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FINAL HEIGHT OF CHILDREN WITH TRUE PRECOCIOUS PUBERTY TREATED WITH GnRH (LRF) AGONISTS.
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GnRH (LRF) agonists effectively suppress gonadotropin and sex steroid production and have become the treatment of choice for young children who have rapidly progressive, true (central) precocious puberty. Although several reports have indicated that predicted adult height improves during GnRH agonist therapy, the limited reliability and accuracy of adult height prediction methods necessitate collection of final height measurements to determine whether final height is improved. We propose to test the hypothesis that GnRH agonist therapy improves the final height of children with true precocious puberty. Final height data will be obtained from selected pediatric endocrinologists around the world. Data from patients will be included: 1) if they have achieved 98 percent or more of their final height (bone age $\geq$ 14 years for girls or $\geq$16 years for boys); 2) if they have no other condition that might alter growth potential; and 3) if compliance and effectiveness of therapy have been felt to be good. Final heights will be compared with: 1) target heights; 2) untreated and treated (progestational agents) historical controls; and 3) predicted adult heights at initiation and completion of therapy. Data regarding length of therapy, the specific drug and route of administration, complications, and length/degree of post treatment suppression will also be sought.

Pituitary and Hypothalamic Tumors

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PITUITARY ADENOMAS IN CHILDHOOD
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Between 1969 and 1992, 2,260 patients underwent surgery for pituitary adenomas, 95 (4.2%) of them before their 19th birthday. According to their endocrine activity, the majority of childhood tumors were endocrine active: PRL 38, ACTH (Cushing's) 33, GH 9, and ACTH (Nelson's) 4. As a group, patients treated for ACTH-secreting tumors were the youngest (12.5 years). The recurrence rates varied with immunotype: PRL 2.6%, ACTH (Cushing's) 9%, endocrine inactive 9%, GH 22%, and ACTH (Nelson's) 0%. Surgical morbidity was minimal, and there were no serious complications or deaths. The distribution of immunotypes and recurrence rates differ from those in adults with pituitary adenomas.

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HYPOTHALAMIC SURGERY AND CHEMOTHERAPY. M.S.B. Edwards, Division of Pediatic Neurosurgery, Departments of Neurosurgery and Pediatrrics, University of California at San francisco, San Francisco, CA 94943, USA

Suprasellar tumors are the second most common supratentorial tumors in children less than 12 years of age. The two most common lesions in this area are the craniopharyngioma and the hypothalamic /chiasmatic astrocytoma. The majority of the astrocytic tumors are histologically low grade, however, they are unpredictable and may act aggressively especially in infants. Our experience with more than 50 children with this tumor indicates that radiation therapy (RT) can delay the time to tumor progression and may even prolong survival. Although RT is effective its side effects in infants is unacceptable. We have shown that various chemotherapy regimens are effective in halting growth or reducing tumor size in approximately 70% of children treated (this is true for children of all ages). Chemotherapy may allow RT to be delayed until after infancy and on rare occassions for extended periods of time even avoiding RT. Surgical debulking is frequently possible witn minimal morbidity and mortality. Long term survival is common in this disorder (5- and 10-year survival has been 93 and 74% respectively in our experince) and neuroendocrine dysfunction is the rule rather than the exception. Our approach to diagnosis, management, and long term outcome will be presented.. Treatment of craniopharyngioma remains controversial but, it is essentially a surgically curable tumor, with 10 year survivals in excess of 90% in those tumors with a post-operative MR scan confirming a total resection. Subtotally resected or recurrent tumors require and respond to RT which delays recurrence and prolongs survival. Neuroendocrine and neuropsychological dysfunction is common in this group of children no matter which form of therapy is employed. If time allows, our experience and recomendations for treatment of craniopharyngioma will also be presented.

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ENDOCRINE OUTCOME
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Dependent on site and size, pituitary hormone deficits may be associated with space-occupying lesions in the pituitary and suprasellar regions (craniopharyngyoma, adenoma and germinoma). Medical awareness of such a lesion however tends to be alerted more quickly to mass effects rather than the associated hormone deficiencies. Apart from the lesion itself, hypopituitarism may be induced by surgery and/or radiotherapy. The deficit with surgery may be transient or permanent but occurs promptly whilst hypopituitarism following irradiation is delayed and dose dependent. The hormone-producing pituitary adenomas met in paediatric practice, albeit rarely, are prolactin, GH and ACTH-secreting. Surgery is the treatment of choice for ACTH and GH-secreting adenomas although debate remains about the definition of cure and recurrence rates. The role of medical therapy is usually adjunctive to surgery or radiotherapy however octreotide, a somatostatin analogue appears to offer a promising new approach for GH-secreting adenomas. Treatment of choice for prolactinomas is contentious but dopamine agonist therapy has a prominent place. In the majority of children treated for hormone-secreting pituitary adenomas endocrine "cure" may be achieved but in a significant proportion hormone replacement therapy will be required permanently.

Resistance Syndromes—Nuclear Receptors

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NUCLEAR HORMONE RECEPTORS: REGULATORS OF GENE EXPRESSION. A. O. Brinkmann, Department of Endocrinology & Reproduction, Erasmus University, Rotterdam, The Netherlands

Over the past three decades, a great deal of evidence has accumulated in favor of the hypothesis that steroid hormones act via regulation of gene expression. The action is mediated by specific nuclear receptor proteins, which belong to a superfamily of ligand-modulated transcription factors that regulate homeostasis, reproduction, development and differentiation. This family includes receptors for steroid hormones, thyroid hormones and hormonal forms of vitamin A and D. All members of this superfamily have a similar functional domain structure: a variable N-terminal region, which is involved in modulation of gene expression. A short well conserved DNA-binding domain, which is crucial for recognition of specific DNA sequences and for receptor dimerization; and a partially conserved C-terminal hormone-binding domain. Hormone-receptor complexes regulate gene expression by binding to hormone-response elements which are located in the 5'-flanking sequences of hormone-responsive genes. Binding of nuclear hormone receptors to their cognate hormone response elements occurs as dimers. Receptors enhance transcription by stabilizing general transcription factors either directly at the TATA-box or through interactions with proteins bound to upstream promoter sequences or via interaction with transcription intermediairy factors which can be considered as coupling proteins between the receptor and other protein components in the transcription initiation complex. Receptor gene defects are frequently the cause of several forms of hormone resistance.

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MUTATIONS IN THE ANDROGEN RECEPTOR GENE CAUSING ANDROGEN RESISTANCE.
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Mutations in the androgen receptor gene cause phenotypic abnormalities of male sexual development that range from a female phenotype (complete testicular feminization) to that of undervirilized or infertile men. These defects have previously been classified according to the abnormality identified in ligand binding studies performed in genital skin fibroblasts. Patients with absent ligand binding (receptor-binding negative), reduced levels of binding, qualitative binding abnormalities, or no ligand binding abnormality have been described. The type of ligand binding abnormality has little relationship to the clinical phenotype. Nucleotide sequence analysis of the androgen receptor coding sequence, coupled with immunoblot assays and assays of receptor function, have permitted the definition of several types of mutation in the androgen receptor gene and their effects on receptor function and abundance. In our patient population, the defects are most often due to nucleotide changes that cause either premature termination codons or single amino acid substitutions within the androgen receptor open reading frame. Premature termination codons have been identified in several coding exons and the amino acid substitutions cluster in the DNA-binding domain and two short segments of the hormone-binding domain. Despite diverse effects on the capacity of the mutant receptors to bind ligand or to target DNA sequences, functional studies and immunoblot assays indicate that the phenotypic abnormalities in patients with androgen resistance are paralleled by decreases in receptor function or abundance or both.