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## NEW IDEAS FOR MEDICAL TREATMENT OF CONGENITAL ADRENAL HYPERPLASIA

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Dramatic improvement has occurred in the lives of patients with congenital adrenal hyperplasia (CAH) during the past 50 years through the introduction of glucocorticoid and mineralocorticoid replacement therapy<sup>16</sup> and luteinizing hormone-releasing hormone (LHRH) agonist treatment to arrest secondary LHRH-dependent precocious puberty.<sup>43</sup> Owing to the discovery of cortisone therapy, patients with classic CAH can have a long lifespan. Despite these advances, existing treatment has failed to normalize the growth and development of many children with CAH, and the clinical management of adults with CAH is often complicated by iatrogenic Cushing's syndrome, inadequately treated hyperandrogenism, or infertility.<sup>8</sup> Many of these unresolved clinical problems exist even when compliance with treatment has been excellent. Recently, adrenalectomy has been proposed as an alternative therapy for CAH that is difficult to manage with medical therapy.<sup>32, 54</sup> Nevertheless, existing therapy has been less effective than hoped, and it is unknown whether new medical approaches can improve on earlier results. This article addresses the clinical problems patients with CAH continue to have and new medical strategies that offer the prospect of an improved outcome of treatment. The goal of new treatment approaches is to normalize the growth and development of children with CAH and to

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optimize the quality of life of adults with CAH. Some of these strategies are being tested, whereas others await medical and technical advances.

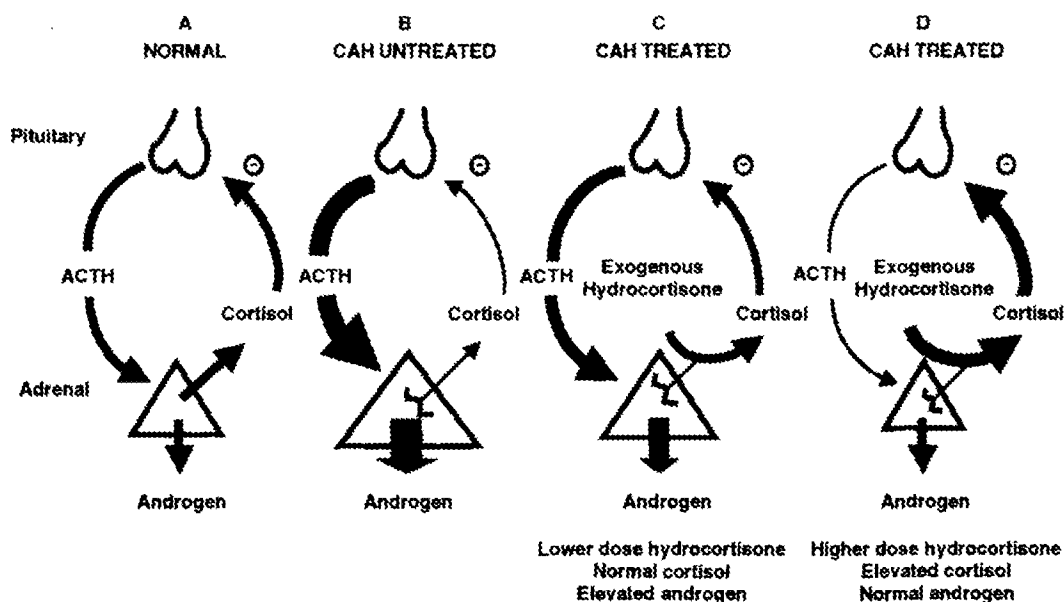
## UNRESOLVED PROBLEMS IN THE TREATMENT OF 21-HYDROXYLASE DEFICIENCY

In their pioneering studies of glucocorticoid therapy for CAH, Bartter<sup>2</sup> and Wilkins<sup>57</sup> and their colleagues reasoned that a defect in the pathway of cortisol biosynthesis led to a compensatory increase in pituitary corticotropin (ACTH) secretion. The resulting increase in ACTH caused the hypersecretion of adrenal androgens. Because ACTH, like other anterior pituitary hormones, is regulated by negative feedback, they hypothesized that the administration of glucocorticoid at physiologic doses would restore the levels of ACTH and adrenal androgen to normal.

Experience during the past 50 years requires certain revisions to this hypothesis. The administration of physiologic hydrocortisone doses does not normalize plasma ACTH levels in patients who have CAH.<sup>8, 33</sup> Exogenous hydrocortisone (divided two or three times daily) fails to replicate the close temporal relationship between ACTH pulses and the subsequent cortisol pulses that would normally restrain ACTH by negative feedback. Moreover, a decreased sensitivity of feedback inhibition is often observed in patients with CAH. Recent studies in mice with 21-hydroxylase deficiency suggest that intrauterine glucocorticoid deficiency results in hyperactivity of the hypothalamic-pituitary-adrenal axis and insensitivity to glucocorticoid feedback.<sup>48</sup> Decreased glucocorticoid sensitivity may further blunt the central effects of glucocorticoid therapy, whereas peripheral glucocorticoid sensitivity is preserved, leading to growth inhibition among other undesirable side effects.

Even the restoration of normal ACTH secretion in CAH cannot normalize androgen production because, with any adrenal activity, the block at 21-hydroxylase shunts a greater than normal proportion of steroid intermediates into the androgen pathway. To overcome the intrinsic tendency of the adrenal gland to overproduce androgens in CAH, the rate of cholesterol side-chain cleavage must be decreased to below normal levels to prevent the excessive accumulation of 17-hydroxyprogesterone and shunting into the androgen pathway. To suppress the rate of cholesterol side-chain cleavage to below normal levels by negative feedback requires supraphysiologic doses of glucocorticoid. Patients with treated CAH may have normal cortisol levels and excessive androgen secretion, excessive cortisol levels and normal androgen secretion, or an intermediate state consisting of mild hypercortisolism and mild hyperandrogenism (Fig. 1).

Conventional medical treatment is often a difficult balancing act between the undesirable states of hypercortisolism and hyperandrogenism. Signs of glucocorticoid excess, such as obesity, poor growth velocity, or other features of Cushing's syndrome, are frequent among treated



**Figure 1.** Relation between androgen production and cortisol production in untreated and treated patients with congenital adrenal hyperplasia (CAH). *A*, Normally, the adrenal gland produces cortisol and androgen, which is regulated by negative feedback. *B*, In the untreated patient with CAH, low levels of cortisol secretion are achieved in most patients through the compensatory hypersecretion of adrenocorticotropic hormone (ACTH) and adrenal hyperplasia. Overproduction of androgen is often massive. *C* Physiologic doses of hydrocortisone reduce androgen production, but not to normal levels. *D*, Supraphysiologic doses of hydrocortisone can normalize androgen levels, but at the expense of exposing the patient to elevated cortisol levels. Mineralocorticoid treatment has been omitted for clarity. (Adapted from Merke DP, Cutler GB: New Approaches to the treatment of congenital adrenal hyperplasia. *JAMA* 277:1073–1076, 1997; with permission.)

patients.<sup>5, 26, 50</sup> The symptoms and signs of hyperandrogenism include virilization of women, precocious virilization of men, and adult short stature in men and women. An additional complication in children is central precocious puberty, which is most likely to develop when the diagnosis of CAH is delayed or when control of adrenal androgen secretion is poor.<sup>43</sup> The premature elevation of gonadal steroid secretion compounds the problem of excess secretion of adrenal androgens.

The adult short stature frequently observed in patients who have CAH may be caused by hypercortisolism, by hyperandrogenism owing to indirect effects on the growth axis caused by hyperestrogenism, or by a combination of both. Retrospective studies indicate that the final height of treated patients is relatively independent of the degree of control of adrenal androgen levels.<sup>11</sup> Adrenal androgen secretion is best controlled in patients in whom the hydrocortisone dose, on average, is highest relative to their individual requirement and thus contributes the most to the ultimate adult short stature. Theoretically, patients with the most nearly physiologic hydrocortisone dose would tend to have the poorest control of adrenal androgen levels and bone maturation rates and, consequently, decreased final height because of early epiphyseal fusion; how-

ever, glucocorticoid excess suppresses growth. A randomized prospective crossover trial showed that patients treated with 15 mg/m<sup>2</sup>/d of hydrocortisone were less likely to show growth suppression when compared with patients taking doses of 25 mg/m<sup>2</sup>/d.<sup>45</sup>

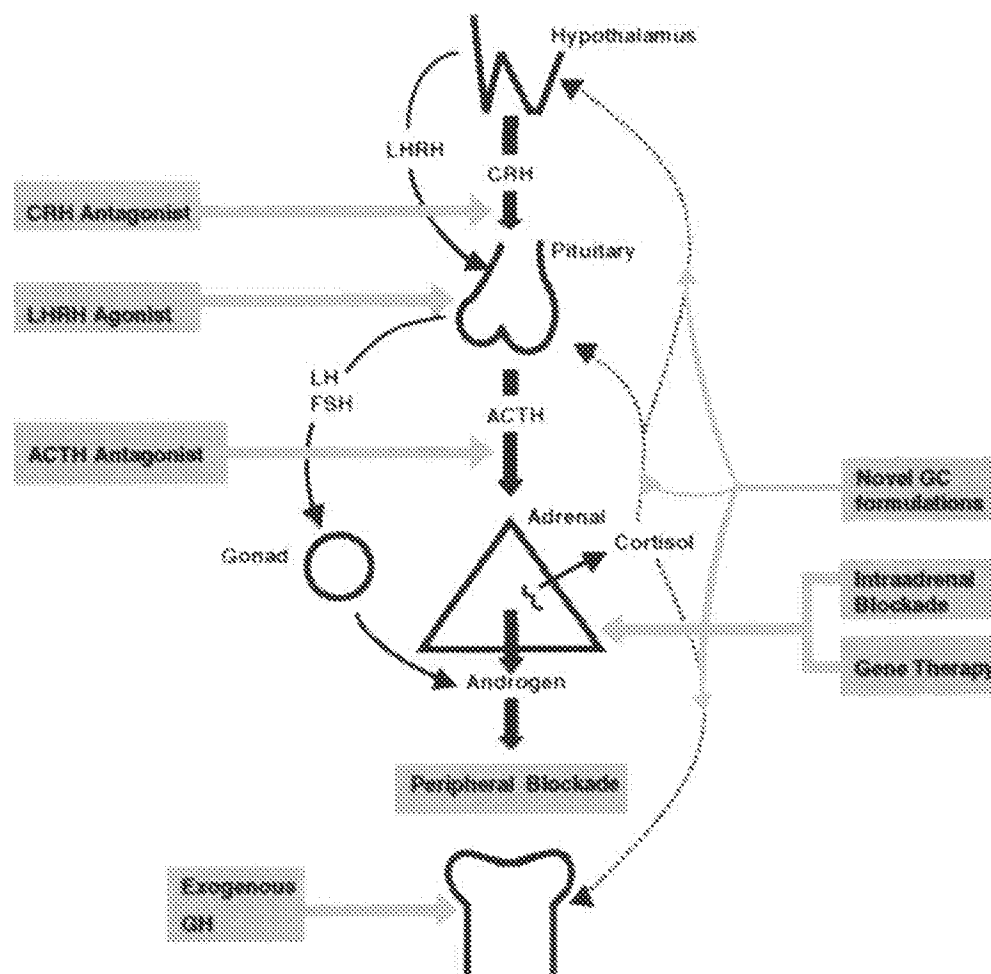
Once growth and development are complete, women with CAH often continue to have problems with hirsutism, amenorrhea, and infertility. Delay of the average age of menarche in girls with classic CAH is common,<sup>25,40</sup> and a polycystic ovarian syndrome (PCOS) type of ovarian dysfunction has been described.<sup>16</sup> Androgens may directly prevent the maturation of follicles or affect the hypothalamic-pituitary-gonadal axis; however, menstrual irregularities, anovulation, and infertility in girls with CAH are not always caused by the undertreated state of hyperandrogenism. Girls with CAH have increased adrenal progesterone secretion<sup>23</sup> and elevated estrogen of adrenal origin.<sup>40</sup> Ovarian dysfunction in girls with CAH may be caused by abnormalities at the hypothalamic, pituitary, or ovarian level, and inadequate control of excessive adrenal sex steroids (androgens, progestins, and estrogens alone or in combination) may contribute to menstrual and reproductive disorders.

Once growth and development are complete, men with CAH may have infertility owing to the development of testicular adrenal rest tumors.<sup>4</sup> Inhibition of gonadotropins owing to excessive adrenal androgens usually does not occur, even in untreated adult patients with classic CAH.<sup>52</sup> The majority of adult men with CAH have normal fertility.<sup>52</sup> As many as 30% of males with classic CAH have evidence of adrenal rest tissue on a screening testicular ultrasound.<sup>1</sup> The clinical significance of small (<5 mm) testicular adrenal rest masses, which are detected only by screening ultrasound, is unknown.

Unresolved clinical problems in the management of classic 21-hydroxylase deficiency include an inadequate response to glucocorticoid and mineralocorticoid replacement therapy, iatrogenic Cushing's syndrome,<sup>5, 26, 50</sup> adult short stature,<sup>9, 38</sup> the activation of ectopic adrenal tissue resulting in adrenal rest tumors,<sup>1</sup> and infertility.<sup>25, 37</sup> Current understanding of the molecular defect in CAH does not permit prevention of the many clinical consequences of this disorder. The following sections describe new ideas for the medical treatment of CAH, which represent potential solutions to these unresolved issues (Fig. 2).

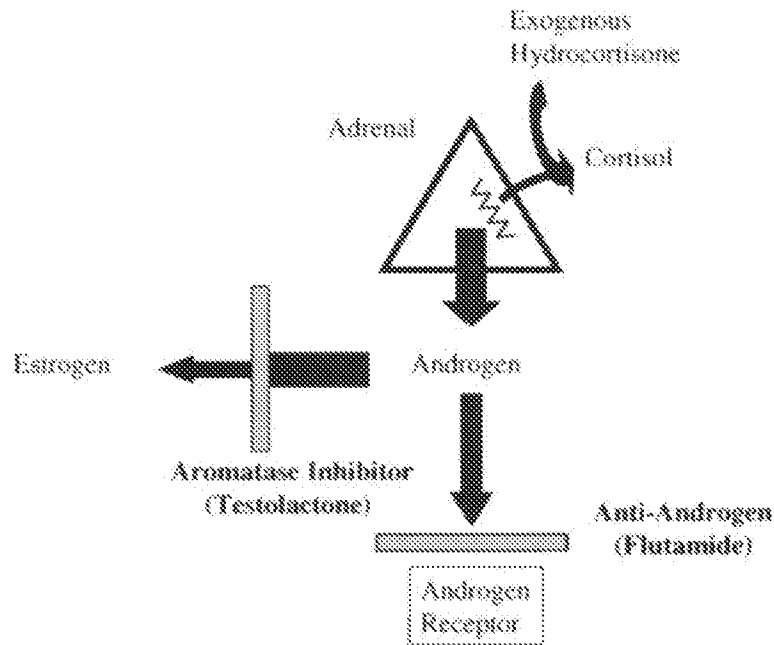
## **PERIPHERAL BLOCKADE OF ANDROGEN ACTION AND ESTROGEN PRODUCTION**

Most of the adverse outcomes in treated children with CAH are attributable to supraphysiologic levels of glucocorticoid, androgen, progestin, or estrogen. Higher doses of glucocorticoid are often needed to achieve satisfactory androgen suppression, which exposes children with CAH to excessive levels of glucocorticoid. Glucocorticoid excess can be avoided by restricting the dose of glucocorticoid to the physiologic range<sup>31</sup>; however, the reduced glucocorticoid dose leads to elevated sex



**Figure 2.** New treatment approaches for congenital adrenal hyperplasia (CAH). The hypothalamic-pituitary-adrenal axis is disturbed in CAH. In the undertreated state, there is increased production of corticotropin-releasing hormone (CRH), adrenocorticotropic hormone (ACTH), and adrenal androgens caused by impaired cortisol production. Exogenous glucocorticoid treatment reduces androgen production by negative feedback on the hypothalamus and pituitary, but higher doses have a direct effect on bone and suppress growth. Promising new treatment approaches include optimization of negative feedback with the use of novel glucocorticoid formulations; intra-adrenal blockade of adrenal androgen production through the use of drugs that inhibit the enzymes of steroid synthesis; correcting the genetic defect through gene therapy; peripheral blockade of androgen action and estrogen production; enhancing growth with exogenous growth hormone; delaying puberty with luteinizing hormone-releasing hormone (LH-RH) agonist therapy; and blocking ACTH or CRH production through the use of antagonists. Stimulatory effects are indicated by solid lines; inhibitory effects are indicated by dashed lines. GC = glucocorticoid; GH = growth hormone.

hormone levels in most children. As an alternative approach to the treatment of CAH, the pathophysiologic effects of elevated androgen could be prevented through the use of an antiandrogen to block androgen action and an aromatase inhibitor to block the conversion of androgen to estrogen<sup>6, 29, 33, 34</sup> (Fig. 3). This treatment approach is based on the earlier successful use of spironolactone, an antiandrogen, and testolac-



**Figure 3.** An investigational approach to the treatment of classic congenital adrenal hyperplasia. Fludrocortisone is given in the usual manner. The hydrocortisone dose is reduced to physiologic levels, resulting in elevated androgen production. An antiandrogen agent is administered to block the effect of the elevated androgen levels, and an inhibitor of androgen-to-estrogen conversion is given to block conversion of the increased amount of androgen to estrogen.

tone, an aromatase inhibitor, for the treatment of familial male-limited precocious puberty.<sup>28, 30</sup>

An investigational regimen of flutamide, testolactone, and reduced hydrocortisone dose (approximately 8 mg/m<sup>2</sup>/d) is being studied at the authors' center in an ongoing clinical trial.<sup>34</sup> Instead of using high-dose hydrocortisone to suppress ACTH and androgens, lower doses of hydrocortisone are used, and androgens are allowed to remain elevated. The effects of androgens are then antagonized with an androgen receptor antagonist, flutamide, and the conversion of androgen to estrogen blocked with an aromatase inhibitor, testolactone. Estrogen blockade is important because estrogens advance bone age and cause children to enter central puberty precociously.

Preliminary 2-year results of this trial are promising.<sup>34</sup> Despite the reduced hydrocortisone dose and the expected increase in the levels of androgens, both of which would be expected to increase the rate of growth and bone maturation, growth and bone maturation rates declined significantly during flutamide and testolactone treatment. This investigational regimen fully normalized growth rate and bone maturation during the 2-year duration of the observations.

Flutamide and testolactone were chosen because of prior experience with these drugs. Although no liver toxicity has been observed in the

subjects studied thus far, vigilance is required to use flutamide safely in children. Ongoing pharmaceutical development of improved antiandrogens and aromatase inhibitors offers the prospect of further improvement in the ability to achieve a peripheral blockade of excessive adrenal androgen. The ultimate test of this treatment is whether it will maintain normal growth and development throughout childhood and adolescence.

Peripheral blockade of androgens may also be useful in women with CAH. Women with CAH have an increase in PCOS,<sup>16</sup> and flutamide, or a similar antiandrogen, may antagonize intraovarian levels of androgens and reduce the incidence of PCOS. The use of an antiandrogen would also permit a lower glucocorticoid dose. Women of reproductive age taking an antiandrogen should be counseled regarding contraceptive use. Taking an antiandrogen during pregnancy may result in ambiguous genitalia in a male fetus. Other potential teratogenic effects are unknown.

### **INTRA-ADRENAL BLOCKADE OF ADRENAL ANDROGEN PRODUCTION**

Intra-adrenal blockade of hormone production represents an additional approach to the medical treatment of patients with CAH. This approach has been successfully used in the treatment of familial male-limited precocious puberty<sup>22</sup> and Cushing's syndrome<sup>47</sup> with the use of ketoconazole. Ketoconazole blocks adrenal steroid production at several enzymatic steps and is effective in achieving a reversible medical adrenalectomy. Although the risk of hepatic toxicity caused by ketoconazole necessitates periodic monitoring of liver function, this risk has not prevented the successful long-term use of this drug in familial male-limited precocious puberty. A regimen of ketoconazole and physiologic hydrocortisone (and fludrocortisone), by reducing adrenal androgen production to normal levels and by avoiding glucocorticoid excess, would be predicted to improve growth and development in children with CAH. To the authors' knowledge, such an approach has not been attempted in patients with CAH.

Drugs have been developed that specifically inhibit many of the enzymes of steroid synthesis,<sup>13</sup> including cholesterol side-chain cleavage, 3 $\beta$ -hydroxysteroid dehydrogenase, 11-hydroxylase, and aromatase. Nevertheless, there is no specific inhibitor of 17,20-lyase activity. With the cloning of the *CYP17* gene that encodes this enzyme and the discovery that serine dephosphorylation of the enzyme greatly reduces 17,20-lyase activity,<sup>59</sup> the development of such inhibitors should eventually be achieved. By blocking the conversion of 17-hydroxyprogesterone to androstenedione, a 17,20-lyase inhibitor could provide a further medical strategy for normalizing adrenal androgen production without resorting to a supraphysiologic glucocorticoid dose.

## LUTEINIZING HORMONE-RELEASING HORMONE AGONIST AND GROWTH HORMONE TREATMENT

A common complication of CAH is central precocious puberty, which is most likely to develop when the diagnosis of CAH is delayed or when control of adrenal androgen secretion is poor. Excess secretion of adrenal androgens and estrogens results in advanced skeletal maturity, which is associated with premature activation of the hypothalamic-pituitary-gonadal axis. The premature elevation of gonadal steroid secretion compounds the problem of excess secretion of adrenal androgens. The result of excessive adrenal androgen production and precocious puberty is adult short stature. Children with CAH and central precocious puberty can be treated with an LHRH agonist to arrest secondary LHRH-dependent precocious puberty.<sup>43</sup> The beneficial effects of this combination of glucocorticoid and mineralocorticoid therapy to suppress adrenal hormone production and LHRH analogue to arrest gonadal activation include regression of the physical signs of puberty, improvement of behavioral changes (personal experience by DPM), and restraint of rapid growth rate and skeletal maturation.<sup>44</sup>

Treatment with an LHRH analogue has been shown to improve adult height in children with LHRH-dependent precocious puberty when compared with the height of untreated historical controls,<sup>42</sup> pretreatment height predictions,<sup>20, 39</sup> or midparental potential height.<sup>20, 39</sup> Nevertheless, adult height is not always fully restored to the patient's genetic potential. Patients who are treated at a younger bone age tend to achieve taller adult height.<sup>42</sup>

Numerous studies support the hypothesis that extended pubertal delay would improve the final adult height of children who have CAH. The adult height of patients with isolated hypogonadotropic hypogonadism and delayed puberty is greater than the normal height of the American population, and final height correlates significantly with the duration of pubertal delay.<sup>53</sup> Rare cases of estrogen insensitivity,<sup>46</sup> and aromatase deficiency<sup>7</sup> show remarkable tall stature with delayed epiphyseal fusion. A randomized double-blind, placebo-controlled clinical trial to determine the efficacy of LHRH analogue treatment on growth in children with non-growth hormone-deficient short stature and normally timed puberty revealed a significant increase in the adult height (average, 6 cm) in the LHRH analogue-induced pubertal delay group.<sup>58</sup> Similarly, a moderate pubertal delay (i.e., to age 13 years in girls and 14 years in boys) would be expected to improve adult height in children with CAH.

Growth hormone therapy in combination with LHRH analogue treatment has also been used to improve the adult height of children with central precocious puberty.<sup>27, 41, 55</sup> Moreover, growth hormone administration can increase adult height in children with idiopathic short stature.<sup>21</sup> Growth hormone may improve the adult height of children with short stature owing to CAH.

A LHRH agonist-induced pubertal delay, with or without the addi-

tion of growth hormone therapy, may improve the final adult height of children who have CAH. Further studies are needed to determine the efficacy of these treatments in CAH.

### ALTERNATIVE GLUCOCORTICOID FORMULATIONS OR DOSE SCHEDULES

Normally, the hypothalamic-pituitary-adrenal axis is controlled by negative feedback. In normal individuals, each ACTH pulse is followed within minutes by a pulse of cortisol that acts to restrain the magnitude and duration of the ACTH pulse by negative feedback. In patients with CAH, exogenous hydrocortisone administration fails to normalize plasma ACTH levels because it lacks the normal close temporal relationship to the ACTH pulses. Alternative methods of administering glucocorticoid, which would provide a greater feedback during the early morning surge of ACTH, hold promise as a strategy to improve treatment outcome. More than a decade ago, a dose schedule in which one third of the glucocorticoid dose was given at 3 AM was found to be much more effective in suppressing 17-hydroxyprogesterone than the daytime administration of the same total dose.<sup>35</sup>

The question remains how to best administer glucocorticoid to suppress the early morning ACTH surge and the tendency toward increased ACTH production in patients with CAH. Randomized clinical trials comparing treatment regimens are lacking. Some clinicians ask their patients to administer a midnight dose. Other physicians administer long-acting glucocorticoids, such as prednisone, at the bedtime dose. Dexamethasone has been used but is avoided in children because of the risk that glucocorticoid excess will suppress growth. A carefully designed clinical research protocol to individualize a nighttime dexamethasone dose, with monitoring of dexamethasone levels, might allow improved control of ACTH without growth suppression.

The development of a delayed-release hydrocortisone formulation may improve ACTH suppression. The development of formulations similar to the delayed-release synthetic glucocorticoids that have been used in inflammatory bowel disease is possible. Hydrocortisone is the preferred steroid rather than the synthetic glucocorticoids because its production rate in children and adults is known,<sup>14, 31</sup> because its metabolic clearance is relatively invariant (except after certain drugs), and because a great deal is known about the total daily dose that can be given without producing the complications of glucocorticoid excess.

Two approaches in the development of delayed-release glucocorticoids have been used for the purpose of delivering glucocorticoids to the colon in patients with inflammatory bowel disease: (1) a pH-dependent methacrylic acid copolymer (Eudragit L or S) coated formulation that dissolves at pH 6 or 7 and that is stable in an acid environment,<sup>15</sup> and (2) the synthesis of steroid esters that are resistant to degradation in the upper gastrointestinal tract.<sup>19</sup> There is an expected 4-hour delay from

Eudragit S,<sup>15</sup> whereas the use of steroid esters is expected to have an approximate 6-hour delay.

Key pharmacokinetic properties of the formulations, such as the time of initial appearance of cortisol in plasma, the time to peak cortisol level, the time course of the decline in cortisol levels, and the bioavailability relative to the standard hydrocortisone formulation, need to be studied. If greater ACTH suppression by the delayed-release formulation is proven, a new treatment regimen can be tested in children with CAH in a randomized crossover design against a regimen using the standard hydrocortisone formulation. Strategies for developing a new hydrocortisone formulation would be expected to improve the suppression of early morning ACTH surge without increasing the total glucocorticoid dose, resulting in improved clinical outcome.

Preliminary studies in adult patients with CAH indicate that carbenoxolone, an inhibitor of the  $11\beta$ -hydroxysteroid dehydrogenase enzyme that inactivates cortisol, can boost endogenous cortisol levels without increasing hydrocortisone dose, leading to improved hormonal control.<sup>24</sup>

## **CORTICOTROPIN-RELEASING HORMONE ANTAGONIST**

Efforts in the treatment of CAH to date have focused on negative feedback by glucocorticoid to control ACTH secretion. This situation is analogous to the use of negative feedback by medroxyprogesterone to control gonadotropin secretion in precocious puberty. In precocious puberty, the effectiveness of treatment was improved dramatically when it became possible to block the hypothalamic LHRH signal by long-acting LHRH agonists.<sup>6</sup> Likewise, an effective antagonist of corticotropin-releasing hormone (CRH) or ACTH would dramatically improve the treatment of CAH by eliminating the need to rely solely on glucocorticoid negative feedback to prevent excessive adrenal androgen production.

What is the current feasibility of a new approach to CAH treatment using ACTH or CRH antagonist? With the cloning of the ACTH family of receptors,<sup>36</sup> new approaches to the development of ACTH antagonists are possible. Preclinical results with a CRH antagonist are promising.<sup>3, 56</sup> A prototype CRH receptor antagonist, antalarmin, binds to the CRH receptor type I and blocks the effects of CRH on that receptor. It acutely and chronically decreases ACTH and cortisol secretion without causing adrenal insufficiency.<sup>3</sup> In rats, chronic treatment with antalarmin is well tolerated. ACTH and corticosterone levels are decreased and adrenal size reduced owing to increased apoptosis in the outer zona fasciculata.

Corticotropin-releasing hormone has an important role in mediating behavioral, autonomic, and inflammatory stress-related response.<sup>10, 12</sup> Extensive preclinical research is exploring the effects of the CRH antagonist class of drugs because of their potential use in a variety of human conditions, including common disorders such as depression and eating

disorders. The use of a CRH antagonist represents a novel therapeutic approach to CAH. Once toxicology studies are complete and human studies are possible, the therapeutic usefulness of a CRH antagonist in the treatment of CAH should be tested.

## GENE THERAPY

Although 21-hydroxylase deficiency is not an appropriate candidate for gene therapy at this time, methodologic advances will eventually make gene therapy safer, more effective, and possibly less expensive than alternative approaches. Pharmacologic approaches are not completely safe or effective, and they are costly in terms of drugs, monitoring, and the quality of life (e.g., the inconvenience of lifelong drug administration). Gene therapy represents a potential solution to the inherent problems of pharmacologic therapy and may be the ideal treatment in the future.

21-Hydroxylase deficiency has several features that may facilitate gene therapy. First, the 21-hydroxylase gene is expressed almost exclusively in the adrenal cortex. Second, because the cortisol pathway is regulated by negative feedback, precise regulation of 21-hydroxylase gene expression is not essential (e.g., heterozygotes for 21-hydroxylase deficiency have no clinical phenotype, and modestly increased expression of the gene would probably not be harmful). Moreover, the ability to remove adrenal glands by laparoscopy, combined with established techniques for adrenal autotransplantation, would make it feasible to perform the gene transfer *ex vivo*.

The 21-hydroxylase-deficient mouse is an ideal model in which to evaluate possible approaches to gene delivery and has proved useful in testing novel therapeutic strategies. As a model system for the treatment of human disease by genetic therapy, a recombinant DNA fragment containing the murine genomic gene for 21-hydroxylase has been successfully introduced into mutant mice.<sup>17</sup> Only 15% of newborns are typically rescued by synthetic steroid therapy, whereas the efficiency of rescue was increased to 80% through the use of gene therapy.<sup>17</sup>

The defective enzyme was recently replaced in the adrenals of the mouse model using an adenoviral vector encoding the genomic sequence of the human *CYP21* gene.<sup>49</sup> In homozygous 21-hydroxylase-deficient mice, intra-adrenal injections of this adenoviral vector allowed expression of human *CYP21* mRNA and 21-hydroxylase activity in the adrenal, normalized plasma hormone levels, and corrected adrenal structural abnormalities. At the same time, the adenoviral vectors induced almost no inflammatory response in the adrenals, suggesting that high local glucocorticoid concentration suppresses the immune response caused by these vectors in other tissues. The adrenal may be a privileged site for gene therapy, an observation made earlier.<sup>51</sup>

In contrast to exogenous hormone replacement therapy, correcting the gene defect in 21-hydroxylase deficiency by adrenal gene transfer

corrects the endocrine abnormalities characteristic of 21-hydroxylase deficiency.<sup>49</sup> The development of novel viral vectors with adrenal-specific promoters will be required to improve the efficiency and duration of gene transfer in the adrenal. With these advances, gene therapy may become a feasible option for the treatment of CAH.

## SUMMARY

During the past 50 years since the discovery of cortisone therapy as an effective treatment for CAH, many advances have been made in the management of 21-hydroxylase deficiency. Despite these advances, the clinical management of patients with CAH is often complicated by abnormal growth and development, iatrogenic Cushing's syndrome, inadequately treated hyperandrogenism, and infertility.

New treatment approaches to classic CAH represent potential solutions to these unresolved issues. At the National Institutes of Health, a long-term randomized clinical trial is investigating a new treatment regimen: a reduced hydrocortisone dose, an antiandrogen, and an aromatase inhibitor.<sup>34</sup> Peripheral blockade of androgens may also be helpful in the adult woman with CAH and PCOS. Other promising new treatment approaches include LHRH agonist-induced pubertal delay with or without growth hormone therapy, alternative glucocorticoid preparations or dose schedules, CRH antagonist treatment, and gene therapy. The applicability and success of these new approaches await the results of current research.

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