REFERENCES


COMMENTARY


Comments by Melvin M. Grumbach, MD, Edward B. Shaw Professor of Pediatrics

ABSTRACT OF ORIGINAL ARTICLE. Three infants with female pseudohermaphroditism attributable to the salt-losing form of congenital adrenal hyperplasia (CAH; adrenogenital syndrome) followed for 14 to 20 months are described in detail. The first infant was admitted at the age of 7 weeks in adrenal crisis and studied intensively during a 557-day hospitalization; the second, an infant 7 weeks of age, was hospitalized for 7 ½ months; and the third, a 9-week-old infant, was studied over a 5-month period.

The effects of cortisone and corticosterone on the suppression of the abnormal adrenals, as reflected in the urinary excretion of 17-ketosteroids (17-KS) and on the electrolyte disturbance as manifested by changes in serum and urinary electrolytes and body weight, are described. Cortisone acetate produced more marked suppression of the adrenal overactivity per milligram (as assessed by the urinary excretion of 17-KS), but less sodium retention than corticosterone. Both steroids, however, improved the electrolyte abnormality significantly.

The possible mechanism of action of cortisone on the disturbed electrolyte metabolism is considered. We suggest that cortisone can serve as a substitute for deficient “Na-retaining hormone,” and/or it may act by suppressing secretions of the abnormal adrenals that possibly cause salt loss actively, either from the production of a specific “Na-losing” factor or from an antagonistic action of some of the steroids secreted by the normal adrenal gland against those hormones that normally regulate electrolyte metabolism. The studies in the three infants lead us to conclude that the electrolyte disturbance in patients with the salt-losing form of CAH is not merely simple deficiency of the adrenal salt hormone that appears to be associated with the zona glomerulosa of the adrenal cortex.

The approach to the initial and long-term management of infants with the salt-losing form of CAH derived from the intensive study of these three infants is described. The critical importance of the use of adequate NaCl and fluids by intravenous administration initially to repair the electrolyte and fluid deficiencies and the hemodynamic abnormalities without the use of deoxycorticosterone acetate (DCA), if possible, in the initial treatment is emphasized because suppression of the adrenal with cortisone seems to alter materially the requirement for DCA. The final combination of the maintenance dose of cortisone acetate (either intramuscularly or orally) after initial high-dose priming, the amount of added NaCl, and the requirements for DCA (as long-acting subcutaneous pellets preferably), however, must be decided in each patient individually. Too high a dose of glucocorticoid resulted in impaired growth and cushingoid features as we described earlier; an inadequate dose of cortisone did not protect the infant from an adrenal crisis and was associated with rapid growth and skeletal maturation and

From the Department of Pediatrics, University of California San Francisco, San Francisco, California.
Received for publication Mar 19, 1998; accepted Mar 19, 1998.
Address correspondence to: Melvin M. Grumbach, MD, Department of Pediatrics, University of California San Francisco, San Francisco, CA 94143-0434.
the undesirable clinical signs of excess androgen production.*

INTRODUCTION

The advances in pediatric endocrinology over the past 5 decades have been legion, and many represent major landmarks in biomedical science and clinical medicine. When Birt Harvey asked me to select one paper that was “the classic” from among the more than 400 papers on a pediatric endocrine subject published in Pediatrics over the past 50 years, my first response was, “He can’t be serious.” How can one choose from this huge cornucopia? To my relief, one contribution stood out. This insightful report, with its compelling observations and analyses, appeared in the fifth year of the publication of Pediatrics and had an enormous impact on the field; it anticipated and stimulated a cascade of later contributions; its therapeutic approach led to a reduction in mortality of the disorder in pediatric endocrine clinics from virtually 100% to ~2% in subsequent years; and it advanced prescient hypotheses and predictions. This paper and others in this series had a significant role in attracting a host of young pediatricians to the field of pediatric endocrinology.

COMMENTARY

It has been almost 5 decades since the simultaneous demonstration by Wilkins and associates at Johns Hopkins and Bartter and colleagues at the Massachusetts General Hospital that cortisone suppressed the abnormal androgen secretion in CAH; it provided the first evidence that deficient glucocorticoid secretion was the key abnormality in the disorder. The Johns Hopkins and the Massachusetts General groups had a friendly but intensely competitive rivalry in the study of the adrenogenital syndrome and in seeking a hormone that would suppress the abnormal androgen secretion in CAH; it provided the first evidence that deficient glucocorticoid secretion was the key abnormality in the disorder. Both groups began the study of the effect of cortisone in December 1949. The preliminary report by the Wilkins’ group of the dramatic decrease in urinary excretion of 17-KS by cortisone treatment of a 15-year-old female pseudohermaphrodite resulting in the classical studies in the field. Between 1951 and 1949 when the partial synthesis of cortisone was achieved by Sarrett at Merck, and it became available in limited quantities for clinical research, the announcement in 1949 by Hench and Kendall (for which they received the Nobel Prize) and their associates of the remarkably ameliorating effect of cortisone and of ACTH in patients with rheumatoid arthritis and rheumatic fever had a striking influence and galvanized a host of research studies on the adrenal cortex and its secretions. It was during this same period that steroid biochemists and organic chemists were unraveling the biogenesis of adrenal steroids and improving methods for the analysis and quantitation of plasma and urinary adrenal steroids, and physiologists were occupied with Selye’s “alarm reaction.” In 1952, the same year of the report of Crigler et al, aldosterone, the long sought, potent, elusive adrenal mineralocorticoid was isolated by Simpson and Tait, and soon thereafter, it was crystallized and its synthesis described. The entire adrenal field was in enormous ferment with exciting new discoveries stimulating clinical investigators to a full court press. With this background and the relatively large number of patients with the adrenogenital syndrome in the Harriet Lane Home Endocrine Clinic, the stage was set for Wilkins to launch his comprehensive investigations on the management of CAH.

The classic clinic manifestations and disordered electrolyte and fluid metabolism of the salt-losing form and the simple virilizing form of CAH had been defined in the decade before 1950. Attention had focused on the role of salt-loss in the adrenal crisis. It was recognized that this life-threatening event occurred most commonly between neonatal days 6 and 14, but sometimes not until weeks 3 to 8. In other patients, it occurred only during a stressful event or illness. Two life-threatening clinical manifestations of salt-losing CAH were appreciated. The most common was that accompanied by nausea, vomiting, anorexia, weight loss or lack of weight gain, loss of skin turgor, hyperkalemia, and hypotension associated with inappropriate natriuresis, hypotenremia, renal acidosis, elevated BUN, and, at times, glucosuria. The second, less common, manifestation was sudden death without apparent signs of dehydration and peripheral circulatory collapse caused by cardiac arrhythmias and arrest attributable to severe hyperkalemia. Wilkins and his coworkers began an intensive, comprehensive, and critical study of the treatment of CAH with cortisone, and the reports that emanated from his group became the classic studies in the field. Between 1951

PROLOGUE

It is awesome to reflect that when I was a medical student in the 1940s, the only adrenal steroid available for the treatment of adrenal insufficiency was the mineralocorticoid, DCA (first synthesized by Reichstein in 1937, a later Nobelist), which, together with supplemental NaCl therapy, was the only treatment for Addison disease. A chemical assay for urinary 17-KS became available for clinical use in the early 1940s. Relatively crude preparations of sheep and porcine adrenocorticotropic hormone (ACTH) and laborious and relatively nonspecific assays for urinary glucocorticoids were beginning to be used in clinical studies. The endocrine pharmacoepoa consisted of desiccated thyroid, insulin, sex steroids, and DCA.

All this, however, changed dramatically in 1948 and 1949 when the partial synthesis of cortisone was achieved by Sarrett at Merck, and it became available in limited quantities for clinical research. The announcement in 1949 by Hench and Kendall (for which they received the Nobel Prize) and their associates of the remarkably ameliorating effect of cortisone and of ACTH in patients with rheumatoid arthritis and rheumatic fever had a striking influence and galvanized a host of research studies on the adrenal cortex and its secretions. It was during this same period that steroid biochemists and organic chemists were unraveling the biogenesis of adrenal steroids and improving methods for the analysis and quantitation of plasma and urinary adrenal steroids, and physiologists were occupied with Selye’s “alarm reaction.” In 1952, the same year of the report of Crigler et al, aldosterone, the long sought, potent, elusive adrenal mineralocorticoid was isolated by Simpson and Tait, and soon thereafter, it was crystallized and its synthesis described. The entire adrenal field was in enormous ferment with exciting new discoveries stimulating clinical investigators to a full court press. With this background and the relatively large number of patients with the adrenogenital syndrome in the Harriet Lane Home Endocrine Clinic, the stage was set for Wilkins to launch his comprehensive investigations on the management of CAH.

The classic clinic manifestations and disordered electrolyte and fluid metabolism of the salt-losing form and the simple virilizing form of CAH had been defined in the decade before 1950. Attention had focused on the role of salt-loss in the adrenal crisis. It was recognized that this life-threatening event occurred most commonly between neonatal days 6 and 14, but sometimes not until weeks 3 to 8. In other patients, it occurred only during a stressful event or illness. Two life-threatening clinical manifestations of salt-losing CAH were appreciated. The most common was that accompanied by nausea, vomiting, anorexia, weight loss or lack of weight gain, loss of skin turgor, hyperkalemia, and hypotension associated with inappropriate natriuresis, hyponatre-
and 1952, five papers appeared that have had a powerful impact.

**ANALYSIS OF THE PAPER**

The first paper to be published in the American pediatric literature, the fourth in this series, was the detailed and well-documented report in the October 1952 issue of *Pediatrics* by Crigler, Silverman, and Wilkins on cortisone treatment and the management of the electrolyte and fluid abnormalities in the salt-losing form of CAH, a disorder that in the past had carried a very high mortality. For example, Iversen (Pediatrics, 1955) reviewed a large number of infants and children with the salt-losing form; all 81 patients who had not received specific therapy died, approximately half in the first 2 months of infancy. Of the remainder, all but one was dead by 13 months of age.

Studies of the management of salt-losing CAH by the Wilkins’ group began in August 1950 and included stringent monitoring of the patient; astute clinical observations; scrupulous attention to the collection of data; and graphic analysis of the changes in weight, serum electrolytes, urinary excretion of 17-KS, intake of Na and K, and effects of manipulating salt intake and doses of cortisone and DCA. There was a determined, compelling commitment to define a practical, if not optimal, therapeutic approach; rushing to publish was not on the agenda. The factors predisposing to an adrenal crisis were monitored, and the relatively extraordinarily large amounts of DCA required to control the salt-losing abnormality in infancy were documented. Once the serum Na and high K concentrations were returned to normal, the contraction of extracellular fluid and plasma volume corrected, and the hemodynamic effects of salt and fluid loss reversed, the initiation of high-dose cortisone acetate treatment (priming) was begun. Cortisone has Na-retaining properties (about 1/25 that of DCA) in addition to its glucocorticoid activity; the latter results through inhibition of ACTH in adrenal androgen suppression. Finally, the daily dose of DCA required to maintain normal serum electrolytes was determined and the number of DCA pellets estimated and implanted subcutaneously. Crigler et al emphasized the variability in the severity of the salt-losing form of CAH in their three patients. Two of the three infants required the implantation of DCA pellets for the maintenance of normal concentrations of serum electrolytes, whereas one infant was controlled satisfactorily with cortisone and the addition of added NaCl to the diet. The effects of too much or too little cortisone, DCA, and salt were described, and the necessity of individualizing the maintenance dose of cortisol was stressed. Intramuscular cortisone acetate and long-acting DCA pellets were recommended to reduce the risk of adrenal crises during intercurrent illnesses, and the necessity of increasing the dose of cortisol during stressful events was indicated. Their hypothesis for the pathogenesis of salt loss, a deficiency of the then putative Na-retaining hormone and/or the secretion by the abnormal adrenal of one or more steroids that actively cause salt loss, was prescient and the foundation of research for the next 2 decades. But more about this aspect below.

**EPILOGUE**

Bongiovanni‡ and Clayton in Wilkins’ laboratory described in 1954 a practical, quantitative method for measuring urinary pregnanetriol, the major metabolite of 17-hydroxyprogesterone (17-OHP), which was adopted widely, along with determination of the urinary excretion of 17-KS, for diagnosing and monitoring the effectiveness of glucocorticoid therapy. In 1952 and 1953, Jaiker proposed that virilizing CAH was caused by an inherited enzymatic defect in the 21-hydroxylation of 17-OHP to 17-deoxycorticisol. As a consequence, the defect causes cortisol deficiency and increased secretion of ACTH and abnormal amounts of non-21-hydroxylated precursors of cortisol such as 17-OHP accumulate, some of which are diverted into the adrenal androgen pathway. This theory of deficient 21-hydroxylation was confirmed by the work of many, including the observation of an impaired plasma cortisol response to ACTH. The deficient biosynthesis of cortisol leads to increased ACTH secretion and high plasma ACTH levels, adrenal hyperplasia, and clinical manifestations of hyperandrogenism in the fetus and throughout life. The vaginogram was developed as a useful approach to the detection of the presence of a urogenital sinus and cervix in infants with ambiguous genitalia. This procedure was supplemented years later by ultrasonography and magnetic resonance imaging of the pelvis. In 1949, Barr discovered sex chromatin (the Barr body in female somatic nuclei), and this distinction between the nuclei of the female and male soon was applied to the determination of the sex chromatin pattern in infants and children with anomalies of sex, initially in skin biopsy specimens and later in smears of the oral mucosa (see Grumbach and Barr, 1958). The latter test was especially useful in helping to identify quickly female pseudohermaphrodism attributable to CAH; later, it was replaced by karyotype analysis on a blood sample.

The pattern of inheritance of CAH was unclear especially because of the reported skewed sex ratio, until 1956, when Childs et al delineated the autosomal recessive pattern of inheritance in virilizing CAH and made the general observation that within families the type of CAH was, with rare exceptions, always the same. In 1977 and 1978, Levine, Dupont, and New discovered the linkage of 21-hydroxylase deficiency with the major histocompatibility complex human leukocyte antigen.

Wilkins et al and Shepherd and Clausen (Pediatrics, 1951) had described a hypertensive form of CAH, and in 1955, Prader and Gurtner recognized congenital lipoid hyperplasia now known to be

‡I am especially indebted to my late friend Alfred Bongiovanni, an inspiring and brilliant colleague who brought to my attention and translated the classic paper in Italian by Luigi De Crecchio in which the author describes the autopsy findings in a female pseudohermaphrodite (with CAH) who lived a rich life as a male. This is the first description of the disorder (De Crecchio L. Sopra un caso di apparenti virili in una donna. Morgagni 1865;7:154–188).
caused by mutations in the gene encoding the steroidogenic acute regulatory protein (StAR).

Eberlein and Bongiovanni (1956), who had left Wilkins’ group in 1954, established that some patients with the salt-losing form of CAH responded to salt restriction, but it did not explain the large dose of DCA required to suppress CAH in the nonglucocorticoid suppressed state.

Progesterone in doses similar to its production rate in the salt-losing CAH was shown in 1958 to have antimineralocorticoid activity, and in 1961, the natural effect of 17-OHP was described. Both of these steroids bind to the renal tubular cortex and act as competitive inhibitors of the action of aldosterone. Even though a unique salt-losing steroid has not been detected in 21-hydroxylase deficiency, the pattern of C21 steroid precursors of cortisol, which are secreted in large amounts, seems to account for the second component of the pathogenesis of naturesis in salt-losing CAH and the increased compensatory aldosterone secretion in children with the untreated simple virilizing form of 21-hydroxylase deficiency.

In the late 1960s, protein binding and radioimmunoassays were developed for the measurement of plasma 17-OHP and this determination was used for the early and rapid diagnosis of 21-hydroxylase deficiency in the newborn. High levels of plasma 17-OHP, found at birth, fell within 18 to 24 hours, whereas full-term infants with 21-hydroxylase deficiency had exceedingly high concentrations (Jenner et al, 1970). Determination of plasma 17-hydroxyprogesterone has replaced urinary steroid determinations in the diagnosis of female pseudohermaphroditism attributable to 21-hydroxylase deficiency in most centers and has an important role, along with the measurement of plasma androstenedione or testosterone, in determining the adequacy of glucocorticoid suppressive therapy.

The renin–angiotensinogen/angiotensin–aldosterone axis was defined in the 1960s, and angiotensin II was identified as the major regulator of aldosterone secretion by the zona glomerulosa; renin is secreted by the kidney in response to hypovolemic states and hyperkalemia. Practical assays for the determination of plasma renin activity (PRA) were developed in the late 1960s, and soon they were applied to the assessment of the adequacy of mineralocorticoid and salt supplementation of patients with salt-losing CAH. As PRA began to be used widely as a new and sensitive indicator of the requirement for mineralocorticoid replacement in salt-losing CAH (Goddard et al, 1968; Imai et al, Pediatrics, 1968), it became apparent that many patients who had been thought to have the simple virilizing form of 21-hydroxylase deficiency had subtle evidence of sodium and volume depletion as reflected in an elevated PRA, despite normal concentrations of serum Na, K, HCO₃, blood urea nitrogen, and the lack of obvious clinical signs of extracellular fluid contraction. Hypovolemia not only stimulates renin secretion, but it leads to increased secretion of vasopressin.
and ACTH and, as a result, to increased release of adrenal androgens. This had two consequences. First, of special importance was the finding that the addition of 9α-fluorohydrocortisone (9α-FF), a potent oral mineralocorticoid synthetic analog, which apart from repairing the hypovolemia and salt defect and decreasing the elevated PRA activity into the normal range indicates too high a dose of mineralocorticoid, hypervolemia, and the risk of hypertension and its untoward effects. Second, it had been thought that ~35% of patients with classic 21-hydroxylase deficiency had the salt-losing form; monitoring of PRA in the simple virilizing form indicated that a significant proportion was mild or less severe salt-losers, so that at present ~75% of all patients with classic 21-hydroxylase deficiency are now classified as salt-wasters. It is current practice to treat patients except with the mildest form of simple virilizing CAH with the mineralocorticoid.

The endogenous secretory rate of cortisol in healthy individuals has served as a yardstick to assess the maintenance dose of glucocorticoid. Early studies suggested that this value was 12.5 mg ± 3 mg/m² of body surface area per day. More recent determinations using improved methods now set the cortisol secretion rate in infancy and childhood at 7 to 8 ± 1 mg/m² per day and consistent with this value, an oral maintenance dose of cortisol of 12 to 18 mg/m² per day. Nevertheless, the oral dose of cortisol (which has replaced oral cortisone acetate) necessary to suppress ACTH and the adrenal and to achieve normal growth and development varies from child to child. In any event, it exceeds the glucocorticoid requirement of children with congenital adrenal hypoplasia or Addison disease. The use of potent long-acting cortisol analogs such as prednisolone and dexamethasone is to be avoided in the treatment of children with CAH, but once growth has ceased, they are a useful approach to adrenal-suppressive therapy.

In summary, in contrast to 1952, the diagnosis in a 2-day-old female with pseudohermaphroditism attributable to 21-hydroxylase deficiency (or in an affected male infant who presents at a later age in crisis) can be established rapidly by the determination of plasma 17-OHP, karyotype analysis, and pelvic sonography, and the presence of the salt-losing form monitored by following serum electrolytes and in older infants and children PRA.

Despite advances in treatment, which have been life-saving for the salt-losers and arrested the progressive virilization of androgen excess, long-term follow-up studies indicate that the mean adult height of both males and females affected is significantly below the normal mean adult height and of the adult height of their unaffected siblings. The fertility rate among sexually active women, especially if they are salt-losers, is low; an inadequate introitus in adult women affected is not uncommon. Recently, an increased prevalence of learning disorders in children with the salt-losing form of CAH has been reported, and changes in the central nervous system white matter visible by magnetic resonance imaging have been detected (Nass et al, 1997). All of these outcomes are leading to reassessment of current therapy and the use of new approaches. The experience of many pediatric endocrine clinics emphasizes the paradox in this disease between the requirement of large doses of glucocorticoids to suppress ACTH and adrenal androgen secretion, which can lead to overt or more commonly subtle cushingoid signs especially decreased growth, and the much lower dose needed for glucocorticoid replacement in adrenalectomized children or those with Addison disease.

Below is a brief consideration of other important advances and some unsolved clinical issues.

**Neonatal Screening for CAH Attributable to P450c21 Deficiency**

Pang et al (1977) developed a blood spot test for 17-OHP that is now used widely for neonatal screening in many states in the United States and in other countries. In the United States, the incidence of newborns affected is 1 in 12,000 to 1 in 18,000 live births; in the Yupik tribe of Alaska it is 1 in 280. This screening procedure, operative in 15 states in the United States, serves to identify not only affected females who are already marked by the genital ambiguity and are at risk for misassignment of sex as a male, but to the early detection of affected males of whom ~75% are salt losers and, in the absence of other affected siblings, may not come to light until an adrenal crisis occurs or later in childhood when signs of sexual precocity appear. The frequency of classic P450c21 deficiency exceeds that of phenyketonuria.

**Prenatal Diagnosis and Dexamethasone Therapy by Determination of Steroids in Amniotic Fluid, HLA Typing of Amniocytes, Karyotype Analysis, and Molecular Genetic Diagnostics on Chorionic Villus Biopsy Samples or Amniocytes**

A spirited discussion is in progress of the pros and cons of oral dexamethasone (a steroid not inactivated by the placenta) treatment of the mother during pregnancy to prevent or modify masculinization of the external genitalia and urogenital sinus of an affected female fetus (Forest et al, 1993; New et al, 1993; Miller et al, 1996). Prenatal treatment, which should begin by 4 to 6 weeks of gestation, reduces the need for surgery and quite likely reduces exposure of the fetal brain of the female to excessive androgens; however, 7 of 8 fetuses—all males and 3 of 4 females—will be treated needlessly for 12 to 18 weeks.

**Psychoendocrinology**

Wilkins encouraged John Money and Joan and John Hampson to study patients with intersexuality, including affected females with virilizing CAH and nurtured the establishment of Money’s Psychohormonal Clinic. Long-term studies of psychosexual orientation and gender identity in this disorder are now available.
Experimental Surgical and Pharmacologic Approaches to Treatment

For the reasons presented above, the less than satisfactory results of long-term glucocorticoid suppressive therapy on growth and other aspects has focused interest on new schemes. The following approaches have been proposed or are under study:

1. In Chapel Hill and Stockholm, a long-term trial of adrenalectomy (which now can be done by laparoscopy) in infants and young children with homozygous or compound heterozygous nonfunctional P450c21 genes (null mutations) is in progress. Such patients have severe glucocorticoid and mineralocorticoid deficiency, and their defective adrenal glands are hyperresponsive to ACTH.

2. Trials are in progress in patients with CAH to determine the effects of aromatase inhibitors that block the conversion of androgens to estrogens, in some studies combined with an antiandrogen. Estrogens are now recognized as the principal sex steroid affecting skeletal maturation.

3. Other potential therapies not yet available include the use of 1) potent antagonists of hypothalamic corticotropin to block ACTH secretion or of antagonists to ACTH itself to block its action on the adrenal, and 2) steroidogenic enzyme inhibitors, especially selective antagonists to 17,20 lyase, an obligatory step in androgen synthesis.

4. Finally, there is the promise of gene therapy to correct the 21-hydroxylase deficiency.

LOOKING AHEAD

The advances in the management and diagnosis of 21-hydroxylase deficiency over almost 5 decades provide a truly extraordinary record of achievement in pediatrics, but the story is far from complete. We need to vigorously address and, through research, overcome these deficiencies and resolve issues that confront us in the care of our patients. These include measures to improve adult height; provide more optimal control of virilization; assist in the counseling of patients and their parents and advance our understanding of psychosexual and psychologic factors and their management; improve compliance in a lifelong chronic disease; assess the functional, not simply anatomic, results of surgical repair of the genitália; and determine the long-term safety of prenatal therapy.

SUGGESTED READINGS


White PC, New MI, Dupont B. HLA-linked congenital adrenal hyperplasia results from a defective gene encoding a cytochrome P450 specific for steroid 21-hydroxylation. Proc Natl Acad Sci USA. 1984;81:7505–7509

The most common reason for antimicrobial use in United States children is treatment of otitis media. Of 44.5 million office-based prescriptions for antimicrobials in 1986 for children younger than 10 years of age, 42% were for otitis media, and of the estimated 20 million visits in 1990 for otitis media by children younger than 14 years of age, antimicrobials were prescribed at >80%. In a recent prospective study, antimicrobial treatment of otitis media accounted for >90% of all antimicrobial use during the first 2 years of life.


From the Department of Pediatrics, University of Pittsburgh School of Medicine, Children’s Hospital of Pittsburgh, Pittsburgh, Pennsylvania. Received for publication Mar 19, 1998; accepted Mar 19, 1998. Address correspondence to: Jack L. Paradise, MD, University of Pittsburgh School of Medicine, Children’s Hospital of Pittsburgh, 3705 Fifth Ave, Pittsburgh, PA 15213-2583.

PEDIATRICS (ISSN 0031 4005). Copyright © 1998 by the American Academy of Pediatrics.
Melvin M. Grumbach and Edward B. Shaw Professor of Pediatrics
Pediatrics 1998;102;215

Updated Information & Services
including high resolution figures, can be found at:
http://pediatrics.aappublications.org/content/102/Supplement_1/215

References
This article cites 29 articles, 2 of which you can access for free at:
http://pediatrics.aappublications.org/content/102/Supplement_1/215.full#ref-list-1

Subspecialty Collections
This article, along with others on similar topics, appears in the following collection(s):
Endocrinology
http://classic.pediatrics.aappublications.org/cgi/collection/endocrinology_sub
Metabolic Disorders
http://classic.pediatrics.aappublications.org/cgi/collection/metabolic_disorders_sub
Pharmacology
http://classic.pediatrics.aappublications.org/cgi/collection/pharmacology_sub
Therapeutics
http://classic.pediatrics.aappublications.org/cgi/collection/therapeutics_sub

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
https://shop.aap.org/licensing-permissions/

Reprints
Information about ordering reprints can be found online:
http://classic.pediatrics.aappublications.org/content/reprints
Melvin M. Grumbach and Edward B. Shaw Professor of Pediatrics
Pediatrics 1998;102;215

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pediatrics.aappublications.org/content/102/Supplement_1/215