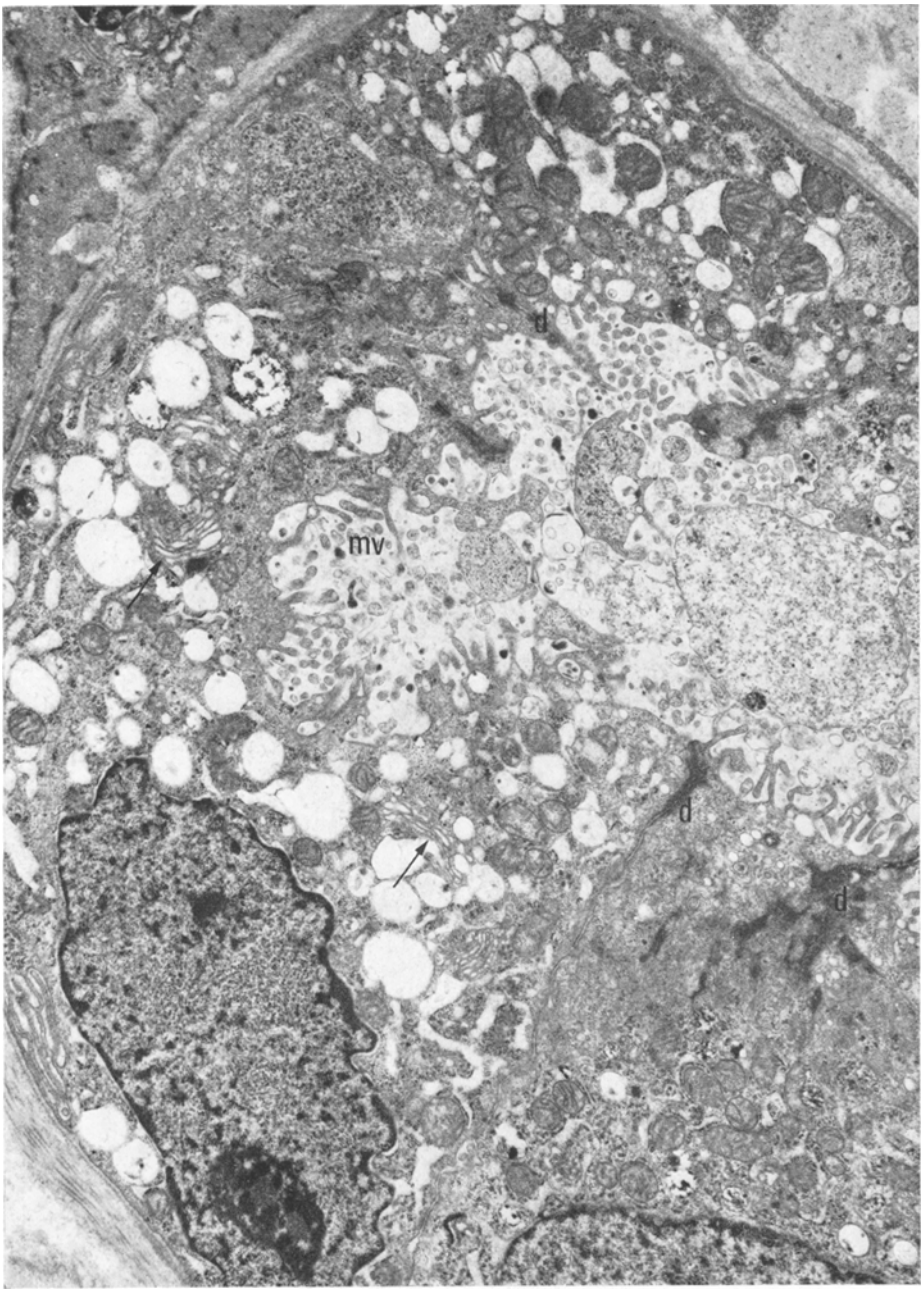

Fig. 3. Tumor acinus with tumor cell type IV: heterochromatic nucleus, loss of polar cytoplasmic architecture, disproportionate increase of organelles (→ multiple Golgi complexes). On surface numerous irregular microvilli (*mv*). *d* desmosomes. × 6,500

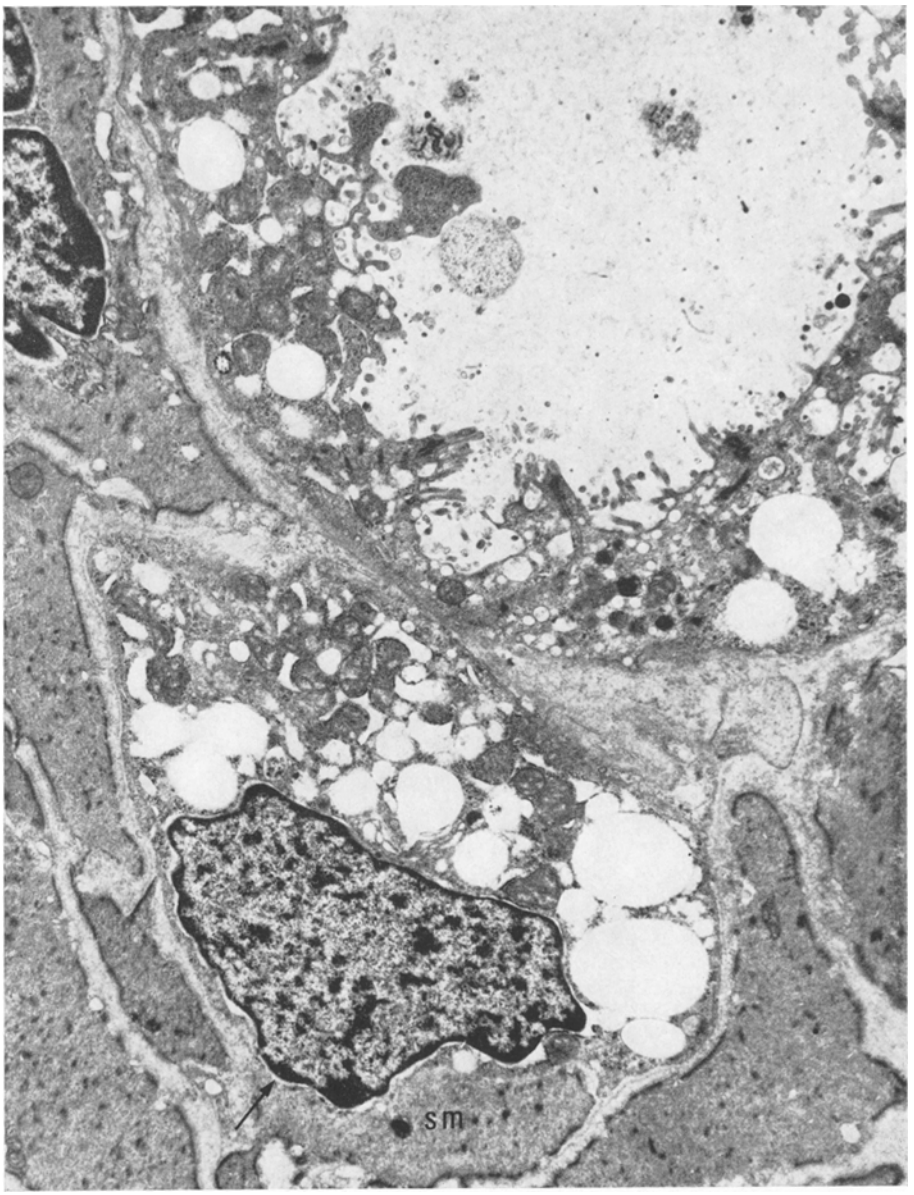

Fig. 4. Early stromal infiltration by glandular tumor structures (cell type IV): splitting up of smooth muscle bundles and adjacency to muscle cell (→) by loss of basement membrane. *sm* smooth muscle cell. × 9,200

At an early stage, a junction of the microacinar tumor structures to the fibromuscular organic stroma is to be seen. The normal architecture is disrupted (Fig. 1, 4). After loss of their basement membrane the tumor cells settle directly

next to the smooth muscle cells; additionally, a destruction of myofibrils occurs by lysis of the plasmalemma. Usually these infiltrating tumor cells are those of Type IV (Fig. 4). With advanced tumor growth and progressive infiltration of the stroma, an increased irregularity of the tumor glands results: these have an eccentrical lumen and are cytomorphologically in advancing degeneration.

2. Solid/Cribriform Pattern. This tumor structure is characterized by the light microscope as a compact bundle of tumor cells, which are sharply divided from the surrounding stroma by a discontinuous layer of small basal cells (Fig. 5). A preexisting ductal structure seems to be filled out with proliferated tumor cells, whereby remaining lumina may fail (solid) or a sievelike perforation of the tumor cell complex is more or less distinctly marked (cribriform). Altogether the cellular pattern seems to be more uniform than the pattern of the glandular tumor structure. Polygonal cell forms with varying broad, light cytoplasm and euchromatic round nuclei predominate (Fig. 5, 6). The cytoplasm is altogether poorly differentiated and shows only attempts to secrete. Depending on their stage of maturation, cytoplasmically more differentiated tumor cells may occasionally exist, whose architecture corresponds to the functionally activated tumor cell types (Type II–IV). Occasionally one can see within the cell complexes formations of true lumina, which may also be found intracytoplasmically (Fig. 7) Furthermore focal necrobiosis of cell complements as well as a widening of the intercellular space cause additional lumina (Fig. 8). Signs of a secretory activity of the cells bordering on a lumen is often not recognizable.

In the periphery lies a partly discontinuous layer of cuneiform basal cells next to the intact basement membrane (Fig. 5). These are characterized by their irregularly shaped and homogenously dense nuclei as well as by a dark, undifferentiated cytoplasm with many free ribosomes and bundles of thin filaments. No sign of secretory activity exists. The basal cells distinctly separate the solid/cribriform tumor cell complexes from the stroma. With further proliferation of the tumor one finds besides the increased features of cytoplasmic degeneration, also an invasive process displacing and finally destroying the organic stroma. Hereby, the solid/cribriform structure of the prostate carcinoma becomes more and more indistinct in its outlines.

3. Anaplastic Pattern. The pattern consists of varying large, solid masses of tumor cells, narrow epithelial rows, and also groups of tumor cells partially with an adenoid formation (Fig. 9). The irregular distribution of the cell complexes with a pronounced infiltration of the organic stroma is distinctly marked: the smooth muscle is split and destroyed (Fig. 9b). The relationship of the anaplastic formation to the previously described proliferative patterns becomes especially clear when examined ultrastructurally: this is manifested by the microlumina which often develop (Fig. 10). At the cellular level one can see a mixed picture of tumor cells (Type I–IV). The number of degenerated tumor cells is enlarged (Type V; Fig. 11). These possess strong heterochromatic, lobular nuclei and a vacuolar degenerated cytoplasm (vacuolar degeneration of mitochondria and of the endoplasmic reticulum, broadening of the Golgi complex, lipid vacuoles).

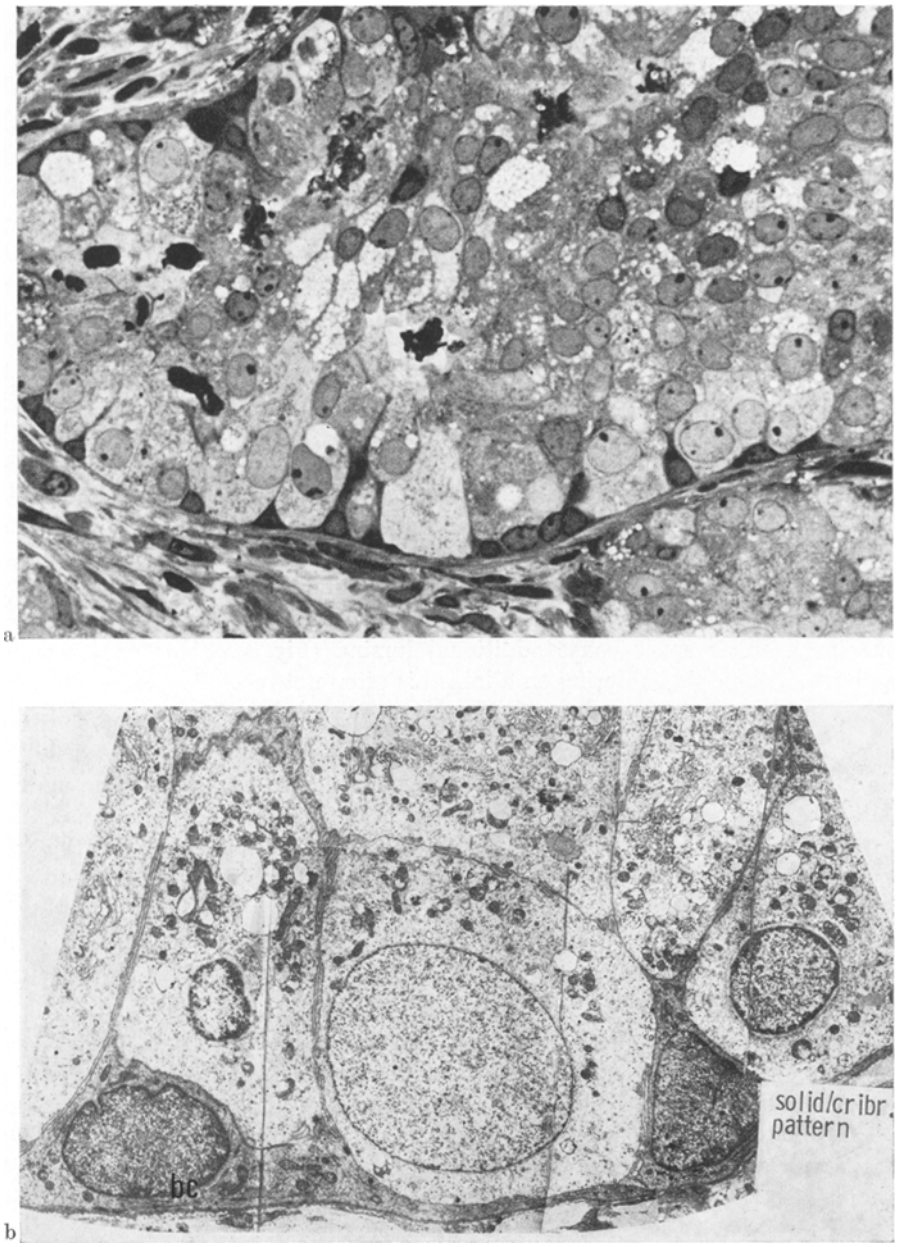

Fig. 5a and b. Solid/cribriform pattern. (a) histology: multilayered proliferation of tumor cells, peripherically demarcated by rim of basal cells from surrounding stroma. Toluidine blue × 600. (b) ultrastructure: periphery of solid/cribriform pattern. Tumor cells above basal cells (*bc*) with dense cytoplasm and nuclei. Basement membrane intact. × 3,000

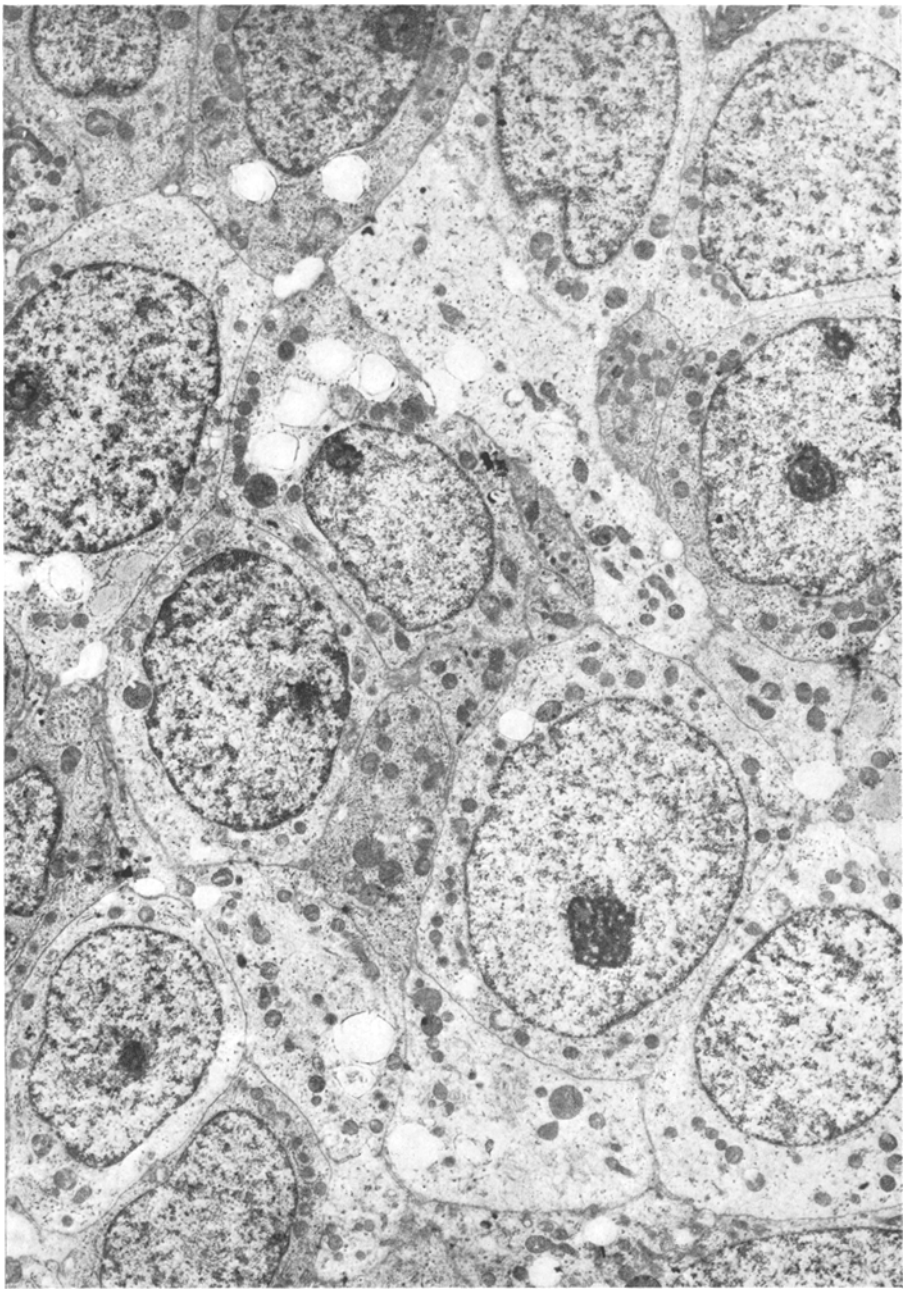

Fig. 6. Ultrastructure of solid pattern: polygonal, light tumor cells with round, large, euchromatic nuclei; poorly differentiated cytoplasm without secret production (Type I). × 5,000

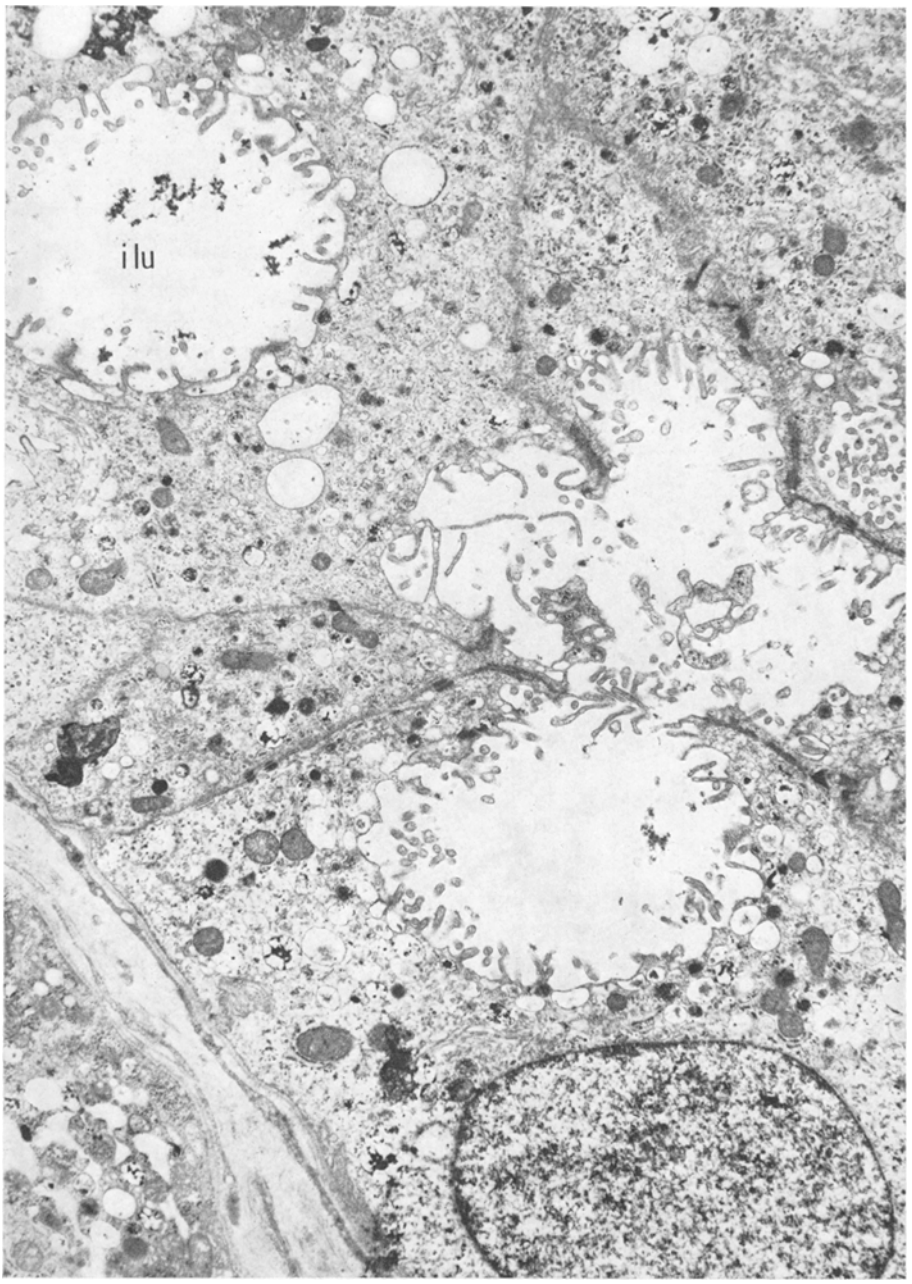

Fig. 7. Ultrastructure of cribriform pattern: some, partly intracytoplasmic lumina within tumor cell complexes; bodering tumor cells (Type II) with long microvilli; no visible secretion. *ilu* intracytoplasmic lumen. × 8,000

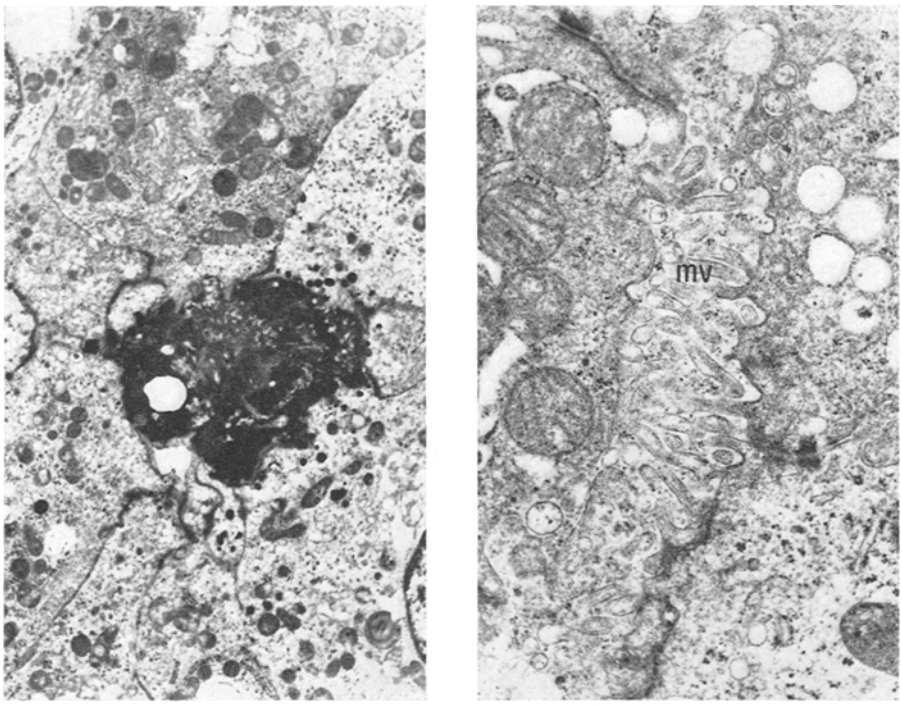

Fig. 8a and b. Formation of lumina by focal necrobiosis (a) or by widening of intercellular space (b). *mv* microvilli. a × 2,700, b × 13,000

Discussion

In a former investigation we already described ultrastructurally different tumor cell forms in the prostate carcinoma (Kastendieck et al., 1973). The single cell types do not present on their own independent races of tumor cells. We rather believe, that they represent different maturation and function stages of a uniform tumor stem cell. This theory is also supported by Foulds (1956) and Ozzello (1971) as in the development of the cancer cells in breast tumors. We would like to explain the cytomorphogenetic process for the prostatic carcinoma as follows. Initially, an undifferentiated epithelial tumor cell exists with the signs of proliferative activity (Type I). Then the tumor cells show a progressive cytoplasmic differentiation (Type II). The formation of a morphologically well-differentiated and functionally mature tumor cell (Type III) is seldom. However, a deranged tumor cell develops very often because of the disturbances in cell differentiation, specifically in tumor cells, and shows defects in the production and release of secretion (Type IV). The cell type V, marked by degenerative change, can principally arise from each of the previously described cell forms, but mostly out of the tumor cell type IV which is overloaded with organelles. Morphologically, we cannot conclude from the signs of the cellular degeneration, that the tumor cells are avital.

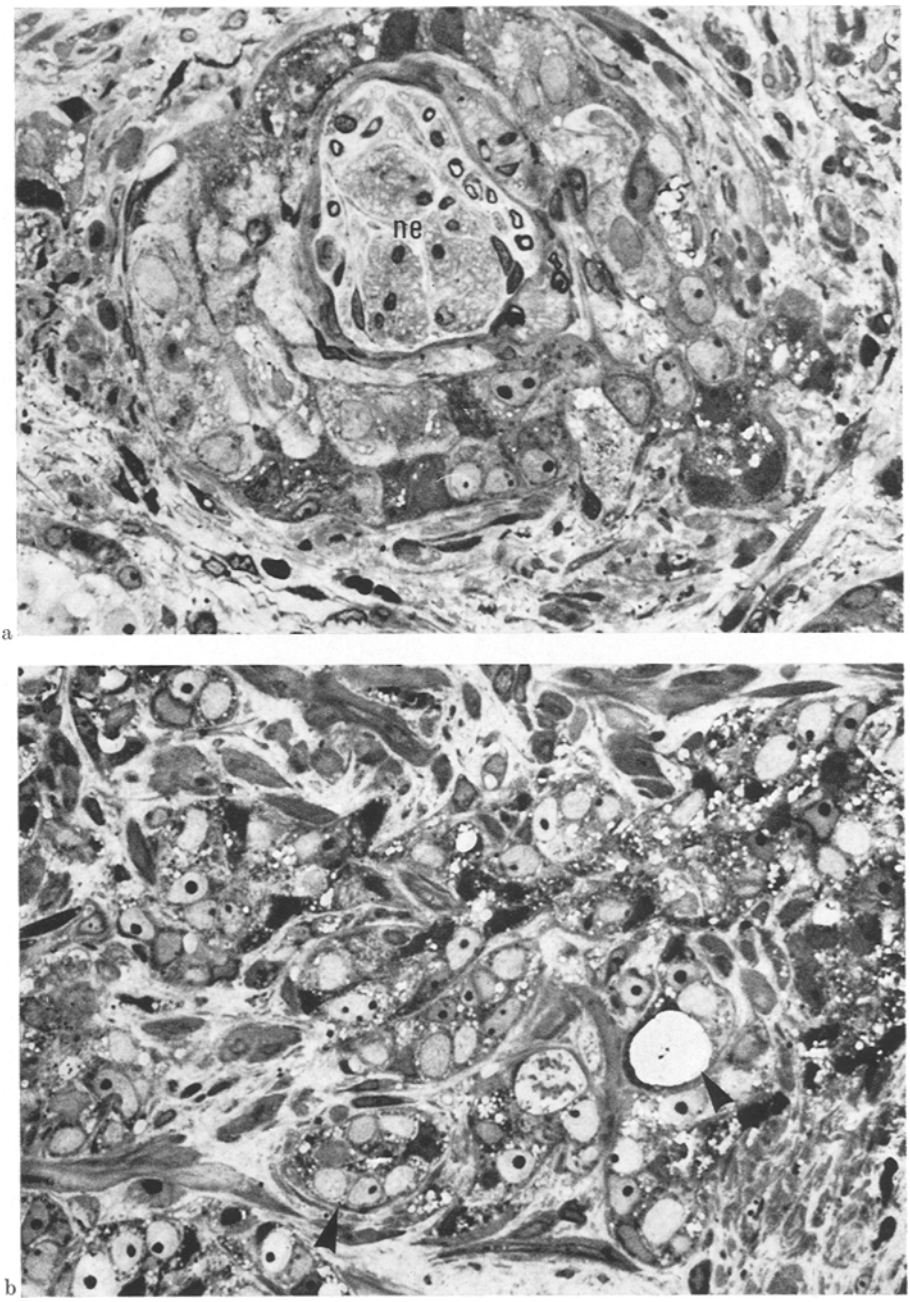

Fig. 9a and b. Histology of anaplastic pattern: (a) perineural growth of solid epithelial tumor cell complexes. *ne* nerve. Toluidine blue. × 600. (b) infiltration and destruction of organic stroma by irregular tumor cell formations as well as by microacinar tumor cell groups (→). Mixed cell picture. Toluidine blue. × 600

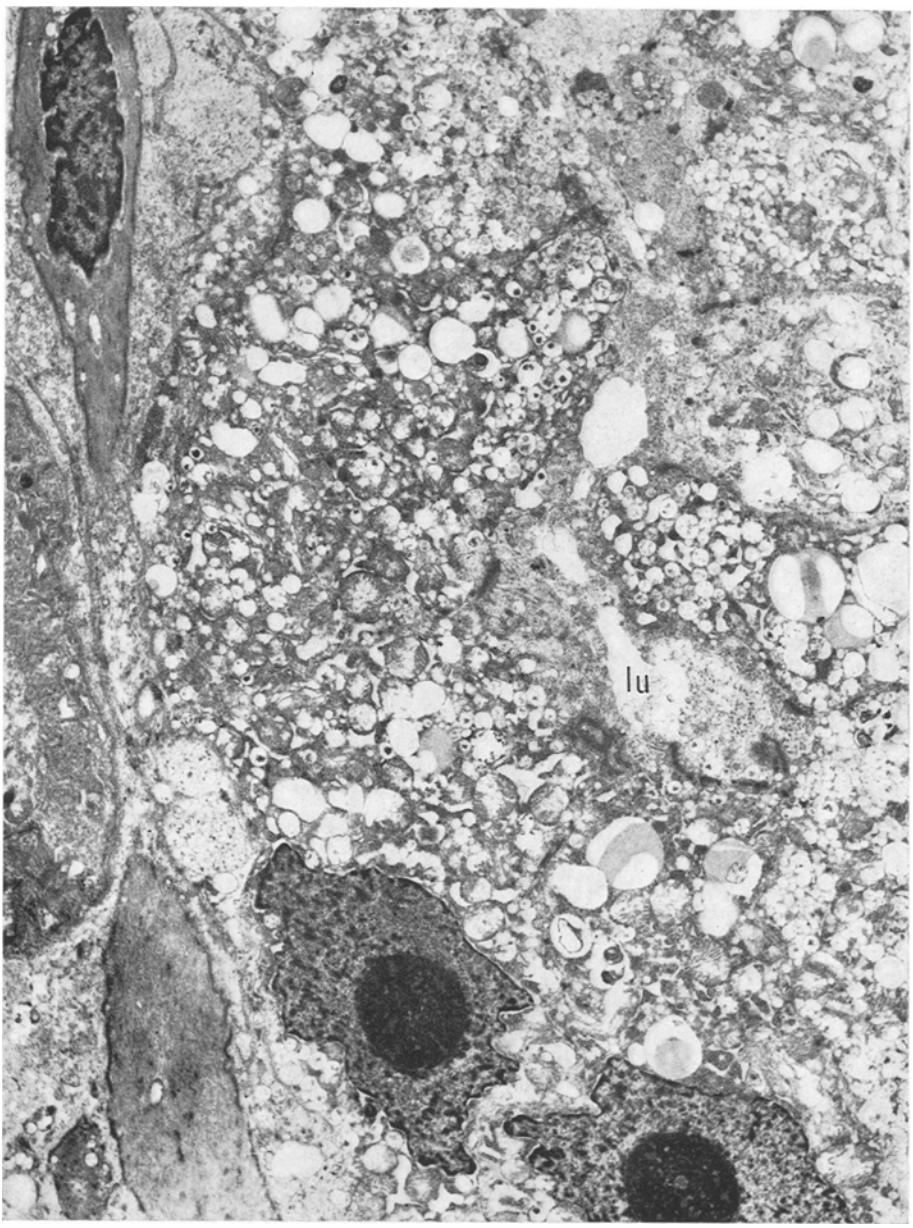

Fig. 10. Ultrastructure of anaplastic pattern: infiltrating tumor cell complex with progressing cellular degeneration (Type IV–V). In cytoplasm numerous, partly vacuolar degenerated organelles and lipid vacuoles. *lu* lumen. × 5,200

The tumor stem cell may possibly be a primary atypical basal or reserve cell. The function of the basal cells in the normal prostate as a reserve or a cell of replacement of the secretory glandular epithelium has been emphasized by the

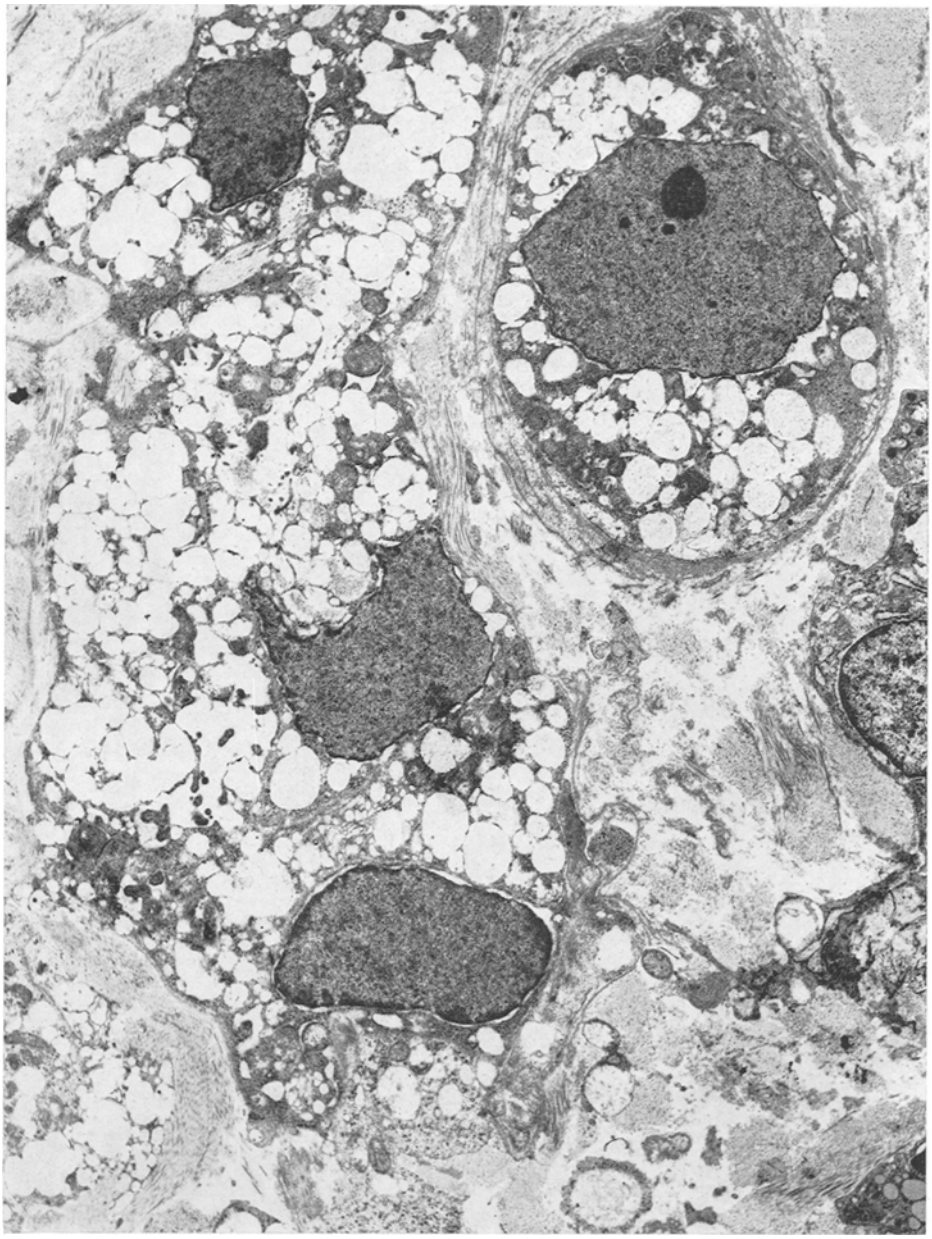

Fig. 11. Anaplastic pattern with narrow rim of epithelial tumor cells and single tumor cell. Advanced degenerative vacuolization of cytoplasm. × 5,500

electron-microscopic findings of Mao and Angrist (1966). With the results of our ultrastructural investigations about the epithelial metaplasia in the human prostate (Kastendieck and Altenähr, 1975), we have been able to show the multiple

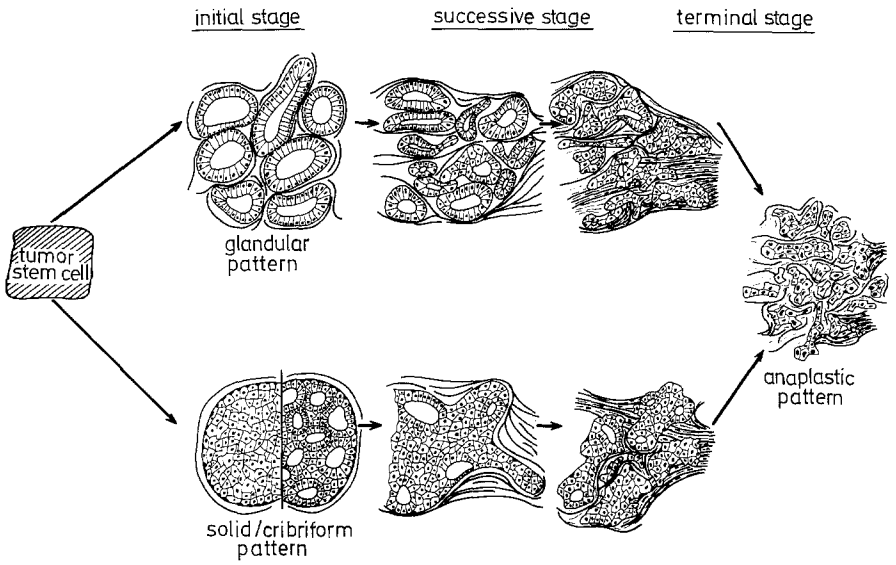

Fig. 12. Prostate carcinoma: phases and stages of development under special consideration of histologic growth patterns

potential of these cytologically undifferentiated basal cells. The formation of the squamous metaplasia and of the greater amount of carcinoma types of the cervix uteri is identical (Stegner and Sachs, 1973).

In the present study we have tried to analyze the histologic growth patterns of the prostate carcinoma based on a uniform formal pathogenesis of the tumor cells. As a result of our findings we have come to the conclusion, that the prostatic carcinoma develops in phases, whereby each stage is characterized by a different histologic pattern. However, it is certainly not possible to correlate the ultrastructural tumor cell types and the single histologic architecture of the carcinoma, exclusively (Mao et al., 1966). Nevertheless, the assessment of the distribution of the tumor cell types in conjunction with their behavior against the fibromuscular organic stroma gives the impression of the morphogenetic process of the prostate carcinoma as follows (Fig. 12): A glandular pattern results when the tumor cells have a predominant trend to differentiate. A solid/cribriform pattern turns out by the proliferation of mainly undifferentiated tumor cells.

First Phase. The *glandular* pattern presents itself in the initial phase as a well formed tumorous acinus with a central lumen and usually with a one-layered glandular epithelium. The tumor cell picture varies, one has the impression that the functionally more matured tumor cells (Type III and in particular Type IV) predominate. This growth pattern resembles the ultrastructural formation of the well-differentiated tubular carcinoma of the breast (Gould et al., 1975). Also characteristic for this phase is the suspension of the well-ordered glandular-stromal architecture. A mark for this is the tumor acini which lie

adjacent to the smooth muscle cells as well as the early signs of stromal infiltration and destruction (Kastendieck et al., 1974). The same procedure has been described for the beginning infiltrating growth of the mammary carcinoma (Goldenberg et al., 1969; Ozzello, 1971, 1974; Gould et al., 1975). The early infiltration of the fibromuscular stroma is probably initiated by the functionally deranged glandular tumor cells which are often found in this pattern (Kastendieck et al., 1975). This finding as well as the absence of basal cells (Mao et al., 1966; Fisher and Sieracki, 1970; Dhom, 1974) speak for a primary centrifugal proliferation of the tumor cells.

In the solid/cribriform growth pattern of the prostate carcinoma the undifferentiated tumor cells (Type I + II) predominante in number and are proliferated toward inside. Hereby they can either fill out completely the glandular lumen (solid), or residual lumina or newly formed lumina exist (cribriform). In the periphery one finds a partially discontinous layer of basal cells. The surrounding stroma has preserved its orderly architecture. This proliferative manner and the resulting structure form are identical with the findings of the intraductal breast carcinoma (Foulds, 1958; Ozzello, 1971; Gould et al., 1975). In the mammary carcinoma, the myoepithelial cells and the remaining unity between glandular epithelium and stroma ("esj": epithelial-stromal-junction by Ozzello, 1971) speak for the centripetal, intraductal proliferation of the tumor cells. In the carcinoma of the prostate, it is the basal cells and the absence of a stroma distorsion that point to this. According to Ozzello's assumption (1971), it is unlikely that the tumor cells imitate a ductlike architecture during their proliferation.

The alternative way of proliferation as described is not always found in an exclusive, "pure" form, so that mixed patterns may occur in this initial phase too.

Second Phase. This is characterized by the invasion, infiltration, and destruction of the organic stroma which we have already described (Kastendieck et al., 1974). Basically the solid/cribriform pattern shows at first mostly a displacing growth, and afterward a destructive growth as in the glandular proliferative pattern. The structure patterns which are still noticeable in the first phase, loose their orderly formation because they squeeze into the preexisting organic stroma, so that eventually an anaplastic picture develops. As in the breast carcinoma (Ozzello, 1971), the stromal elements accordingly possess an essential importance for the structural organization and behavior of the tumor. The expression "anaplastic" is not in accordance with reality as one can identify ultrastructurally glandular and solid structures. Furthermore, an increased cellular anaplasia is missing. The anaplasia is simulated, whereby, on the one hand mechanical factors (counterpressure of the organic stroma) and on the other hand the deterioration of the nutritive supply—visible in the advanced degeneration of the tumor cells—play an important role.

The described phases of development explain the findings of the high percentage of prostate carcinomas in the clinical stage 0, presented as "highly differentiated adenocarcinomas" (Dhom and Hautumm, 1975). The light-microscopic impression of an increasing anaplasia of prostate carcinoma with the increase of the tumor volume (Howald, 1948; McNeal, 1969; Gleason et al., 1974; Dhom and Hautumm, 1975) is also understandable.

The theories about the pathogenesis of the prostate carcinoma are numerous: its origin from senile atrophy of the glands (Andrews, 1945), from the glandular proliferation in the surroundings of atrophic glandular ducts (Franks, 1954), or the derivation from the so-called postatrophic hyperplasia (Moore, 1935) are only some attempts of interpretation. On the other hand, McNeal (1965) presents a much more causal connection between active glandular epithelium and prostate carcinoma. Edwards et al. (1953) and McNeal (1965) have tried to show a histologic relationship between the glandular structures and tumorous growth patterns in the human prostate carcinoma. Leav and Ling (1968) have tried to do this with the canine prostatic carcinoma.

Despite the presented cyto- and morphogenesis of the prostate carcinoma, we cannot make any definite statement about the pathogenesis of the tumor. Further investigations with the electron microscope as well as with the light microscope on large research series (biopsy and autopsy material) are necessary, in order to answer the question about the changes in the prostatic glands as being precancerous or carcinoma in situ lesions.

References

Andrews, G. S.: Latent carcinoma of the prostate. J. clin. Path. **2**, 197–208 (1949)

Brandes, D., Kirchheim, D., Scott, W. W.: Ultrastructure of the human prostate: normal and neoplastic. Lab. Invest. **13**, 1541–1560 (1964)

Dhom, G.: Differentialdiagnostische Probleme des Prostatacarcinoms (Erfahrungen mit dem Prostatacarcinomregister). Beitr. Path. **153**, 203–220 (1974)

Dhom, G., Hautumm, B.: Die Morphologie des klinischen Stadium 0 des Prostatacarcinoms (incidental carcinoma). Urologe A **14**, 105–111 (1975)

Edwards, C. N., Steinthorsson, E., Nicholson, D.: An autopsy study of latent prostatic cancer. Cancer (Philad.) **6**, 531–554 (1953)

Esposti, P. L.: Cytologic malignancy grading of prostatic carcinoma by transrectal aspiration biopsy. Scand. J. Urol. Nephrol. **5**, 199–209 (1971)

Fisher, E. R., Jeffrey, W.: Ultrastructure of human normal and neoplastic prostate. Amer. J. clin. Path. **44**, 119–134 (1965)

Fisher, E. R., Sieracki, J. C.: Ultrastructure of human normal and neoplastic prostate. Path. Ann. (S. C. Sommers, ed.), 1–26 (1970)

Foulds, L.: The histologic analysis of mammary tumors of mice. J. nat. Cancer Inst. **17**, 701–801 (1956)

Foulds, L.: The natural history of cancer. J. chron. Dis. 8, 2–37 (1958)

Franks, L. M.: Latent carcinoma of the prostate. J. Path. Bact. **68**, 603–616 (1954)

Franks, L. M.: Atrophy and hyperplasia in the prostate proper. J. Path. Bact. **68**, 617–621 (1954)

Gleason, D. F.: Classification of prostatic carcinoma. Cancer Chemother. Rep. **50**, 125–128 (1966)

Gleason, D. F., Mellinger, G. T., and the Vacurg: Prediction of prognosis for prostatic adenocarcinoma by combined histological grading and clinical staging. J. Urol. (Baltimore) **111**, 58–64 (1974)

Goldenberg, V. E., Goldenberg, N. S., Sommers, S. C.: Comparative ultrastructure of atypical ductal hyperplasia, intraductal carcinoma and infiltrating ductal carcinoma of the breast. Cancer (Philad.) **24**, 1152–1169 (1969)

Gould, V. E., Miller, J., Jao, W.: Ultrastructure of medullary, intraductal, tubular and adenocystic breast carcinomas. Amer. J. Path. **78**, 401–416 (1975)

Howald, R.: Die Morphogenese der Hypertrophie und des Karzinoms der Prostata und ihre Bedeutung für die Klinik. Helv. chir. Acta **15**, Ser. B, Suppl. IV, 1–40 (1948)

Kastendieck, H., Altenähr, E., Burchardt, P.: Elektronenmikroskopische Untersuchungen zur Zelldifferenzierung in Prostata-Carcinomen. Virchows Arch. Abt. A **361**, 241-256 (1973)

Kastendieck, H., Altenähr, E., Burchardt, P.: Zur Ultrastruktur der Tumor-Stromabeziehungen im Prostatacarcinom. Z. Krebsforsch. **81**, 85–100 (1974)

Kastendieck, H., Altenähr, E.: Morphogenese und Bedeutung von Epithelmetaplasien in der menschlichen Prostata. Eine elektronenmikroskopische Studie. Virchows Arch. Abt. A **365**, 137–150 (1975)

Kirchheim, D., Bacon, R. C.: Elektronenmikroskopische Untersuchungen der normalen Prostata, der Prostatahypertrophie und des Prostatacarcinoms. Urologe **7**, 292–305 (1968)

Kudo, S.: Electron microscopic studies on the prostatic epithelium. II. Fine Structures of the human prostatic cancer. Kumamoto med. J. **20**, 86–101 (1967)

Leav, I., Ling, G. V.: Adenocarcinoma of the canine prostate. Cancer (Philad.) **22**, 1329–1345 (1968)

Mao, P., Angrist, A.: The fine structure of the basal cell of human prostate. Lab. Invest. **15**, 1768–1782 (1966)

Mao, P., Nakao, K., Angrist, A.: Human prostatic carcinoma: an electron microscopic study. Cancer Res. **26**, 955–973 (1966)

McNeal, J. E.: Morphogenesis of prostatic carcinoma. Cancer (Philad.) **18**, 1659–1666 (1965)

McNeal, J. E.: Origin and development of carcinoma in the prostate. Cancer (Philad.) **23**, 24–34 (1969)

Mellinger, G. T., Gleason, D. F., Bailar, J.: The histology and prognosis of prostatic cancer. J. Urol. (Baltimore) **97**, 331–337 (1967)

Moore, R. A.: The morphology of small prostatic carcinoma. J. Urol. (Baltimore) **33**, 224–234 (1935)

Mostofi, F. K.: Carcinoma of the prostate. In: Modern trends in urology (E. Riches, ed.), pp. 231–263. London: Butterworths 1969

Mostofi, F. K., Price, E. B.: Tumors of the male genital system. Atlas of tumor pathology. Sec. Ser. Fasc. 8. Washington, D. C.: A.F.I.P. 1973

Murad, T. M.: A proposed histochemical and electron microscopic classification of human breast cancer according to cell of origin. Cancer (Philad.) **27**, 288–299 (1971)

Murad, T. M., Scarpelli, D. G.: The ultrastructure of medullary and scirrhous mammary duct carcinoma. Amer. J. Path. **50**, 335–360 (1967)

Ozzello, L.: Ultrastructure of the human mammary gland. Path. Ann. (S. C. Sommers, ed.) **6**, 1–59 (1971)

Ozzello, L.: Electron microscopic study of functional and dysfunctional human mammary glands. J. invest. Derm. **63**, 19–26 (1974)

Sinha, A. A., Blackard, C. E.: Ultrastructure of prostatic benign hyperplasia and carcinoma. Urology **2**, 114–120 (1973)

Slemmer, G.: Interactions of separate cell types of cells during normal and neoplastic mammary gland growth. J. invest. Derm. **63**, 27–47 (1974)

Stegner, H.-E., Sachs, H.: Gynäkologische Zytologie. Stuttgart: F. Enke 1973

Takayasu, H., Yamaguchi, Y.: An electron microscopic study of the prostatic cancer cell. J. Urol. (Baltimore) **87**, 935–940 (1962)

Utz, D. C., Farrow, G. M.: Pathologic differentiation and prognosis of prostatic carcinoma. J. Amer. med. Ass. **209**, 1701–1703 (1969)

Wiederanders, R. E., Stuber, R. U., Mota, C., O'Connell, D., Haslam, G. J.: Prognostic value of grading prostatic carcinoma. J. Urol. (Baltimore) **89**, 881–888 (1963)

Dr. Hartwig Kastendieck
Priv.-Doz. Dr. Eberhard Altenähr
Institute of Pathology
University of Hamburg
Martinistr. 52
D-2000 Hamburg 20
Federal Republic of Germany