Effect of growth hormone and resistance exercise on muscle growth in young men

KEVIN E. YARASHESKI, JILL A. CAMPBELL, KENNETH SMITH, MICHAEL J. RENNIE, JOHN O. HOLLOSZY, AND DENNIS M. BIER

Department of Medicine, Washington University School of Medicine, St. Louis, Missouri 63110; and Department of Anatomy and Physiology, University of Dundee, Dundee DD1 4HN, United Kingdom

Yarasheski, Kevin E., Jill A. Campbell, Kenneth Smith, Michael J. Rennie, John O. Holloszy, and Dennis M. Bier. Effect of growth hormone and resistance exercise on muscle growth in young men. Am. J. Physiol. 262 (Endocrinol. Metab. 25): E261-E267, 1992.—The purpose of this study was to determine whether growth hormone (GH) administration enhances the muscle anabolism associated with heavy-resistance exercise. Sixteen men (21–34 yr) were assigned randomly to a resistance training plus GH group (n = 7) or to a resistance training plus placebo group (n = 9). For 12 wk, both groups trained all major muscle groups in an identical fashion while receiving 40 μg recombinant human GH·kg⁻¹.·day⁻¹ or placebo. Fat-free mass (FFM) and total body water increased (P < 0.05) in both groups but more (P < 0.01) in the GH recipients. Whole body protein synthesis rate increased more (P < 0.03), and whole body protein balance was greater (P = 0.01) in the GH-treated group, but quadriceps muscle protein synthesis rate, torso and limb circumferences, and muscle strength did not increase more in the GH-treated group. In the young men studied, resistance exercise with or without GH resulted in similar increments in muscle size, strength, and muscle protein synthesis, indicating that 1) the larger increase in FFM with GH treatment was probably due to an increase in lean tissue other than skeletal muscle and 2) resistance training supplemented with GH did not further enhance muscle anabolism and function.

Recent evidence suggests that short-term growth hormone (GH) treatment acutely increases forearm amino acid uptake (12) and whole body protein synthesis (19) in normal adults. Prolonged GH treatment increases fat-free mass (FFM) in athletes (6) and elderly men (31) and increases muscle mass and strength in GH-deficient adults (7). However, the alterations in the rates of whole body protein synthesis and breakdown that produce an increase in FFM in normal adults during prolonged GH treatment are not known. Furthermore, it is not clear whether the increase in FFM is due to an increase in muscle protein.

Despite clinical observations that acromegalis have larger but not stronger muscles (25), GH administration has been used in conjunction with heavy-resistance exercise training in an effort to maximize skeletal muscle protein anabolism and strength. The protein anabolic effects of resistance exercise training are well documented (21). Besides anecdotal reports, no controlled published study has examined whether GH administration potentiates the anabolic effects of resistance exercise training.

Therefore the purpose of this double-blind placebo-controlled study was to examine whether GH supplementation enhances the anabolic response to resistance exercise training by measuring GH and exercise effects on FFM, muscle strength, the rates of whole body protein turnover, and quadriceps muscle protein synthesis.

METHODS

Eighteen healthy young [21–34 (mean 27 ± 1) yr] untrained men of normal height (177 ± 2 cm) and weight (73.7 ± 2.3 kg) were recruited for this study, which was approved by the Human Studies Review Board at Washington University School of Medicine. Informed consent was obtained after the purpose and procedures were described.

On entry, the subjects underwent a medical history, physical examination, and measures of oral glucose tolerance (OGTT), body composition, muscle strength, an overnight GH profile, and serum insulin-like growth factor I (IGF-I) levels as described below. These were followed by a 10-day controlled protein diet, at the end of which whole body and skeletal muscle protein kinetics were measured as described below.

All subjects then underwent a 12-wk heavy-resistance exercise training program consisting of moderate to high-intensity (75–90% maximum strength) low (4–8)-repetition exercise performed for 4 sets/session 5 days/wk. The weight training was done on Nautilus equipment, involved all major muscle groups, and alternated daily between lower and upper body exercises. Subjects were assigned randomly to the resistance exercise training plus placebo injection (Genentech excipient in sterile water) group (n = 9) or to a group (n = 9) that trained in an identical fashion but received an injection of 40 μg recombinant human GH·kg⁻¹.·day⁻¹ (Genentech) after each exercise session. The subcutaneous injections were given 5 days/wk in a double-blind fashion, and their administration was rotated daily among four (2 arm and 2 thigh) injection sites. Injections were administered after each exercise session to match the possible anabolic effects of GH with the enhanced muscle protein synthesis that occurs during recovery from exercise (4).

After 6 wk of treatment, the OGTT and serum IGF-I measures were repeated. After 12 wk of treatment, measures of OGTT, body composition, muscle strength, an overnight GH profile, and serum IGF-I levels were repeated. During the final 10 days of exercise and injections (weeks 11–12), the subjects consumed a controlled protein diet, and whole body and skeletal muscle protein kinetics were measured within 18–20 h of the last exercise session and 13–15 h of the last injection. One month after treatment had ended, the OGTT and serum IGF-I measures were repeated.

Overnight GH profile and serum IGF-I levels. Subjects were admitted to the General Clinical Research Center (GCRC) for an overnight GH profile (2100–1300 h), during which venous blood samples were drawn every 30 min and analyzed for serum GH by radioimmunoassay (18). The final GH profile was done immediately after the daily injection. Serum IGF-I was deter-
mined (14) in the morning after an overnight fast.

OGTT. At least 12 h after the last injection, oral glucose tolerance was measured as described by the National Diabetes Data Group (NDDG; see Ref. 27). Plasma glucose (glucose oxidase reaction) and insulin (17) concentrations were determined before and at 30, 60, 90, 120, and 180 min after ingesting 75 g glucose.

Body composition and anthropometry. Body density, fat mass, and FFM were determined by hydrodensitometry using previously described methods (1, 3, 40). Circumferential measurements of the upper arm, thigh, and chest were made (≥12 h after exercise) to estimate changes in muscle cross-sectional area.

Total body water (TBW) was determined using the dilution of deuterium oxide in body fluid. Plasma samples taken before and 2, 3, and 4 h after oral administration (250 mg $^2$H$_2$O/kg), were analysed for $^2$H$_2$O abundance using proton nuclear magnetic resonance spectroscopy, and TBW was calculated as previously described (30).

Muscle strength assessment. Muscle strength was determined from the maximum amount of weight lifted on each of the Nautilus exercise devices and as the maximum force (N·m) produced by the knee extensor and flexor muscles during maximum voluntary concentric (60°/s) and isometric contractions on a Cybex dynamometer (32).

Dietary control. A research dietitian designed a 10-day meal plan that consisted of 1.5 g protein and 130–176 kJ (31–42 kcal)·kg body wt·day$^{-1}$ and served the meals (3 daily meals and snacks) to each subject on the GCRC. The subjects were instructed to eat no other food and to eat all the food provided. Any small amount not consumed was weighed, and the daily intake record was corrected. During the training program the subjects returned to their normal eating habits, but their dietary intake was monitored by the research dietitian using 3-day records. Calculated from these records, the subjects were consuming 160±8 kJ (38±2 kcal)·kg$^{-1}$·day$^{-1}$, 1.5±0.1 g protein·kg$^{-1}$·day$^{-1}$, 15±1% calories from protein, 51±2% from carbohydrate (CHO), and 33±1% from fat, values no different from the 10-day controlled diet period and no different between the two groups. Furthermore, none of the subjects lost weight during the study.

Whole body protein turnover and fractional muscle protein synthesis rate. Whole body protein turnover was measured by two methods. First, $[^{15}$N$]$glycine was administered orally (0.5 mg $^{15}$N/kg$^{-1}$·day$^{-1}$) every 3 h during the last 60 h of each 10-day controlled protein diet period. Each individual urinary void was collected during this 60-h period, the $^{15}$N enrichment in total urinary N was determined, and the rates of whole body protein turnover, synthesis, and breakdown were calculated as previously described (37).

Second, on the morning after each 10-day period of controlled dietary protein intake, the rates of leucine turnover, oxidation, nonoxidative disposal (i.e., protein synthesis rate), and protein breakdown were measured during a 6-h constant infusion of [1-13C]leucine (1 mg·kg$^{-1}$·h$^{-1}$; see Refs. 22, 23, 33). At 30-min intervals during this test, the subjects ate a portion (1/2) of the daily breakfast and lunch meals, identical in composition to those consumed during the 10-day meal plan. In separate 6-h control experiments (data not shown), we determined that this approach resulted in constant breath $^{13}$CO$_2$, plasma [13C]leucine, and α-[13C]ketosocaproate (KIC) enrichment values.

The percutaneous muscle biopsy technique was used to remove a sample (50–100 mg) of muscle tissue from the vastus lateralis at the beginning and at the end of the [13C]leucine infusion, and the in vivo fractional incorporation rate of leucine into protein (i.e., muscle protein synthesis; %/h) was determined using plasma [13C]KIC as the precursor as previously described (26, 35).

Statistical analysis. To assess between-group differences, delta scores (final − initial) were computed for each measure and compared using Student’s t test. To determine whether changes existed within a group, the initial and final measures were compared using a paired t test. When measures were made initially, at 6 and 12 wk and 1 mo posttreatment, a two-group repeated-measures analysis of variance with Tukey’s analysis of individual comparisons was used. Means ± SE are reported.

RESULTS

During the study, two of the GH recipients developed symptoms of carpal tunnel compression and were withdrawn from the study. This occurred after only 16 injections and exercise sessions in 1 subject and after 9 wk of treatment in another. The symptoms subsided after GH administration and resistance training were discontinued, but one case required several weeks to completely resolve. Therefore the results of 16 young men (9 placebo, 7 GH treated) are reported.

GH, IGF-I, glucose, and insulin levels. The area under the serum GH curves averaged 38±6 ng·ml$^{-1}$·16 h$^{-1}$ in the placebo group before training and was unchanged (39±11 ng·ml$^{-1}$·16 h$^{-1}$) after 12 wk of training. Additionally, serum IGF-I values in the placebo group remained constant before, after 6 and 12 wk of training, and 1 mo after training, averaging 0.76±0.08, 0.72±0.10, 0.80±0.10, and 0.79±0.15 U/ml, respectively. In the GH-treated group, the area under the overnight GH curves averaged 52±10 ng·ml$^{-1}$·16 h$^{-1}$ before treatment [not significant (NS) vs. placebo] and increased (P < 0.05) to levels six times greater (250 ± 25 ng·ml$^{-1}$·16 h$^{-1}$) than in the placebo group after the last injection. Within 2.5 h after a GH injection, serum GH levels peaked at an average 29.0±1.4 ng/ml and remained >10 ng/ml for 10 h after injection. The elevated GH values were physiologically significant because the average serum IGF-I values in the GH-treated group at 6 and 12 wk of training (2.85±0.56 and 2.78±0.67 U/ml, respectively) were greater (P < 0.001) than in the placebo group but returned to initial levels (0.68±0.13 U/ml) 1 mo after treatment was discontinued.

Fasting plasma glucose and insulin levels were not affected by training or GH treatment (Figs. 1 and 2), and oral glucose tolerance remained normal (ND11G criteria) in all subjects. However, after 12 wk of training, the area under the insulin curve for the placebo group was lower (P < 0.02) than the corresponding pretraining curve. In the GH-treated group, on the other hand, the areas under the insulin curve for the placebo group was lower (P < 0.01) than the corresponding pretraining curve. In the GH-treated group, the area under the overnight GH curves averaged 52±10 ng·ml$^{-1}$·16 h$^{-1}$ before treatment [not significant (NS) vs. placebo] and increased (P < 0.01) than in the placebo group but returned to initial levels (0.68±0.13 U/ml) 1 mo after treatment was discontinued.

Body composition. Initially, the two groups did not differ significantly with respect to height (178 ± 2 vs. 175 ± 2 cm) or weight (76.0 ± 2.3 vs. 70.6 ± 3.7 kg). After 12 wk of treatment, body weight increased in both groups, but the increment in body weight was not significantly different between groups. By hydrodensitometry, FFM increased significantly in both groups, but the increment was greater (P < 0.01) in the GH-treated group (Table 1). Because FFM is principally water, TBW measured by $^2$H$_2$O dilution also increased in both groups, but, again, the increment was greater (P < 0.01) in the GH-treated group (Table 1). The ratio of the increase in
TBW to increase in FFM at the end of treatment was similar (0.9) in both groups, implying that an equal proportion of fluid was retained per kilogram FFM, but the observed ratio was slightly greater than expected (0.7–0.8; see Ref. 20). On the basis of the observed rapid body weight gain (1.90 ± 0.04 kg) during the first 10 GH injections and the subsequent weight loss (−0.61 ± 0.22 kg) over the weekends when injections were not given, it is likely that a portion of the increment in FFM in the GH group was due to fluid retention. After treatment, the fat mass in the GH group tended to be lower (P = 0.056) than before treatment, but this decrement was not greater than the small change in the placebo group.

Muscle strength improvements. In both groups, muscle strength improved on all weight-lifting exercises (P < 0.01, Table 2), and the relative percent improvement on each exercise (placebo range = 26–73% vs. GH = 33–71%) and average improvement for all exercises (placebo = 50 ± 5% vs. GH = 54 ± 5%) were identical for each group. Furthermore, although the concentric force-producing capabilities of the knee extensor and flexor muscles increased in both groups (Table 3; P < 0.05), these increases and the increments in isometric force production were not greater in the GH-treated group.

Whole body protein turnover and fractional muscle protein synthesis rate. At the completion of training, whole body protein synthesis and breakdown rates were significantly elevated (P < 0.05) in the GH-treated group (Table 4) when measured with the [15N]glycine tracer over the final 3 days of the 10-day controlled diet. The whole body protein synthesis rate increased more (P < 0.03) in the GH-treated group (0.5 ± 0.1 g protein·kg FFM⁻¹·day⁻¹) than in the placebo group (0.1 ± 0.1 g protein·kg FFM⁻¹·day⁻¹). In addition, body protein balance (calculated as the difference between synthesis and breakdown rates) increased more (P = 0.01) in the GH-treated group (0.26 ± 0.08 g protein·kg FFM⁻¹·day⁻¹) than in the placebo group (0.01 ± 0.04 g protein·kg FFM⁻¹·day⁻¹). Finally, total urinary N decreased more (P < 0.05) in the GH-treated group (−2.8 ± 0.9 mmol·kg FFM⁻¹·day⁻¹) than in the placebo group (−0.2 ± 0.4 mmol·kg FFM⁻¹·day⁻¹), providing additional support for a greater increase in protein anabolism in the GH-treated group.

Similar results were obtained from the [13C]leucine tracer experiments conducted in the postabsorptive state (Table 4). In the GH-treated group, the leucine oxidation rate decreased significantly (P < 0.05), whereas the nonoxidative leucine disposal rate (estimated protein
Table 1. Body composition and circumferences

<table>
<thead>
<tr>
<th></th>
<th>Exercise + Placebo</th>
<th>Exercise + GH</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Body wt, kg</td>
<td>76.0±2.3</td>
<td>77.4±2.1</td>
</tr>
<tr>
<td>Fat mass, kg</td>
<td>12.6±1.8</td>
<td>12.4±1.5</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>63.4±2.1</td>
<td>65.0±1.7*</td>
</tr>
<tr>
<td>Total body water, liters</td>
<td>46.7±1.5</td>
<td>48.1±1.6†</td>
</tr>
<tr>
<td>Chest, cm</td>
<td>97.7±1.9</td>
<td>100.2±2.0†</td>
</tr>
<tr>
<td>Upper arm, cm</td>
<td>34.6±0.9</td>
<td>36.1±0.8†</td>
</tr>
<tr>
<td>Thigh, cm</td>
<td>57.1±1.2</td>
<td>57.5±1.0</td>
</tr>
<tr>
<td>Midthigh, cm</td>
<td>54.0±1.0</td>
<td>54.6±0.8*</td>
</tr>
</tbody>
</table>

Values are means ± SE; * P < 0.05 vs. initial; † P < 0.01 vs. initial. ‡ Increase for growth hormone (GH)-treated group greater than (P < 0.01) increase for placebo.

Table 2. Muscle strength improvement

<table>
<thead>
<tr>
<th></th>
<th>Exercise + Placebo</th>
<th>Exercise + GH</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Delta</td>
<td>%Change</td>
</tr>
<tr>
<td>Shoulder press</td>
<td>5.3±0.5</td>
<td>53±6</td>
</tr>
<tr>
<td>Bench press</td>
<td>6.1±0.7</td>
<td>43±6</td>
</tr>
<tr>
<td>Deltoids</td>
<td>4.4±0.3</td>
<td>47±7</td>
</tr>
<tr>
<td>Bicep curl</td>
<td>4.4±0.3</td>
<td>36±3</td>
</tr>
<tr>
<td>Latissimus</td>
<td>6.5±0.4</td>
<td>58±5</td>
</tr>
<tr>
<td>Flys</td>
<td>6.5±0.4</td>
<td>73±8</td>
</tr>
<tr>
<td>Knee extension</td>
<td>9.7±0.9</td>
<td>62±10</td>
</tr>
<tr>
<td>Leg press</td>
<td>4.9±0.7</td>
<td>26±4</td>
</tr>
<tr>
<td>Knee flexion</td>
<td>4.1±0.4</td>
<td>47±8</td>
</tr>
<tr>
<td>Average</td>
<td>5.8±0.6</td>
<td>50±4.8</td>
</tr>
</tbody>
</table>

Values are means ± SE. Final strength score greater (P < 0.01) than initial for all exercises in both groups. Delta scores represent absolute increase in no. of 4.5-kg wts lifted. Average and individual delta and %change scores were not different between groups.

Discussion

These findings indicate that prolonged GH treatment, in combination with resistance exercise training, produced no greater increase in muscle strength, size, or fractional muscle protein synthesis rate than an identical exercise program without GH treatment. The GH treatment dose used in this study was two to four times the daily adult GH secretion rate (38) and induced significant elevations in serum IGF-I levels. Thus our results indicate that pharmacological doses of GH given to young men with normal GH secretory function do not enhance skeletal muscle protein accretion or muscle function more than resistance training without GH treatment.

The greater increase in FFM and whole body protein synthesis rate observed in the GH-treated group indicates that these individuals accumulated additional lean tissue. However, on the basis of the greater body water accumulation, and no greater increase in fractional muscle protein synthesis rate, muscle strength, or limb and torso circumferences, it appears unlikely that the additional lean tissue was skeletal muscle. This suggests that, with resistance exercise, muscle protein synthesis is stimulated near some limit, and the addition of another anabolic stimulus (GH) does not further enhance muscle protein synthesis, but other proteins (not activated by exercise) can increase their synthesis rates. Therefore the rationale for the use of GH (administered in the dose regimen described here) to amplify exercise-induced muscle growth, and thus enhance muscle force production, appears to have no foundation in fact.

Both amino acid tracers demonstrated that GH treatment enhanced FFM by increasing the rate of whole body protein synthesis more than the rate of whole body protein breakdown and by reducing the rate of leucine oxidation. One possible interpretation of this finding relates to the ability of GH to increase plasma FFA concentration and the rate of FFA oxidation (28), such
prolonged GH treatment studied here. Our findings are but not IGF-I levels, may differ from the effects of consistent with others (39) who observed no change in intravenous hypercaloric feeding, which elevates insulin protein, and the acute effect of a GH infusion during mRNA do not always indicate increased synthesis of the thesis is enhanced during a 6-h infusion of methionyl protein turnover, synthesis, or catabolic rates were ob-

suggested (11) that human skeletal muscle myosin syn-

are surprising because, in growing rats, GH-induced muscle growth is well established (16), and it has recently been suggested (11) that human skeletal muscle myosin synthesis is enhanced during a 6-h infusion of methionyl human GH. However, increased levels of muscle myosin mRNA do not always indicate increased synthesis of the protein, and the acute effect of a GH infusion during intravenous hypercaloric feeding, which elevates insulin but not IGF-I levels, may differ from the effects of prolonged GH treatment studied here. Our findings are consistent with others (39) who observed no change in muscle fiber diameter after 6 mo of GH treatment in GH-deficient adults. In addition, if the rate of muscle proteolysis decreased in either of the groups, this can also account for an increase in muscle protein mass. But again, since the increments in muscle strength and accre-
cision indicates that GH treatment did not result in tol-

tors (i.e., amino acids) intended to potentiate GH release from the normally functioning pituitary, even if they do result in elevations in circulating GH and IGF-I, may not be effective muscle growth enhancers. How-

One possible reason for the lack of an additional anab-

Table 4. Whole body amino acid and protein turnover

<table>
<thead>
<tr>
<th>Rate</th>
<th>Leucine Kinetics, (\mu\text{mol.kg FFM}^{-1}.\text{h}^{-1})</th>
<th>Protein Kinetics, (\text{g protein.kg FFM}^{-1}.\text{day}^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>Intake</td>
<td>89±6</td>
<td>86±6</td>
</tr>
<tr>
<td>Turnover</td>
<td>172±5</td>
<td>177±4</td>
</tr>
<tr>
<td>Oxidation</td>
<td>61.4±4.7</td>
<td>48.2±5.0†</td>
</tr>
<tr>
<td>Synthesis</td>
<td>110±5</td>
<td>128±2</td>
</tr>
<tr>
<td>Breakdown</td>
<td>83±7</td>
<td>91±6</td>
</tr>
</tbody>
</table>

Exercise + placebo

Exercise + GH

Values are means ± SE. Leucine kinetics were measured during a 6-
h constant \([^{14}\text{C}]\text{leucine infusion in postprandial condition (see METHODs). FFM, fat-free mass. Protein kinetics were measured with \([^{13}\text{N}]\text{glycine during a 60-h period while subjects consumed an isocaloric controlled protein diet (see METHODS)). Total urinary N excretion \(\times 6.26, \dagger P<0.05 \text{ vs. initial. †} P<0.01 \text{ vs. initial. ‡} P<0.05 \text{ vs. initial. ‡} P<0.01 \text{ vs. initial. §} \text{Initial — final change greater than } (P<0.05) \text{ placebo.}

that other energy substrates are displaced (29). The higher plasma glucose levels and the lower leucine oxida-
dation rate support this notion. Additionally, insulin stimulates amino acid incorporation into protein in humans when amino acid availability is sufficient (13), and thus the contribution of small increments in circulating insulin (or possibly IGF-I) in the GH-treated subjects might also have contributed to the whole body anabolic response observed. However, all the interactions of ele-

ated GH, insulin, glucos, IGF-I levels, and exercise on whole body protein turnover are not understood com-
pletely and need to be elucidated.

In the placebo group, no changes in the whole body protein turnover, synthesis, or catabolic rates were ob-
erved. Our data demonstrate, therefore, that after ad-
aptation to resistance training lean tissue accumulates at the same relative rates of protein synthesis, oxidation, and catabolism per kilogram FFM as those measured before initiation of training. It is important to note, however, that these measurements were made after 12 wk of resistance training, and it is possible that changes in body and muscle protein turnover occurred at the beginning of the training program or immediately after an exercise session that were different in magnitude and/or direction from those observed.

The similar changes in fractional muscle protein syn-
thesis rate (placebo = 38%, GH = 46%) were somewhat surprising because, in growing rats, GH-induced muscle growth is well established (16), and it has recently been suggested (11) that human skeletal muscle myosin synthesis is enhanced during a 6-h infusion of methionyl human GH. However, increased levels of muscle myosin mRNA do not always indicate increased synthesis of the protein, and the acute effect of a GH infusion during intravenous hypercaloric feeding, which elevates insulin but not IGF-I levels, may differ from the effects of prolonged GH treatment studied here. Our findings are consistent with others (39) who observed no change in

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lasting insulin resistance. Increases in glucose and insulin levels with GH treatment are consistent with previous studies (34), but the increments in the present study are somewhat lower. In agreement with others (5), resistance training with an increase in FFM reduced the insulin response to oral glucose, which implies an improvement in insulin sensitivity. The present findings suggest that resistance training may provide some protection against the insulin resistance typically associated with GH administration.

In summary, resistance exercise training with or without GH administration increases FFM and muscle size and strength. The combination of resistance training and GH administration is no more effective in increasing muscle size and strength and the rate of muscle protein synthesis than resistance training without GH. GH administration with resistance training results in a greater increase in the rate of whole body protein synthesis than resistance training without GH supplementation, but our findings suggest that the proteins synthesized are not skeletal muscle proteins. Resistance exercise training combined with chronic GH administration in an attempt to increase muscle anabolism and function was not supported.

We thank the General Clinical Research Center (GCRC) dietitians (Norma Janes, Rita Telkin, and Rebecca Blair), the GCRC nurses and staff, and the subjects for their devotion and effort. We thank Genentech, and especially Dr. Barry Sherman and Dr. Neil Gesundheit, for their support and expertise. Dr. Andre D’avignon and Dr. Jeff Kao assisted with the 3H2O analyses. Dr. Kenneth Schechtman provided statistical advice.

This project was supported by National Institutes of Health Grants AG-00078, RR-00036, RR-00954, and DK-20579 and by a grant from Genentech.

Address for reprint requests: K. E. Yarasheski, Washington Univ. School of Medicine, Metabolism Div., Box 8127, St. Louis, MO 63110.

Received 28 May 1991; accepted in final form 31 October 1991.

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