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Electron microscopical morphometry of well-differentiated and undifferentiated ACTH secreting adenomas in Cushing's disease and Nelson's syndrome*,**

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Summary. Adrenocorticotrophic hormone (ACTH)-secreting adenomas of patients with Cushing's disease (undifferentiated and well-differentiated ACTH-cell adenomas) were studied ultrastructurally and analysed morphometrically by a computer-supported quantitative image-analysing system. They were compared with identically prepared ACTH tumours (undifferentiated and well-differentiated ACTH-cell adenomas) of pituitaries from bilateral adrenalectomised patients with Nelson's syndrome. The aim of our study was to look for significant differences in ultrastructure and to evaluate these findings statistically regarding adenoma types and clinical syndromes. Clinical syndromes aside, more secretory granules and larger-sized prosecretory granules were measured in the well-differentiated ACTH-cell adenomas. The undifferentiated adenomas showed a greater content of nucleoli and prosecretory granules. Within the adenoma types, comparison of well-differentiated ACTH-cell adenomas showed that the clinical group of Cushing's disease contained larger areas of cytofilaments, whereas the clinical group of Nelson's syndrome had a larger tumour size and more lysosomes. Comparing the undifferentiated adenomas of both clinical groups the adenomas in Cushing's disease contained larger nuclei and more lysosomes, whereas the adenomas in Nelson's syndrome were larger in tumour size and contained larger prosecretory granules. Comparison of well-differentiated and undifferentiated adenomas in Cushing's disease showed more secretory granules and bigger prosecretory granules in well-differentiated adenomas whereas in undifferentiated adenomas the total area of the nuclei is larger, the nucleoli increase in number and size and the lysosomes are more frequent. Comparison of well-differentiated and undifferentiated adenomas in Nelson's syndrome demonstrated more lysosomes in well-differentiated adenomas and a larger total area of the nuclei in undifferentiated adenomas. The differences between the well-differentiated adenomas (mainly more secretory granules and larger prosecretory granules) and undifferentiated adenomas (mainly more and larger nuclei and nucleoli and more prosecretory granules) prove the clear separability between the adenoma types, not demonstrated in the literature up to now. The significant differences between adenomas in Cushing's disease (mainly more cytofilaments) and Nelson's syndrome (mainly more ribosomes and larger prosecretory granules) may be interpreted as different cell reactions due to the hypercortisolism present in Cushing's disease and lacking in Nelson's syndrome following adrenalectomy. Despite the fact that both clinical syndromes are based on the same adenoma types, indistinguishable by light microscopy, significant morphometrical findings in ultrastructure allow a clear discrimination of both clinical types.

Key words: Pituitary – ACTH-cell adenoma – Morphometry – Cushing's disease – Nelson's syndrome

Introduction

The definition of the grade of differentiation, the immunohistological hormone content and clinical findings are important in the classification of pituitary adenomas. The grade of differentiation is evaluated by comparison with normal pituitaries. Well-differentiated adenomas show a great similarity with regular cells which is lacking in undifferentiated adenomas. Immunohistology (Challa et al. 1985; Charpin et al. 1982; Osamura et al. 1984; Saeger et al. 1986) provides information about hormone content. For a more specific and sophisticated classification (Kovacs and Horvath 1986), detailed ultrastructural investigations are mandatory.

In our collection we use two grades of differentiation in the adrenocorticotrophic hormone (ACTH)-secreting

* Dedicated to Prof. Gerhard Seifert on the occasion of his 70th birthday

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Table 1. Clinical and histological data

Case no.	Specimen journal no.	Age (years)		Sex	Adenoma size (mm)	Immunohistology					
						ACTH	PRL	GH	TSH	LH	FSH
Well-differentiated ACTH-cell adenomas in Cushing's disease											
1	62/80	38		F	6	+	−	−	−	−	−
2	83/81	46		M	3	+	−	−	−	−	−
3	107/81	55		F	4	+	−	−	(+)	−	−
4	31/82	20		F	7	+	+	+	−	−	−
5	10/83	20		M	4	+	−	−	−	−	−
6	61/83	53		F	2	+	−	−	−	−	−
7	32/83	48		F	3	+	−	−	−	−	−
8	92/83	40		F	7	+	−	−	−	−	−
9	107/83	57		F	8	+	−	−	−	−	−
10	105/84	22		F	10	+	−	−	−	−	−
11	69/86	53		M	9	+	−	−	+	−	−
12	47/88	39		F	4	+	−	−	−	−	−
Undifferentiated mucoid cell adenomas in Cushing's disease											
13	73/83	61		F	5	+	+	−	−	−	−
14	134/83	23		M	5	+	−	−	−	−	−
15	139/83	55		F	4	+	+	−	−	+	−
16	3/84	8		F	9	+	−	−	−	−	−
17	74/84	36		F	11	+	+	−	−	−	−
18	110/84	28		M	3	+	−	+	−	+	−
19	46/85	28		F	4	[a]					
20	279/85	37		F	6	+	−	−	−	−	−
21	109/86	41		M	5	+	+	−	+	−	−
Well-differentiated ACTH-cell adenomas in Nelson's syndrome											
22	71/73	31	4[b]	F	9	[a]					
23	38/77	53	10[b]	M	11	[a]					
24	87/79	25	7[b]	F	[a]	+	−	−	−	−	−
25	43/81	46	15[b]	F	8	+	−	−	−	−	−
26	71/81	39	5[b]	F	11	+	−	−	−	−	−
27	73/82	43	6[b]	F	8	+	−	−	−	−	−
28	25/83	23	12[b]	F	[a]	+	+	−	+	+	+
29	99/84	36	6[b]	F	12	+	−	−	−	+	−
Undifferentiated mucoid cell adenoma in Nelson's syndrome											
30	38/72	34[b]	7[b]	F	9	+	−	−	−	−	−
31	102/78	42	8[b]	F	12	+	+	−	−	−	−
32	45/80	41	18[b]	F	20	+	−	−	−	−	−
33	14/85	41	6[b]	F	12	+	−	−	−	−	−

ACTH, Adrenocorticotrophic hormone; FSH, follicle stimulating hormone; GH, growth hormone; LH, luteinizing hormone; PRL, prolactin; TSH, thyroid stimulating hormone

[a] No data available

[b] Interval in years between bilateral adrenalectomy and hypophysectomy

(and immunohistologically ACTH-positive) adenomas. The classification of an adenoma as well-differentiated or as undifferentiated is often difficult (Saeger 1973; Saeger et al. 1988) and based on qualitative interpretation as well as on subjective evaluation of the findings. Intensive morphometric studies, the most accurate and predicative method to evaluate distinct and significant alterations in light microscopic or ultrastructural features (Saeger et al. 1986, 1987; Schottke et al. 1986), are too time-consuming for routine diagnosis.

The aim of this study was to determine whether significant differences exist between the ultrastructure of well-differentiated ACTH-cell and undifferentiated adenomas of Cushing's disease and Nelson's syndrome, which is defined as an ACTH-secreting pituitary adenoma developing in patients with Cushing's disease after treatment by bilateral adrenalectomy, or not. Light microscopical differences have not been demonstrated in both states of ACTH hyperfunctions.

Materials and methods

Twenty-one pituitary adenomas with the clinical diagnosis of Cushing's disease and 12 with the clinical diagnosis of Nelson's syndrome were classified histologically. Of the cases with Cushing's disease there were 12 well-differentiated ACTH-cell adenomas

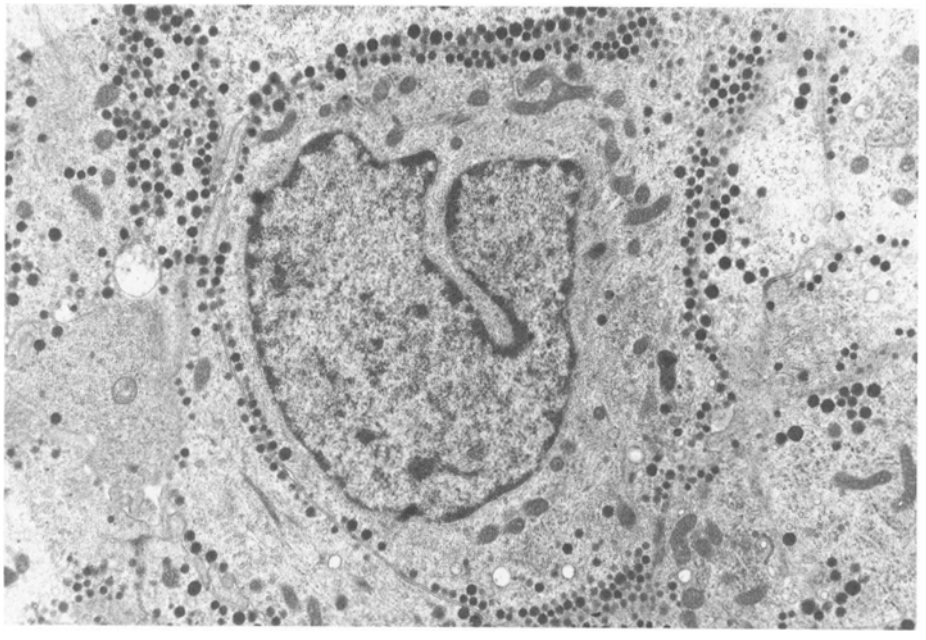

Fig. 1. Well-differentiated ACTH-cell adenoma in Cushing's disease (69/86): slightly elongated cell, indented nucleus, perinuclear cytofilament, various mitochondria in different forms and sizes, peripherally localised dense secretory granules. ×7100

(group 1) and 8 cases (group 3) of Nelson's syndrome, all defined by their close similarity to regular ACTH cells and their density of secretory granules. Undifferentiated adenomas [9 with Cushing's disease (group 2) and 4 with Nelson's syndrome (group 4)] were defined by their proliferative activity by rate of mitoses, loss of similarity to normal ACTH cells, signs of regression and sparseness of the granules. The specimens came from a 20-year collection of surgically removed pituitary adenomas. Clinical data are listed in Table 1.

The material was obtained using the transnasal-transsphenoidal surgical approach and was processed for light microscopic and electron microscopic studies as well as for immunohistological classification. For light microscopic studies material was fixed in Bouin's solution, embedded in paraffin and stained with haematoxylin and eosin and periodic acid-Schiff reaction. For electron microscopy small portions of each adenoma were fixed in glutaraldehyde for 2 h, postfixed in osmium tetroxide and embedded in epon 812. Ultrathin sections were stained with lead citrate and uranyl acetate. Twenty ultrathin sections of each case were photographed in the electron microscope (Zeiss EM 9 S2) at a constant primary magnification (×4000) by random sampling. For electron microscopic studies, the final photographic magnification (size 17×18 cm) was ×10500. For morphometry, 657 photographs (238 well-differentiated ACTH-cell adenomas in Cushing's disease, 159 well-differentiated ACTH-cell adenomas in Nelson's syndrome, 180 undifferentiated adenomas in Cushing's disease and 80 undifferentiated adenomas in Nelson's syndrome) were analysed for number, area, perimeter and maximum diameter of different organelles using a computer-supported semi-quantitative image analysing system (Videoplan; Kontron, Munich, FRG). We identified structures such as nuclei, nucleoli, mitochondria, secretory granules, rough endoplasmic reticulum, Golgi fields, cytofilaments, lysosomes, ribosomes, prosecretory granules and cellular membranes. The measurement of the cellular membranes revealed the total size of the cells. The differentiation between lysosomes and secretory granules was based on irregularity in shape and electron density and the generally larger volume of the lysosomes. Intracellular spaces, capillaries, areas of necrosis, fibrosis and haemorrhage were not taken into account. The average value (in mm, ×10500) and standard deviation were calculated. The results of the four groups were statistically evaluated (Kruskall-Wallis test, Wilcoxon's test) by using the SPSS statistical software package (IBM) on an IBM personal computer (IBM PC 286). Values were interpreted as significantly different at a level of $P<0.05$.

Results

Two patients were younger than 12 years, 2 patients older than 55 years. The average age was 38.2 years; 78.8% were female and 21.2% male. The tumour size measured by the surgeon was between 2 mm and 5 mm in 36%, between 6 mm and 10 mm in 43%, between 11 mm and 15 mm in 17%, and in only 1 case (4%) measured 20 mm in diameter. Significant differences were found between adenomas with Cushing's disease and Nelson's syndrome (Table 1); 67% (20 cases) were monohormonally ACTH-secreting adenomas, 23% (10) cases were plurihormonal adenomas containing mainly ACTH. The collection of undifferentiated adenomas in Cushing's disease contained significantly more plurihormonal adenomas (62.5% plurihormonal, 37.5% monohormonal) (Table 1). There were no significant differences for the time period between bilateral adrenalectomy and hypophysectomy in Nelson's syndrome regarding the grade of differentiation.

Ultrastructurally, well-differentiated ACTH-cell adenomas usually consist of medium-sized, mostly elongated cells with an ovaloid shaped nucleus. The nucleoli are round and located in the periphery. The cytoplasm is densely granulated. Mitochondria are monomorphic, oval and vary in number. The arrangement of secretory granules, between 250–450 nm in diameter, is diffuse or peripheral. The rough endoplasmic reticulum sometimes appears in widened fragments. The Golgi fields, often missing, show few and small prosecretory granules. Cytofilamentous areas are located close to the nucleus and vary in size and number. Lysosomes are larger than secretory granules and vary in size, structure and density. Free ribosomes are numerous (Fig. 1, 3).

Undifferentiated adenomas show enlarged pleomorphic cells. The nuclei are larger. The nucleoli are augmented and enlarged. The cytoplasm is sparsely granulated. The secretory granules are relatively sparse

Table 2. Morphometric comparison of well-differentiated ACTH-cell adenomas and undifferentiated mucoid cell adenomas

	Cushing's disease				Nelson's syndrome		
	well-differentiated ACTH cell adenoma		undifferentiated adenoma		well-differentiated ACTH cell adenoma		undifferentiated adenoma
	Significant differences		Significant differences		Significant differences		Significant differences
Cells							
Counts	106.08	NS	105.00	NS	133.00	NS	89.50
Area	6261.12	NS	7631.06	NS	5380.73	NS	8753.78
	(7226.12)		(7208.60)		(6166.41)		(7850.02)
Nuclei							
Counts	44.67	NS	56.56	NS	52.38	NS	67.00
Area	2342.62	NS	2662.94	NS	2192.18	NS	2354.53
	(1901.47)		(2275.01)		(2081.53)		(1851.21)
Nucleoli							
Counts	19.42	NS	16.11	NS	11.13	NS	15.00
Area	120.25	<	231.04		118.14	>	95.34
	(74.01)		(163.73)		(86.94)		(52.18)
Mitochondria							
Counts	1484.67	NS	1303.56	NS	1752.00	NS	1224.00
Area	17.43	NS	25.15	NS	19.62	NS	25.65
	(17.23)		(20.29)		(17.02)		(20.19)
Secretory granules							
Counts	8663.66	>	5036.33	NS	7185.75	>	7075.00
Area	5.05	NS	5.05	NS	4.70	NS	5.42
	(3.32)		(7.30)		(3.30)		(3.64)
R.E.R.							
Counts	813.66	NS	823.33	NS	1090.87	NS	1234.50
Area	30.31	NS	15.93	NS	17.27	NS	17.33
	(71.32)		(21.25)		(34.70)		(35.21)
Golgi fields							
Counts	46.58	NS	72.55	NS	64.75	NS	58.25
Area	181.77	NS	175.21	NS	130.42	NS	170.06
	(176.47)		(186.29)		(91.49)		(191.40)
Cytofilaments							
Counts	129.18	NS	208.22	NS	75.28	NS	106.75
Area	21.06	NS	29.37	>	3.95	NS	11.43
	(44.04)		(60.83)		(6.80)		(24.14)
Lysosomes							
Counts	43.58	<	86.77	NS	66.75	>	38.25
Area	57.52	NS	169.00	NS	58.52	NS	41.89
	(67.41)		(206.86)		(91.79)		(42.16)
Ribosomes							
Counts	751.50	NS	386.85	<	962.38	NS	1243.75
Area	0.90	NS	1.65	NS	0.91	NS	0.92
	(0.79)		(1.03)		(0.44)		(0.52)
Prosecretory granules							
Counts	22.83	<	224.11	>	29.75	NS	66.75
Area	4.22	>	1.51	<	5.14	NS	5.68
	(2.59)		(7.01)		(3.39)		(5.77)

Mean values (mm^2) and standard deviation ( ) of area of cell organelles ($\times 10500$ magnification). Level of significance $P<0.05$. NS, not significant; <, significantly smaller; >, significantly bigger; RER, rough endoplasmic reticulum

and vary in size. Mitochondria and rough endoplasmic reticulum are sometimes enlarged. Golgi fields appear larger sometimes. Prosecretory granules are augmented. Lysosomes are variable. Necrosis, fibrosis and a higher rate of mitoses are more often demonstrable (Fig. 2, 4).

Morphometric data (counts, average value and standard deviation) of the organelles are listed in Table 2. Table 3 lists average area percentages of the organelles for all four groups. Significant results are described in the following passage; results are listed in Tables 2 and 3.

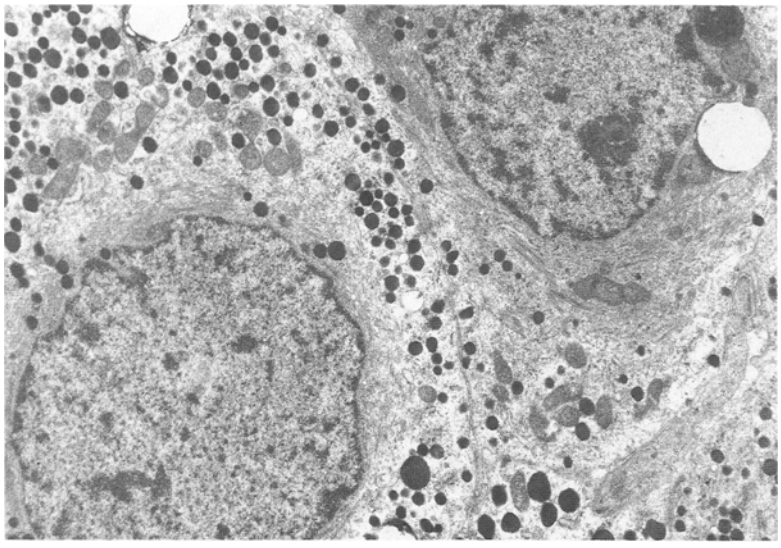

Fig. 2. Undifferentiated mucoid cell adenoma in Cushing's disease (74/84): large nuclei, varying mitochondria, sparse rough endoplasmic reticulum, small paranuclear Golgi fields, masses of perinuclear cytofilaments. ×7100

Table 3. Morphometric comparison of well-differentiated ACTH-cell and undifferentiated mucoid adenomas

	Cushing's disease			Nelson's syndrome			
	Well-differentiated ACTH cell adenoma		Undifferentiated adenoma	Well differentiated ACTH cell	Undifferentiated adenoma		
Area %							
Protoplasm	67.87		65.6		67.52		67.12
Nucleus	15.6	<	20.1	NS	17.8	<	19.5
Nucleolus	0.2	<	0.4	>	0.19	NS	0.18
Mitochondria	3.9	NS	4.3	NS	4.8	NS	4.0
Secre. granules	6.6	>	3.3	NS	4.8	NS	4.7
RER	3.7	NS	1.7	NS	2.9	NS	2.7
Golgi fields	1.3	NS	1.7	NS	1.2	NS	1.3
Cytofilaments	0.35	NS	0.8		0.04	NS	0.15
Lysosomes	0.37	<	1.9		0.6	>	0.2
Ribosomes	0.1	NS	0.07	NS	0.12	NS	0.1
Prosecretory granules	0.01	<	0.05	<	0.03	NS	0.05

Average sum values in area percentage. Level of significance $P<0.05$. NS, not significant; <, significantly smaller; >, significantly bigger

The greater numbers of nucleoli (Tables 2, 3) are significantly different in the undifferentiated adenomas in comparison with the well-differentiated adenomas. The nucleoli of undifferentiated adenomas in Cushing's disease are significantly larger than those of the undifferentiated adenomas in Nelson's syndrome.

Secretory granules (Tables 2, 3) ranging from a maximum size of 5.42 mm^2 to a minimum of 4.70 mm^2 are significantly more numerous in well-differentiated adenomas: 8863.66 in well-differentiated adenomas and 5036.33 in undifferentiated adenomas in Cushing's disease.

Well-differentiated adenomas in Cushing's disease (Fig. 1) contain significantly more cytofilaments (Tables 2, 3) than those in Nelson's syndrome (Fig. 3). Differences between the adenoma types within the two clinical groups are not significant.

No significant differences for lysosomes (Tables 2, 3) appear between adenoma types, but do exist within the clinical groups. Well-differentiated adenomas in Nelson's syndrome contain more lysosomes than undifferentiated ones (Fig. 4), but the reverse is true of adenomas in Cushing's disease.

Adenomas in Nelson's syndrome contain a significantly larger number of ribosomes (Tables 2, 3).

Significant differences exist in the size (1.51 mm^2 and 5.68 mm^2) of the prosecretory granules (Tables 2, 3) between undifferentiated adenomas of both clinical groups. Comparing both adenoma types well-differentiated adenomas contain significantly larger prosecre-

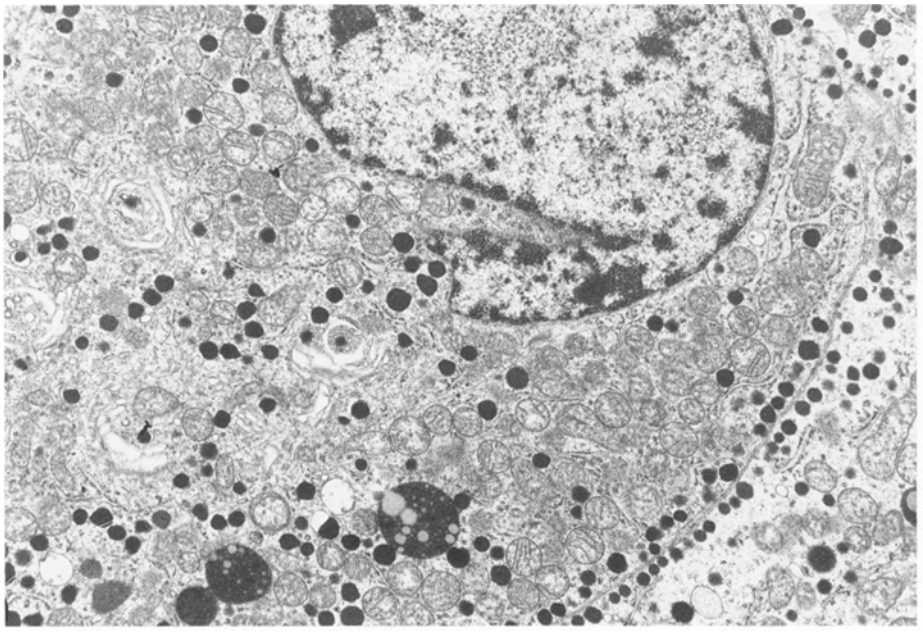

Fig. 3. Well-differentiated ACTH-cell adenoma in Nelson's syndrome (43/81): ovaloid indented nucleus, numerous mitochondria (artificial alterations due to processing), diffusely and peripherally localised secretory granules, Golgi fields, few prosecretory granules, sparse rough endoplasmic reticulum, some electron-dense lysosomes. ×7100

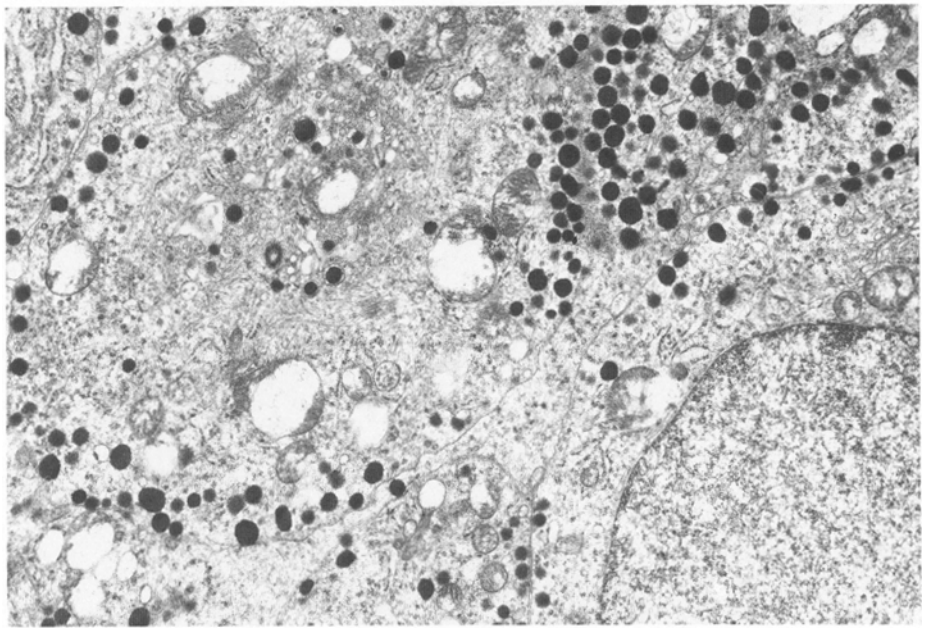

Fig. 4. Undifferentiated mucoid cell adenoma in Nelson's syndrome (38/72): large nucleus, medium amount of secretory granules, few enlarged mitochondria, scattered membranes of rough endoplasmic reticulum, Golgi fields, and large prosecretory granules, few large lysosomes. ×7100

tory granules whereas the undifferentiated adenomas contain more prosecretory granules.

Discussion

ACTH-producing adenomas of the pituitary gland have been extensively studied in the literature (Bergland and Torack 1969; Horvath and Kovacs 1976, 1980; Kovacs and Horvath 1986; Kovacs et al. 1976, 1977; Landolt 1978; Landolt and Hosbach 1974; Lloyd et al. 1986; Olivier et al. 1975; Reuss 1991; Robert et al. 1978; Saeger 1973, 1974; Saeger et al. 1986, 1988).

Perinuclear cytofilaments are typical features in ACTH-producing tumours in Cushing's disease (Challa et al. 1985; Robert et al. 1978; Saeger 1973, 1974). ACTH-secreting adenomas in Nelson's syndrome harbour fewer cytofilaments (Horvath and Kovacs 1976; Kovacs et al. 1976; Landolt 1978; Saeger 1973), which seems to be the only difference between the adenomas in both clinical hyperfunctional states.

Our results provide evidence that the number of perinuclear cytofilaments correlates with the clinical type of an ACTH hyperfunction. Hypercortisolism as the suppressive factor in Cushing's disease is the cause of augmented numbers of cytofilaments in ACTH-cell ad-

enomas (Kovacs et al. 1976; Saeger et al. 1988). An influence of the hypothalamus on the development of cytofilaments has been discussed (Challa et al. 1985). The absence of hypercortisolism in ACTH-producing tumours in Nelson's syndrome leads to fewer perinuclear cytofilaments (Kovacs et al. 1976; Landolt 1978; Saeger 1973; Saeger et al. 1988).

Our findings of a greater number of free ribosomes and larger prosecretory granules in adenomas in Nelson's syndrome are interpreted as indicating accelerated synthesis combined with the increased secretion of prosecretory granules from lack of suppressive increased cortisol (Kovacs et al. 1976).

Comparison of adenoma types shows that well-differentiated adenomas contain significantly more secretory granules and larger prosecretory granules, suggesting intensified secretory activity (Horvath and Kovacs 1980; Kovacs and Horvath 1986). The undifferentiated adenomas contain more nucleoli, fewer secretory granules and more prosecretory granules also suggesting an increased proliferation. Significantly more lysosomes in well-differentiated adenomas than in undifferentiated adenomas in Nelson's syndrome (a finding reversed in Cushing's disease) are possible signs of increased crinophagia of secretory granules or inactive polypeptides.

The significant polyhormonal activity of undifferentiated adenomas in Cushing's disease (Saeger et al. 1988) was not demonstrable in undifferentiated adenomas in Nelson's syndrome. The significantly greater tumour size of the adenomas in Nelson's syndrome (Saeger et al. 1988) is a result of the clinical selection, since the tumour size is an indication for surgical removal of the adenoma. We could not find statistically significant values as for the time elapsed between bilateral adrenalectomy and hypophysectomy and the grade of differentiation of the adenomas in Nelson's syndrome.

Our morphometric findings clearly confirm the classification of ACTH-producing adenomas into well-differentiated and undifferentiated adenoma types as performed by light microscopic examination. Significant ultrastructural findings allow the separation into adenomas of the morphological type of Cushing's disease or the type of Nelson's syndrome, which are induced by the presence (in Cushing's disease) or the absence (in Nelson's syndrome) of hypercortisolism.

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