Virchows Arch. A Path. Anat. and Histol. 387, 307–317 (1980)

Virchows Archiv A

The Biological Significance of Atypical Hyperplasia of the Prostate

Burkhard Helpap*
Institute of Pathology, University of Bonn, Federal Republic of Germany

Summary. In tissue biopsies and resection material (TUR) of the prostate a high coincidence (49.4%) was found between atypical primary hyperplasia with atypical-dysplastic microglandular, adenomatous and cribriform structures on the one hand and carcinomas on the other. The frequency of atypical hyperplasia in prostatic tissue without carcinoma was 2.8%. Microglandular pattern predominates in atypical hyperplasia combined with differentiated adenocarcinomas. A high coincidence between cribriformly structured glands of atypical primary hyperplasia and solid anaplastic – cribriform carcinomas can be observed.

Autoradiographically the labeling index of atypical hyperplasia was three times as high as that of simple hyperplasia. The mean labeling index of atypical hyperplasia, however, was similar to that of poorly differentiated adenocarcinomas and cribriform carcinomas. The similar proliferation pattern of atypical hyperplasia and carcinomas as well as the high coincidence between both indicate that severe atypical primary hyperplasia is a precancerous lesion.

Therefore, those patients with primary atypical hyperplasia with distinct cellular and structural atypia but without manifest carcinomas in prostatic biopsy or resection material should be followed up at short intervals.

Key words: Atypical hyperplasia, prostate gland, proliferation pattern.

Introduction

The high coincidence of atypical primary hyperplasia of the prostate and carcinomas has intensified the discussion on whether the lesion is precancerous or

* Supported by Landesamt für Forschung, Minister für Wissenschaft und Forschung des Landes Nordrhein-Westfalen, Düsseldorf

Offprints request to: Prof. Dr. B. Helpap, Pathologisches Institut der Universität Bonn, Postfach 2120, D-5300 Bonn, Federal Republic of Germany

0340-1227/80/0387/0307/$02.20

not (Mostofi and Price 1973; Kastendieck et al. 1976; Altenähr et al. 1979; Dhom 1979; Kastendieck and Henke 1979).

The different histological patterns of atypical hyperplasia of the prostate and their possibly premalignant nature have been described more recently (Dhom 1979; Kastendieck 1980). In most cases cellular and structural atypia in hyperplastic gland is only slight or moderate, but in cases of severe atypical hyperplasia, markedly atypical or dysplastic cells and an unusual proliferation pattern are observed. Sometimes atypical hyperplasia with microglandular clear cell pattern has the cytological character of clear cell carcinoma (Franks 1954).

Histological investigations on atypical hyperplasia have previously been performed exclusively on total prostatectomies (Kastendieck et al. 1976; Altenähr et al. 1979; Kastendieck and Henke 1979). There are no exact data on the frequency and histological pattern, with cytological grading of atypical hyperplasia in transurethral resection material or needle biopsies. Furthermore, in spite of the important differential diagnosis between atypical primary hyperplasia and carcinoma, proliferative potential has not been studied in detail.

We therefore investigated the distribution of atypical hyperplasia in TUR and biopsy material of the prostate, with and without carcinoma. Autoradiographic investigations using radioactively labeled thymidine were then performed. This enabled us to compare the labeling index and the duration of the DNA-synthesis phase of simple and atypical hyperplasia, with those of carcinomas and thus to evaluate the possible biological significance of atypical hyperplasia of the prostate. The cell kinetic results have been partially reported (Helpap and Stiens, 1979).

Methods

Transurethral resection material (TUR), transrectal biopsies and tissue from a few total prostatectomies were fixed in formalin and embedded in paraplast. Slides were stained with haematoxylin and eosin, PAS and by the van Gieson and Gomori method. Prostatic carcinomas were classified in accordance with the prostate cancer registry Homburg/Saar (Hohbach and Dhom 197?

Besides simple nodular hyperplasia and postatrophic hyperplasia (Franks 1954), cases with atypical hyperplasia were differentiated in those of slight (I), moderate (II) and severe (III) cellular and structural atypia. Furthermore, the histological pattern of atypical hyperplasia was correlated with the different histological pattern of the carcinomas.

In the dynamic studies approximately 1 mm thick prostatic tissue biopsies, obtained with the TRU cut biopsy needle (Travenol) from different areas of the gland, were incubated in autologous plasma under 2.2 atm carbogen pressure (95% O_2 and 5% CO_2) and a constant temperature of 37° C. During the first hour of incubation ^{3}H-thymidine was added to the plasma (5.0 µCi/ml; specific activity 20.0 Ci/mmol; NEN Chemicals, Boston, Mass. USA). After washing the biopsies in an inactive medium or plasma the tissue biopsies were subsequently incubated for another hour in plasma containing ^{14}C-thymidine (0.5 µCi/ml; specific activity 56 mCi/mmol).

The biopsies were fixed in 4% neutral formalin and embedded in paraplast. Stripping film (AR 10, Kodak, Stuttgart) and G 5 (Ilford, London) emulsion autoradiograms were made in the usual manner. The exposure time was 10 days for G 5 and 30 days for stripping film autoradiograms.

In the autoradiograms stained with haematoxylin the percentages of radioactively labeled nuclei of the glandular epithelia or tumor cells were determined (labeling index). On the average 1,000 cells were counted per slide.

With the double labeling method using ^{3}H- and ^{14}C-thymidine the percentage of both ^{3}H- and ^{14}C-labeled cell nuclei as well as those of only ^{3}H- and of only ^{14}C-labeled cell nuclei were determined and the duration of the DNA-synthesis phase (S-phase) was calculated by the following relationship:

$$\text{S-phase} = \frac{\text{number of all cells with } ^{14}C}{\text{number of cells with } ^{3}H \text{ only}} \Delta t$$

(Hilscher and Maurer 1962; Helpap and Maurer 1969; Helpap et al. 1973, 1974, 1976; Helpap and Stiens 1979).

Results

Histology

Findings in Atypical hyperplasia without Carcinoma. In 4341 tissue biopsies of the prostate, 122 cases of atypical hyperplasia with a microglandular, papillary clear cell or adenomatous/intraglandular-cribriform pattern were found (2.8%, Figs. 1–3).

In 37.9% of these cases slight cellular atypia was visible (Table 1). Moderate atypia was observed in 35.7%. In 13.9% marked cellular and structural atypia could be detected. 12.4% revealed a transition from severe atypical hyperplasia to carcinoma of the prostate after serial sections of the material (Figs. 4–6). The most frequent histological structures in atypical hyperplasia are microglandular or papillary clear cell formations. There are no significant differences between cases of slight, moderate and severe atypia (Table 1).

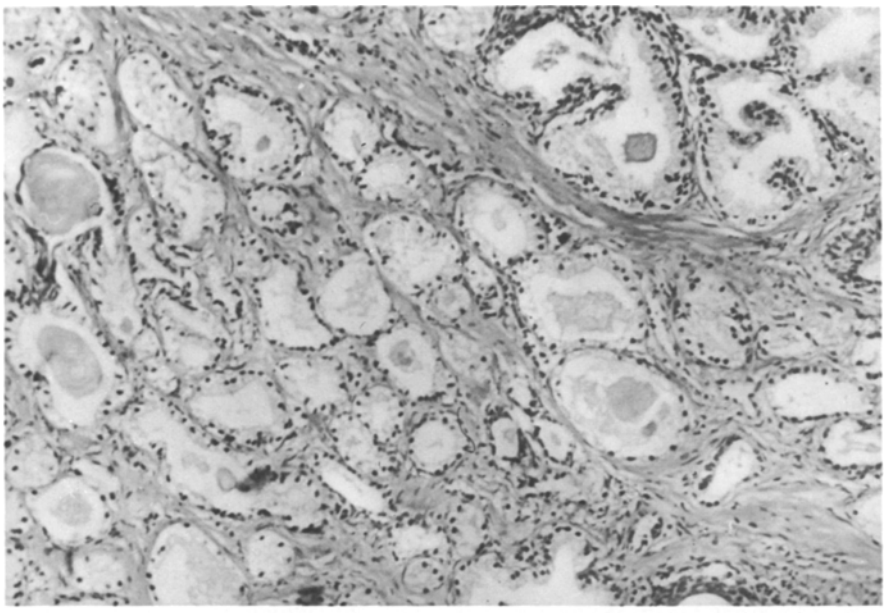
Atypical Hyperplasia and Carcinoma. 524 prostatic carcinomas were analysed histologically. In 49.4% atypical hyperplasia was combined with prostatic carcinoma (Table 2).

Table 3 shows the correlation between the different histological pattern of carcinomas and the grading of atypical hyperplasia. Differentiated adenocarcinomas most frequently are combined with slight or moderate, microglandular clear cell or papillary atypical hyperplasia. In contrast, there is a high coincidence of severe atypical hyperplasia with predominant cribriform pattern and solid anaplastic and cribriform carcinomas (Tables 2, 3).

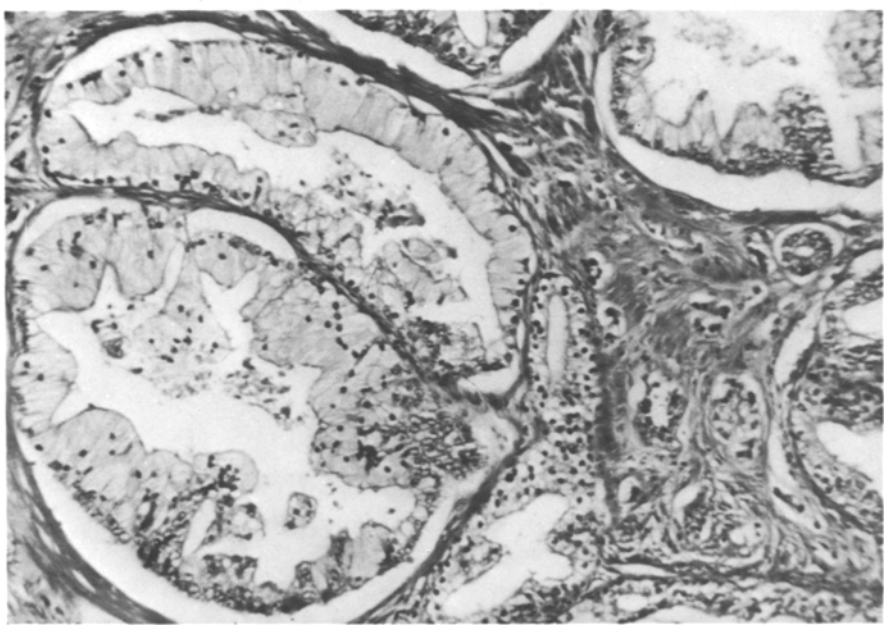
Cell Kinetic Findings. Mitotic figures were extremely rare in simple hyperplasia, less than 0.01%. In severe atypical hyperplasia the average mitotic index was 0.06%. Glandular carcinomas showed mitotic indices of 0.02% and cribriform carcinomas of 0.04–0.06% (Table 4).

The average labeling index in 65 cases of simple glandular hyperplasia was $0.49 \pm 0.4\%$. There was no significant difference from three cases which had an accompanying unspecific focal inflammation with a labeling index of $0.60 \pm 0.04\%$.

In 11 cases of postatrophic hyperplasia with cellular atypia but without carcinoma an average labeling index of $1.60 \pm 0.8\%$ could be calculated. In atypical primary hyperplasia with strong cellular and structural atypia in the



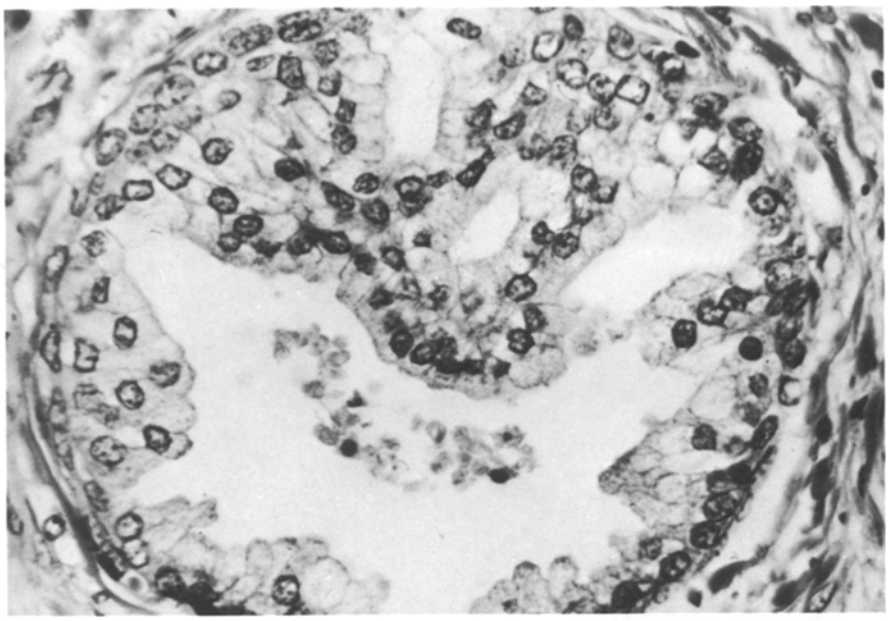
1



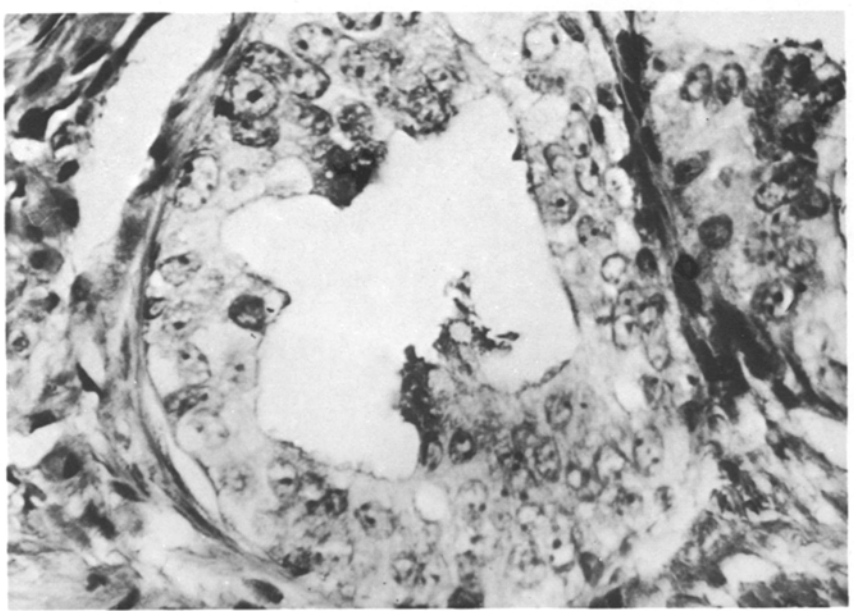
2

Fig. 1. Atypical primary hyperplasia with microglandular clear cell structures and moderate atypias H.E. ×122

Fig. 2. Atypical hyperplasia with papillary structures and moderate atypias of clear cells in vicinity of prostatic carcinoma H.E. ×122



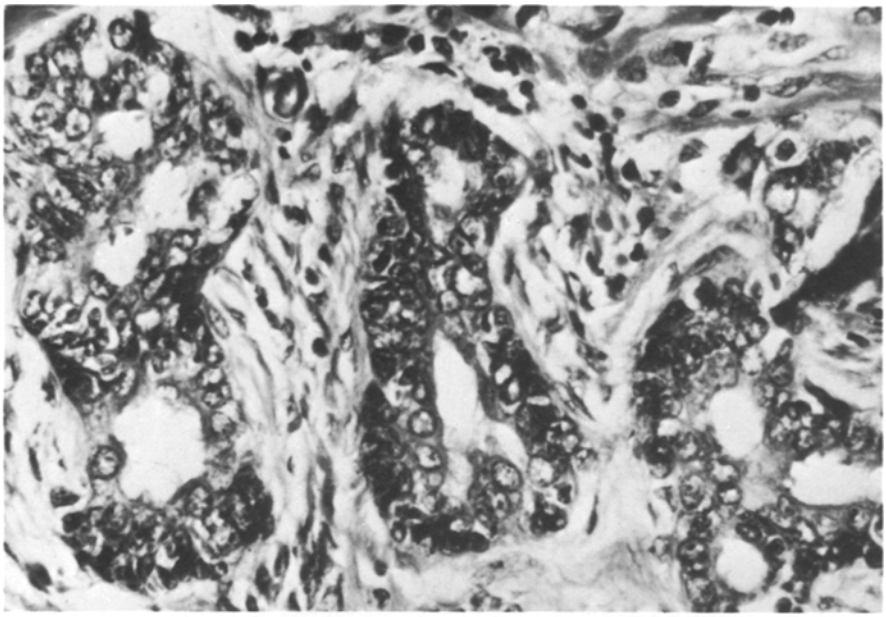
3



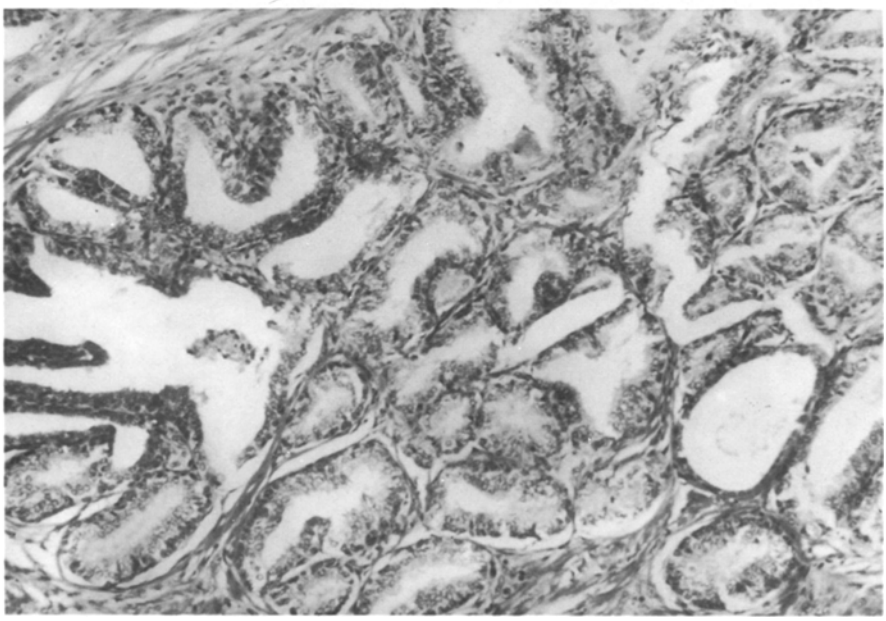
4

Fig. 3. Atypical hyperplasia with moderate cellular atypías and cribriform pattern H.E. ×307

Fig. 4. Severe atypical hyperplasia of the prostate H.E. ×307



5



6

Fig. 5. Transition from atypical hyperplasia to carcinoma of the prostate H.E. ×307

Fig. 6. Severe atypical hyperplasia in combination with carcinoma H.E. ×122

Table 1. Correlation between histological pattern and cytological grading of atypical hyperplasia of the prostate, $n=122$

Histological pattern of atypical hyperplasia	Cytological grading of atypical hyperplasia of the prostate			
	Slight (I) $n=45$ (37.9%)	Moderate (II) $n=43$ (35.7%)	Severe (III) $n=18$ (13.9%)	Transition to Ca $n=16$ (12.4%)
Microglandular/papillary clear cell	93.4%	93.0%	94.4%	93.8%
Intraglandular cribriform and adenomatous	2.2%	4.7%	5.6%	–
Other combinations	4.4%	2.3%	–	6.2%

Table 2. Coincidence of atypical hyperplasia and carcinoma of the prostate gland

Histological differentiation	*n*	*n*	%
	Uniform carcinoma	Atypical hyperplasia	
Highly differentiated adenocarcinoma	80	38	47.5
Poorly differentiated adenocarcinoma	187	86	45.9
Cribriform carcinoma	23	10	43.5
Papillary-intraductal carcinoma	8	3	75.0
Solid anaplastic carcinoma	30	–	–
Urothelial carcinoma	2	–	–
Squamous epithelial carcinoma	1	–	–
	Pluriform carcinoma		
Highly and poorly diff. adenocarcinoma	40	23	57.5
Cribriform-anaplastic carcinoma	23	10	43.5
Cribriform pattern in other carcinoma	121	80	66.3
Other combination	9	3	33.3
	524	259	49.4

vicinity of adenocarcinomas a labeling index of $1.50 \pm 0.84\%$ was determined (Fig. 7). The single values ranged from 0.2–4.1%. This labeling index is comparable to that of poorly differentiated adenocarcinomas (0.2–2.4%) and cribriformly structured carcinomas (0.4–5.7%). The average duration of the DNA-synthesis phase was 9.5 hours and is not significantly different from simple and atypical primary hyperplasia or from carcinomas (Table 4).

Discussion

Atypical hyperplasia of the prostate may show numerous histological glandular formations which can verge on a carcinomatous pattern. This atypical hyperplastic configuration may represent a biological trend of the cells or glands towards

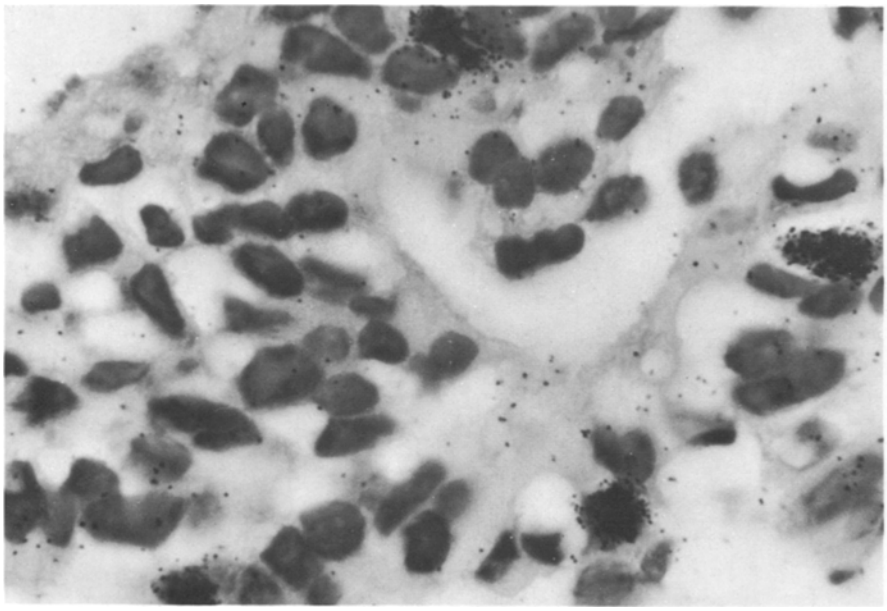


Fig. 7. Radioactively labeled nuclei of atypical hyperplasia of the prostate gland. Strippingfilm autoradiogram H.E. ×490

Table 3. Histological pattern and cytological grading of atypical hyperplasia of the prostate correlated with the histological classification of carcinomas

Histological pattern of atypical hyperplasia	Slight atypical hyperplasia			Moderate atypical hyperplasia			Severe atypical hyperplasia		
	adeno ca. *n* 307	crib. ca. *n* 144	solid anapl. ca. *n* 62	adeno ca. *n* 307	crib. ca. *n* 144	solid anapl. ca. *n* 62	adeno ca. *n* 307	crib. ca. *n* 144	solid anapl. ca. *n* 62
Micro-glandular/ papillary clear cell	13.0%	0.7%	–	9.1%	3.5%	3.2%	2.9%	2.8%	3.2%
Intraglandular cribriform and adenomatous	0.9%	–	–	2.3%	4.9%	–	5.5%	39.6%	14.5%
Other combination	2.9%	–	–	6.6%	1.4%	–	4.9%	9.7%	4.8%

Table 4. Autoradiographic results of prostatic biopsies after incubation with ^{3}H- and ^{14}C-thymidine

Histological differentiation	*n*	Mitotic index %	Labeling index %	S-phase (h)
Atrophy	17	–	0.24±0.08	–
Postatrophic hyperplasia	11	0.03	1.60±0.80	9.2±1.7
Simple hyperplasia				
without focal inflammation	65	<0.01	0.49±0.40	9.9±3.2
with focal inflammation	3	–	0.66±0.04	–
Atypical hyperplasia in the vicinity of carcinomas	15	0.06	1.50±0.84	9.4±3.5
Poorly diff. adenocarcinomas	13	0.02	0.88±0.65	8.9±3.9
Cribriform carcinomas	11	0.04–0.06	2.70±1.90	10.4±2.3

malignancy (Mostofi and Price 1973; Tannenbaum 1977). Cases of atypical hyperplasia with slight or moderate cellular atypia should be seperated from cases with severe atypia and an unusual proliferation pattern, i.e. development of glands in glands, cribriform, microglandular structures with single layers of clear cells, and cellular atypia with prominent nucleoli combined with disintegration of the morphological unity between prostatic glands and stroma (Baron and Angrist 1941; Akazaki and Stemmermann 1973; Kastendieck et al. 1976; Altenähr et al. 1979; Dhom 1979; Kastendieck and Henke 1979; Kastendieck 1980).

The analysis of prostatic carcinoma and atypical hyperplasia has shown that severe atypical hyperplasia is correlated with carcinoma in 26%. In those cases cribriform glandular structures predominate in atypical hyperplasia. Slight or moderate atypical hyperplasia with predominant microglandular clear cell pattern is combined with carcinoma in 10% and 12% respectively.

These results support the conclusion that in at least 25% of the cases of atypical hyperplasia without carcinoma, a malignant transformation may occur in the future, or an overt carcinoma is in the vicinity. Atypical hyperplasia of the prostate, especially with severe cellular and structural atypia may therefore be classified as a precancerous lesion.

This histological and cytological finding is additionally supported by the cell kinetic analysis of atypical hyperplasia. Our own cell kinetic investigations have shown that proliferative activity of postatrophic hyperplasia with isolated cellular atypia without carcinoma and of atypical primary hyperplasia in the vicinity of carcinomas, is more than three times as high as that in simple hyperplasia (Helpap and Stiens 1979). This increased proliferative activity of severe atypical hyperplasia is in very close relationship to that of poorly differentiated adenocarcinomas and cribriform carcinomas.

Similarly increased proliferative activities in regions of precancerous cellular atypia in the vicinity of already manifest carcinomas are known to exist in the mucosa of the urinary bladder, the stomach and in the large bowel (Deschner et al. 1966; Hainau and Dombernowsky 1974; Bleiberg and Galand 1976; Bleiberg et al. 1977; Maskens and Deschner 1977; Murphy et al. 1979). The

similar labeling indices, i.e. the similar proliferative pattern of atypical hyperplasia and carcinomas of the prostate, also suggest that severe atypical hyperplasia is a precancerous lesion.

Thus, in discussing the histogenesis of prostatic carcinoma not only proliferating postatrophic – hyperplastic processes but also active proliferating atypical primary hyperplastic glands should be considered (Franks 1954; Liavag 1969; Mc Neal 1969; Tannenbaum 1977; Dhom 1979; Kastendieck 1980).

The histological diagnosis of atypical primary hyperplasia from TUR or needle biopsy material of the prostate, means that a potentially malignant transformation of the glands has occured and/or that an already manifest carcinoma may exist in other parts of the gland not sampled in the material investigated.

Patients with primary atypical hyperplasia with severe cellular and structural atypia in microglandular, adenomatous, papillary or cribriform parts of the prostate, even without a discernable carcinoma in the biopsy or resection material, should therefore be followed up at short intervals. This could lead to an earlier detection of prostatic carcinoma.

Finally, it should be mentioned that atypical primary hyperplasia per se is no indication for any therapeutic measures.

Acknowledgement: The cowork in autoradiographic findings of Dr. R. Stiens, M.D., the valuable assistance of Mrs. Inge Heim and of Mrs. K. Ellinger is gratefully acknowledged.

References

Akazaki K, Stemmermann GN (1973) Comparative study of the latent carcinoma of the prostate among Japanese in Japan and Hawai. J Natl Cancer Inst 50:1137–1144

Altenähr E, Kastendieck H, Siefert H (1979) Koinzidenz von Prostatacarcinom und Dysplasie bei totalen Prostatektomien und bei Autopsien. Verh Dtsch Ges Path 63:415–418

Baron E, Angrist A (1941) Incidence of occult adenocarcinoma of the prostate; After fifty years of age Arch Pathol 32:787–793

Bleiberg H, Galand P (1976) In vitro autoradiographic determination of cell kinetic parameters in adenocarcinomas and adjacent healthy mucosa of the human colon and rectum. Cancer Res 36:325–328

Bleiberg H, Salhadin A, Galand P (1977) Cell cycle parameters in human colon. Comparison between primary and recurrent adenocarcinomas, benign polyps and adjacent unaffected mucosa. Cancer 39:1190–1194

Deschner EE, Lipkin M, Solomon C (1966) Study of human rectal epithelial cells in vitro. II 3-H-thymidine incorporation into polyps and adjacent mucosa. J Natl Cancer Inst 36:849–855

Dhom G (1979) Frühe neoplastische Veränderungen der Prostata. Verh Dtsch Ges Path 63:218–231

Franks LM (1954) Atrophy and hyperplasia in the prostate proper. J Pathol Bacteriol 68:617–621

Hainau B, Dombernowsky P (1974) Histology and cell proliferation in human bladder tumors. An autoradiographic study. Cancer 33:115–126

Helpap B, Maurer W (1969) Autoradiographische Untersuchung zur Frage der Vergleichbarkeit des Einbaus von markiertem Thymidin unter in vivo-Bedingungen und bei Inkubation von Gewebsproben. Virchows Arch Zellpath B 4:102–118

Helpap B, Stiens R, Grouls V (1973) Autoradiographische Untersuchungen zum Thymidin-Einbau nach mehrstündiger Inkubation von Rattenlebern. Histochemie 34:305–316

Helpap B, Stiens R, Brühl P (1974) Autoradiographische Untersuchungen an inkubierten Prostatapunktaten nach Doppelmarkierung mit 14-C- und 3-H-Thymidin. Beitr Path 151:65–74

Helpap B, Stiens R, Brühl P (1976) The proliferative pattern of the prostatic carcinoma before and under hormonal treatment. Z Krebsforsch 87:311–320

Helpap B, Stiens R (1979) Autoradiographische Befunde bei atypischer Prostatahyperplasie. Verh Dtsch Ges Path 63:419–422

Hilscher W, Maurer W (1962) Autoradiographische Bestimmung der Dauer der DNS-Verdopplung und ihres zeitlichen Verlaufs bei Spermatogonien der Ratte durch Doppelmarkierung mit C-14- und H-3-Thymidin. Naturwissenschaften 49:352–354

Kastendieck H (1980) Prostatic carcinoma. Aspects of Pathology, prognosis, and therapy. J Cancer Res Clin Oncol 96:131–156

Kastendieck H (1977) Ultrastrukturpathologie der menschlichen Prostatadrüse. In: Büngeler W, Eder M, Lennert K, Peters G, Sandritter W, Seifert G (eds) Veröffentlichungen aus der Pathologie, vol 106. Stuttgart: Fischer

Kastendieck H, Henke A (1979) Morphologische Studien zur Frage der Beziehungen zwischen atypischer Hyperplasie und Carcinom der Prostata. Verhdl Dtsch Ges Path 63:515

Kastendieck H (1980, in press) Correlations between atypical primary hyperplasia and carcinoma of the prostate. Histologic studies on 180 total prostatectomies due to manifest carcinoma Path Res Pract

Kastendieck H, Altenähr E, Hüsselmann H, Bressel M (1976) Carcinoma and dysplastic lesions of the prostate. A histomorphological analysis of 50 total prostatectomies by step-section technique. Z Krebsforsch 88:33–54

Maskens AP, Deschner EE (1977) Tritiated thymidine incorporation into epithelial cells of normal-appearing colorectal mucosa of cancer patients. J Natl Cancer Inst 58:1221–1224

Mostofi FK, Price EB (1973) Tumors of the male genital system. Fasc 8. Washington, D.C.: Armed Forces Institute of Pathology

Murphy WM, Nagy GK, Rao MK, Soloway MS, Parija GC, Cox CE, Friedell GH (1979) "Normal" urothelium in patients with bladder Cancer. A preliminary report from the national bladder cancer collaborative group A. Cancer 44:1050–1058

Steenbeck L, Wolff G (1971) Histoautoradiographische Untersuchungen der menschlichen Magenschleimhaut bei chronischer Gastritis und Magenkarzinom. Arch Geschwulstforsch 38:132–138

Tannenbaum M (1977) Urologic pathology: The prostate. Philadelphia: Lea and Febiger

Accepted April 2, 1980