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Massive Crooke's Hyalinization in Corticotroph Cell Adenomas of the Human Pituitary
A Histological, Immunocytological, and Electron Microscopic Study of Three Cases

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With 5 Figures

Summary
Three women with Cushing's disease caused by ACTH-producing adenoma, underwent transsphenoidal tumour resection. Many adenoma cells showed massive accumulation of microfilaments indistinguishable from Crooke's hyaline material by light and electron microscopy. We believe that these tumours represent variants of ACTH-producing adenomas, and the accumulation of microfilaments is due to cortisol dependency.

Introduction
Microfilaments are cytoplasmic structures that have been the subject of several studies in the last two decades. They have been described in numerous cell types of various organs, and have been related to many different functions. Several factors, such as drugs and toxic agents, may be involved in their formation. Their significance is still unknown, but it is believed that they play an important role in the transport of secretory products, cell movement, and maintenance of cell shape. Filaments are constituents of the cytoskeleton, and are thought to represent a contractile apparatus. They have been found to increase in number in cellular aging.

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As revealed by transmission electron microscopy, a massive accumulation of microfilaments is the paramount cytoplasmic finding in Crooke's hyalinization of the non-tumourous human pituitary. This change is due to glucocorticoid excess, and it occurs in the cytoplasm of corticotroph cells in patients with hyperadrenocorticism associated with Cushing's disease or ectopic ACTH syndrome, and following protracted medication with pharmacological doses of glucocorticoids. In Cushing's disease, accompanied by pituitary corticotroph cell adenoma, Crooke's hyalization is conspicuous in the cytoplasm of non-tumourous corticotrophs, whereas it is claimed to be undetectable in the adenoma cells.

We describe here three pituitary corticotroph cell adenomas associated with Cushing's disease, in which a massive accumulation of cytoplasmic microfilaments was a prominent finding.

Case Reports

Clinical Findings

The first patient was a 66-year-old woman with a long history of Cushing's disease. She presented with hypertension, abdominal striae, hirsutism, diabetes mellitus, and osteoporosis. She had configurational abnormality of the pituitary fossa on the right side, and underwent transsphenoidal adenoma resection. Before operation her plasma cortisol was 13.3 mg/dl a.m., and 25 mg/dl p.m.; blood ACTH was 1,400 pg/ml. There was a loss of diurnal variation in plasma cortisol levels. No ACTH was detected in the blood following suppression with 8 mg of Dexamethasone.

The second patient was a 17-year-old girl with a one-year history of Cushing's disease. She presented with obesity, acne, and abdominal striae. Before surgery plasma ACTH was elevated at 185 pg/ml 8 a.m., 75 pg/ml 8 p.m. Following 2 mg of Dexamethasone, plasma cortisol, 17-hydroxycorticosteroids, and 17-ketosteroids were suppressed, whereas plasma ACTH was 80 pg/ml. Sella X-ray revealed slight enlargement. Transsphenoidal resection of pituitary adenoma was performed.

The third patient was a 25-year-old woman with a two-year history of Cushing's disease. Preoperatively, blood ACTH levels were high at 250 pg/ml and her urinary free cortisol was elevated. A pituitary adenoma was removed by the transsphenoidal route.

Materials and Methods

For light microscopy, pieces of the three tumours were fixed in 10% buffered formalin, and embedded in paraffin. Sections of 4-6 μm thickness were stained with haematoxylin-phloxine-saffron, PAS, and lead haematoxylin. For the immunocyto logic demonstration of ACTH and related peptides, the immunoperoxidase technique was used on 4-6 μm thick paraffin-embedded sections, described in detail elsewhere. The following primary antibodies were applied: anti-1-39 ACTH (purchased from Wellcome Reagents Ltd., Beckenham, England), anti-β-LPH (donated by Dr. M. Chretien and Dr. M. Lis, Clinical Research Institute, Montreal, Quebec, Canada), anti-α-endorphin (donated by Dr. J. M. Polak, Department of Histochemistry, Postgraduate Medical School, Hammersmith Hospital, London, England), and anti-β-endorphin (donated by Dr. G. M. Brown, Department of