

## Growth Hormone: Metabolic Clearance Rates, Integrated Concentrations, and Production Rates in Normal Adults and the Effect of Prednisone

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### Research Article

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The mean ICGH for 22 premenopausal females on no medication was  $3.0 \pm 1.6$  ng/ml (sd) which is significantly lower ( $P < 0.005$ ) than the mean of  $6.6 \pm 2.9$  for 10 women receiving oral contraceptives and significantly higher than the means of  $1.5 \pm 0.75$  for 5 postmenopausal females ( $P < 0.05$ ) and  $1.8 \pm 1.0$  for 16 adult males ( $P < 0.01$ ) which are comparable. The mean GHPR's in mg/24 hr per  $m^2$  for the four groups are: normal females =  $0.52 \pm 0.24$  (sd), females receiving contraceptive pills =  $1.65 \pm 0.58$  ( $P < 0.005$ ), postmenopausal females =  $0.26 \pm 0.12$  ( $P < 0.025$ ), and adult males  $0.35 \pm 0.23$  ( $P < 0.025$ ).

Three untreated acromegalic patients had ICGH's of 59, 82, and 93 ng/ml and GHPR's ranging from 14.5 to 17.9 mg/24 hr.

Prednisone in a dose of 20 mg t.i.d. for 8 days significantly decreased both the ICGH and GHPR. Alternate day prednisone (60 mg in a single q.o.d. dose) resulted in less consistent inhibition of GH release which may play a role in the more normal growth seen in children receiving q.o.d. prednisone.

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# Growth Hormone: Metabolic Clearance Rates, Integrated Concentrations, and Production Rates in Normal Adults and the Effect of Prednisone

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**ABSTRACT** A constant withdrawal pump was used to determine the integrated concentration of growth hormone (ICGH) which was used in conjunction with the metabolic clearance rate (MCR) of growth hormone (GH) to calculate the GH production rates (GHPR) in normal adults, acromegalics, and normal controls receiving prednisone.

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## INTRODUCTION

Accurate determinations of the production rates of human growth hormone (HGH)<sup>1</sup> have not been possible using the previously available techniques. Urinary methods, as used for many steroids, are not applicable for growth hormone (GH) production studies because of the insignificant amount of GH excreted in urine (1). Although the constant intravenous infusion method of Tait (2) has been utilized to determine the metabolic clearance rate of GH (3-5), a truly accurate production rate cannot be calculated from the data obtained because plasma GH concentrations may fluctuate rapidly. Therefore, the mean GH concentration obtained from multiple samples collected over only a 3.5-4 hr period by Taylor, Finster, and Mintz (4) and used to determine production rate does not necessarily represent the mean GH concentration that is present in serum over a 24 hr period. The same criticism applies to the studies of MacGillivray, Frohman, and Doe (5), who drew serum samples from fasting and resting individuals every 20 min during a 6-7 hr period and utilized a mean of these samples to calculate GH production rates. In both studies the investigators could have missed the documented changes related to sleep (6), exercise (7), and eating.

Constant blood collection would obviate the problems related to obtaining multiple samples by allowing the determination of a true mean or integrated concentration of growth hormone (ICGH). McKendry (8) and Frantz and Holub (9) have described devices that accomplish

<sup>1</sup> *Abbreviations used in the paper:* GH, growth hormone; GHPR, growth hormone production rate; HGH, human growth hormone; ICGH, integrated concentration of growth hormone; MCR, metabolic clearance rate.

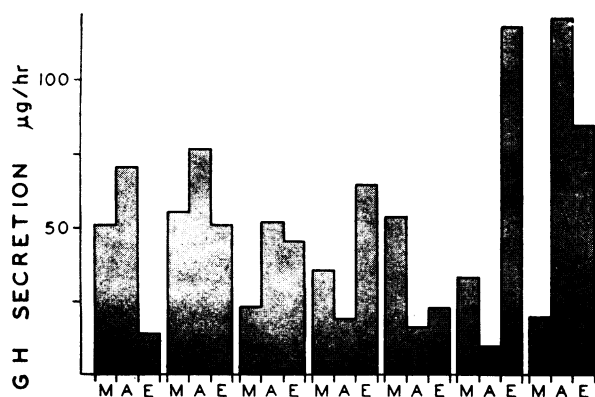


FIGURE 1 GH production in normal adults females during morning, afternoon and early evening, and night collection periods. The variation between collection periods is not constant between individuals.

such collections, but the constant withdrawal pumps proposed by them discourage ambulation and normal activity. The development of a portable constant withdrawal pump to circumvent these problems has allowed us to measure the true integrated concentrations of GH in plasma, and to calculate the true production rate of GH (GHPR) in normals (10).

This technique has been used to study the GHPR and the ICGH during 24-hr periods in normal adults, the diurnal variation of the production rate and the integrated concentration, the variation of these parameters between sexes at different ages, the GHPR and ICGH in acromegalics, and the effect of prednisone on the GHPR and the ICGH. The data obtained in these studies form the basis of this report.

## METHODS

**Patient selection.** 37 adult women between 23 and 62 yr of age and 16 adult men between 31 and 71 yr of age volunteered for the studies. 10 females were receiving oral contraceptive drugs and 5 were postmenopausal. All volunteers were in good health and were taking no medication other than oral contraceptives. The volunteers were all within  $\pm 15\%$  of ideal weight for height (11). Four acromegalic subjects between the ages of 23 and 29 were also studied.

TABLE I  
Metabolic Clearance Rates of GH in liters/day per  $m^2$   
in Normal Adults

| Subjects                            | Mean $\pm$ SD | Range   |
|-------------------------------------|---------------|---------|
| Normal females (22)*                | 190 $\pm$ 53  | 111–294 |
| Females on contraceptive pills (10) | 241 $\pm$ 57† | 174–369 |
| Postmenopausal females (5)          | 161 $\pm$ 65  | 83–280  |
| Normal males (16)                   | 216 $\pm$ 36  | 150–280 |

† Significantly different from normal females ( $P < 0.05$ ).

\* Numbers in parentheses refer to number of subjects.

**Clinical studies.** Volunteers were admitted to the Pediatric Clinical Research Unit for 36 hr. All received ad lib diets with meals being served at a constant time. Normal activity was encouraged but not controlled.

The constant withdrawal of blood was started on admission and continued for 16–24 hr. The metabolic clearance rate (MCR) of HGH- $^{125}$ I was determined on day 2 of the study, as previously described (10).

All patients received thyroidal blocking doses of SSKI (saturated solution of potassium iodide) before and after administration of HGH- $^{125}$ I.

Five adult women of menstrual age volunteered to return for repeat studies while taking prednisone. The prednisone was started 6 days before retesting in a dose of 20 mg t.i.d. and was continued during the 36 hr hospitalization. An additional five adult women returned for repeat studies while taking prednisone, 60 mg in a single dose every other day. The prednisone was started 7 days before admission and continued as a single 60 mg dose every other day during their hospitalization. The MCR of HGH- $^{125}$ I was determined on the morning of admission after the fourth dose of q.o.d. prednisone (day 7). After completion of the MCR, the constant withdrawal was initiated and continued for 48 hr which provided a 24-hr sample on the day of prednisone, and a 24-hr sample on the day when no medication was received. Immediately after the completion of the constant withdrawal, an MCR, representing a day of no medication, was determined.

The prednisone studies were not begun immediately after completion of the control study. After obtaining a menstrual history from each subject, the repeat studies were scheduled so that all studies were completed during the same portion of the menstrual cycle.

**Methods.** A Sigmamotor constant withdrawal pump (Sigmamotor, Inc., Middleport, N. Y.) was used as described in our previous report (10). Further experience with this system demonstrated the desirability of changing the collection bag every 6 hr because of the excessive hemolysis which occurred when the sample was left in the collection bag for longer periods of time.

The MCR, utilizing HGH- $^{125}$ I, was determined in each patient using the method previously described (10). GH was iodinated using the chloramine T method of Greenwood, Hunter, and Glover (12). After appropriate antibody testing and millipore sterilization, the HGH- $^{125}$ I (12–18  $\mu$ Ci) was infused using a Harvard constant infusion pump (Harvard Apparatus Co., Inc., Millis, Mass.) over a 3-hr period. Multiple samples were obtained beginning 2 hr after initiation to confirm that a plateau of immunologically reacting HGH- $^{125}$ I had been reached. The plasma concentration of immunoprecipitable HGH- $^{125}$ I in cpm/ml and the rate of infusion of immunoprecipitable HGH- $^{125}$ I in cpm/min were determined using the excess antibody system previously described (10). The MCR is calculated by dividing the rate of infusion (cpm/min) by the plasma concentration (cpm/ml) as described by Tait (2).

The MCR was previously found to vary minimally with change in posture from lying to normal walking, although standing completely still did significantly reduce the MCR (10). Simultaneous infusions of HGH and HGH- $^{125}$ I (10) in hypopituitary patients demonstrated that iodination of HGH had no effect on the MCR. Changes in endogenous levels of GH did not effect the MCR. It is, therefore, feasible to use the MCR of HGH- $^{125}$ I in conjunction with the integrated concentration of plasma GH collected over any period of

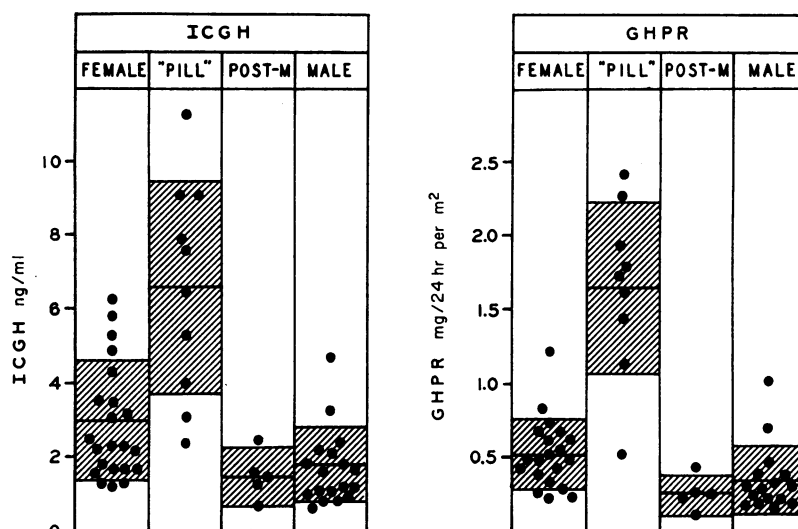


FIGURE 2 ICGH and GHPR in the four groups of normals studied: premenopausal females on no medication (females), women taking oral contraceptives (pill), postmenopausal females (post-M) and normal males. The shaded area represents mean  $\pm 1$  SD.

time to determine the actual production rate of GH for that period.

The assay for HGH was performed on the constant withdrawal samples by using the double antibody technique described by Schalch and Parker (13). All integrated concentrations (ICGH) were determined using 100, 200, and 300  $\mu$ l of serum. Triplicate determinations were used at each level permitting nine values to be calculated on each serum analyzed. The results were accepted only if the triplicate specimens at each concentration gave comparable results and a plot of the three concentrations paralleled the standard curve. The GH standard used (GH HS 1394) has growth activity of 2.0 IU/ml. This standard was used for all determinations in this report.

The production rate was calculated by multiplying the MCR in ml/min by the ICGH in ng/ml giving the production rate in ng/min. The actual amount of GH produced during each withdrawal period was then calculated by multiplying the MCR  $\times$  ICGH  $\times$  the time of the study. Correction for body surface area was made using the Scientific Tables nomogram (14).

## RESULTS

**Diurnal variation of GH production.** Multiple 6-hr integrated samples were collected during 24-hr periods. This method was used in preference to a single 24 hr sample to determine if HGH production is constant throughout the day or if a consistent diurnal variation occurs. The morning, afternoon, and night production rates, in  $\mu$ g/hr, in seven normal females are shown in Fig. 1. GHPR are not constant from one collection period to another and the variation is not consistent in magnitude or direction of change between patients.

**Integrated concentrations of GH in normal adults.** The mean 24 hr ICGH was calculated for each individual from the multiple samples obtained. These ICGH's

for normal adults are shown in Fig. 2. The mean ICGH for premenopausal females on no medication is significantly lower ( $P < 0.005$ ) than the women taking oral contraceptives and significantly higher than postmenopausal females ( $P < 0.05$ ) and normal adult males ( $P < 0.01$ ). A 32-yr old mother of two children with hypopituitarism had an ICGH of only 1.0 ng/ml compared to the range of 1.3–6.3 ng/ml for age-matched normal females. She also had GH deficiency documented by failure to respond to either arginine infusion or insulin-induced hypoglycemia.

**MCR's in normal adults.** There was marked variability in the MCR's within each group as seen in Table I. Variability of the MCR was evaluated in 11 individuals who had MCR's determined on multiple occasions. The MCR usually remained constant in each person as shown in Table II. The marked variation in D. E. is without explanation and further testing is not possible. L. D. was tested on five occasions during the menstrual cycle with values of 167, 170, and 167 liters/day per  $m^2$  at 1, 2, and 3 wk after menses while the MCR within 24 hr of the onset of menses was 262 and 217 liters/day per  $m^2$  during consecutive menstrual periods.

Variation of MCR's between individuals is marked even when calculated on the basis of surface area. This variation between individuals remained constant when individuals were retested. Four of the controls (G. M., S. G., W. L., and H. C.) had consistent MCR's in the very low or very high range.

**GH production rates in normal adults.** Normal premenopausal females on no medications had a mean GHPR of  $0.85 \pm 0.36$  mg/24 hr (SD), with a range of

TABLE II  
Variations of MCR on Repeat Determinations

| Subject | Sex | Interval after initial study | MCR<br>liters/<br>day per m <sup>2</sup> |
|---------|-----|------------------------------|------------------------------------------|
| G. M.   | F   |                              | 255                                      |
|         |     | 2 days                       | 245                                      |
|         |     | 7 months                     | 250                                      |
| S. G.   | F   |                              | 189                                      |
|         |     | 3 days                       | 123                                      |
|         |     | 4 months                     | 142                                      |
|         |     | 4 months                     | 132                                      |
| M. D.   | F   |                              | 184                                      |
|         |     | 3 days                       | 189                                      |
| D. E.   | M   |                              | 305                                      |
|         |     | 2 days                       | 180                                      |
| A. T.   | F   |                              | 218                                      |
|         |     | 2 days                       | 201                                      |
| W. L.   | M   |                              | 280                                      |
|         |     | 1 day                        | 274                                      |
| A. L.   | F   |                              | 159                                      |
|         |     | 2 days                       | 181                                      |
| H. C.   | M   |                              | 174                                      |
|         |     | 3 days                       | 150                                      |
| M. J.   | F   |                              | 230                                      |
|         |     | 18 months                    | 229                                      |
| P. M.   | F   |                              | 199                                      |
|         |     | 8 months                     | 192                                      |
| L. D.   | F   |                              | 262*                                     |
|         |     | 1 wk                         | 167                                      |
|         |     | 2 wk                         | 170                                      |
|         |     | 3 wk                         | 167                                      |
|         |     | 4 wk                         | 217*                                     |

\* 1 day after onset of menses.

0.42–1.88 mg/24 hr. The mean GHPR for women taking oral contraceptives was  $2.59 \pm 0.85$  mg/24 hr with a range of 0.83–3.68 mg/24 hr. Postmenopausal females ranged from 0.24–0.74 mg/24 hr with a mean of  $0.43 \pm 0.19$ . The GHPR in normal adult males ranged from 0.25 to 2.01 mg/day with a mean of  $0.68 \pm 0.46$ . Women taking oral contraceptives have significantly higher ( $P < 0.005$ ) production rates and postmenopausal females have significantly lower ( $P < 0.025$ ) production rates than premenopausal females who are not taking birth control pills. While men have a lower mean production rate than normal females not taking oral contraceptives, this difference is not statistically significant when the production rate is not calculated on a surface area basis.

The mean  $\pm$ SD GHPR in mg/24 hr per m<sup>2</sup> is shown for the four groups in Fig. 2. The GHPR for premenopausal females is significantly higher than postmenopausal females ( $P < 0.025$ ) and normal males ( $P < 0.025$ ) and significantly lower than women taking oral contraceptives ( $P < 0.005$ ).

*ICGH and GHPR in acromegalic patients.* The ICGH's in three untreated acromegalic patients were 59, 82, and 93 ng/ml. An additional patient (H. G.) was initially tested 2 yr after irradiation therapy and retested 15 months after transphenoidal hypophysectomy (3.5 yr after irradiation). His ICGH was 28 ng/ml before surgery and 10 ng/ml after surgery.

The GHPR in the four ranged from 14.5 to 17.9 mg/24 hr. The MCR's in the three untreated females of 108, 121, and 133 liters/day per m<sup>2</sup> were lower than in normal females who had a mean  $\pm$ SD of  $190 \pm 53$  liters/day per m<sup>2</sup> (SD).

*Effect of prednisone on ICGH, MCR, and GHPR in normal females.* Four of the five normal females who previously had GHPR determinations, and who were retested after taking prednisone 20 mg t.i.d. to evaluate the effect of prednisone on GHPR, had decreased MCR's while receiving prednisone. The four who had complete studies (including the one with an increased MCR) had both a decreased ICGH and GHPR as shown in Fig. 3. The mean ICGH of 2.5 ng/ml while receiving prednisone is significantly lower ( $P < 0.05$ ) than the mean of 5.75 for the control period. The decrease of the mean GHPR from 2.10 to 0.74 mg/24 hr is also significantly lower ( $P < 0.025$ ).

Prednisone given in a single dose every other day has less effect on GH than when given daily in divided doses, as seen in Fig. 3. The mean ICGH of 3.1 ng/ml on the day after prednisone is significantly lower than the control of 4.9 ng/ml, while the mean of 3.9 ng/ml for the day of prednisone is not statistically different. The mean GHPR's for the 3 days (control 1.45 mg/24 hr, day of medication 1.28, and day of no medication 0.70) are not statistically different.

## DISCUSSION

The development of the radioimmunoassay has allowed accurate measurement of GH in plasma. However, a method to accurately measure the 24 hr production rate under normal ambulatory conditions has not been readily available. A small constant withdrawal pump (10) which allowed normal activity was used in these studies, thus allowing determination of GHPR under physiologic conditions.

This procedure will have advantages over previously used stimulation tests for routine diagnostic testing, but, because of the complexity of the procedures and the time required, screening of large number of pa-



the sampling period was brief, and normal stimuli such as exercise and sleep were not included in Taylor's study. This difference is also true when the results of MacGillivray et al. (5) are compared to ours. These authors reported no sex-related difference in GHPR's under the conditions of their study. However, examination of their data agrees with our finding that adult men have lower GHPR's than adult women. When the four children who had increased integrated concentrations of GH are excluded from their group of males, the mean GHPR for the remaining five adult males is 0.29 mg/24 hr per m<sup>2</sup> (or 199 ng/min per m<sup>2</sup> in their designation) compared to a mean of 0.47 mg/24 hr per m<sup>2</sup> (329 ng/min per m<sup>2</sup>) for females. Their data are not in conflict with our results or with our conclusion regarding the effect of estrogen on GH.

MCR's of HGH were shown by Taylor et al. (4) to not vary in a diurnal pattern when they studied four subjects at 8:00 a.m. and 8:00 p.m. of the same day. Similar studies have not been done with longer intervals between studies. This information is necessary before the effects of medications on production rate and clearance rate can be evaluated. The MCR must remain fairly constant over long periods if meaningful data are to be accumulated on the effects of various medications on GH production. The variation of the MCR over periods of several months was insignificant in the majority, but not all, of our cases.

Variation of the MCR during the menstrual cycle could occur, since higher MCR's were seen in women receiving oral contraceptive drugs. Therefore, a normal 20-yr old female who was not taking oral contraceptives was tested on five occasions at different stages of her menstrual cycle. Her MCR was very constant (167, 170, 167 liters/day per m<sup>2</sup>) when tested at 1, 2, and 3 wk after menses (Table II). However, when tested on two occasions on the day after initiation of menses, her MCR's were 217 and 255 liters/day per m<sup>2</sup>. This elevation of the MCR at the time of menses cannot be explained by estrogen stimulation, as estrogen levels are low at this time. This series of tests, obviously, has to be repeated in additional normal females because of the implications involved. If this variation in MCR during the menstrual cycle is the normal occurrence, it will add a variable to the study of drug effects on GH production which will be difficult to control.

The variation between the four groups of normals was seen when either the integrated concentrations of the true production rate was evaluated (Fig. 2). This was true despite the wide variation in MCR's seen within each group. Therefore, the determination or MCR may not be necessary for some studies and determinations of the integrated concentrations of GH can be used alone for most studies.

The growth-inhibiting effect of corticosteroids has been well documented (23), but the mechanism of this inhibition has been in dispute. Morris, Jorgenson, and Jenkins (24) found no inhibition of insulin-induced GH release in children receiving various doses of prednisone, while others (25-27) have found suppression of GH release after insulin administration in adults receiving prednisone. A recent study showed that dexamethasone, when given to young adult males, resulted in no suppression of arginine-induced GH release but did suppress the insulin-induced GH release (28). This discrepancy between two stimulation tests (28) is a possible explanation for the previous conflicting results. The significant decrease in both the ICGH and the GHPR was demonstrated without the use of artificial stimuli, and, therefore, should represent more physiologic conditions than previous studies. There can be little doubt from our results (Fig. 3) that prednisone does significantly reduce the production of GH. It should be noted that our patients who received prednisone included women who were taking oral contraceptives which explains the control value obtained. They remained on the oral contraceptives during the prednisone portion of the test.

The use of prednisone in a single dose every 48 hr is much less growth retarding than when given in divided doses (29). The mechanism of this has been unclear. The every-other-day regimen could allow more normal GH production during part of the 48 hr period, or the inhibition to the peripheral action of GH (30) could be decreased during part of the 48 hr. Three of the five women studied before and during every-other-day prednisone therapy had little change in ICGH and no decrease of GH production on the day of prednisone (Fig. 3). The decrease in GHPR with prednisone given every other day is less consistent than when given in daily divided doses. This could play a role in the more normal growth seen in patients receiving corticosteroids every other day. It should be noted that, while both dose schedules represent definite pharmacologic doses, the total amount of prednisone received by the two groups was not equal. The possibility that there is decreased inhibition on the peripheral effect of GH when prednisone is given q.o.d. was not investigated in our study.

The integrated concentrations and the production rates of the four acromegalic patients document their clinical diagnosis. The decreased MCR seen in the three untreated patients is in agreement with the prolonged half-life of GH reported by Refetoff and Sonksen (31). The sequential tests on HG done before (ICGH = 28 ng/ml) and after surgery (ICGH = 10 ng/ml) indicate the valuable information available with this technique in the follow-up of therapy of acromegaly.

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