Influence of Several Hormones on Erythropoiesis and Oxygen Consumption in the Hypophysectomized Rat

By James W. Fisher and Jerry J. Crook

Recent evidence indicates that the kidney is the primary site of formation of erythropoietin. However, other investigators have good evidence for the existence of extrarenal erythropoietic factors. We have postulated that the partial response of the bilaterally nephrectomized animal to erythropoietic stimuli such as hypoxia may be due to the discharge of several hormones which alone or in combination produce an erythropoietic effect. In this study, we have tested this postulate by determining the erythropoietic effects of several hormonal substances, some of which are known to be released during hypoxia. The hypophysectomized rat was selected as the test animal because of its known sensitivity to hormonal treatment. In an attempt to relate the ratio of tissue metabolic oxygen demand to supply with erythropoiesis, the influence of these compounds on oxygen consumption was also determined.

The hormonal substances studied were adrenocorticotropic hormone, growth hormone, thyroid stimulating hormone, 3,5,3'-triiodothyronine, angiotensin, adrenocortical extract, corticosterone, 11-dehydrocorticosterone, 17-OH corticosterone, aldosterone and testosterone.

Materials and Methods

Male rats of the Sprague Dawley strain were used in all studies, usually 10 in each assay. The procedure of Fried and co-workers was followed for the radioactive iron incorporation in RBC studies. Six-week old animals were hypophysectomized by a standard technic and two to three weeks later were used for assay. The hypophysectomized rats that were used in the adrenalectomy experiments were lightly anesthetized with ether and the adrenals removed through bilateral lumbar incisions. The animals were adrenalectomized three days prior to being used in an experiment and were maintained on 0.9 percent sodium chloride as drinking fluid throughout the test period. They were maintained on a diet consisting of milk, fresh vegetables and Rockland mouse diet ad libitum. The total dose of all test substances was injected subcutaneously, except angiotensin which was injected intravenously, in two daily injections. On the third day 1 ml. of saline containing 1 μc of Fe was given intravenously to each rat and standards were prepared for later counting. Sixteen hours later, one ml. of blood was obtained by cardiac aspiration, and the Fe incorporation into red cells was calculated according to the following formula:

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*Obtained from Hormones Assay Laboratories, Chicago, Ill.
In these experiments, the blood volume was assumed to be five per cent of the body weight. The statistical analysis was performed with the use of the technic of analysis of variance.

Total circulating red cell volume was determined with Cr$^{51}$ tagged erythrocytes. Each animal was anesthetized with ether and 0.2 ml. of a tagged red cell suspension was injected into the saphenous vein and allowed to mix for 10 minutes, at which time blood was removed via cardiac aspiration and delivered into a heparinized tube. The Cr$^{51}$ was assayed on a 1.0 ml. aliquot of this blood with the aid of a scintillation counter. Hematocrits were determined on the cardiac blood with heparinized capillary tubes.

Bovine growth hormone (Armour Lot 50109) having a potency of approximately 1.0 U.S.P. units per mg. and containing less than 0.02 U.S.P. units per mg. of TSH as a contaminant was dissolved in 0.85 per cent saline before injection. ACTH injection (Parke-Davis Corticotropin Injection solution, Lot No. 35-98-1) containing 5 mg. aminoacetic acid per 40 units and standardized in terms of U.S.P. corticotropin standard was dissolved in 0.85 per cent saline before injection. The bovine thyroid stimulating hormone (TSH) preparation (Armour Lot No. 216-174-1), having a potency of approximately 0.9 U.S.P. units per mg. and being negligibly contaminated with the remaining pituitary tropins, was dissolved in 0.85 per cent saline before injection. Each ml. of N.F. adrenocortical extract (Parke-Davis Lot No. A505) contained biological activity equivalent to that of 100 μg. of U.S.P. hydrocortisone standard, contained less than 1 per cent of solid extractive material, was substantially free of the medullary hormone (less than one part in 1,000,000) and also contained 0.8 per cent sodium chloride. 17-hydroxycorticosterone acetate (Upjohn Lot No. LT697 GL), corticosterone (Upjohn Lot No. U-0569) were suspended in 0.85 per cent sodium chloride solution before injection. D-aldosterone-21-acetate injectable (Ciba Lot No. E6409) was dissolved in sesame oil before injection. Lyophilized crystals of angiotensin (Ciba-Hypertensmn Lot No. E6286B) were dissolved in 0.85 per cent saline before injection. 3,5,3'-triiodothyronine (Smith, Kline and French Liothyronine Sodium Lot No. RM 7310) was dissolved in .01 N NaOH solution, placed in 0.85 per cent NaCl solution and pH adjusted to 9.0 before injection. An aqueous suspension of testosterone (Ayerst Labs. Lot No. 332188) with maximum impurity for lead of 0.005 per cent was dissolved in 0.85 per cent saline before injection.

The oxygen consumptions were determined by a modified Watts and Gourley procedure with a commercially available servo-activated apparatus. The oxygen consumption chamber contained a mixture of soda lime and calcium chloride as the carbon-dioxide absorbent and desiccant and was partially immersed in a water bath maintained at 37 C. After the rat was placed in the chamber, the gas cylinder of the spirometer was filled as the system was flushed with oxygen. After allowing a five-minute equilibration period, ten determinations, each of which were one minute in duration, were made with the animal resting quietly in the chamber. The mean was used for calculating ml. oxygen consumed per 100 Gm. body weight per hour. The measurements were made on each rat during the afternoon 18-24 hours prior to the Cr$^{51}$ red cell volume determination.

**RESULTS**

1. **Effects of Anterior Pituitary Hormones on the Incorporation of Fe$^{59}$**

Fe$^{59}$ incorporation in red cells was measured in hypophysectomized rats receiving saline, growth hormone (4 mg./Kg.), thyrotropic hormone (4 mg./Kg.), and [other hormones as mentioned].
Table 1.—Effects of Several Hormones and Cobalt on Radioactive Iron Incorporation in RBC of Hypophysectomized Rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total Dose* (per Kg. b.w.)</th>
<th>No. Rats</th>
<th>Body Wt. (Gm.)</th>
<th>% Fe59 Incorporated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior Pituitary Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>—</td>
<td>25</td>
<td>138 ± 4.9†</td>
<td>6.9 ± 0.51</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>4 mg.</td>
<td>17</td>
<td>151 ± 5.08</td>
<td>8.4 ± 1.27</td>
</tr>
<tr>
<td>ACTH</td>
<td>25 units</td>
<td>10</td>
<td>127 ± 2.61</td>
<td>21.9 ± 4.30§</td>
</tr>
<tr>
<td>TSH</td>
<td>4 mg.</td>
<td>10</td>
<td>118 ± 2.56</td>
<td>10.0 ± 1.12§</td>
</tr>
<tr>
<td>Adrenocortical Hormones</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenocortical extract</td>
<td>380 μg.</td>
<td>8</td>
<td>141 ± 3.70</td>
<td>12.2 ± 2.54§</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>380 μg.</td>
<td>5</td>
<td>151 ± 2.86</td>
<td>9.2 ± 1.43</td>
</tr>
<tr>
<td>Hydrocortisone acetate</td>
<td>380 μg.</td>
<td>5</td>
<td>157 ± 1.50</td>
<td>11.3 ± 1.98§</td>
</tr>
<tr>
<td>Hydrocortisone acetate</td>
<td>4000 μg.</td>
<td>10</td>
<td>118 ± 1.98</td>
<td>4.3 ± 0.46§</td>
</tr>
<tr>
<td>11-dehydrocorticosterone</td>
<td>380 μg.</td>
<td>6</td>
<td>155 ± 2.07</td>
<td>11.3 ± 0.96§</td>
</tr>
<tr>
<td>Aldosterone acetate</td>
<td>380 μg.</td>
<td>7</td>
<td>153 ± 2.67</td>
<td>6.3 ± 0.87</td>
</tr>
<tr>
<td>Thyroid Hormone, Testosterone and Cobalt</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3,5,3′-triiodothyronine</td>
<td>700 μg.</td>
<td>16</td>
<td>113 ± 1.73</td>
<td>25.0 ± 1.74§</td>
</tr>
<tr>
<td>Cobalt</td>
<td>83 μM</td>
<td>10</td>
<td>139 ± 7.02</td>
<td>42.9 ± 4.35§</td>
</tr>
<tr>
<td>Testosterone</td>
<td>2 mg.</td>
<td>5</td>
<td>166 ± 2.32</td>
<td>6.2 ± 1.07</td>
</tr>
</tbody>
</table>

*Divided into two daily injections.
†0.5 ml. adrenocortical extract per rat is equivalent to the biological activity of 380 μg./Kg. of hydrocortisone.
‡± = standard error of the mean.
§Significantly different from hypophysectomized controls at the 5 per cent level.

mg./Kg.), and ACTH (25 units/Kg.). Table 1 indicates the mean per cent radioactive iron incorporation in these four groups of rats.

Fe59 incorporation in both the ACTH and TSH treated rats was significantly greater than the saline injected controls. ACTH was the most potent of the anterior pituitary hormones assayed and these results are in accord with the findings of Van Dyke et al.12,13 Growth hormone injections resulted in a slight but not significant elevation in Fe59 incorporation.

2. Effects of Adrenocortical Steroids on the Incorporation of Fe59

The mean radioactive iron incorporations in RBC of hypophysectomized rats receiving adrenocortical extract (0.5 ml. per rat or 380 μg. hydrocortisone equivalent/Kg.), and 380 μg./Kg. respectively of corticosterone, hydrocortisone acetate, 11-dehydrocorticosterone and aldosterone acetate are given in table 1. Adrenocortical extract, hydrocortisone acetate and 11-dehydrocorticosterone injections resulted in a significant increase in Fe59 incorporation. Corticosterone injections produced a slight but not significant increase in Fe59 incorporation. Adrenocortical extract was slightly more potent than either of the adreno-
cortical steroids tested separately. A dose of 4000 μg./Kg. of hydrocortisone acetate was tested and resulted in a significant decrease in Fe^{59} incorporation in RBC. Aldosterone acetate failed to produce any change in radioactive iron incorporation in RBC.

3. Effects of Thyroid Hormone, Testosterone and Cobalt on Fe^{59} Incorporation

Radioactive iron incorporation in RBC of hypophysectomized rats receiving 3,5,3'-triiodothyronine (700 μg./Kg.), cobaltous chloride (83 μM/Kg.) and testosterone (2 mg./Kg.) are also shown in table 1. Cobalt and 3,5,3'-triiodothyronine injections resulted in significantly greater Fe^{59} incorporation than the saline treated controls and were the most potent compounds tested. Testosterone failed to produce a significant change in Fe^{59} incorporation and is in agreement with the findings of Prentice et al.5

4. Effects of Angiotensin on Fe^{59} Incorporation

The effects of angiotensin (100 μg./Kg.) on radioactive iron incorporation in RBC of hypophysectomized and hypophysectomized-adrenalectomized rats may be seen in table 2. Angiotensin produced a significant elevation (123 per cent) in Fe^{59} incorporation when injected into hypophysectomized rats. When angiotensin was injected into the hypophysectomized-adrenalectomized rat, it also produced an increase in Fe^{59} incorporation when compared with saline injected hypophysectomized-adrenalectomized controls. The baseline Fe^{59} incorporation in the hypophysectomized-adrenalectomized rats (8.0 per cent) was greater than the hypophysectomized controls (5.6 per cent). These results indicate that angiotensin stimulates erythropoiesis in the absence of the adrenals and therefore it may be concluded that the erythropoietic response to angiotensin is not entirely the result of its stimulatory action on the adrenal cortex.

5. Effects of Hormones and Cobalt on Total Circulating Red Cell Volume and Oxygen Consumption

As may be seen from table 3, hypophysectomized rats injected for 14 days with saline exhibited a significant decrease (8 per cent) in circulating RBC.
Table 3.—Influence of Several Hormones and Cobalt on Total Circulating Red Cell Volume, Oxygen Consumption and Hematocrit in Hypophysectomized Rats

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. Rats</th>
<th>Dose (per Kg./day)</th>
<th>Body Wt. (Gm.)</th>
<th>Final</th>
<th>RBC Volume$\uparrow$</th>
<th>O$_2$ Consumption (ml./100 Gm./hr.)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Initial</td>
<td>Final</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonhypophysectomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>21</td>
<td>—</td>
<td>161.4 ± 2.79t</td>
<td>186.7 ± 7.42</td>
<td>47.5 ± 0.64</td>
<td>2.44 ± .044</td>
</tr>
<tr>
<td>Hypophysectomized</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saline</td>
<td>19</td>
<td>—</td>
<td>130.8 ± 2.48t</td>
<td>128.9 ± 2.46</td>
<td>45.2 ± 1.03</td>
<td>2.13 ± .09</td>
</tr>
<tr>
<td>3,5,3'-triiodothyronine</td>
<td>6</td>
<td>350 pg.</td>
<td>134.8 ± 4.49t</td>
<td>120.7 ± 2.55</td>
<td>48.8 ± 1.89</td>
<td>3.32 ± .17t</td>
</tr>
<tr>
<td>TSH</td>
<td>16</td>
<td>2 mg.</td>
<td>121.8 ± 1.50t</td>
<td>133.9 ± 2.42</td>
<td>42.8 ± 0.55</td>
<td>2.12 ± .04</td>
</tr>
<tr>
<td>ACTH</td>
<td>12</td>
<td>5 units</td>
<td>125.6 ± 4.68</td>
<td>126.9 ± 3.71</td>
<td>50.2 ± 1.52</td>
<td>2.75 ± .009$\ddagger$</td>
</tr>
<tr>
<td>Adrenocortical extract*</td>
<td>13</td>
<td>380 pg.</td>
<td>131.7 ± 4.24t</td>
<td>131.8 ± 3.12</td>
<td>47.6 ± 0.90</td>
<td>2.47 ± .20$\ddagger$</td>
</tr>
<tr>
<td>Corticosterone</td>
<td>5</td>
<td>380 pg.</td>
<td>127.2 ± 1.74t</td>
<td>133.8 ± 2.36</td>
<td>42.2 ± 3.20</td>
<td>2.28 ± .09</td>
</tr>
<tr>
<td>Hydrocortisone acetate</td>
<td>7</td>
<td>380 pg.</td>
<td>128.0 ± 2.79t</td>
<td>117.3 ± 2.48</td>
<td>50.3 ± 1.21</td>
<td>2.42 ± .054$\ddagger$</td>
</tr>
<tr>
<td>11-dehydrocorticosterone</td>
<td>6</td>
<td>380 pg.</td>
<td>114.2 ± 4.74t</td>
<td>121.8 ± 2.96</td>
<td>45.2 ± 1.68</td>
<td>2.39 ± .15</td>
</tr>
<tr>
<td>Cobalt</td>
<td>5</td>
<td>20 M</td>
<td>136.8 ± 2.18t</td>
<td>132.2 ± 4.59</td>
<td>53.8 ± 1.53</td>
<td>3.48 ± .161</td>
</tr>
<tr>
<td>Angiotensin</td>
<td>12</td>
<td>100 pg.</td>
<td>136.8 ± 2.93t</td>
<td>128.1 ± 3.78</td>
<td>50.9 ± 2.04</td>
<td>2.57 ± .131</td>
</tr>
</tbody>
</table>

$^{*}$0.5 ml. adrenocortical extract per rat is equivalent to the biological activity of 380 pg./Kg. of hydrocortisone standard.

$\uparrow$Standard error of the mean.

$\ddagger$Significantly different from hypophysectomized controls at the 5 per cent level.

$\S$RBC volumes calculated on the basis of final body weight.

...volume, accompanied by a significant decrease (28 per cent) in oxygen consumption. Hypophysectomized rats injected daily for 14 days with 3,5,3'-triiodothyronine (350 pg.), ACTH (5 units), adrenocortical extract (0.5 ml. per rat or 380 pg. hydrocortisone equivalent per Kg.) and hydrocortisone acetate (380 pg.) induced a significant elevation in both RBC volume and oxygen consumption. Corticosterone and 11-dehydrocorticosterone produced a slight increase in RBC volume and a moderate elevation in oxygen consumption, while TSH failed to produce an elevation in RBC volume but resulted in a marked elevation in oxygen consumption.

Three hundred and fifty pg./Kg./day of 3,5,3'-triiodothyronine is quite toxic to hypophysectomized rats because four of the 10 rats injected died during the 14 days of treatment. This may account for the disproportionate rise in RBC volume as compared with the increase in oxygen consumption. Treatment with angiotensin resulted in a significant increase in RBC volume but failed to elevate oxygen consumption. On the other hand, cobalt produced the most significant increase in RBC volume of any of the compounds tested but resulted in a significant depression of oxygen consumption. The effect of the thyroid, anterior pituitary and adrenocortical hormones on erythropoiesis is apparently correlated with their effect on oxygen consumption. However, cobalt and angiotensin must exert their effects on erythropoiesis through a mechanism which does not depend upon an increase in tissue oxygen demand.

**DISCUSSION**

The present study re-affirms and extends, using additional parameters, previous descriptions of the erythropoietic effects of ACTH, thyrotropic hor-
Adrenocortical, thyroid, and cobaltous chloride in hypophysectomized rats. However, this is apparently the first report of an erythropoietic action of angiotensin. Approximately 123 per cent augmentation of Fe incorporation in RBC was found in hypophysectomized rats treated with angiotensin. The finding that angiotensin exerts an erythropoietic effect in hypophysectomized-adrenalectomized rats indicates that angiotensin is not dependent upon the adrenal cortex for its influence on erythropoiesis. Carpenter et al. found that angiotensin infusions into hypophysectomized-nephrectomized dogs resulted in the release of aldosterone and several other Porter-Silber chromagens. Our findings that adrenalectomy does not abolish the erythropoietic effect of angiotensin, that aldosterone does not stimulate erythropoiesis in the hypophysectomized rat and that angiotensin fails to stimulate oxygen consumption in hypophysectomized rats indicate that the effect of angiotensin on adrenocortical steroid release is independent of its effects on erythropoiesis. The juxtaglomerular apparatus is assumed to be the site of formation of renin, the protein which interacts with hypertensinogen to give rise to angiotensin. If this view is correct, renal ischemia produced by shock or experimental mechanical constriction of the kidney should result in an erythropoietic response. Testing this hypothesis, Mantz et al. found erythropoietic activity in blood from the renal vein after producing partial ischemia of the rat kidney.

The discharge of multiple target organ hormones has been postulated to explain the partial response of the nephrectomized animal to erythropoietic stimuli. Although none of the work included in the present study is concerned with the kidney per se, it seems quite conceivable that one or more of the hormones assayed, excluding angiotensin, may be responsible for the erythropoietic response of the nephrectomized animal exposed to hypoxia. In this regard it would be of interest to know if hypoxic stimuli alone would provoke erythropoietin release in an animal in which nephrectomy has been combined with hypophysectomy, adrenalectomy or thyroidectomy.

Cobalt has been shown previously to repair the anemia of hypophysectomy. Furthermore the increase in red cell volume was of the same magnitude as that reported for normal rats. Cobalt injections also result in a significant elevation in plasma erythropoietin titers but failed to exert a characteristic erythropoietic effect in the absence of the kidney. Our finding that cobalt depresses oxygen consumption concurrently with increasing circulating red cell volume in hypophysectomized rats may help to explain how cobalt stimulates erythropoietin production. It has been postulated that the dynamic equilibrium of the erythron is regulated by erythropoietin in circulating blood, and that the quantity of this hormone is in some way determined by the relationship of tissue oxygen supply to oxygen demand. Cobalt may belong to the class of erythropoietic stimuli which produces histotoxic hypoxia, perhaps in the kidney, and may stimulate erythropoietin production by interfering with the metabolic oxygen requirements of this end-organ. The finding that adrenocortical extract as well as some individual corticoids stimulate Fe incorporation was not unexpected in view of previous work in which the corticoids produced...
an increase in RBC volume\textsuperscript{15} and a reticulocytosis.\textsuperscript{16} The erythropoietic activity of ACTH in hypophysectomized rats has been attributed by other investigators to the activity of the adrenal steroids.\textsuperscript{12} The finding that a total dose of 380 $\mu$g. of hydrocortisone produced an increase in Fe\textsuperscript{59} incorporation while the 4000 $\mu$g. dose resulted in a decrease is difficult to interpret. This inhibitory effect of high doses of hydrocortisone may be related to the finding that large doses of cortisone inhibit protein synthesis.\textsuperscript{24}

The mechanism by which the adrenocortical steroids stimulate erythropoiesis may be related to their effect on metabolic rate. Evans et al.\textsuperscript{25} have shown that ACTH increases metabolic rate in the hypophysectomized rat in the absence of the thyroid, but not in the absence of adrenals. In addition, these investigators found that hydrocortisone, injected into hypophysectomized rats, elevates the suppressed basal metabolic rate. The glucocorticoids tested in the present study produce a significant increase in oxygen consumption in the hypophysectomized rat. These steroids may produce an imbalance in the ratio of oxygen supply to demand and thus stimulate red cell formation by the same mechanism as that postulated for thyroxin.\textsuperscript{17}

At present one can only speculate concerning the nature of the erythropoietically active substances found by Gurney et al.\textsuperscript{26} in human plasma. This activity was lost after boiling the plasma and filtering the precipitate. The stimulatory effect of human plasma in the hypophysectomized, but not in the starved rat, may be due to the presence of anterior pituitary, thyroid and adrenocortical hormones. We find that the hypophysectomized rat is more sensitive to the erythropoietic effects of these hormones than the starved rat.

The primary site of action of the thyroid and adrenocortical hormones in stimulating erythropoiesis is not presently known. Cobalt apparently exerts its action through release of kidney erythropoietin.\textsuperscript{18} Utilizing recent advances in technics for maintaining the life of nephrectomized animals, it should be possible to assay the corticoids and thyroid hormones in this preparation. It is also possible that these hormones exert a direct effect on erythroid tissue unrelated to their effects on metabolic rate. In this regard it would be of interest to know if these hormones could stimulate erythroid hyperplasia when perfused through the bone marrow of in isolated hind limb.

\textbf{SUMMARY}

Adrenocorticotropic hormone (ACTH), thyroid stimulating hormone (TSH), adrenocortical extract (ACE), hydrocortisone (F), corticosterone (B), 11-dehydrocorticosterone and 3,5,3'-triiodothyronine (T-3) induced a moderate to marked erythropoietic effect in the hypophysectomized rat as indicated by an increase in both Fe\textsuperscript{59} incorporation in RBC and total circulating red cell volume. A corresponding increase in oxygen consumption was also observed. Angiotensin increased red cell volume and radioactive iron incorporation in RBC of hypophysectomized rats and stimulated Fe\textsuperscript{59} incorporation in hypophysectomized-adrenalectomized rats, but did not exert a significant effect on oxygen consumption. Cobalt injections resulted in a significant increase in red cell volume and Fe\textsuperscript{59} incorporation in RBC of hypophysectomized rats.
but produced a significant decrease in oxygen consumption. The significance of these findings is discussed.

**SUMMARIO IN INTERLINGUA**

In rattos hypophysectomisate, hormon adrenocorticotrophic, hormon thyroido-stimulante, extracto adrenocortical, hydrocortisona, corticosterona, 11-dishydrocorticosterona, e 3,5 3'-triiodothyronina induceva un moderate a marcate effecto erythropoietic que esseva indicate per un augmento in le incorporation de Fe59 in le erythrocytos e per un augmento in le volume total de circulante erythrocytos. Esseva etiam observate un correspondente augmento in le consumo de oxygeno. Angiotensina resultava in un augmento de (1) le volume de erythrocytos e (2) le incorporation de ferro radioactive in le erythrocytos de rattos hypophysectomisate e stimulava le incorporation de Fe59 in rattos hypophysectomisate e adrenalectomisate sed non exerceva un effecto significative super le consumo de oxygeno. Injectiones de cobalt resultava in un augmento significative in le volume de erythrocytos e le incorporation de Fe59 in le erythrocytos de rattos hypophysectomisate sed produceva un significative reduction in le consumo de oxygeno. Es discutite le signification de iste constatationes.

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