Recombinant growth hormone and insulin-like growth factor I do not alter gonadotrophin stimulation of the baboon testis in vivo*

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In vitro studies indicate a physiological role for insulin-like growth factor I (IGF-I) in paracrine regulation of testicular function and recent clinical studies suggest a potential role for growth hormone (GH) and/or IGF-I in the treatment of hypogonadotrophic states in males. This study aimed to examine the effects of pretreatment with recombinant human GH (rhGH) or rhIGF-I on the response to gonadotrophins of the non-human primate testis in vivo. Using a balanced Latin square design with repeated measures, six prepubertal male hamadryas baboons (Papio hamadryas hamadryas) were treated in a cross-over sequence for periods of 18 days with daily im injections of rhGH (0.4 IU·kg⁻¹·day⁻¹), rhIGF-I (0.1 ng·kg⁻¹·day⁻¹) or saline with a 2-week washout period between each treatment. A single im injection of hCG (1500 IU) increased serum testosterone (p = 0.0002) but neither rhGH nor rhIGF-I influenced the timing or magnitude of this response (p > 0.5). A single im dose of FSH (75 IU) stimulated immunoreactive inhibin (p = 0.01) but also was unaffected in magnitude or timing by pretreatment with rhGH or rhIGF-I (p > 0.2). Circulating IGF-I levels were increased independently by hCG (p = 0.01) and FSH (p < 0.0001) administration. These findings indicate that neither GH nor IGF-I pre-treatment enhance acute gonadal responses to gonadotrophin stimulation of the prepubertal non-human primate testis in vivo. These findings suggest that GH or IGF-I treatment of hypogonadotrophic men without somatotrophin deficiency is unlikely to be beneficial.

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Although sexual maturation during puberty and mature reproductive function are dependent primarily upon gonadal stimulation by pituitary secretion of LH and FSH, in vitro studies show that growth hormone (GH) and insulin-like growth factor I (IGF-I) may influence gonadal function, particularly in a paracrine and/or autocrine fashion (1). The testis is a site of IGF-I synthesis (1) under regulation by both GH (2, 3) and gonadotrophins (1). Testicular receptors for GH (4) and IGF-I (5, 6) have been demonstrated and intratesticular IGF-I may exert a paracrine role in regulating Leydig cell function (1) and spermatogenesis (7, 8). In contrast, an in vivo role of GH and IGF-I in augmenting gonadotrophin-dependent testicular steroidogenesis or spermatogenesis remains less clearly established (8). Evidence such as delayed puberty in children with GH deficiency (9), impaired gonadal function in GH-deficient adults (10, 11) and reduced seminal plasma IGF-I concentrations in azoospermic men (12) indicate the potential importance of the GH/IGF-I axis but direct clinical studies examining a role for GH in gonadotrophin stimulation of the human testis have been controlled inadequately owing to ethical and practical constraints on human experimentation (13–15). If GH has effects on the testis, it then becomes relevant to examine whether IGF-I also can replicate these effects. No in vivo studies of IGF-I effects on the mammalian testis have been reported.

This study was designed to determine whether GH and/or IGF-I modify testicular responses to gonadotrophins in non-human primate testis as indicated by the testosterone response of Leydig cells to hCG and the inhibin response of Sertoli cells to FSH. The studies were conducted in hamadryas baboons (Papio hamadryas hamadryas), which provide a closer model of human growth and sexual maturation than subprimate models, including rodents. Among non-human primates, hamadryas baboons exhibit distinct advantages, including lack of reproductive seasonality and large body size (16). In seasonal breeders, including rhesus macaques, cyclic changes in testis size and spermatogenesis (17) can confound treatment effects under observation. The relatively large body size of baboons makes physiological studies technically easier to perform and even in

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Methods

Experimental design (Table 1)
The study was designed to determine whether pretreatment with GH or IGF-I would influence testicular responses to hCG and FSH. In order to reduce the variability due to endogenous GH, IGF-I, gonadotrophin and testosterone secretion, and to provide an unstimulated background on which to observe testicular responses to exogenous gonadotrophins, the study was carried out in prepubertal baboons. In order to optimize the efficiency of primate usage, we utilized an extensive cross-over Latin square design for repeated measures (18). Weight-matched pairs of monkeys rotating through each treatment (GH, IGF-I, saline) acted as their own controls for temporal changes. In a randomized sequence, each monkey received daily injections of rhGH, rhIGF-I or saline for 18 days, followed by a 2-week washout period between each hormone treatment. Within each 18-day treatment assignment, monkeys underwent a single dose stimulation by one of hCG, FSH or saline during separate weeks during the daily hormone injections. Thus, at the end of the experiment each baboon had received every treatment, providing N = 6/treatment group for each stimulation (hCG, FSH, saline), as well as balance in the order of treatment administration with respect to time (18).

Treatments and sampling schedule
Both rhGH (Genotropin®) and rhIGF-I were provided by Pharmacia (Australia) Pty Ltd., North Ryde, Australia. Vials of lyophilized rhGH (12 IU) were reconstituted, as required (at least every 4 days), in 3 ml of distilled water containing 0.25% m-cresol. Recombinant hIGF-I was supplied as a solution of 2 g/l in phosphate-buffered saline (0.5 ml/vial). Human chorionic gonadotrophin (Pregnyl®) was purchased from Organon (Australia) Pty Ltd., Sydney, Australia and highly purified urinary FSH (Metrodin®) from Serono Australia Pty Ltd., Frenchs Forest, Sydney, Australia. All hormones were stored in the dark at 4°C. Injections were given into the thigh muscle at midday on each day.

Six prepubertal male baboons were treated in a cross-over design where each monkey was exposed sequentially to 18-day periods of treatments with recombinant human GH (rhGH) (0.4 IU·kg⁻¹·day⁻¹), rhIGF-I (0.1 mg·kg⁻¹·day⁻¹) or saline in ≤0.7 ml in a random sequence, with a 14-day washout period between treatments. Hormone doses were calculated on the mean body weight of a pair at the beginning of each treatment cycle. In the second and third week of each 18-day treatment cycle, standard gonadotrophin stimulations were performed, consisting of an im injection of 1500 IU of hCG on day 8 and 75 IU of FSH on day 15, measuring testosterone and inhibin responses, respectively. Following hCG and FSH stimulation, blood samples were taken at 0, 24, 48 and 72 h and, for hCG only, also at 96 h. The samples were taken immediately prior to the next daily treatment injection, i.e. 24 h after the last injection. A baseline blood sample also was taken prior to commencing each treatment phase. At the end of the experiment, samples were assayed for testosterone, inhibin and IGF-I.

Animals and venipuncture
The baboons in this study live in a self-sustaining breeding colony of hamadryas baboons maintained by the Department of Renal Medicine, Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia. Animals have free access to water and are fed each afternoon on a diet of fresh fruit, bread, peanuts, sunflower seeds and primate pellets. Animals are housed in a number of adjoining wire mesh cages, each with a large outdoor and a smaller indoor section.
connected overhead by wire passages, or races, leading to a squeeze-back cage (19).

The six baboons involved in the study were housed in the same cage (7.5 m × 5 m × 3 m) for the duration of the study. Animals were anaesthetized with ketamine (5–7.5 mg/kg, im) and blood samples (3–4 ml) were taken by venipuncture from the cubital vein. Blood samples were centrifuged in a refrigerated table-top centrifuge (Sorvall, Technospin) and the serum was removed and transported on ice to the laboratory, where it was stored at −20°C until assay. The study was approved by the Animal Care Ethics Committees of the Royal Prince Alfred Hospital and the University of Sydney under National Health and Medical Research guidelines for animal experimentation.

Assays

Testosterone. Testosterone was measured by radio-immunoassay (RIA) after solvent extraction from serum. Serum samples (50 μl) were extracted with hexane–ethyl acetate (3:2, v/v) in glass tubes, air-dried and reconstituted in warm phosphate-buffered saline with gelatin (1.0 g/l). No correction was made for extraction losses because recovery of added tritiated testosterone was consistently greater than 90% (mean 95 ± 2%, N = 13). Aliquots of 100 μl (15 μl serum equivalent/tube) were assayed in duplicate. Tritiated testosterone and dilutions of the SGT-1 antibody (raised against testosterone-3-oxime–BSA by Dr BV Caldwell, Yale University, CT) were added to sample or standard and incubated overnight at 4°C. Separation was by dextran-coated charcoal. The detection limit (B/B₀ = 0.90) was 0.9 nmol/l. For samples at testosterone levels of 5 and 20 nmol/l, within-assay coefficients of variation (CVs) were 6.6% and 6.1%, respectively, and between-assay CVs were 8.2% and 6.2%, respectively.

Inhibin. Inhibin was measured by a double antibody RIA, previously validated for non-human primates (20, 21). Reagents, provided by Dr G Bialy, CBD, NICHD, were: a rabbit antibody to bovine inhibin (rAs-1989); purified 31-kD inhibin from bovine follicular fluid for iodination (bLNH-R-90/1); and bovine inhibin standard (bLNH-R-90/1). To validate the use of these reagents for baboons, parallelism of serial dilutions of baboon serum (pooled from the three highest samples in this study) to the standard curve was demonstrated. Non-equilibrium conditions were used, with an overnight preincubation of serum samples (100 μl in duplicate) with antibody prior to addition of 125I-labelled inhibin. As castrate baboon serum (containing negligible amounts of circulating inhibin (20)) inhibited tracer binding to antibody, the standard curve was blanked with castrate baboon serum to equalize serum protein concentrations in assay tubes. The detection limit (B/B₀ = 0.90) was 19.5 ng/l, which was the value assigned to any samples below this level (5.4% of samples). For samples at inhibin levels of 90, 200 and 390 ng/l, within-assay CVs were 1.8%, 3.0% and 5.0%, respectively, and between-assay CVs were 31.1%, 7.3% and 7.4%, respectively.

Insulin-like growth factor I. Baboon serum samples (50 μl) were assayed for IGF-I after acid–ethanol (AE) extraction (22). The immunoreactive IGF-I levels from six baboon serum samples following AE extraction were compared with the results obtained following removal of IGF-binding proteins by the reference method (23) of high-performance liquid chromatography (HPLC) under acid conditions as described previously (24). The IGF-I values (range 34–320 nmol/l) using AE extraction corresponded very closely with results obtained by acid HPLC (p = 0.9; multivariate ANOVA). Recovery of added rhIGF-I (1 mg/l) was 97 ± 4% for HPLC (N = 3) and 98 ± 5% (N = 7) for AE. The extracted baboon serum also diluted in parallel to the human IGF-I standard.

Neutralized supernatant after AE extraction was diluted 1/15 with assay buffer (0.95 μl serum equivalent/tube) prior to RIA in duplicate using reagents provided by Professor Robert C Baxter (25). Briefly, incubations in 0.5 ml of final volume consisted of antiserum (Tr10 at 1:50 000 final dilution), 125I-labelled IGF-I (approximately 10 000 cpm/tube) and rhIGF-I standards in the range 0.05–5.0 ng/tube. After a 16-h incubation at 4°C, bound and free tracers were separated by the addition of second antibody, rabbit serum and polyethylene glycol in saline. The detection limit (B/B₀ = 0.90) of the assay was 7 nmol/l. For samples at IGF-I levels of 28 and 126 nmol/l, within-assay CVs were 6.3% and 6.9%, respectively, and between-assay CVs were 9.5% and 9.6%, respectively. Parallelism of diluted extracts with the IGF-I standard curve was assessed by the computer program ALLFIT (26).

Data analysis

Data were analysed by analysis of variance (ANOVA) for repeated measures adapted to the balanced Latin square design (18, 27). Responses to gonadotrophins were analysed in terms of peak hormone levels (using suitable linear contrasts), as peak/basal ratio as well as in time of peak hormone levels. Testosterone and inhibin values were log-transformed to stabilize variance prior to analysis. A two-tailed p value of <0.05 was regarded as statistically significant. Data are presented as means (SEM).

Results

Animals (Table 2)

At entry into the study, the prepubertal male baboon pairs were closely matched for body weight although the ages ranged from 1.8 to 3.0 years. All had low
Table 2. Age, body weight and serum testosterone, inhibin and IGF-I levels of the six male baboons at entry into the studya.

<table>
<thead>
<tr>
<th>Baboon no.</th>
<th>Age (years)</th>
<th>Body wt (kg)</th>
<th>Testosterone (nmol/l)</th>
<th>Inhibin (ng/l)</th>
<th>IGF-I (nmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pair A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>3.03</td>
<td>7.59</td>
<td>2.3</td>
<td>140.5</td>
<td>91.7</td>
</tr>
<tr>
<td>2</td>
<td>2.99</td>
<td>6.43</td>
<td>4.5</td>
<td>73.3</td>
<td>74.5</td>
</tr>
<tr>
<td>Pair B</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>2.08</td>
<td>4.36</td>
<td>3.6</td>
<td>19.5</td>
<td>25.6</td>
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<tr>
<td>4</td>
<td>1.80</td>
<td>5.13</td>
<td>2.7</td>
<td>58.9</td>
<td>32.5</td>
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<tr>
<td>Pair C</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>5</td>
<td>1.85</td>
<td>3.24</td>
<td>4.8</td>
<td>73.1</td>
<td>11.2</td>
</tr>
<tr>
<td>6</td>
<td>1.79</td>
<td>3.36</td>
<td>4.0</td>
<td>133.3</td>
<td>20.3</td>
</tr>
<tr>
<td>Mean (SEM)</td>
<td>2.26 (0.24)</td>
<td>5.02 (0.71)</td>
<td>3.7 (0.4)</td>
<td>83.1 (18.8)</td>
<td>42.6 (13.3)</td>
</tr>
</tbody>
</table>

aBaseline data.

circulating testosterone levels and testis volumes of ≤1 ml, indicative of prepubertal status based on our prior studies of this colony (28). Serum IGF-I levels in the two older baboons, however, were higher than the other baboons, which reflected their closer chronological proximity to puberty (28). The wide interindividual variation in baseline serum inhibin levels was unrelated to age. There were no significant differences in the pretreatment baseline serum testosterone, inhibin or IGF-I levels between the three treatment cycles (all p > 0.6).

Testosterone (Fig. 1)

Testosterone levels were stimulated markedly by hCG (p = 0.0002) but the overall time course did not differ according to pretreatments (treatment p = 0.56; treatment × time interaction, p = 0.98). The magnitude of testosterone response to hCG, expressed as either an increment (median 56.1 nmol/l, range 28.7–108.3 nmol/l) or a peak/basal stimulation ratio (median 16.6 times, range 6–64.7), did not differ according to pretreatment. Similarly, peak testosterone levels

![Testosterone](https://via.placeholder.com/150)

**Fig. 1.** Serum testosterone levels in six prepubertal male baboons treated with rhGH (■), rhIGF-I (□) or saline (○). Gonadotrophin stimulation tests (1500 IU of hCG and 75 IU of purified urinary FSH) were given intramuscularly on days 8 and 15, respectively, as marked by arrows. Error bars represent SEM where they exceed the symbol in size.
occurred at a median of 72 h (range 24–96 h) after hCG stimulation without any significant difference in timing between treatments. Testosterone levels returned towards baseline 1 week after hCG administration, although on day 15 the testosterone levels remained marginally above pretreatment baseline values (6.6 ± 0.5 vs 4.0 ± 0.4 nmol/l; p = 0.0003).

Inhibin (Fig. 2)
Inhibin levels initially were unchanged, with a delayed decrease following administration of hCG that had not returned to baseline 1 week after hCG administration (p < 0.0001). Thereafter, considering serum inhibin levels on day 15 as the baseline, FSH stimulated serum inhibin levels (p = 0.01) in all groups without any significant difference (treatment and treatment × time interactions, p > 0.2) between treatments (rhGH, rhIGF-I or saline). The median increment in inhibin levels, following FSH stimulation, was 86.3 ng/l (range 16.1–229.5 ng/l) and the peak/basal stimulation ratio was 3.2-fold (range 1.6–12.8-fold). There was no difference between treatment groups in the timing of peak inhibin levels (median 24 h, range 24–72 h after FSH administration).

There was no evidence of immunoneutralization of human gonadotrophins because the serial responses to the three consecutive gonadotrophin stimulations were undiminished in magnitude.

Insulin-like growth factor I (Fig. 3)
Serum IGF-I levels were higher at 24 h after rhGH injections (p < 0.0001) but not after rhIGF-I injections (p = 0.13). The IGF-I levels in the rhIGF-I-treated
baboons were similar to saline controls over the duration of the experiment and also prior to gonadotrophin stimulation after 7 days of rhIGF-I administration (p = 0.99).

Circulating IGF-I levels were stimulated by administration of hCG (p = 0.01) and FSH (p < 0.0001) but without significant differences between rhGH, rhIGF-I or saline treatments (treatment × time interaction, F = 0.62, df 18/90, p = 0.88). After hCG stimulation, IGF-I levels were increased by a median increment of 19.8 nmol/l (range 1.1–81.4 nmol/l) or a stimulation of 1.9-fold (range 1.0–3.7-fold). For the FSH stimulation, the corresponding values were 31.1 nmol/l increment (range 1.0–77.7 nmol/l) or 2.3-fold stimulation (range 1.0–3.6-fold). Serum IGF-I levels after hCG stimulation followed a similar time course to that of testosterone, peaking at a median of 72 h (range 24–168 h). In addition, peak IGF-I levels prior to day 15 correlated significantly with peak testosterone levels (r² = 0.67; p = 0.0001, N = 18); however, the correlation between peak increments in IGF-I levels with testosterone was not as strong (r² = 0.27; p = 0.03). Following FSH stimulation, IGF-I levels peaked at a median of 48 h (range 24–48 h).

Discussion

This study examined the effects of rhGH and rhIGF-I on the testicular response to gonadotrophin stimulation in an immature non-human primate. We utilized rhGH and rhIGF-I doses based on regimens used clinically in non-GH-deficient humans (29, 30) and examined their influence on testicular responses to gonadotrophin stimulation by maximal doses used in the treatment of hypogonadotropic men. The principal finding of this study is that pretreatment with rhGH or rhIGF-I did not augment either the Leydig cell testosterone response to hCG or the Sertoli cell inhibin response to FSH.

The negative results of this study imply that circulating GH and IGF-I have negligible effects on testicular responses to gonadotrophins, in contrast with in vitro studies (8). Alternative explanations for our negative findings, including inadequate study power, insufficient GH and/or IGF-I doses and the prepubertal, non-GH-deficient status of the monkeys, are considered unlikely to invalidate this conclusion. The serial crossover study design was efficient to minimize usage of non-human primates. By rotating baboons through each treatment (rhGH, rhIGF-I or saline), each animal underwent all six combinations of stimuli, thus minimizing the effects of between-animal variability while providing internal control for time-related changes in environmental and other unidentified potentially confounding variables. For these reasons, this design has greater power than the comparable parallel group design with six groups of six monkeys (18).

The doses used in this study were based on those used clinically in non-GH-deficient humans (29, 30) and could be expected to achieve adequate circulating hormone levels. Although circulating IGF-I levels 24 h after the last dose remained elevated after rhGH, they had returned to baseline 24 h after the last rhIGF-I dose. This contrasts with a similar human study where the same IGF-I dose produced total and free IGF-I levels that remained elevated above baseline 24 h after the last injection (30). This discrepancy may be related to the route of hormone administration because increased thigh blood flow due to the vigorous physical activity of juvenile baboons may have enhanced hormone clearance from the injection site and thereby shortened the duration of action of GH or IGF-I in baboons compared with the use of the subcutaneous route in humans (30). The short circulating transit time and rapid renal clearance of GH and IGF-I, whereby urinary IGF-I levels return to baseline by 24 h after rhIGF-I injection in humans (31, 32), leave open the possibility that dose fractionation into multiple daily doses, or, preferably, continuous infusions of GH or IGF-I may have greater effects than observed in this study. Also, it cannot be excluded that the intratesticular levels of GH/IGF-I achieved in the present study using systemic administration may have been inadequate to activate fully the paracrine mechanisms described in vitro (8). Under these circumstances, however, systemic administration of GH or IGF-I would be unlikely to be effective therapeutically.

The intact somatotropic axes of the prepubertal baboons in this study may have ensured that endogenous GH and IGF-I, albeit low in immature primates, already had exerted maximal effects on prepubertal testicular function. An analogous interpretation has been proposed for the effects of rhGH and rhIGF-I treatment in augmenting hCG-induced testosterone secretion in GH-deficient but not non-GH-deficient mice (33). Thus, although the present study cannot exclude a physiological effect of GH and/or IGF-I on testicular function, it remains unlikely that any therapeutic benefit of exogenous GH and/or IGF-I might arise during testicular stimulation by gonadotrophins in non-GH-deficient primates. The high gonadotrophin doses used in this study potentially could obscure subtle shifts in gonadotrophin dose–response sensitivity, which would require even more complex experimental designs elaborating dose–response curves in the baboons. Such subtle changes, however, may not be relevant to clinical gonadotrophin regimens in hypogonadotropic regimens in hypogonadotropic men, where maximal gonadotrophin doses usually are used.

The glycoprotein hormone inhibin has been used as a marker of Sertoli cell function in human (34) and non-human (35) primates. Classically, inhibin secretion is stimulated by FSH action on Sertoli cells, although recent studies also suggest that LH/hCG acting on Leydig cells may increase immunoreactive inhibin output (36) in rats (37) and humans (34) but not in
rams (38). The depressed circulating immunoreactive inhibin levels several days after hCG administration observed in our study may reflect the indirect effects of elevated testosterone levels in suppressing pituitary FSH secretion, the normal stimulus maintaining testicular inhibin output. A single FSH injection stimulates circulating immunoreactive inhibin in adult rhesus monkeys (35) with a time lag of 50–60 h, in contrast to the prompt rise in inhibin levels peaking at 24 h in our study. This more rapid time course also may be due to the presumed suppression of endogenous FSH by hCG in our study, which effectively would create a lower background for a steeper basal/peak stimulation by exogenous FSH.

The present study also demonstrates significant increases in serum IGF-I levels following stimulation with either hCG or FSH, unrelated to rhGH or rhIGF-I pretreatment. The source of the increased circulating IGF-I remains unclear but the enhancement of hepatic IGF-I output by testosterone (39) and the temporal correlation between the hCG-induced testosterone rise and circulating IGF-I levels suggest a predominantly hepatic origin during hCG stimulation. It is harder to postulate a mechanism whereby FSH could alter hepatic IGF-I output because FSH does not increase circulating testosterone levels and FSH and inhibin do not have receptors in the liver. An alternative possibility is that gonadotrophin stimulation may increase the testicular contribution to circulating IGF-I, although the gonadal IGF-I output is usually negligible (40). The failure of GH and IGF-I to augment the testosterone response to hCG contrasts with in vitro studies demonstrating IGF-I stimulation of basal and hCG-stimulated testosterone production by cultured Leydig cells (1). Similarly, the inability of rhGH and rhIGF-I to alter FSH-induced inhibin secretion is consistent with a previous in vitro study in rat Sertoli cells (41) but not in granulosa cell cultures (42). Our negative results suggest, however, that, in contrast to the paracrine effects of GH and IGF-I, circulating GH and IGF-I have negligible effects on testicular hormone output compared to gonadotrophins.

The present findings provide a more systematic experimental basis on which to evaluate claims of a potential role of GH and/or IGF-I in the treatment of male hypogonadotropic states (14, 15). One recent study reported increased sperm density and serum testosterone in gonadotrophin-deficient men who had rhGH treatment added to continuing gonadotrophin regimes (14). The lack of concurrent non-GH-treated controls makes it impossible to exclude the alternative explanation that the observed effect was due to continued gonadotrophin treatment, which has characteristically slow effects (43), rather than to GH administration. Another study demonstrated a modest reduction in hCG-stimulated testosterone secretion following cessation of rhGH therapy in four males with multiple pituitary hormone deficiency (15). The limited sample size and lack of appropriate controls hampers the interpretation of findings from both studies.

We conclude that the failure of exogenous rhGH or rhIGF-I treatment to augment gonadotrophin effects on testicular hormonal secretion in vivo suggests that such treatments may not be beneficial in hypogonadotropic non-GH-deficient boys with delayed puberty or post-pubertal hypogonadotrophic hypogonadism. The non-human primates and the efficient experimental design used in this study represent a valuable non-human primate paradigm in which to test for drug effects where human studies are constrained by ethical and pragmatic difficulties and lower species do not model adequately human physiology.

Acknowledgments. This study is dedicated to the memory of Professor Andrew Phippard, a colleague and friend, whose generous vision made the baboon colony possible and whose premature death is a deep loss. The authors gratefully acknowledge the technical assistance of Julie Simpson and Jennifer Spaliviero and the help of Dr Adrian Gillin. The efforts of Ms S Hammond, RN, Clinical Research Associate, in facilitating the study and the support of Pharmacia (Australia) Pty Ltd. also are gratefully acknowledged.

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