Effect of Growth Hormone upon Body Weight and Incidence of Bacterial Endocarditis in Rats Exposed to Hypoxia

By FRANKLIN E. ROTI, PH.D., AND C. WALTON LILLEHEI, PH.D., M.D.

Somatotropic hormone (STH) administration accelerated the rate of gain of body weight in normal rats, and effectively neutralized the inhibitory effect of hypoxia on gain in body weight. STH administration caused a nonsignificant reduction in the incidence of bacterial endocarditis. STH had no detectable effect upon the usual hypertrophy of the adrenal glands and cardiac ventricles resulting from the stressful exposure. A sex difference was noted in the weight gain response of rats receiving STH.

CHRONIC exposure of the rat to hypoxia produces damaging effects upon the heart and other organs, as well as a general failure to gain weight at a rate comparable to normal animals. Simpson, Evans and Li have shown that growth hormone (STH, somatotropic hormone) will increase the weight gain in normal animals far above that of untreated controls. However, there is controversy over the ability of STH to prevent the catabolic effects of stress when rats are exposed to cold, or injected with turpentine. Moreover, Selye has reported that STH has certain "anti-infective" properties in that it antagonized the development in the rat of bacterial lesions in various organs following overdosage with cortisone.

In an attempt to resolve some of these reported differences in the effects of the anabolic and possible "anti-infective" properties of growth hormone, this substance has been utilized in a series of studies upon experimental bacterial endocarditis produced in the rat by chronic discontinuous exposure to hypoxia together with the injection of bacteria. Observations have been made of the effects of STH on the incidence of endocarditis, on body weight responses, and on adrenal and cardiac ventricular weight alterations in rats exposed to hypoxia and given intravenous bacterial infections.

MATERIALS AND METHODS

The method employed to produce bacterial endocarditis was essentially similar to that of Highman and Alland. Forty rats of the Holtzman-Rolfs-meyer strain, 60 days of age, were divided into five groups each consisting of four males and four females and designated by Roman numerals (I to V). The mean weight of the males and females was 223 ± 8.1 Gm. and 172 ± 6.5 Gm. respectively. All animals were allowed Purina Fox Chow and tap water ad libitum. The animals subjected to hypoxia (groups II, IV, and V) were put into a decompression chamber four hours per day, seven days per week, and exposed to a simulated altitude of 25,000 to 26,000 feet (252 to 270 mm. Hg) for 30 consecutive days. The chamber temperature varied from 25 to 30 C.

After this preparatory period of 30 consecutive days, exposure to hypoxia was continued while a series of four injections of bacteria into the tail vein were made over seven days into each of the animals of the hypoxia exposed groups (II, IV, V). The animals of groups I and III (not exposed to hypoxia) likewise received the same series of injections of the same bacterial organism. Each injection consisted of 0.5 cc. of an 18-hour broth sus-
FIG. 1. Effect of STH and stress (exposure to hypoxia and bacterial injections) upon body weight gain and incidence of bacterial endocarditis.

* STH started 10 days before injection of bacteria. STH 1.0 mg. per rat per day (intramuscularly).

### Table 1: Significance of Weight Gains Between Selected Groups (Period A). Eight Rats per Experiment

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Av. gain in Wt./100 Gm. Body Wt. ±S.D.</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal</td>
<td>35 ± 7.6</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>II</td>
<td>Hypoxia</td>
<td>24 ± 4.0</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Normal</td>
<td>35 ± 7.6</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>III</td>
<td>STH*</td>
<td>44 ± 3.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>IV</td>
<td>Hypoxia + STH*</td>
<td>25 ± 6.7</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>V</td>
<td>Hypoxia + STH*</td>
<td>19 ± 3.6</td>
<td></td>
</tr>
</tbody>
</table>

* STH injections started 10 days before bacteria.

The STH* used was a partially purified, lyophilized preparation of pituitary growth hormone. It was injected intramuscularly in a dose of 1.0 mg. per rat per day in 0.1 cc. of sterile saline.

A more detailed description of the division of the rats into these five treatment groups and of the procedure periods follows. Reference may also be made to figure 1 wherein the treatment procedures are graphically depicted.

**Period A. Initial period of 30 days (before intravenous bacterial injections were started)**

Group I. Normals.
Group II. Exposed to hypoxia only.
Group III. Normals treated with STH (1.0 mg. per rat per day starting 10 days before bacterial injections).
Group IV. Exposed to hypoxia and treated with STH (1.0 mg. per rat per day starting 10 days before bacterial infections).
Group V. Exposed to hypoxia only.

**Period B. Next 12 Days (after intravenous bacterial injections were started)**

Group I. Injected with bacteria only.
Group II. Exposed to hypoxia + bacterial injections.
Group III. Treated with STH (1.0 mg. per rat per day + bacterial injections).
Group IV. Exposed to hypoxia + STH (1.0 mg. per rat per day) + bacterial injections.
Group V. Exposed to hypoxia + STH (1.0 mg. per rat per day starting coincidentally with bacterial injections) + bacterial injections.

All gains or losses in body weight for either period A or B are expressed as grams per 100 Gm. of initial body weight preceding any given procedure.

**RESULTS**

In figure 1 the division of the treatment groups and their weight responses to each of the five procedures employed in periods A and B are diagrammatically portrayed.

In table 1 the weight gains of each of the five groups in period A are compared, and a statistical analysis of the significance of the comparison of the average weight gains between selected groups is also shown.

An analysis of these data during the 30 days of the study designated as period A (figure 1 and table 1) has indicated the following observations:

TSH (Thyroid Stimulating Hormone) = On iodine depletion in the day old cockerel. 0.32 ± 0.098 activity μg/mg.
Period A

Normal animals (group I) gain more weight than those exposed to hypoxia for 30 days (group II) (P < 0.01). Animals receiving only STH (group III) gain more weight than do normals (group I). This difference appears significant (P < 0.02). Animals exposed to hypoxia for 30 days and receiving STH from the twentieth to the thirtieth day (group IV) fail to show a significant gain in weight above those exposed for 30 days to hypoxia only (group V), (P > 0.05). However, during the 10 days of STH injections (fig. 3, table 2) the animals of group IV showed a much greater weight gain than that observed in the untreated group (group V) during the equivalent time period (P < 0.01). These group IV animals also gained almost the same weight as normals during this same period (P > 0.2).

It is therefore evident that STH significantly increased the rate of weight gain of both normal and hypoxia treated animals during the 10-day period of its administration.

During the subsequent 12-day period of this study (designated period B, fig. 1) during which time bacteria were injected, the following observations were made:

Period B

From figure 1 it may be seen that both the normal and STH-treated groups (I and III) show a comparable weight loss which suggests the inability of STH to prevent the catabolic effects secondary to the injections of bacteria in the group III animals. However, the normal animals (group I) had a 13 per cent incidence of endocarditis, while the STH-treated animals (group III) had no incidence of the disease.

Group II animals subjected to both hypoxia and bacterial injections showed the greatest weight loss and the highest incidence of bacterial endocarditis (88 per cent).

However, when STH was added to the regimen of the two groups of animals exposed to hypoxia and receiving bacterial injections (groups IV and V), there was only a slight reduction in the incidence of endocarditis from that observed in the group II animals, but both groups (IV and V) showed a continued weight gain during their period of stress-exposure in

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**Table 2.—Significance of Weight Gains Between Selected Groups During the Ten Days of STH Administration (Period A). Eight Rats per Experiment**

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment</th>
<th>Av. Gain in Wt./100 Gm.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Normal</td>
<td>7.3 ± 2.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>III</td>
<td>STH</td>
<td>11.0 ± 2.8</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Normal</td>
<td>7.3 ± 2.7</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>V</td>
<td>Hypoxia</td>
<td>3.7 ± 1.9</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>Normal</td>
<td>7.3 ± 2.7</td>
<td>&gt;0.2</td>
</tr>
<tr>
<td>IV</td>
<td>Hypoxia + STH</td>
<td>8.8 ± 1.1</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>Hypoxia</td>
<td>3.7 ± 1.9</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

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Fig. 2. Effect of STH and stress (exposure to hypoxia and bacterial injections) upon the weight of the adrenal glands and heart ventricles.

* STH started 10 days before injection of bacteria. † STH started with bacteria. STH 1.0 mg. per rat per day (intramuscularly).

striking contrast to the weight loss observed in group II animals (which differed only in not having received STH). This anabolic effect of STH in bringing about a weight gain in the rats exposed to hypoxia and given bacterial injections is statistically significant.*

The slight reduction in the incidence of endocarditis observed in the STH-treated animals (group IV, 63 per cent, and group V, 57 per cent when compared with the incidence (group II 88 per cent) in the animals subjected to the same stress but without STH, was not found to be significant.

This apparent anabolic effect of STH in

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* For period B (fig. 1), comparison of body weight changes:
  - Group II and group IV ..................... P < .01
  - Group II and group V ..................... P < .01
FIG. 3. Sex difference in weight gain response to hypoxia and STH over a ten-day period (A, fig. 1).

All animals of groups III and IV received 1.0 mg. STH per day (intramuscularly). The difference between the calculated mean dose of STH per kilogram for the males and the females in each group is shown.

animals which had been exposed to hypoxia and bacteria (groups IV and V) in contrast with the absence of such an effect of STH in animals who received bacteria, but who had not been subjected to the stress of hypoxia (group III), appears somewhat paradoxical and is not understood at this time.

In figure 2 are depicted graphically the weight changes reflecting the typical hypertrophy of the cardiac ventricles and the adrenal glands which occurred when animals were exposed to hypoxic stress. There was no apparent effect on these weights attributable to the administration of STH.

It was observed that there was an apparent disparity in the rate at which the males and females gained weight within groups III and IV during period A. Therefore, the 10-day duration of STH injections was subjected to analysis as to weight gain and calculated mean dose of STH per kilogram of body weight (fig. 3 and table 2). In group III (fig. 3) it may be seen that the females received a mean dose of 4.60 ± 0.17 mg. per kilogram, and the males 3.28 ± 0.10 mg. per kilogram. This dose difference was due to the fact that the male animals were heavier on the average. In group IV the females received 4.84 ± 0.2 mg. per kilogram, and the males 4.01 ± 0.18 mg. per kilogram. Thus, in both groups III and IV the females received a larger dose of STH per unit of body weight, and in both groups the females gained more weight. This difference in growth hormone dose on a milligram per kilogram basis may or may not be sufficient to explain the observed sex difference in weight gain during this 10-day period of its administration. No comparisons were made during period B in regard to this sex difference in weight gain because the addition of bacterial injections to all the groups introduced variability in weight response, depending upon the incidence of endocarditis and the resultant severity of the valvular lesions.

DISCUSSION

It has been suggested that in animals under stress there is a "shift in anterior pituitary hormone liberation" in favor of corticotropin and at the expense of less urgently needed STH. As shown by Sayers and Sayers, there is an increased liberation of corticotropin as well as retardation of growth in rats exposed to various stresses like cold or histamine injections. In our experiment, where the stress was hypoxia and bacterial injections, both the impaired growth and adrenal hypertrophy were evident.

The question of reduced release of STH by the pituitary in animals under stress is not answered here, but if true it might be expected that administered STH would remedy the failure of animals exposed to hypoxia to gain weight normally. Because STH did cause a significantly greater weight gain in treated animals during the 10 days of its administration, we are inclined to agree with the suggestion that STH does help to counteract the catabolic effects of hypoxic stress.

Although STH did not show any dramatic "anti-infective" properties in the hypoxia-bacteria treated groups, there was evidence of a small reduction in the incidence of endocarditis (in groups IV and V) under the conditions of its use in these experiments. Also, rats who received only bacteria injections have regularly shown a small incidence of endocarditis (13 to 20 per cent). With the addition of STH to the regimen of the bacteria treated rats (group III in this experiment), there was no incidence of this disease. These observations suggest some mild antibacterial effects for STH, but the numbers and alterations involved were too small to be significant. Further investigations
of the use of STH in varying doses and for longer periods of administration should be feasible.

**Summary**

In a dose of 1.0 mg. per rat per day for 10 days, STH caused a significantly accelerated rate of growth over normal in young rats during the period of its administration.

Young rats exposed to hypoxia for four hours per day, seven days a week, exhibited a significant inhibition in their growth rate when compared with normal controls. STH administration effectively neutralized this inhibitory effect. The rate of weight gain of STH treated animals exposed to hypoxia was equal to that observed in normal controls, but was not as great as the weight gain in normal rats receiving STH.

Young rats exposed to hypoxia over a period of 42 consecutive days and receiving intravenous bacterial injections during the last 12 days of this period showed a high incidence (88 per cent) of bacterial endocarditis and a net loss in body weight. The administration of STH to these animals resulted in a nonsignificant reduction in the incidence of endocarditis and a gain in body weight.

Thus, under the conditions of these experiences, we are unable to substantiate any dramatic “anti-infective” properties for STH, but its effectiveness in counteracting the catabolic effects upon body weight of certain types of stress was demonstrated.

STH administration in the doses used did not influence the hypertrophy of the cardiac ventricles and the adrenal glands that occurred when animals were exposed chronically to hypoxia and given bacterial injections.

STH caused more weight gain in female than in male rats. This might be explained by the fact that females received slightly larger doses per gram body weight.

**REFERENCES**

6. **Ershoff, B.:** Failure of growth hormone to promote weight increment in immature rats under conditions of low environmental temperature. Endocrinology 48: 111, 1951.
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