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# Interactions between normal and tumoral tissues at the boundary of human anterior pituitary adenomas

## An immunohistochemical study

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**Abstract** We studied the boundary between adenoma and peritumoral anterior pituitary tissues in order to understand their mutual interactions during tumour progression. We selected 18 adenomas of different secretory type, grade and invasiveness in which fragments of peritumoral anterior pituitary were still attached to the adenoma. Immunohistochemistry was performed on serial sections with markers of the basement membranes (type IV collagen), the hormone-producing cells of the normal and neoplastic anterior pituitary, and the folliculo-stellate cells (S–100 protein). In passing from tumour to gland, localized areas of passive compression of the normal gland were seen in only 3 cases. In all the tumours, the boundary consisted partly or solely of a transitional zone characterized by the presence of enlarged cell-cords. Openings in the basement membrane of these enlarged cell-cords were seen in contact with the tumour tissue. Normal and neoplastic cells intermingled in the transitional zone. Normal residual cells could be seen in the central area of the tumour but no adenomatous cells were observed in the gland around the tumour. Folliculo-stellate cells were concentrated in the vicinity of the transition zone. These findings favour the existence of an active process of adenoma expansion within the normal parenchyma, without noticeable infiltration of tumour cells into surrounding gland.

**Key words** Pituitary adenoma · Human anterior pituitary · Tumour progression · Folliculo-stellate cells Immunocytochemistry

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## Introduction

Human pituitary adenomas are the most frequent intracranial neoplasms and may be responsible for different endocrine and tumoral symptoms. In most instances, hormonal hypersecretion is associated with cellular proliferation. In non-secreting pituitary tumours, however, which represent at the most 20% of the cases, a mass effect is the only symptom that reveals the neoplasm (Racadot et al. 1975; Kovacs and Horvath 1986). The majority of pituitary tumours are considered to be benign and slow-growing (Landolt et al. 1987) and metastatic pituitary carcinomas are exceptional (Kovacs and Horvath 1986; Mountcastle et al. 1989). However, radiological, macroscopic and microscopic findings show that a large proportion of these benign tumours display locally aggressive behaviour, invading surrounding structures such as the dura mater, the optic chiasm, the diaphragma sellae and the sphenoidal or cavernous sinus (Jefferson 1954; Martins et al. 1965; Lundberg et al. 1977; Scheithauer et al. 1986; Selman et al. 1986; Sautner and Saeger 1991). Few studies have been devoted to the interactions between adenoma and surrounding anterior pituitary tissues during adenoma growth.

In previous work (Farnoud et al. 1992, 1994) using antibodies against different components of the basement membrane (BM) and stroma we showed great differences between normal and tumoral tissue architectures. In the normal anterior pituitary, two different sets of BMs were seen: one was the epithelial or parenchymatous BMs limiting the cell-cords comprising the various endocrine cells and the other was the vascular BMs surrounding the portal venules, the numerous sinusoids and the veins interspersed between the cell-cords. In contrast, in adenomas, we found an absence of the regular cell-cords, resulting from a complete disorganization of the parenchymatous BMs regardless of the secretory type, grade or invasiveness of the tumour. In contrast, continuous vascular BMs surrounded all adenoma neovessels. In particular, neoarteries, the development of

which is specific for adenoma tissue (Racadot et al. 1986; Gorczyca and Hardy 1988; Schechter et al. 1988b), were prominently stained.

The present work pursues the study of the difference of organization of adenoma versus normal gland by focusing attention on the boundary between adenoma and peritumour anterior pituitary tissues in order to understand their mutual interactions during tumour progression. For this purpose, we selected surgical specimens in which fragments of anterior pituitary were still attached to the adenoma and studied them by immunohistochemistry with a marker of the BMs, type IV collagen (CIV), the hormonal markers of the different endocrine cell-types of the anterior pituitary and a marker of the folliculo-stellate cells, the S–100 protein.

## Materials and methods

We selected 18 specimens from our routinely stained sections in which adenoma tissue was attached to fragments of peritumour anterior pituitary tissue.

These 18 adenomas were obtained from 11 women (19–65 years old) and 7 men (22–72 years old) operated on between 1990 and 1993 at the neurosurgery units of Hôpital Foch, Suresnes, France and of Hôpital Pitié-Salpêtrière, Paris, France. Based upon the clinical symptoms and the biological data, the samples included 8 prolactin (PRL), 2 bihormonal PRL and growth hormone (GH), 1GH, 2 corticotropin (ACTH) secreting adenomas. The other 5 tumours were not associated with clinical or biological evidence of anterior pituitary hormone hypersecretion. The tumours were graded according the classification of Guiot (1973) and included 9 microadenomas (grade 0), 2 macroadenomas of grade I, 6 macroadenomas of grade II and 1 macroadenoma of grade III. Invasion of the dura mater and/or cavernous sinus was found in 6 cases by the neurosurgeons (for more details see Table 1).

The pathological specimens were fixed in Gérard's fluid consisting of a mixture of Bouin-Hollande fixative and saturated aqueous mercuric chloride (9v/1v) and embedded in Paraplast. At least 30 serial 4-µm-thick sections were obtained from the 18 specimens. Indirect immunoperoxidase (Li et al. 1992) was performed with the following rabbit polyclonal antibodies and mouse monoclonal antibodies which were used at the specified dilutions. Polyclonal antibodies included: anti-CIV antiserum (Institut Pasteur, Lyon, France) 1:500, anti-GH antiserum (batch 5976, from Dr. Y. Tillet, Nouzilly, France) 1:2000, anti-β lipotropin (β LPH) antiserum (batch 4053, from Dr. Y. Tillet) 1:1000, anti-$ACTH_{17-39}$ (batch 19524, from Dr. Y. Tillet) 1:2000, anti-PRL (batch 51.53.55, from Dr. C. Rougeot, Institut Pasteur, Paris, France) 1:500, anti-βLH antiserum (AFP 54 372, NIDDK, Bethesda, USA) 1:1000 and anti-S-100 protein antiserum (Dako, Paris, France) 1:500. Monoclonal antibodies (Immunotech, Marseille, France) were raised to the α-subunit of the glycoprotein hormones (clone 6E4, working dilution 1:500), to the β-subunit of FSH (clone 300.10E, working dilution 1:200) and to the β-subunit of TSH (clone 27.18.4, working dilution 1:200). Goat anti-rabbit immunoglobulin antiserum and rabbit anti-mouse immunoglobulin antiserum, both conjugated to horseradish peroxidase (Biosys, Paris, France), were used at a 1:200 dilution. This panel of antibodies was used for the immunohistochemical characterization of the 18 specimens (Table 1). For the purpose of the present study, at least 6 sets of 3 serial sections were systematically immunostained for type IV collagen, the principal hormonal product of the adenoma and one of the other anterior pituitary hormones or hormone subunits. Immunostaining specificity was checked by omitting the primary antibody and by replacing the antibodies either by non-immune rabbit serum or by irrelevant mouse immunoglobulins.

The sections were examined with a Zeiss photomicroscope and pictures were taken on APX25 Agfa film. Pictures of homologous fields on each set of serial sections of the boundary between the adenoma and the peritumoral gland immunostained with the various antibodies were compared.

**Table 1** Clinical and pathological data (*PRL* prolactin; *GH* growth hormone; *ACTH* corticotrophin; *FSH* follicle stimulating hormone; *α-su* α-subunit)

| Case no. | Sex | Age (years) | Grade[a] | Local[b] invasion | Immunohistochemistry |
|---|---|---|---|---|---|
| PRL-secreting adenoma | | | | | |
| 1 | F | 27 | 0 | – | PRL |
| 2 | F | 29 | 0 | – | PRL, α-su |
| 3 | F | 33 | 0 | – | PRL |
| 4 | F | 33 | 0 | – | PRL |
| 5 | M | 34 | 0 | – | PRL, α-su |
| 6 | M | 33 | 0 | cs | PRL |
| 7 | F | 21 | I | – | PRL, α-su |
| 8 | F | 24 | II | – | PRL |
| PRL/GH-secreting adenoma | | | | | |
| 9 | M | 22 | II | – | PRL, GH |
| 10 | F | 29 | II | cs | PRL, GH, α-su |
| GH-secreting adenoma | | | | | |
| 11 | F | 61 | 0 | – | GH, α-su |
| ACTH-secreting adenoma | | | | | |
| 12 | F | 37 | 0 | – | ACTH |
| 13 | F | 65 | 0 | – | ACTH |
| Non-secreting adenoma | | | | | |
| 14 | M | 53 | II | – | ACTH, α-su[c] |
| 15 | F | 19 | II | cs | – |
| 16 | M | 65 | II | d | βFSH, α-su[d] |
| 17 | M | 72 | II | d | α-su |
| 18 | M | 63 | III | d+cs | α-su |

[a] 0, Microadenoma; I, tumour which reaches the optic chiasm; II, suprasellar extension amputating the anterior recess of the third ventricle; III, tumour which reaches the foramen of Monro (Guiot 1973)

[b] –, No invasion; d, dura mater invaded; cs, cavernous sinus invaded

[c] Silent corticotropic adenoma

[d] Immunoreactive FSH-producing cells without clinical or biological manifestations

## Results

Observation of normal anterior pituitary tissue at distance from the tumour confirmed the presence of two different BMs regularly stained by the anti-CIV antiserum: the epithelial or parenchymatous and the endothelial BM (Fig. 1a, b, e, f). The common feature of all tumours was an absence of the regular parenchymatous BM. The parenchymatous BM was either completely absent (Fig. 1e) or consisted of variably fragmented strips of BM that did not define a consistent cordonal structure (Fig. 1a). The other difference between normal and tumour tissue was the presence of arterial neovascularization in all the adenomas (Fig. 1e).

At the boundaries between the tumour and surrounding anterior pituitary tissues, there was absence of a connective tissue capsule (see also Hardy 1969, 1975). In only 3 cases out of 18 (Table 2, Fig. 1a), a pseudocapsule, resulting from the condensation of the BMs of compressed peritumour cell-cords, was observed. Even in these rare cases, the pseudocapsule was only present in focal areas of the border of the tumour and the remainder of the border was similar to that observed in the other cases. In all cases, a transition zone distinct from the pseudocapsule was seen between the normal and tumour tissue. This transitional tissue had unique features. It was made of a few rows of enlarged cell-cords (17 cases out of 18; Figs. 1b, f, 2a, 3a, d). These enlarged cord-like structures were surrounded by continuous parenchymatous BMs. Very often (15 cases out of 18), the last row of cell-cords which abutted on the tumour itself were not entirely delineated by parenchymatous BMs. Openings in their BMs faced the tumour tissue (Figs. 1b, f, 3a). The BMs of the cell-cords in this area frequently looked thinner and were less intensely stained by the anti-CIV antiserum (Fig. 1b). On the other side of the transition zone, cell-cords of normal size adjacent to the enlarged cell-cords displayed other modifications (Table 2). In 9 cases, an abnormal accumulation of BMs was seen in the pericapillary connective tissue spaces of these cell-cords (Figs. 1a, b, 2a, 3d). Moreover, in 8 out of these 9 cases, the contour of these cell-cords was outlined by irregular, wrinkled BMs (Figs. 1a, b, 3d). None of these modifications was correlated with the secretory activity, the grade or the invasive behaviour of the tumour.

Comparison of homologous fields of serial sections stained for type IV collagen, the main hormonal product of the adenoma and the different anterior pituitary hormones allowed us to study to which degree normal and adenoma cells intermingled at the junction of the surrounding gland and the adenoma. In general, adenomatous cells immunoreactive for a given antibody were distinguishable from their normal counterparts by the cell shape, size or intensity of staining (Fig. 1h). However, in adenomas that did not react to any of the hormonal markers used in the study (Table 3, case 15), this approach applied only to normal cells in the tumour.

With regard to the adenoma cells, apart from case 1, they were systematically observed in the enlarged and open cell-cords of the transition zone (Figs. 1b, d, 1f, h, 2a, c, 3a, c). They were particularly numerous in the enlarged cell-cords limited by thin and weakly stained BMs (Fig. 1b, d). In contrast they were never found in the juxtatumour cell-cords of normal size adjacent to the transition zone (Figs. 1b, d, 1f, h, 2a, c, 3a, c; Table 3).

Non-tumour hormone-producing cells had a distri-

**Table 2** Staining patterns of type-IV collagen in the transition zone and the surrounding anterior pituitary tissue

| Case no. | Pseudo-capsule | Transition zone | | Adjacent peritumour tissue | |
|---|---|---|---|---|---|
| | | Enlarged cell-cords | Open cell-cords | Wrinkled BMs | Accumulation of BM material |
| 1 | —[a] | + | + | — | — |
| 2 | — | + | + | — | — |
| 3 | — | + | — | — | — |
| 4 | — | + | + | + | + |
| 5 | — | + | + | — | — |
| 6 | — | + | + | — | — |
| 7 | — | + | + | + | + |
| 8 | — | + | + | + | + |
| 9 | — | — | + | — | — |
| 10 | — | + | + | — | + |
| 11 | — | + | + | — | — |
| 12 | — | + | + | + | + |
| 13 | + | + | + | + | + |
| 14 | — | + | + | — | — |
| 15 | — | + | + | + | + |
| 16 | + | + | — | — | — |
| 17 | + | + | — | + | + |
| 18 | — | + | + | + | + |
| Frequency | 3/18 | 17/18 | 15/18 | 8/18 | 9/18 |

[a] +, Presence; —, absence

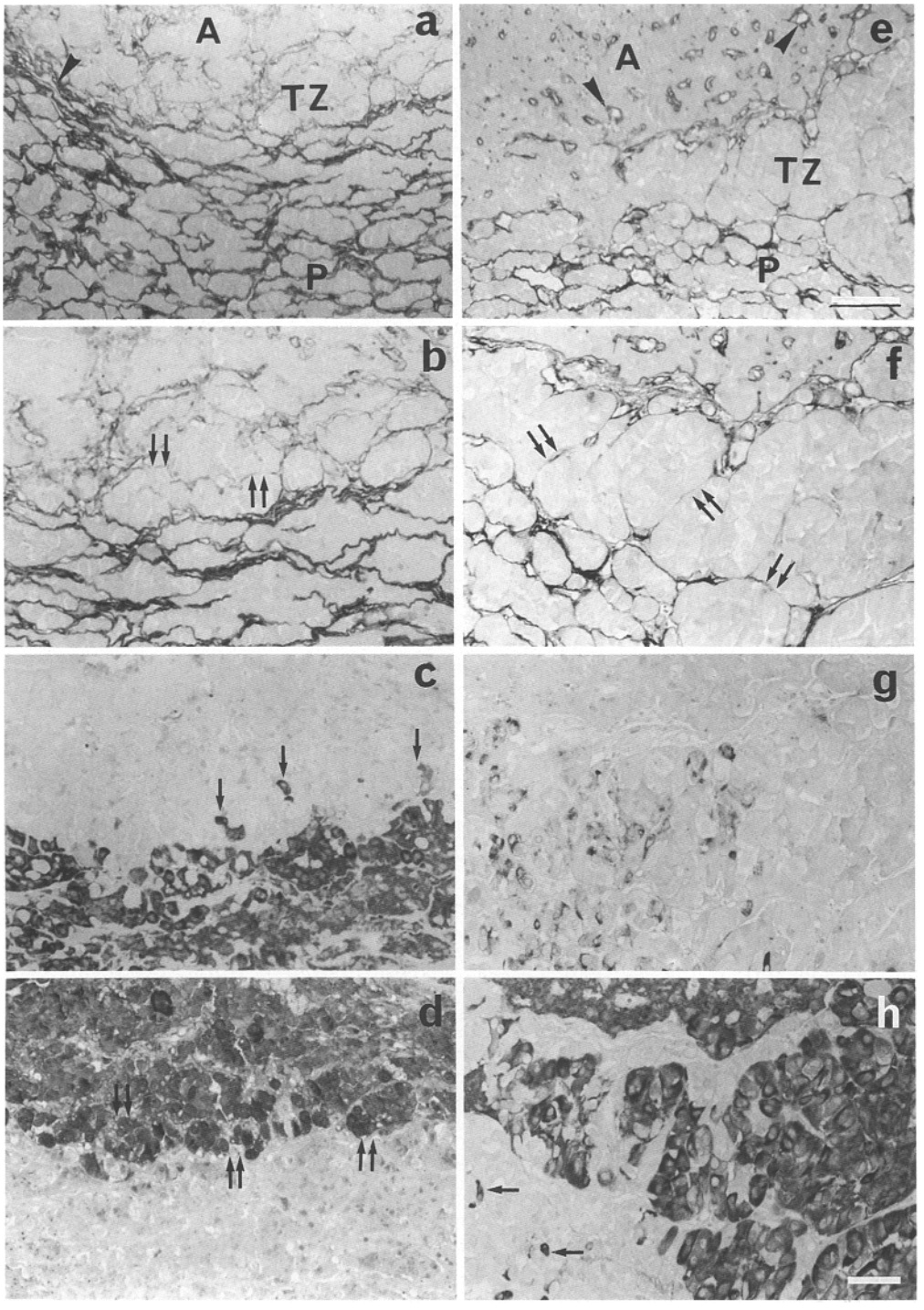


**Fig. 1a–h** Boundaries of 2 pituitary adenomas (**a–d** case 13, corticotroph adenoma; **e–h**, case 11, somatotroph adenoma. **a** Case 13, type IV collagen (CIV) immunostaining. The adenoma (*A*) is separated from the peritumoral gland (*P*) by a focal area of pseudocapsule (*arrowhead*) and a transition zone (*TZ*). Note the accumulation of basement membranes (BMs) between the peritumoral cell-cords having wrinkled contours. **b–d** Higher magnification of the transition zone shown in **a**. Serial sections (**b** anti-CIV; **c** anti-GH; **d** anti-$ACTH_{17-39}$). In the transition zone (**b**), note the presence of enlarged cell-cords and open cell-cords, some enlarged cell-cords being surrounded by thin and weakly stained BMs (*double arrows*). Comparison of the serial homologous fields **b** and **d** shows that, while adenomatous corticotrophs are present in the open cell-cords (**b** and **d**, *double arrows*), they are absent from the peritumour cell-cords of normal size. Comparison of the serial homologous field **b**, **c** and **d** shows that normal somatotrophs are numerous in the gland around the tumour, a few of them (**c** *arrows*) being entrapped between adenomatous cells in the transition zone. **e** Case 11, CIV immunostaining. Adenoma (*A*) rich in arterioles (*arrowheads*). Peritumoral gland (*P*). Transition zone (*TZ*). **f–h** Higher magnification of the transition zone shown in **e**. Serial sections (**f** anti-CIV; **g** anti-PRL; **h** anti-GH). In the transition zone, thin and weakly stained BMs (**f** *double arrows*) around some enlarged cell-cords. Adenomatous somatotrophs are present in the enlarged and the open cell-cords (compare **f** and **h**). They are absent from the peritumoral cell-cords of normal size. Rare small non-tumoral somatotrophs in the peritumoral gland (**h** *arrows*). Presence of numerous normal lactotrophs in the peritumoral gland. In the transition zone, they intermingle with adenomatous somatotrophs (compare **f**, **g** and **h**). Indirect immunoperoxidase, **a** and **e** × 100, *bar* = 100 μm; **b–d** and **f–h** × 160, *bar* = 50 μm

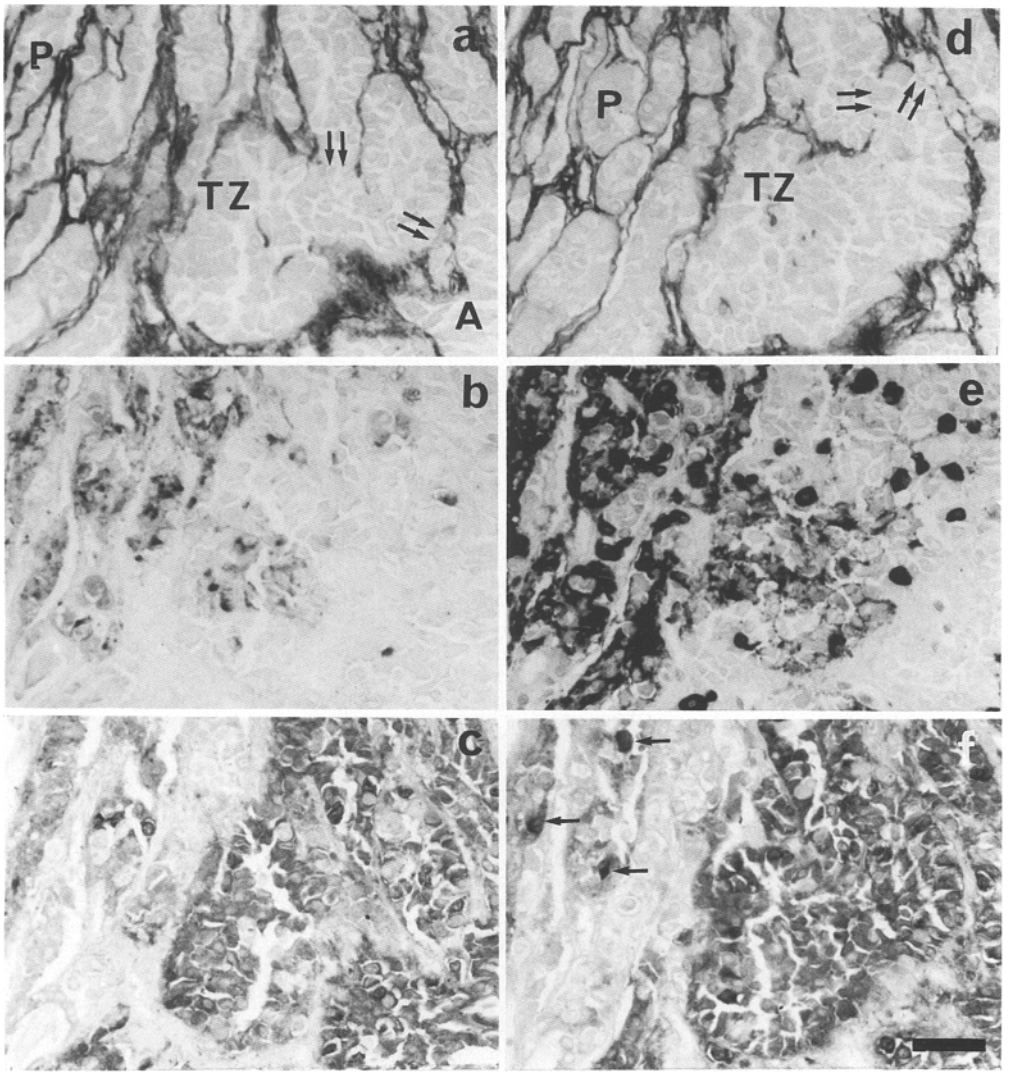


**Fig. 2a–f** Boundary of a corticotroph adenoma (case 12). **a**, **d** CIV immunostaining. Adenoma (*A*). Peritumoral gland (*P*). Transition zone (*TZ*). Openings of the enlarged cell-cords BMs (*double arrows*). Accumulation of BMs between peritumoral cell-cords. **a–c** Serial sections (**a** anti-CIV; **b** anti-PRL; **c** anti-$ACTH_{17-39}$). Several normal lactotrophs are present in the peritumoral gland and in the transition zone. Adenomatous corticotrophs are present in the open and enlarged cell-cords. **d–f** Serial sections (**d** anti-CIV; **e** anti-GH; **f** anti-$ACTH_{17-39}$). Non-tumoral somatotrophs are numerous in the peritumoral gland and many of them are entrapped between adenomatous corticotrophs in the transition zone. Only few strongly stained normal corticotrophs (**f** *arrows*) are seen in the peritumoral cell-cords of normal size. Indirect immunoperoxidase, ×200, *bar* = 50 μm

**Table 3** Intermingling of tumoral and normal hormone-producing cells in adenoma, transition zone and surrounding anterior pituitary

| Case no. | Normal cells towards adenoma | | Adenoma cells towards surrounding gland | |
|---|---|---|---|---|
| | Enlarged and open cell-cords | Central area of adenoma | Enlarged and open cell-cords | Peritumoral cell-cords |
| 1 | GH, PRL, LH, FSH | GH | – | – |
| 2 | GH, PRL, ACTH, LH, FSH, TSH | GH, ACTH, TSH | PRL, α-su | – |
| 3 | GH, PRL, ACTH, LH, FSH, TSH | GH, ACTH | PRL | – |
| 4 | PRL, LH, FSH | – | PRL | – |
| 5 | GH, PRL, ACTH, LH, FSH | – | PRL | – |
| 6 | GH, PRL, ACTH, LH, FSH | GH, PRL, ACTH, LH, FSH | PRL | – |
| 7 | GH, ACTH, LH, FSH | GH, ACTH, LH, FSH | PRL | – |
| 8 | GH, ACTH, LH, FSH | GH, ACTH, LH, FSH | PRL | – |
| 9 | GH | GH | PRL | – |
| 10 | ACTH, LH, FSH | ACTH | GH, PRL, α-su | – |
| 11 | PRL, ACTH, LH, FSH, TSH | PRL | GH, α-su | – |
| 12 | GH, PRL, LH, FSH | GH, PRL, LH, FSH | ACTH | – |
| 13 | GH, PRL, LH, FSH | – | ACTH | – |
| 14 | GH, PRL, ACTH | GH, PRL, ACTH | ACTH | – |
| 15 | GH, PRL, ACTH, LH, FSH | GH, ACTH, LH, FSH | – | – |
| 16 | PRL | – | FSH | – |
| 17 | PRL, ACTH | – | α-su | – |
| 18 | GH, PRL, ACTH, LH, FSH, TSH | GH, PRL, TSH | α-su | – |

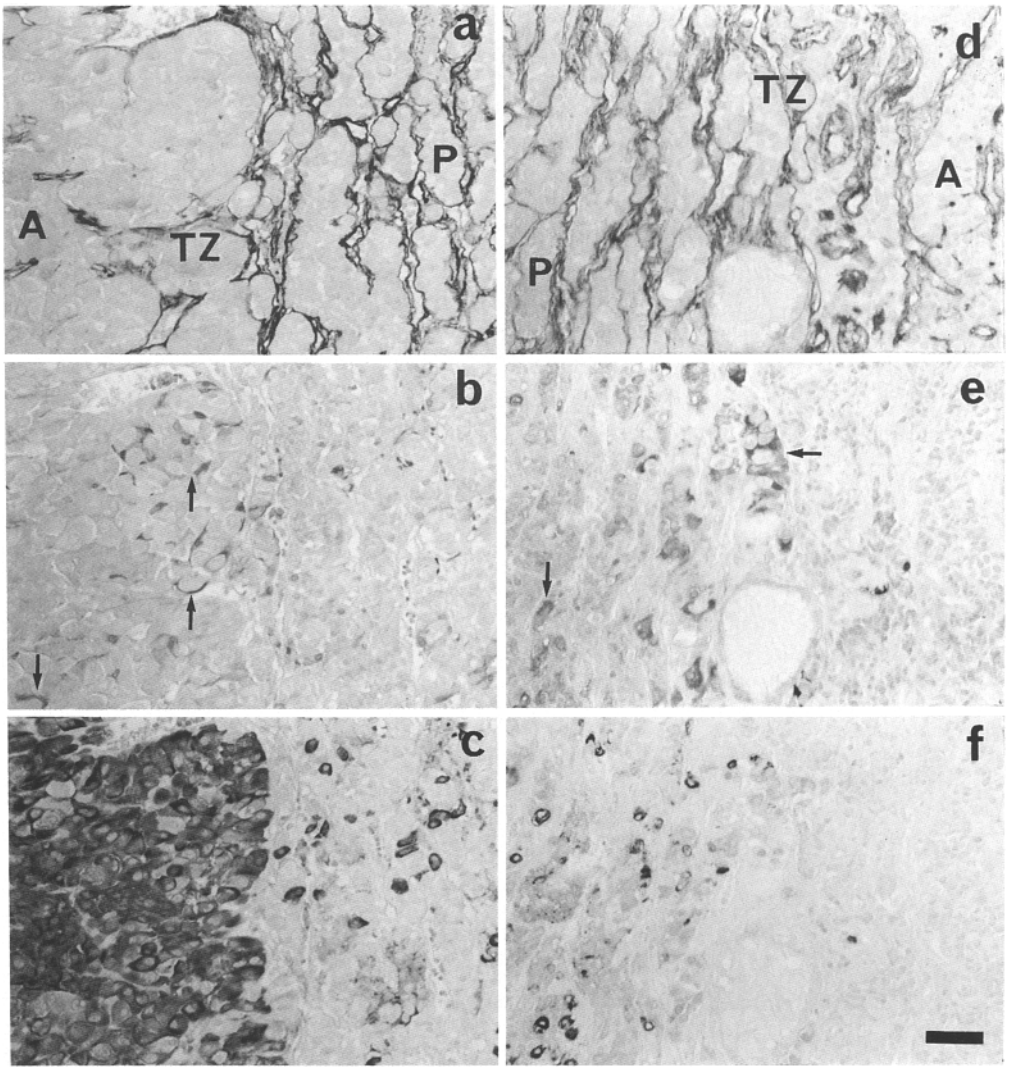


**Fig. 3** Boundaries of 2 pituitary adenomas (**a–c** case 11, somatotropic adenoma; **d–f** case 15, non-secreting adenoma). **a**, **d** CIV immunostaining. Adenoma (*A*). Peritumoral gland (*P*). Transition zone (*TZ*). Accumulation of BMs between peritumour cell-cords having wrinkled contours. **a–c** Serial sections (**a** anti-CIV; **b** anti-S–100; **c** anti-GH). S–100 immunoreactive folliculo-stellate cells in the surrounding gland are very few. They are numerous in the open cell-cords of the transition zone and in the adenoma, intermingling with and surrounding adenomatous somatotrophs (*arrows*, compare **b** and **c**). Note the small normal somatotrophs in the gland around the tumour (**c**). **d–f** Serial sections (**d** anti-CIV; **e** anti-S–100; **f** anti-PRL). The folliculo-stellate cells are present in the cell-cords around the tumour and in the transition zone (*arrows*). They are absent in the adenoma. Non-tumour lactotrophs are scattered in the surrounding gland and in the transition zone (compare **d** and **f**). Indirect immunoperoxidase, × 160, *bar* = 50 μm

bution which was not restricted to the cell-cords of normal size in the surrounding gland. They were systematically found in the enlarged and open cell-cords of the transition zone (Figs. 1b, c, 1f, g, 2a, b, 2d, e, 3d, f). Moreover, in 13 cases out of 18, they were present in adenoma tissue (Table 3; Fig. 2a, b, d, e). They made a small subpopulation of cells in the transition zone and their number decreased gradually towards the core of the tumour. Non-tumour cell-types were not systematically represented in the transition zone and adenoma tissue. The types of entrapped non-tumour cells did not seem to be associated to the secretory type of the adenoma (Table 3).

The distribution of S-100 immunoreactive cells was also studied on serial sections and compared with that of the BMs and the various endocrine cells (Table 4, Fig. 3).

S–100 immunoreactive cells had the characteristic slender processes of the folliculo-stellate cells and were distinct from the various types of anterior pituitary hormone producing cells (Fig. 3b, c, e, f). They were present in normal cell-cords of the gland at distance of the adenoma as rare dispersed cells (Table 4). Their occurrence deep in the adenomas was noted in 6 out of 18 cases (Table 4). In almost all the cases (17 cases out of 18), immunoreactive cells, scattered or often in small clusters, were observed in the transition zone or in its vicinity (Fig. 3). According to the case, they were concentrated either in the open cell-cords of the transition zone and in the outer area of the adenoma (Fig. 3b) or in the enlarged cell-cords and peritumour cell-cords of normal size (Fig. 3e).

## Discussion

As expected from our previous work (Farnoud et al. 1992) immunostaining of type IV collagen, by delineating the BMs in the normal connective tissue compartment and tumour stroma, clearly distinguished the surrounding anterior pituitary tissue from the adenoma. In addition, this immunostaining turned out to be very efficient in defining a transition zone between the tumour and peritumour tissues. This zone comprised a few rows of enlarged and open cell-cords. These results conflict with studies claiming that adenomas are demar-

cated from normal tissue by a pseudocapsule resulting from the compression of the peritumour cell-cords (Velasco et al. 1977). In our cases, when such a pseudocapsule existed, it was restricted to focal areas of the border. The enlargement of the cell-cords in the transition zone and the opening of those in direct contact with the tumour do not favour the existence of a compressive effect of the expanding tumour as the only interaction of adenoma with the adjacent normal parenchyma. In addition, in half of the cases, alterations of the BMs were seen in the peritumour gland adjacent to the transition zone (wrinkling of the BMs or accumulation of immunoreactive material between the cell-cords). These alterations suggest that the proximity of the tumour may affect the connective tissue compartment of the surrounding gland.

Our results on the distribution of adenomatous and normal endocrine cells support our data on the delineation of the transition zone by type IV collagen immunohistochemistry. On the one hand, the intermingling of normal and tumour endocrine cells in the transition zone is in accordance with the absence of a sharp demarcation between the tumour and the normal tissue, on the other, our results showed an uneven distribution of adenomatous versus normal cells with regard to the transition zone. Normal cells were not only found in the transition zone but they were still seen deep into adenomatous tissue. Such an observation has been reported elsewhere (Kovacs and Horvath 1986). In contrast, adenoma cells were never seen beyond the last row of enlarged cell-cords of the transition zone. These data show that adenomatous and normal cells intermingle over a wide area only on the adenomatous side of the transition zone and that the adenomatous cells do not infiltrate surrounding normal cell-cords. A tentative scheme of these results is proposed in Fig. 4.

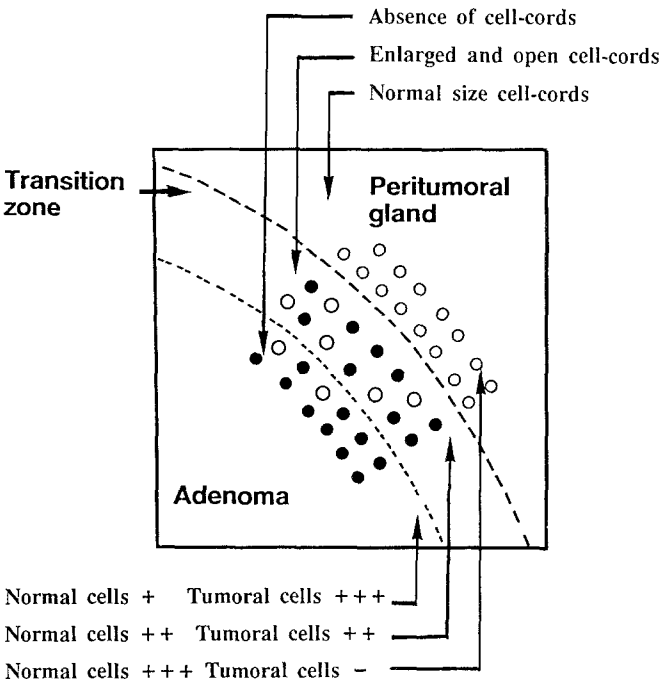


**Fig. 4** Tentative scheme of pituitary adenoma progression in normal gland

**Table 4** Staining patterns of S-100 protein in adenoma, transition zone and peritumour anterior pituitary

| Case no. | Peritumour cell-cords | Enlarged and open cell-cords | Central area of adenoma |
|---|---|---|---|
| 1 | +[a] | ++ | + |
| 2 | + | + | + |
| 3 | + | + | — |
| 4 | + | ++ | — |
| 5 | + | + | — |
| 6 | + | + | — |
| 7 | + | ++ | — |
| 8 | + | ++ | +++ |
| 9 | + | ++ | — |
| 10 | + | ++ | + |
| 11 | + | ++ | + |
| 12 | + | + | + |
| 13 | + | — | — |
| 14 | + | ++ | — |
| 15 | + | + | — |
| 16 | + | + | — |
| 17 | + | + | — |
| 18 | + | + | — |
| Frequency | 18/18 | 17/18 | 6/18 |

[a] —, Absence; +, rare dispersed cells; ++, cell clusters; +++, numerous cell clusters

Our results are at variance with other observations reporting that, even when a boundary could be seen between the two tissues, there could be gross interchange of cells on both sides of the boundary (Wrightson 1978, 1980; Sautner and Saeger 1991). The well-established efficiency of conservative resection of pituitary adenomas can be explained on the basis of our morphological data which imply that, provided that the transition zone is removed together with the tumour tissue, no nests of tumour cells remain.

Our results show that invasive and non-invasive pituitary adenomas share the ability to progress into adjacent normal anterior pituitary tissue. This observation does not, however, preclude the fact that invasive adenomas are endowed with additional modalities of expansion into non-pituitary neighbouring structures.

The pattern of S–100 immunoreactivity described here agrees with other reports on folliculo-stellate cell distribution in normal and neoplastic human anterior pituitaries (Velasco et al. 1982; Vila-Porcile and Olivier 1984; Iwaki et al. 1986; Turpin et al. 1988; Sbarbati et al. 1991; Marin et al. 1992). The frequent association of folliculo-stellate cells with the interface between the adenoma and the adjacent normal gland has been stressed by other groups (Velasco et al. 1982; Marin et al. 1992). Several authors have suggested that folliculo-stellate cells show signs of increased activity under pathological or experimental situations (Iwaki et al. 1986; Schechter et al. 1988a). They might play a role in both trophic and catabolic processes (for review see Allaerts et al. 1990).

Among these roles, the phagocytic activity and the production of angiogenic growth factors by folliculo-stellate cells is of potential importance in the process of adenoma expansion. The preferential localization of these cells in close association with the transition zone suggests that in this area folliculo-stellate cells could be involved in BM remodelling and tumoral neovascularization.

Our results favour the existence of an active process of adenoma expansion within the normal parenchyma. Its existence is based upon the absence of signs of passive compression of the normal gland by the neoplasm; the existence of a transition zone characterized by a remodelling of the cord-like organization typical of the normal gland; the presence of tumour cells in the transition zone, resulting in an intermingling of tumour and non-tumour cells on the adenoma side of this zone; the presence of residual normal anterior pituitary cells in the central area of the tumour and the concentration of folliculo-stellate cells in the vicinity of the transition zone. Through such an active expansion process, adenoma tissue would, step by step, progress into the normal parenchyma without the presence of tumour cell clusters in the surrounding gland.

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