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Light microscopical morphometry of prolactin secreting adenomas under treatment with dopamine agonists*

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Summary. In order to study the light microscopical alterations of pituitary tumours under dopamine agonist treatment, three groups of a total of 18 large or small cell chromophobe adenomas were analysed by light microscopical, immunohistological and morphometrical methods.

They were all removed by transsphenoidal surgery. 6 of them were treated preoperatively with dopamine agonists, bromocriptine and/or lisuride, for various periods of time. 8 adenomas remained preoperatively untreated. 4 additional untreated tumors were small cell inactive adenomas for comparison. One case was excluded from the final evaluation of the data because it appeared to be a typical non-responder, clinically as well as histologically.

Immunohistological positivity for prolactin was to be found in all cases in various degrees. Clinically active adenomas contained many prolactin positive cells, whereas in inactive adenomas only scattered cells were prolactin positive.

The morphometric analysis revealed a reduction of the cytoplasmic area in a statistically significant degree in the group of adenomas under treatment, which explains adequately the shrinkage of the entire adenoma and the reduction of prolactin plasma levels. The morphometric data of treated adenomas resembled those of untreated inactive adenomas.

Key words: Pituitary adenomas - Prolactin - Dopamine agonists - Morphometry

Introduction

Certain effects of dopamine agonists (DA) on prolactinomas are described in the following literature, such as the well known suppression of the normal lactation post partum (Varga et al., 1972; MacLeod et al., 1977) and the observation in cases with prolactinomas that a remarkable reduction of tumour size under DA-treatment occurs in many cases (Corenblum et al., 1975; McGregor et al., 1979; Nissim et al., 1982; Rengachary et al., 1982; Johnston et al., 1983; Liuzzi et al., 1983; Lüdecke et al., 1983).

The tumour shrinkage as an effect of DA is combined with a reduction of the prolactin plasma level. This effect was found to be reversible after cessation of the DA-medication (Thorner et al., 1978; Kuhn et al., 1985).

The probably antiproliferative effect of DA could be taken as an explanation for the clinical findings (Eversman et al., 1977; Chiodini et al., 1981), but because of the relatively low rate of mitoses within untreated prolactinomas, a further decrease after treatment is hardly noticeable (Rengachary et al., 1982).

Electron microscopical studies showed that the decrease of cell size is combined with a decrease of cytoplasmic compartments, such as the Golgi complex, the ribosomes and the rough endoplasmic reticulum (Nissim et al., 1982; Tindall et al., 1982; Schottke et al., 1986).

A further theory concerns an increase of necrobioses within the tumour under treatment, implicating a direct cytocidal effect of DA (Lüdecke et al., 1983; Moritetsu et al., 1983). An increase of lysosomes which may cause a higher autophagolytic activity within the cells was described by Anniko et al. (1981).

The aim of our study was to demonstrate alterations in different groups of adenomas under DA-treatment by light microscopical morphometry under single blind conditions.

Materials and methods

18 patients, both male and female, divided into three groups with macroadenomas (diameter > 10 mm) and one microadenoma (< 10 mm) were studied. They

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differed in their histopathological classification which is listed in Table 1.

The clinical findings, the immunohistochemical evaluations and the mode of treatment are also summarized in Table 1.

14 patients showed a preoperative increase of the prolactin plasma level. Their tumours were defined as clinically active adenomas (prolactinomas). In 6 of these cases, DA-treatment was performed preoperatively. The other 8 cases remained preoperatively untreated by DA.

4 patients who had never been treated with DA suffered from inactive tumours or showed a borderline increase of the prolactin plasma level. The prolactin level of one patient was not checked because the hypophysectomy was performed due to a cancer of the prostate. This operation revealed an incidental adenoma.

The mean prolactin plasma levels are also shown in Table 1.

For light microscopy the specimens were fixed in 3 % glutaraldehyde and cacodylate buffer, postfixed in osmium-tetroxyde buffered with cacodylate, dehydrated and embedded in Epon 812. Semi-thin sections were stained with toluidin blue.

The photographs were taken with a «Leitz-Orthoplan»-microscope. The morphometric analysis was performed on the basis of 284 single photographs taken of 18 adenomas at identical magnification (objective 40 x) in the attempt to cover the whole area of each adenoma. The final photographic magnification was 820, the size of the photos being 18 x 24 cm. The analyses were performed with a Videoplan-computer (Kontron Inc., Munich, Western Germany) which is a semi-automatic quantitative image analysing system.

The photographs were examined by one observer under single blind conditions.

As the membranes of the cells were not to be identified on the photographs, the shapes of the nuclei and of the adenoma tissue on the photograph have been taken into account for the measurement. The area of the whole cell, including cytoplasm, was calculated by division. Further parameters were: «A» for area, «p» for perimeter, «D-circle» for area-equivalent diameter.

The parameters for shape are «FAr» and «FPe»; they indicate to what extent a structure resembles a circle or an ellipse as far as its shape is concerned. The formulae of these factors are the following:

$$FAr = \frac{\text{Area}}{\frac{\pi}{4} A \times B}$$

A: maximal diameter of an ellipse

B: minimal diameter of an ellipse

$FAr = 1$ (for circle or ellipse)

$FAr < 1$ (for formless structures)

$$FPe = \frac{4\pi \times \text{Area}}{\text{circumference}^2}$$

$FPe = 1$ (for circle)

$FPe < 1$ (for ellipse or formless structures)

The standard deviation and the mean values were also calculated for each parameter of the program.

The results were checked for statistical significance by means of the Krouskal and Wallis analysis of variance and ranks (Sachs, 1970).

Results

Light microscopical findings of the untreated prolactinomas

Our light microscopical studies reveal that the group of untreated prolactinomas consists of mostly large cell chromophobe adenomas (Table 1). One tumor has to be classified a small cell chromophobe adenoma. In a further case, large and small cell parts are detectable. Some adenomas show bleedings and liquefactions.

The amount of nuclear chromatin is average. In case 9 (Fig. 1) the nuclei containing relatively little chromatin are nearly round, others are slightly indented and show a higher density of nuclear chromatin which is also found in case 12. The nucleoli are of medium size. Plurinuclear cells and cases with mitoses are rarely to be found. The cellular borders can hardly be distinguished.

Light microscopical findings of the adenomas treated with DA

Three of them (cases 1, 2, 3) are classified as large cell chromophobe adenomas (Table 1) and show regressive changes to a relatively high extent. The tumours 4 and 5 (Fig. 2) are small cell chromophobe adenomas with remarkable regressive changes. In both cases, collagenous connective tissue with hyalinisations is distinctly developed. Liquefactions are present in case 1 and 3. The nuclei of the large cell adenomas are mainly round with varied nucleoli. One adenoma (case 5) containing also small cell parts, shows nuclei of slightly irregular shape with dense nuclear chromatin. On the whole, the cell borders are not detectable. Mitotic figures are rarely demonstrable. In cases 1 and 2, a few plurinuclear cells are present.

Light microscopical findings of the inactive untreated adenomas

The adenomas 15 (Fig. 3) and 16 are small cell chromophobe adenomas (Table 1). Case 17 has additional oncocytic parts. These three adenomas contain bleedings and liquefactions. Tumour 18 is a chromophobe microadenoma. The nuclei of cases 15 and 16 are mostly oval, in the latter case more elongated. The nucleoli are small, the content of nuclear chromatin is average. The cell membranes are detectable in different degrees. Only very few plurinuclear cells or mitoses are visible.

Statistical analyses

A comparison between the morphometric data of the treated and the untreated prolactinomas shows that the

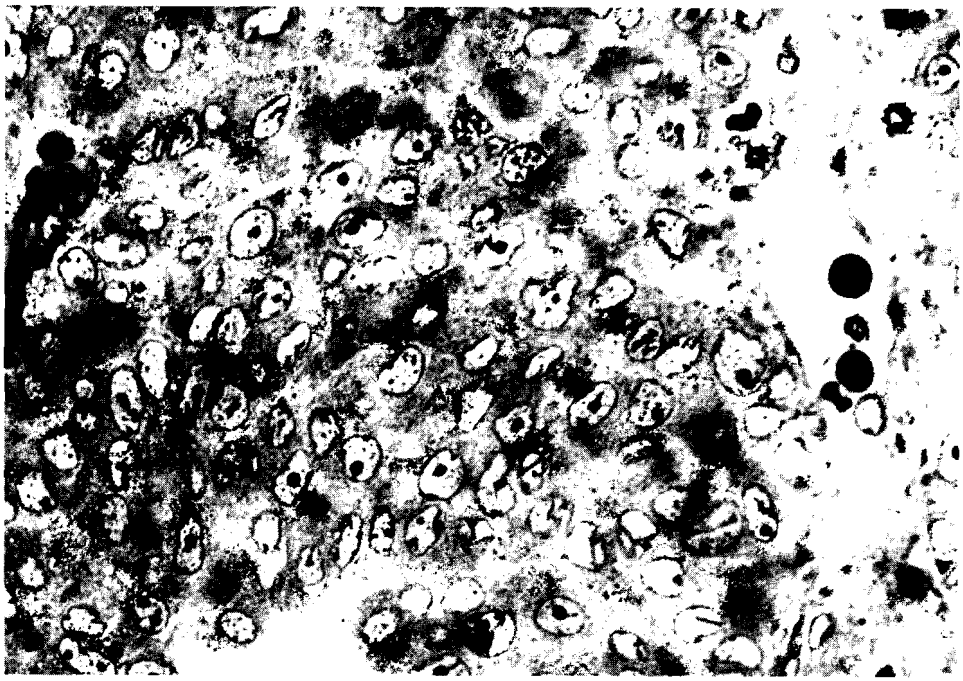

Fig. 1. (case 9) Large cell chromophobe adenoma untreated with DA: slightly indented nuclei, undetectable nucleoli, hardly distinguishable cell borders. Semi-thin section, toluidin blue. ×610

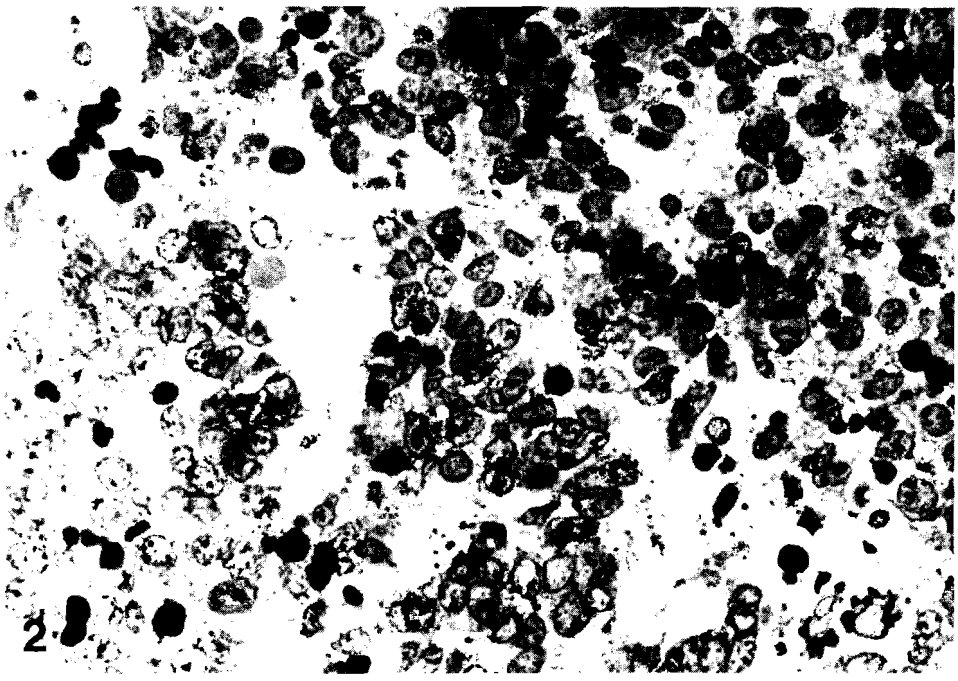

Fig. 2. (case 4) Small cell chromophobe adenoma after treatment with DA: irregular shape of the nuclei, hardly distinguishable cell borders, collageneous connective tissue. Semi-thin section, toluidin blue. ×610

nuclei as well as the entire volume of the cells have shrunken. The cells of the treated prolactinomas resemble those of the untreated inactive adenomas.

When compared statistically by the Krousal and Wallis analysis of variance and ranks (Sachs, 1970), all these groups differ significantly only in their cell volume (level of significance of 5 %).

The significant differences between the treated and the untreated prolactinomas were also checked with the U-test. Here, a significant difference of 2 % is to be found. This also applies to the parameters concerning the cell volume, such as the area of the whole cell and the area of the cell without caryoplasm.

The cellular area does not always correlate with the amount of the endocrinological activity, but is generally considered to be a direct parameter for it, as we showed in former studies (Schottke et al., 1986).

Therefore, in our cases the extent of cellular area

Table 1. Clinical and morphologicval data of prolactinomas and inactive adenomas

Case Number	Age / Sex	Preoperative treatment	Period of treatment	Prolactin plasma level before treatment	Prolactin plasma level after DA-treatment	Type of tumour	Estimated percentages of immunohistological PRL-positive adenoma cells
			Treated prolactinomas				
1	m 35 ys.	Lisuride 4 × 0.2 mg	51 days	670 ng/ml	187 ng/ml	chromophobe, mainly large cell	70 %
2	m 15 ys	Bromocriptine 3 × 1.25 mg and 3 × 2.5 mg	1½ months, 2 days preop.	807 ng/ml	207 ng/ml	large cell chromophobe regressive changes	70%
3	f 32 ys	Lisuride 2 × 0.2 mg	9 days, 1 day preop.	507.5 ng/ml	79 ng/ml	large cell chromophobe	90%
4	f 38 ys	Lisuride 3 × 0.2 mg	7.5 months	3660 ng/ml	180 ng/ml	small cell chromophobe regressive changes	45%
5	f 32 ys	Bromocriptime 5 × 2.5 mg	no data available	297 ng/ml	2.5 ng/ml	mainly small cell regressive changes	90%
6	m 41 ys	Bromocriptine 3 × 2.5 mg Lisuride 3 × 0.2 mg	B. 1 year L. 5 months	200 ng/ml	125 ng/ml	large cell chromophobe regressive changes	60%
			Untreated prolactinomas				
7	m 35 ys			4700 ng/ml	post-operative 60.5 ng/ml	large and small cell chromophobe regressive changes	70%
8	m 47 ys			398 ng/ml	185 ng/ml	large cell chromophobe	90%
9	f 31 ys			800 ng/ml	82.9 ng/ml	large cell chromophobe regressive changes	90%
10	f 34 ys			97 ng/ml	5.5 ng/ml	large cell chromophobe	90%
11	f 39 ys			423 ng/ml	11 ng/ml	large cell chromophobe regressive changes	60%
12	m 67 ys			201 ng/ml	162.6 ng/ml	small cell chromophobe regressive changes	80%
13	m 67 ys			> 200 ng/ml	47.6 ng/ml	large cell chromophobe regressive changes	70%
14	f 26 ys			255 ng/ml	28 ng/ml	large cell chromophobe regressive changes	35%
			Untreated inactive adenoma				
15	m 56 ys			10.1 ng/ml		small cell chromophobe regressive changes	4%
16	m 21 ys			18.5 ng/ml	14.65 ng/ml	small cell chromophobe regressive changes	25%
17	m 44 ys			2.5 ng/ml		chromophobe oncocytic parts	1%
18	m 70 ys			incidental adenoma at hypophysectomy due to cancer of the prostate		chromophobe microadenoma	5%

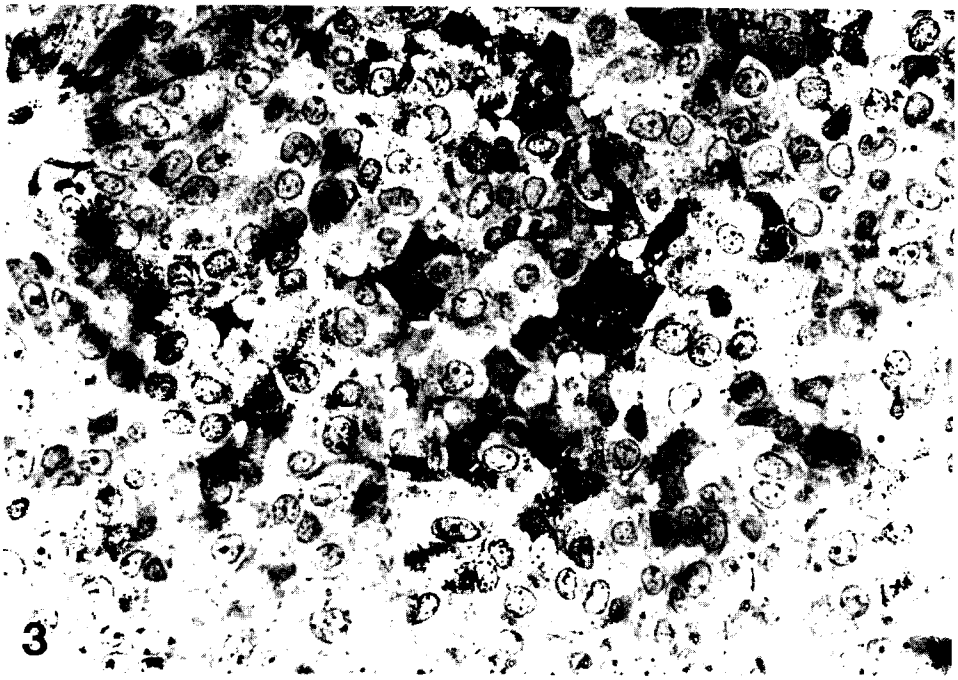

Fig. 3. (case 15) Inactive small cell chromophobe adenoma, untreated with DA: oval nucleoli, detectable nucleoli, partly visible cell borders. Semi-thin section, toluidin blue. ×610

Table 2. Statistical analyses

U-test

Comparison between treated prolactinomas (5 cases) and untreated prolactinomas (8 cases). (without non-responder case 6)

Parameter	U	Significance
A (Area)	10	n.s.
P (Perimeter)	11	n.s.
FAr	15.5	n.s.
FPe	10	n.s.
D-Circle (Area equivalent diameter)	8	n.s.
Area of whole cell	0	s. (0.2%)
Area of cell without caryoplasm	0	s. (0.2%)

For $U \leqslant 0$ the significance for the difference between the two groups (α) is 0.002.

Analysis of variance and ranks

Comparison between treated prolactinomas (5 cases), untreated prolactinomas (8 cases) and an untreated inactive comparison group (4 cases). (without non-responder case 6).

Parameter	H	Significance
A (Area)	1.228	n.s.
P (Perimeter)	2.449	n.s.
FAr	0.695	n.s.
FPe	3.282	n.s.
D-Circle (Area equivalent diameter)	4.179	n.s.
Area of whole cell	9.129	s. (1%)
Area of cell without caryoplasm		s. (5%)

For H 5.99 the significance of difference between the three groups is 5%.
For H 9.21 the significance of the difference is 1%.

Table 3. Morphometrical results

	Nuclei	Area	Standard-deviation of area	Perimeter	Standard-deviation of Perimeter	Factor for the Shape Pe	Standard-deviation of factor for the shape Pe	Factor for the shape Ar	Standard-deviation of factor for the shape Ar	Area-equivalent diameter	Standard-deviation of area equival. diameter	Area of whole cell	Area of whole cell without caryoplasm
Treated prolactinomas													
case 1	8,245	39.300	10.600	23.780	3,780	0.860	0.093	0.970	0.035	6.84	0.970	93.190	54.540
case 2	627	47.123	11.015	26.136	3.208	0.858	0.076	0.988	0.0116	7.675	0.900	106.596	59.510
case 3	757	36.990	8.880	22.947	3.135	0.877	0.085	0.985	0.027	6.812	0.815	76.912	39.927
case 4	4,128	35.032	7.310	21.010	3.040	0.880	0.090	0.990	0.050	6.23	0.740	55.820	24.900
case 5	230	31.252	9.572	21.202	3.404	0.858	0.096	0.982	0.024	6.208	0.998	72.316	41.066
case 6	2,267	44.262	9.840	24.562	3.163	0.908	0.075	0.993	0.032	7.461	0.813	143.576	99.226
Mean value	2,709	38.993	9.536	23.272	3.288	0.873	0.085	0.984	0.0299	6.871	0.864	91.401	55.299
Sum	16,254	–	–	–	–								
Treated prolactinomas (without non-responder Case 6)													
Mean value	2,797.9	37.939	9.475	23.015	3.289	0.866	0.088	0.983	0.029	6.753	0.875	80.960	43.980
Sum	13,987	–	–	–	–								
Untreated prolactinomas													
case 7	5,018	37.850	11.810	24.780	4.180	0.838	0.095	0.975	0.035	7.166	1.032	129.877	88.252
case 8	2,231	43.824	10.296	24.717	3.313	0.896	0.074	0.990	0.017	7.415	0.872	120.729	76.904
case 9	5,757	46.113	13.483	25.785	4.315	0.856	0.088	0.977	0.031	7.572	1.111	135.477	89.391
case 10	2,125	45.210	11.655	25.214	2.594	0.886	0.083	0.983	0.026	7.520	0.966	126.666	81.454
case 11	2,515	37.918	7.280	22.718	3.026	0.917	0.066	0.990	0.020	6.907	0.684	165.681	127.747
case 12	3,339	39.472	9.713	23.440	3.341	0.895	0.080	0.988	0.042	7.033	0.875	128.098	88.601
case 13	1.099	46.376	10.137	25.020	3.175	0.920	0.060	0.990	0.019	7.626	0.872	240.410	194.383
case 14	2,066	45.099	11.304	25.189	3.868	0.886	0.083	0.986	0.027	7.512	0.964	169.390	124.290
Mean value	3,018.75	42.732	10.709	24.607	3.476	0.886	0.078	0.984	0.027	7.343	0.922	152.041	108.877
Sum	24,150	–	–	–	–								
Untreated inactive adenomas													
case 15	2,936	31.610	8.405	21.745	3.173	0.884	0.083	0.985	0.027	6.481	0.844	142.844	109.078
case 16	2,388	36.434	9.880	22.786	3.451	0.869	0.083	0.981	0.039	6.739	0.947	120.727	84.291
case 17	2.053	44.790	12.430	25.150	4.210	0.875	0.096	0.987	0.024	7.470	1.046	145.030	102.160
case 18	96	43.205	10.355	24.775	2.965	0.875	0.070	0.985	0.015	7.365	0.880	93.135	49.930
Mean value	1,868.25	39.009	10.265	23.614	3.449	0.876	0.083	0.985	0.026	7.014	0.929	125.426	86.365
Sum	7,473	–	–	–	–								

stands for the success of treatment. There are few exceptions. Case 2, for example, shows relatively large cells. Therefore the exception is purely morphological since the clinical findings reveal a decrease of the prolactin plasma level.

By contrast, case 6 of the same group is a typical non-responder. As the relatively high prolactin plasma level remains undiminished even after operative treatment, this is correlated to unusually large nuclei and cells after treatment.

With regard to these findings, further statistical tests were made after excluding the non-responding case 6 from the treated group for comparison of those tumours which responded clinically as well as morphologically. The mean value for the nuclear area of the treated group of prolactinomas —excluding case 6— is 37,939; for the prolactinomas which remained untreated, 42,732. The treated prolactinomas resemble the untreated inactive group which shows the following mean value for area: 39,009 (Table 3).

These results are much clearer when the whole cytoplasmic area is taken into account. The cytoplasmic area of the DA-treated prolactinomas with the mean value of 80,960 is significantly smaller than that of the untreated prolactinomas with an average of 152,041 (Table 3).

The analyses of variance and ranks (Table 2) shows a significance of difference of 5 % for the parameter «area of the cell without caryoplasm». For the area of the whole cell, the significance of the difference is 1 %. According to the U-test, the significance for the difference between the two groups of treated and untreated prolactinomas concerning both cell-size parameters is 0.2 %.

Discussion

Our study compares the light microscopical structures and morphometric data of prolactin secreting adenomas with untreated adenomas and with adenomas which partially show a borderline enhancement of prolactin plasma levels.

In one case (No. 6) neither the removal of the adenoma, nor the treatment with DA could achieve a decrease of the prolactin plasma level. This case which did not show an extremely high level of prolactin, 200 ng/ml before the operation, was characterized morphologically and clinically as an adenoma typically non-responding to DA-treatment.

Similar findings are also described by other authors (Chiodini et al., 1981; Nissim et al., 1982). Due to its untypical reaction, this case was excluded from the final statistical evaluation.

The other adenomas which had been treated with DA showed significantly smaller cells than those of untreated adenomas. The latter resembled the structures of the clinically inactive tumour group. The nuclei themselves were not shrunken significantly under DA-treatment.

Further conclusions are not to be drawn from the clinical data, above all no correlation between the duration and success of therapy can be found.

The only non-responder of the group, for example, had required the longest DA-treatment of all. Bromocriptine was given for one year and Lisuride for five months. On the other hand, this could also be the reason for the failure of therapy. According to Barrow et al. (1984) the most tumour shrinkage occurs after three weeks of therapy. A continuation could possibly mean a further reduction of tumour size, but also an increase of fibrosis within the tissue so that the final removal of the tumour will become more difficult (Landolt and Osterwalder, 1984).

Similar results concerning the shrinking of the cytoplasmic area are achieved by Rengachary et al. (1982). At the electron microscopical level, the reduction of cytoplasmic compartments, such as rough endoplasmic reticulum, Golgi complex and ribosomes is said to be the main reason for the obvious reduction of cell volume. This phenomenon is not correlated to reduction of the nuclei themselves (Nissim et al., 1982; Barrow et al., 1984). But there are also studies showing both the shrinking of cell and nuclei area (Tindall et al., 1982).

The ultrastructural changes of those organella identified by many authors (Rengachary et al., 1982; Tindall et al., 1982; Barrow et al., 1984; Schottke et al., 1986), as well as a decrease of exocytoses can be considered as the morphological correlation for the decrease of the prolactin plasma levels.

The disminishing of the cell volume causes tumour shrinkage. This can be demonstrated not only with the electron microscope but also at the light microscopical level as we showed by our morphometrical anaylses.

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