0021-972X/97/$03.00/0
Journal of Clinical Endocrinology and Metabolism

Vol. 82, No. 7
Printed in U.S.A.

EXTENSIVE PERSONAL EXPERIENCE

Childhood Adrenocortical Tumors*

ROMOLO SANDRINI, RAUL C. RIBEIRO, AND LUIZ DELACERDA

Department of Pediatrics, Division of Pediatric Endocrinology, Clinics Hospital, Federal University of Parana (R.S., L.D.L.), Curitiba, Parana, Brazil; and the Department of Hematology-Oncology (R.C.R.) and the International Outreach Program (R.C.R., R.S.), St. Jude Children's Research Hospital; and the Department of Pediatrics, University of Tennessee College of Medicine (R.C.R.), Memphis, Tennessee 38105

The problem

From 1966–1996, 73 children under 16 yr of age with adrenocortical tumor were admitted to the Division of Pediatric Endocrinology at the Clinics Hospital, Federal University of Parana, in the city of Curitiba, State of Parana, in southern Brazil. The Clinics Hospital is a tertiary referral center for approximately 10 million inhabitants, 3.5 million of whom are children less than 15 yr of age. With 12–14 new cases of childhood adrenocortical tumor (ACT) diagnosed in the State of Parana each year, the annual incidence of ACT within this region can be estimated to range from 3.4–4.2/million children below the age of 15 yr. Remarkably, patients 4 yr of age or less account for the vast majority of cases seen at the Clinics Hospital (Fig. 1). This finding as well as those from other southern Brazilian states suggest an increased incidence of ACT in children (1). By comparison, the annual worldwide incidence of childhood ACT ranges from only 0.3–0.38/million children below the age of 15 yr (2, 3).

Definitive explanations for this apparent excess of ACT cases in southern Brazil are presently lacking. The Parana region is located below the Tropic of Capricorn and has no known endemic transmissible diseases. The population is mainly of European extraction (Italy, Poland, and Germany), locales in which the incidence of ACT in children has not been unduly increased. Moreover, compared with other regions of Brazil, this southern state has had the least native Indian influence during colonization. A genetic predisposition toward cancer, which appears to play a role in many childhood tumors, is not a common feature among southern Brazilian families of children with ACT (4).

Industrial pollutants, a major contributor to increased rates of solid tumor development, cannot be accorded more than a minor role in the Parana cases due to the slow pace of industrial expansion in this region. However, because of the extensive agricultural activities in southern Brazil, it is possible that environmental pollutants, such as pesticides, may pose a substantial health hazard. Agricultural pesticides are widely used in Parana, usually without safety guidelines. In this regard, British investigators found an association between an increased incidence of ACT and pesticide use in northwestern England (5), whereas in Norway, Kristensen *et al.* (6) noted an almost 2-fold increase in the relative risk for cancer among children 0–4 yr of age whose parents were engaged in agriculture. Taken together, these findings suggest that environmental pollutants may play a causative role in the excessive incidence of childhood ACT in southern Brazil.

Clinical and laboratory features

We have reviewed in detail the presenting features and outcome of 58 cases of childhood ACT treated at the Clinical Hospital between 1966–1992 and will use these data to discuss various aspects of the disease.

There were 17 boys and 41 girls in this series (Fig. 1). The median age at diagnosis was 4.3 yr (range, 3 days to 15.7 yr); 42 patients were younger than 5 yr. Girls predominated over boys (5.3:1) until 4 yr of age. Thereafter, the distribution was similar (0.8:1) for both sexes, suggesting different disease etiologies for each age group. Clinical manifestations of the tumor were present at birth in 4 cases. One girl presented with an abdominal mass at 3 days of age, and 3 other children had signs of virilization. Two additional patients with congenital tumors, not included in our series, were diagnosed in other hospitals in Curitiba (7).

Virilization was the only presenting feature in 40% of the group. Isolated signs of Cushing's syndrome were rare (3% of the patients), occurring most often (50%) in combination with clinical signs of an increased secretion of androgens (Table 1). Three patients had an abdominal mass and increased blood pressure without any other signs of virilization or Cushing's syndrome, and another patient had only a palpable abdominal mass.

An elevated blood pressure was noted in 55% of the patients, 12% (seven patients) of whom had hypertensive crises associated with seizures. Hypertension was common in patients with glucocorticoid-secreting tumors (Cushing or mixed type); it also occurred in half of the patients with signs of virilization only and in three patients with palpable ab-

Received August 16, 1996. Revision received March 10, 1997. Accepted March 20, 1997.

Address all correspondence and requests for reprints to: Dr. Romolo Sandrini, Department of Pediatrics, Division of Endocrinology, Rua General Carneiro 181, Curitiba, Pr. Brazil 80060–900.

* This work was supported in part by NCI Cancer Center Core Grants P30-CA-21765 and PO1-CA-20180, and the American Lebanese Syrian Associated Charities.

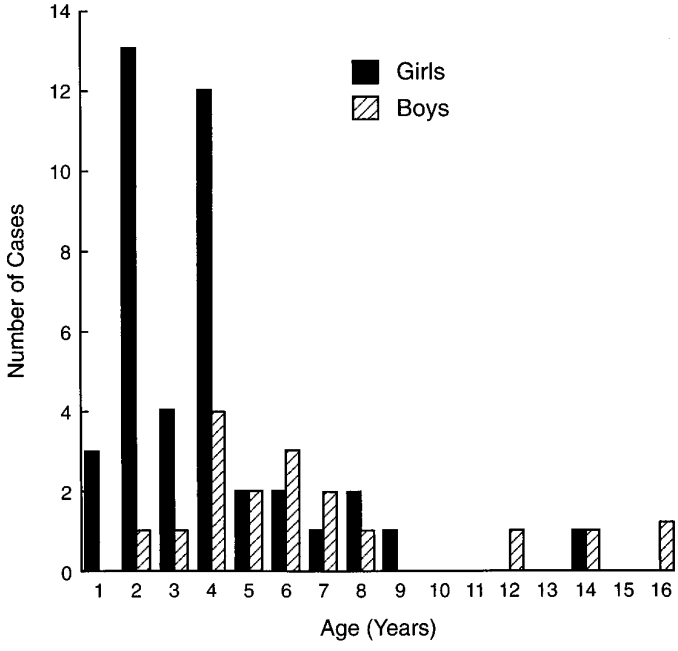

FIG. 1. Distribution of 58 cases of childhood adrenocortical tumor by age and gender.

dominal mass only. Hypertension without increased secretion of glucocorticoids might appear to be unusual; however, many virilizing tumors, although producing one type of hormone predominantly, can secrete other substances with the potential to cause hypertension (8). Although serum electrolytes abnormalities were not common in our patients with hypertension, seven children (three with the mixed form, three with the virilizing form, and one with Cushing's syndrome) had serum potassium levels below 3.5 mEq/L; these three patients with virilization had serum sodium values of 148, 148, and 154 mEq/L, reflecting increased mineralocorticoid activity. One child died in hypertensive crisis (highest blood pressure, 280/240 mm Hg), whereas another with diffuse cerebral hemorrhage from her hypertensive episode recovered and remains disease-free for 8 yr after diagnosis. Treatment of hypertension in patients with ACT can be challenging. In general, our patients have responded well to captopril, either alone or in combination with furosemide or ketoconazole.

An abdominal mass was palpable in 48% of the patients. All tumors were unilateral; the left and right adrenal glands were affected equally.

The heights and weights of these children often exceeded the 50th percentile (Fig. 2). Patients with height SD scores above that of the target height included not only those with the virilizing form of ACT, but also those with the mixed form (9). Bone age was advanced more than 1 yr in 68% of the patients.

In many instances, the increased somatic growth of these children, their generally healthy appearance, and the lack of a palpable abdominal mass diverted pediatricians from the possibility of a malignancy. The resulting delay in diagnosis can be appreciated from the long median interval (10 months; range, 3 days to 61 months) between the first clinical manifestations of ACT and its diagnosis. Hence, in our region, we consider pubarche in children under 4 yr of age a feature of ACT until proven otherwise.

TABLE 1. Signs and symptoms of adrenocortical tumors in 58 children

Feature	n	%
Pubic hair	53	91
Hypertrophy		84
Clitoris	36	62
Penis	13	22
Acne	42	72
Deep voice	32	55
Hypertension	32	55
Facial hair	29	50
Facial hyperemia	28	48
Palpable tumor	28	48
Wt gain	22	38
Hirsutism	21	36
Moon face	19	33
Accelerated growth velocity	17	29
Centripetal fat distribution	14	24
Buffalo hump of the neck	11	19
Seizures	07	12

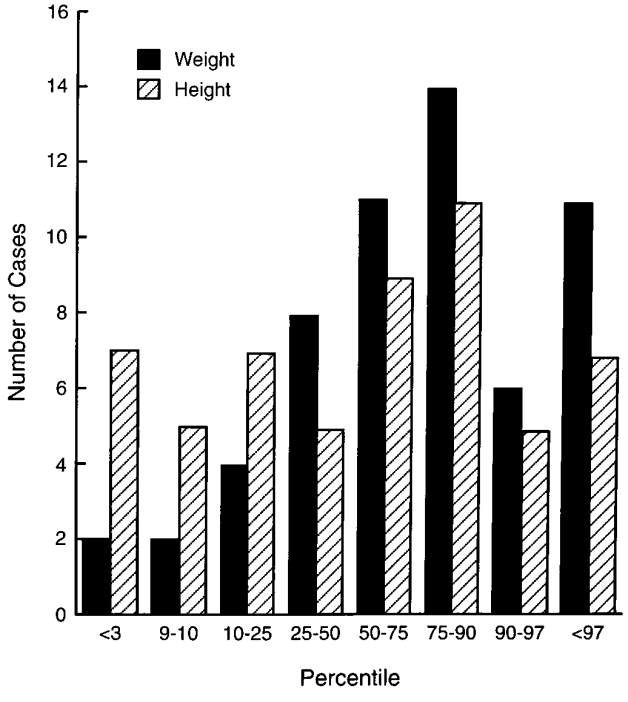

FIG. 2. Distribution of 58 cases of childhood adrenocortical tumor by weight and height percentile.

The absence of certain signs is noteworthy: 1) no patient showed striae; 2) there were no cases of hemihypertrophy or Beckwith-Wiedemann syndrome; and 3) none of the patients had the feminizing form of ACT.

Diagnosis

Urinary 17-ketosteroids (17-KS) frequently provided the pivotal clue to a diagnosis of ACT. 17-KS levels were elevated in 48 of the 49 patients tested, whether their tumors caused mainly Cushing's syndrome or virilization. Plasma dehydroepiandrosterone (DHEA) sulfate levels were abnormal in 90% of the 20 patients tested, suggesting their value as a

second sensitive tumor marker. Abnormal urinary DHEA concentrations were less sensitive, occurring in only 23 (74%) of the 31 patients tested. Urinary 17-hydroxycorticosteroid (17-OHCS) levels were elevated in all cases with clinical signs of excessive glucocorticoids. Other adrenal steroids were measured too infrequently to allow meaningful inference as to their diagnostic utility. A dexamethasone suppression test was rarely necessary. The presence of elevated levels of glucocorticoid and androgen was a strong indication of adrenal tumor in our experience.

At present, our routine laboratory evaluation for patients suspected of having ACT includes measurements of urinary 17-KS, 17-OHCS, and free cortisol, as well as plasma cortisol, DHEA sulfate, testosterone, androstenedione, 17-hydroxyprogesterone, aldosterone, PRA, deoxycorticosterone, and other 17-deoxysteroids precursors. This comprehensive panel of tests not only contributes to the diagnosis, but also provides useful markers for the detection of tumor recurrence.

Several different imaging modalities were used to establish the diagnosis of ACT. Until 1982, plain radiographs, excretory urography, and nephrotomograms were the principal modalities. More recently, we have shifted to computed tomography (CT), ultrasonography, and magnetic resonance imaging. In 28 of our patients evaluated with both ultrasonography and CT, the sonograms did not indicate abnormalities in 3 cases (11%), each of which was detected by CT scanning. We recommend that all patients suspected of having an adrenal tumor should be examined by CT or magnetic resonance imaging.

The diagnosis of adrenocortical tumor was made on the basis of the gross and histological appearance of tissue obtained at surgery. Tumor samples from 51 patients were reviewed and classified by a single pathologist (G.A.S.) using previously reported classification schemes (10–14). Only 1 tumor specimen met the criteria for benign in all 3 systems, whereas the tumors from 2 patients were classified as benign in 2 systems and those from 2 others were classified as benign in only 1 system. Tumor specimens from 2 and 11 patients were considered of indeterminate nature in the classification of van Slooten *et al.* (12) and Hough *et al.* (11), respectively. The remaining tumors without benign or indeterminate histology met the criteria for malignancy in at least 2 of the 3 criteria. These data underscore the difficulties in characterizing the ACT histology as being of malignant or benign potential.

Treatment and outcome

Surgery. Surgery is the single most important procedure in successful treatment of ACT and was considered for each or our patients. Because of tumor friability, rupture of the capsule and tumor spillage were frequent (20% of cases during the initial procedure and 43% after local recurrence). In one case, the presenting clinical manifestations were those of an acute abdomen due to spontaneous tumor rupture; Lack *et al.* (15) reported a case of adrenocortical tumor with similar presenting features. Infiltration of the vena cava could be expected to make radical surgery difficult in some cases, although successful complete resection of the tumor thrombus has been reported in patients undergoing cardiopulmonary bypass (16). Our experience with tumor thrombi extending into the vena cava is limited to two patients. One had tumor extension into the inferior vena cava and right atrium and was considered too ill to undergo surgery. She died 1 week after admission despite treatment with mitotane. The remaining child, who also had an inoperable tumor extending into the vena cava and right atrium, received two courses of combination chemotherapy (ifosfamide, carboplatinum, and etoposide) without response.

Surgery required careful and precise perioperative planning. All patients with a functioning tumor were assumed to have suppression of the contralateral adrenal gland, so that steroid replacement therapy was given to those patients. Special attention to electrolyte balances, hypertension, surgical wound care, and infectious complications was imperative. There were no perioperative deaths in this series.

Surgical resection was complete in 98% of the 48 operable cases and partial in the remaining 2%. Of the 10 patients whose tumors were considered inoperable, 1 patient with localized disease had a substantial oncolytic response to mitotane, permitting complete resection of the mass. This child is alive and free of disease 5 yr after definitive surgery.

Surgery was also attempted in six patients with local recurrences, five of whom eventually died from metastatic disease. One patient, who in addition to a third surgical procedure received adjuvant chemotherapy that included cisplatin and etoposide, has been alive for 8 yr.

Chemotherapy. The role of chemotherapy in the management of childhood ACT has not been established. Mitotane [1,1-dichloro-2-(*O*-chlorophenyl)-2-(*p*-chlorophenyl)-ethane, or *o,p*′-DDD], an insecticide derivative that produces adrenocortical necrosis, has been used extensively in adults with ACT, but its efficacy in children is not known. Since 1990, we have been conducting a multinstitutional study to determine the efficacy and toxicity of mitotane as an adjuvant therapy for newly diagnosed children at high risk of relapse (see below). However, it is still too early to reach conclusions as to the efficacy of this compound. Mitotane toxicity has been dose dependent and considerable. The most important toxicity was gastrointestinal and neurological, with nausea, vomiting, diarrhea, and abdominal pain also present in a high proportion of patients. Less frequent reactions included somnolence, lethargy, ataxic gait, depression, and vertigo. Of interest, all prepubertal patients developed gynecomastia or thelarche. Another shortcoming of mitotane treatment is that it significantly alters steroid hormone metabolism, so that steroid measurements in blood and urine cannot be used as a marker of tumor relapse. Thus, mitotane should be considered an experimental agent in the treatment of children with ACT. Other antineoplastic drugs, including the combination of cisplatin with etoposide, 5-fluorouracil with leucovorin, and ifosfamide and carboplatinum with etoposide were used in too few patients to permit meaningful conclusions. Adjuvant radiation therapy was not attempted in this group of patients.

Outcome. Of the 54 patients with known outcomes, 24 (44%) died, and 30 (56%) have been disease free for periods of 1–214

TABLE 2. Outcome by disease stage in 58 patients with adrenocortical tumors

Feature	Disease stage (no. of patients)	Cause of death
Early death	I (1)	Hypertensive encephalopathy
Inoperable tumor	III (3)	Progressive disease
Metastatic disease	IV (8)	Progressive disease
Relapse	II (11)	Progressive disease
Death in remission	I (1)	Choroid plexus carcinoma
Alive in complete remission	I (17)	
	II (11)	
	III (1)	
Lost to follow-up	(4)	

months from diagnosis (median, 63 months). The survival rate in our series is similar to that reported by others (17).

All but 2 of the 24 deaths were attributable to the primary ACT (Table 2). One child died from a second neoplasm (choroid plexus carcinoma), and another as the consequence of encephalopathy that developed during a hypertensive crisis. Sites of metastasis were confined mainly to the liver, lungs, and regional lymph nodes. The time to tumor recurrence ranged from 1–48 months postsurgery (median, 6 months). Only 2 of 15 patients relapsed more than 1 yr from the initial surgery, (1.8 and 4.0 yr, respectively). Recurrences were rapidly fatal in nearly all cases (median time from relapse to death, 5 months; range, 2–11 months). It should be noted that local relapse in these patients always preceded distant metastasis.

Markers of growth and development have consistently remained within the normal range in long term survivors. In most cases, the initial predicted adult height was smaller than the target height; however, due to a "catch-down" effect that was more pronounced for bone age than for growth velocity, the final predicted adult height did not differ from the target height (9). True precocious puberty was noted in only one patient, who lacked a period of bone age catch-down.

Prognostic factors

Because of the heterogeneity and rarity of ACTs, prognostic factors have been difficult to establish. The prognostic importance of histology has been controversial (13, 14, 18). However, none of the patients with tumor specimens classified as of adenoma or benign histology (in any of the 3 classification schemes above mentioned) died of disease. These findings have been corroborated in another study of 54 patients from our and 2 other Brazilian institutions (18). In that study, none of 11 patients with tumors of adenoma histology or diploid DNA content died from disease. However, cure was often possible for patients whose tumor specimens were classified as carcinoma or had an aneuploid DNA content (18).

In an effort to identify at last marginal predictors of outcome, we retrospectively analyzed 40 cases from our institution in which treatment was essentially uniform (10). The presence of metastases at diagnosis or failure to completely resect the tumor was associated with an extremely poor outcome. Among patients without metastatic disease, a univariate statistical analysis indicated several clinical and laboratory variables with an adverse impact on outcome: age more than 3.5 yr, interval of more than 6 months between the first signs and diagnosis, urinary excretion of 17-OHCS of 4 $mg/m^2 \cdot day$ or more, tumor volume of 200 cm^3 or greater, and tumor weight of 80 g or more. Tumor size was highly correlated with a delay in diagnosis and, to a lesser degree, with older age, indicating that patients diagnosed more than 6 months after the first symptoms and/or older than 3.5 yr tended to have larger tumors. Multivariate analysis indicated that only tumor size was independently associated with disease-free survival.

TABLE 3. Staging criteria for childhood adrenocortical tumor

Stage	Description
I	Tumor totally excised, tumor vol <200 cm^3, absence of metastasis, normal hormone levels after surgery
II	Microscopic residual tumor, tumor >200 cm^3, tumor spillage during surgery, or persistence of abnormal hormone levels after surgery
III	Gross residual or inoperable tumor
IV	Distant metastasis

On the basis of these results, we proposed a set of staging classifications of childhood ACT (19) (Table 3). The staging criteria are highly predictive of outcome among patients with either stage I or stage IV disease, that is 90% or more of patients with stage I disease are long term survivors (median follow-up time of 6.2 yr; range, 1.4–13.7 yr) compared with virtually none of those with stage IV disease. Predicting outcome for patients with intermediate stages of disease is much more difficult. In this regard, only 52% (12 of 23) of the patients with stage II disease remain alive and free of disease (median, 6.3 yr; range, 0.1–17.8 yr). Among 4 patients with stage III disease, only 1 remains alive and has been free of disease for 6 yr. This patient's tumor regressed with mitotane and could be completely excised.

In summary, two distinct prognostic groups of patients with ACT can be recognized: one with very poor prognosis (patients with metastatic disease or gross residual tumor) and one with a very good prognosis (patients with completely resected tumor of small size or adenoma histology). Together, these later patients represent 40% of newly diagnosed children with ACT.

Future plans

Because so few cases of childhood ACT are encountered outside southern Brazil, we have established an international registry by which information on children with this tumor is collected, stored, and updated yearly. We believe that the availability of such data will allow us to clarify many of the puzzling aspects of this disease. We are also analyzing the results of a recent clinical trial designed to determine the efficacy and toxicity of mitotane used in adjuvant treatment of ACT. To add to the list of useful prognostic factors and possibly improve the current system of risk classification, we have begun to investigate the relation of telomerase activity (20) to treatment outcome in childhood ACT.

Acknowledgments

The authors are grateful to Dr. Izrail Cat for leadership, to Dr. Gilberto A. Sampaio for reexamining the histopathological material, and to Dr.

Claude Migeon for reviewing the manuscript. Editorial assistance provided by John Gilbert and preparation of the manuscript by Peggy Vandiveer are greatly appreciated.

References

1. **Marigo C, Muller H, Davies JNP.** 1968 Survey of cancer in children admitted to a Brazilian charity hospital. J Natl Cancer Inst. 43:1231–1240.
2. **Young Jr JL, Ries LG, Silverberg E, Horm JW, Miller RW.** 1986 Cancer incidence, survival, and mortality for children younger than age 15 years. Cancer. 58:598–602.
3. **Stiller CA.** 1994 International variations in the incidence of childhood carcinomas. In: Cancer Epidemiol Biomarkers Prev. 3:305–310.
4. **Sandrini R, Pianovski MA, Gabardo J, et al.** Childhood adrenocortical tumor (ACT) in southern Brazil: lack of association with familial cancer syndromes [Abstract P3–668]. Proc of the 10th Int Congr of Endocrinol. 1996; 921.
5. **Birch JM, Blair V.** 1988 Increase in childhood carcinomas in Northwest England [Letter]. Lancet. 1:833.
6. **Kristensen P, Adersen A, Irgens LM, Bye AS, Sundheim L.** 1996 Cancer in the offspring of parents engaged in agricultural activities in Norway: incidence and risk factors in the farm environment. Int J Cancer. 65:39–50.
7. **Artigas JRL, Niclewicz ED, Silva APG, Ribas DB, Athayde SL.** 1976 Congenital adrenal cortical carcinoma. J Pediatr Surg. 11:247–252.
8. **Kater CE, Biglieri EG, Brust N, Chang B, Hirai J, Irony I.** 1989 Stimulation and suppression of the mineralocorticoid hormones in normal subjects and adrenocortical disorders. Endocr Rev. 10:149–164.
9. **Schmit-Lobe MC, DeLacerda L, Ribeiro RC, Kohara SK, Sandrini R.** 1990 Patterns of growth and development in 26 children operated for adrenocortical carcinoma (ACC) and disease-free for more than one year [Abstract 5]. Pediatr Res. 38:622.
10. **Ribeiro RC, Sandrini Neto RS, Schell MJ, Lacerda L, Sambaio GA, Cat I.** 1990 Adrenocortical carcinoma in children. A study of 40 cases. J Clin Oncol. 8:67–74.
11. **Hough AJ, Hollified JW, Page DL, Hartmann WH.** 1979 Prognostic factors in adrenal cortical tumors. A mathematical analysis of clinical and morphologic data. Am J Clin Pathol. 72:390–399.
12. **van Slooten H, Schaberg A, Smeenk D, Moolenar AJ.** 1985 Morphologic characteristics of benign and malignant adrenocortical tumors. Cancer. 55:766–773.
13. **Weiss LM.** 1984 Comparative study of 43 metastasizing and nonmetastasizing adrenocortical tumors. Am J Surg Pathol. 8:163–169.
14. **Weiss LM, Medeiros LJ, Vickery AL, Jr.** 1989 Pathologic features of prognostic significance in adrenocortical carcinoma. Am J Surg Pathol. 13:202–206.
15. **Lack EE, Mulvihill JJ, Travis WD, Kozakewich HP.** 1992 Adrenal cortical neoplasms in the pediatric and adolescent age group. Clinicopathologic study of 30 cases with emphasis on epidemiological and prognostic factors. Pathol Ann. 27:1–53.
16. **Godine LB, Berdon WE, Brash RC, Leonidas JC.** 1990 Adrenocortical carcinoma with extension into inferior vena cava and right atrium: report of 3 cases in children. Pediatr Radiol. 20:166–168.
17. **Chudler RM, Kay R.** 1989 Adrenocortical carcinoma in children. Urol Clin North Am. 16:469–479.
18. **Bugg MF, Ribeiro RC, Roberson PK, et al.** 1994 Correlation of pathologic features with clinical outcome in pediatric adrenocortical neoplasia. A study of a Brazilian population. Brazilian Group for Treatment of Childhood Adrenocortical Tumors. Am J Clin Pathol. 101:625–629.
19. **Sandrini R, DeLacerda L, Sampaio G, et al.** 1993 Adrenocortical tumors (ACT) in children: relationship between disease stage and outcome. Pediatr Res. 33(Suppl):S22:110.
20. **Kim NW, Piatyszek MA, Prowse KR, et al.** 1994 Specific association of human telomerase activity with immortal cells and cancer. Science. 266:2011–2014.