Studies on the Defense Mechanism of the Body and the Neurohumoral Regulation

Report IV. Further Studies on the Neurohumoral Regulation of the Adrenal Cortex

By

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In the III. report we1) have already reported that the stimulation of the N. splanchnicus caused a remarkable increase of the chemocorticoid substance in the adrenal venous blood only on the stimulated side and given our opinion in respect to the possibility that the secretory mechanism of the adrenal cortex might be regulated not only by the humoral, but also by the neural control.

In this paper we are going to report the results obtained from our further experimental studies concerning this problem.

Experimental

The Effect of the Stimulation of the N. Splanchnicus on the Chemocorticoid Content in the Adrenal Venous Blood of Hypophysectomized Dog

We extirpated pituitary glands on five dogs beforehand. The post-mortem examination revealed that the pituitary glands had been extirpated completely in two dogs and partially in three dogs (one half of the gland extirpated in two cases and one-third in one.)

From one to five days after the extirpation of the pituitary gland we stimulated the N. splanchnicus on the left side by the same method mentioned in the former III. report.

The method of extraction and determination of the chemocorticoid substance in adrenal venous blood was given also in the III. report (modified Heard-Sobel's method).

The result of this series of experiment is given in the following Table I.
TABLE I
Chemocorticoid Content in the Adrenal Vein,
Effect of N. Splanchnicus Stimulation in
Hypophysectomized Dogs
(γ per 10 cc. adrenal venous blood)

<table>
<thead>
<tr>
<th>Time (min.)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. 1.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis partially extirpated.</td>
<td></td>
<td>53</td>
<td>60</td>
<td>345</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>+292</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 2.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis partially extirpated.</td>
<td></td>
<td>138</td>
<td>147</td>
<td>180</td>
<td>288</td>
<td></td>
<td></td>
<td>+150</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 3.</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis partially extirpated.</td>
<td></td>
<td>90</td>
<td>258</td>
<td>175</td>
<td>120</td>
<td>110</td>
<td></td>
<td>+168</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 5.</td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis totally extirpated.</td>
<td></td>
<td>100</td>
<td>177</td>
<td>400</td>
<td></td>
<td></td>
<td></td>
<td>+300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exp. 5.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypophysis totally extirpated.</td>
<td></td>
<td>80</td>
<td>115</td>
<td>145</td>
<td>160</td>
<td>145</td>
<td>80</td>
<td>+80</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

As this Table I indicates, the chemocorticoid content in the adrenal venous blood on the stimulated side is remarkably increased by the splanchnic nerve stimulation, amounting to the maximum between 5–30 minutes after the end of the stimulation.

This result is quite similar with that obtained from the nonhypophysectomized cases (p. 157 in the III. report). Only there is a slight tendency that the chemocorticoid content reaches its maximum a little more slowly in the hypophysectomized dogs (compare with the table in page 157 of the III. report).

The Histological Studies of the Adrenal Cortex in the Case of the Stimulation of the N. splanchnicus

Immediately after the end of the above experiment, the adrenal glands were examined histologically by the Sudan III staining comparatively on the stimulated, non-stimulated side and also adrenal of the normal untreated animal. And marked difference was confirmed in histological features between both sides as follows, the sudanophilic lipid granules in the adrenal cortex on the stimulated side showed a remarkable change, they are clearly decreased in number in all zones, become fine granular, and thus these zones appear brightly, especially noticeably in the reticular and fascicular zones.
The so-called transitional zone between the glomerular and fascicular zones (sudanophobe zone) (Bennett\(^2\) 1939), which is regarded as the presecretory zone and appear brightly in the normal condition owing to its poor sudanophilic granules, was filled with fine lipid granules and therefore became undiscriminative.

This histological feature corresponds just to the state of the elevated function of the adrenal cortex, as has already been pointed out by Selye,\(^3\) Deane\(^4\) and other authors (Fig. 1). The sudanophilic granules in the adrenal cortex of the non-stimulated side are gross and numerous and the transitional zone was clearly visible on the contrary, suggesting rest and accumulation of the cortical activity. (Fig. 2).

Fig. 1. Adrenal cortex of the N. splanchnicus-stimulated side. Sudan III ×50 (dog)

In comparison with the untreated normal dog, the histological features of the adrenal cortex on the non-stimulated control side of the experimented dog showed a small difference: the most outside layer, the zona glomerulosa, of the non-stimulated as well as of the stimulated side contained lipid granules relatively abundantly as compared with that layer of the untreated normal dog.

We also examined the adrenal cortex histologically in the rabbit whose one side splanchnic nerve had been sectioned thirty days previously. In this case the lipid granules of the cortical layers on the sectioned side
Fig. 2. Adrenal cortex of the non-stimulated control side. Sudan III staining ×50 (dog)

Fig. 3. Adrenal cortex of the N. splanchnicus sectioned side. Sudan III staining ×50 (rabbit)

showed features just as the type of rest and accumulation as compared with the control side, suggesting the reduced secretory activity of the cortical hormones. (Figs. 3 and 4).

In the previous report (III. report) we have published that the stimulation of the N. splanchnicus caused a remarkable increase of the
chemocorticoid substance in the adrenal vein blood on the stimulated side, and suggested that there might be some neural or neurohumoral control in respect to the secretory mechanism of the adrenal cortex, besides well known humoral control through the anterior pituitary gland. The above experimental results give a further important knowledge, indicating that the increased chemocorticoid substance in the adrenal venous blood confirmed in the time of stimulation of the N. splanchnicus might be evoked without the existence of the pituitary gland. In this paper we could confirm furthermore the histological appearance of the adrenal cortex after the stimulation of the N. splanchnicus suggesting the increased activity of cells in the cortical layers, just corresponding to the increase of the chemocorticoid substance in the adrenal venous blood.

On the Influence of the Epinephrine-injection upon the Chemocorticoid Substance in the Adrenal Venous Blood

In this set of experiments the influence of the intravenous injection of epinephrine on the chemocorticoid output in the adrenal venous blood was studied on the normal as well as on the hypophysectomized dogs.

A. Experiments on the normal dogs

0.35-0.5 cc. of 0.1% epinephrine-solution was injected into the femoral vein at one time and the chemocorticoid in the adrenal venous blood was estimated several times between 5 and 60 minutes after the injection.

The result is given in the Table II.

As the Table shows, the chemocorticoid content was increased from 585 γ/10 cc. blood to 933 γ in forty-five minutes (No. 1), from 200 γ
TABLE II

Chemocorticoid Content in the Left Adrenal Vein in Dogs.
Effect of Intravenous Injection of Epinephrine
(γ per 10 cc. blood)

<table>
<thead>
<tr>
<th>Exp. No.</th>
<th>Method of Injection</th>
<th>Time (min.)</th>
<th>0</th>
<th>5</th>
<th>10</th>
<th>15</th>
<th>20</th>
<th>30</th>
<th>40</th>
<th>45</th>
<th>60</th>
<th>Rate of Increase</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.5 cc. 0.1% Epineph. intrav.</td>
<td>585 500 550 535 933 617</td>
<td>1.6 times (+348)</td>
<td>1.0 times (+24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.</td>
<td></td>
<td>564 456 468 588 468</td>
<td>1.9 times (+173)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.</td>
<td>0.3 cc. &quot;</td>
<td>200 373 213 350 320</td>
<td>2.5 times (+282)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.</td>
<td>0.2 cc. infusion (in 100 cc. of phys. saline)</td>
<td>130 320</td>
<td>2.5 times (+282)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.</td>
<td>0.5 cc. infusion (in 200 cc. of Ringer solut.)</td>
<td>250 392 541 350 625</td>
<td>2.3 times (+583)</td>
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<tr>
<td>6.</td>
<td>ACTH 10 mg. infusion (in 200 cc. of phys. saline)</td>
<td>467 733 300 1050</td>
<td>1.0 times (+0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control-Experiment</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>Spalon 2 mg. intraven.</td>
<td>564 486 486 564</td>
<td>1.0 times (+0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.</td>
<td>Spalon 4 mg. intraven.</td>
<td>317 233 300 283</td>
<td>0.9 times (+0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9.</td>
<td>Physiol. saline solut. 0.3cc. (directly in 1. adrenal cortex)</td>
<td>242 233 250</td>
<td>1.0 times (+8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The chemocorticoid substance was not increased (from 564 γ to 588 γ) in No. 2, in which the blood flow coming from the direction of the diaphragm had not been checked by venous ligation exceptionally; the result is presumably due to the fact that the blood from the adrenals may be diluted by far greater amount of blood flow running down from the direction of the diaphragm.

In the No. 4 and No. 5 cases, the epinephrine (0.2–0.5 cc. mixed respectively in 100 cc. and 200 cc. of the physiologic saline solution was infused into the femoral vein for an hour.

In these cases the chemocorticoid was increased from 130 γ to 320 γ in 15 minutes (No. 4, 2.5 times) and from 250 γ to 625 γ in 60 minutes (No. 5, 2.5 times), after the epinephrine-infusion. The chemocorticoid increase through the same dose of epinephrine seems to be greater in the cases of infusion than those of rapid injection.

In the No. 7 case, the dose of 10 mg. ACTH dissolved in 200 cc. of physiologic saline solution was infused intravenously for one hour. The chemocorticoid was raised from 467 γ to 1050 γ in one hour (2.3 times). The rate of increase in the case of ACTH-infusion is almost the
same as in the cases of the epinephrine infusion contrary to our expectation.

The control experiment was performed in the No. 8, 9 and 10 cases. Namely, 2 and 4 mg. of Spalon (Neocyanocor: photosensitizing drug) in 5 and 20 cc. of distilled water was injected into the femoral vein or 0.3 cc. of physiologic saline solution was injected directly in the left adrenal cortex. The chemocorticoid content in the adrenal vein blood remained almost unchanged after the injection (from 564 γ to 564 γ and from 317 γ to 300 γ, and from 242 γ to 250 γ).

From these findings it is almost certain that the epinephrine-injection causes an increase of chemocorticoid substance in the adrenal venous blood, suggesting probably the increased hormonal secretion from the adrenal cortex.

B. Experiments on the Hypophysectomized Dogs

Epinephrine (0.3–0.5 cc. of 0.1% solution) was similarly injected on the hypophysectomized dogs between 1 and 7 days after the extirpation of the pituitary glands and the chemocorticoid substance was measured in the adrenal venous blood in these animals.

The results are given in Table III. As this Table indicates, the chemocorticoid content was increased after the epinephrine-injection, the average rate of increase amounting to 1.9 times as much as before the injection. The table shows also that the rate of increase of chemocorticoid by the epinephrine injection shows a tendency of gradual decrease, beginning from the third day after the extirpation of hypophysis. The former level of the chemocorticoid before the epinephrine injection tends also to reduce gradually from the third day after the operation, particularly, it is on the lowest level on the 7th and 8th days, suggesting that the adrenal cortex may begin to undergo atrophic change approximately from the third day after the hypophysectomy.

In the No. 8 case in Table III, the rise of the chemocorticoid was especially remarkable after the ACTH-injection (from 18 γ/10 cc. to 72 γ/10 cc.—4 times), as compared with the case of epinephrine-injection, though the former level was very low.

DISCUSSION

The humoral control over the adrenal cortex by the pituitary gland (through ACTH-liberation) has been generally accepted. Concerning the mechanism of the ACTH-liberation from the anterior pituitary glands acting on the adrenal cortex there are several theories (epinephrine theory of Long,5 peripheral-humoral mechanism of Sayers6). According to Long, an organism, confronted by stress or, mobilized epinephrine from its adrenal medulla as an emergency reaction by Cannon. Thus secreted epinephrine promotes the ACTH-release by acting on the anterior pituitary
Chemocorticoid Content in the Left Adrenal Vein in Hypophysectomized Dogs. Effect of Intravenous Injection of Epinephrine

(γ per 100 cc. blood)

| No. | Method of Injection | Days after extirpation | Time (min.) | 0  | 5  | 10 | 15 | 20 | 25 | 30 | 40 | 45 | Rate of increase
<table>
<thead>
<tr>
<th></th>
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<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>0.4 cc. 0.1% Epinephrine Intraven.</td>
<td>1</td>
<td>384</td>
<td>880</td>
<td>320</td>
<td>600</td>
<td>376</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.3 times (+496)</td>
</tr>
<tr>
<td>2.</td>
<td>0.3 cc. &quot;</td>
<td>2</td>
<td>174</td>
<td>186</td>
<td>207</td>
<td>252</td>
<td>318</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.8 times (+144)</td>
</tr>
<tr>
<td>3.</td>
<td>0.5 cc. &quot;</td>
<td>3</td>
<td>112</td>
<td>120</td>
<td>168</td>
<td>300</td>
<td>336</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.0 times (+288)</td>
</tr>
<tr>
<td>4.</td>
<td>0.3 cc. &quot;</td>
<td>3</td>
<td>300</td>
<td>414</td>
<td></td>
<td>414</td>
<td>564</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.9 times (+264)</td>
</tr>
<tr>
<td>5.</td>
<td>0.5 cc. &quot;</td>
<td>3</td>
<td>387</td>
<td>477</td>
<td></td>
<td>372</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2 times (+90)</td>
</tr>
<tr>
<td>6.</td>
<td>0.5 cc. &quot;</td>
<td>4</td>
<td>170</td>
<td>270</td>
<td>250</td>
<td>230</td>
<td>300</td>
<td>260</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7.</td>
<td>0.3 cc. &quot;</td>
<td>8</td>
<td>116</td>
<td>136</td>
<td>96</td>
<td>112</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.2 times (+20)</td>
</tr>
<tr>
<td>8.</td>
<td>ACTH 10 mg.</td>
<td>8</td>
<td>18</td>
<td>54</td>
<td>30</td>
<td>72</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0 times (+54)</td>
</tr>
</tbody>
</table>

gland by means of humoral way, which in turn causes the secretion of adrenocortical hormone. The reason of adopting epinephrine instead of ACTH in the Thorn's test bases its argument on this Long's theory.

In respect to the epinephrine action upon the ACTH-mobilization from the anterior pituitary, there have appeared already many experimental investigations (Vogt7) 1947, Paschkis8) 1950, Corcoran and Page9) 1948, Hechter10) 1949). But, we think that there have been no definite findings which gave a conclusive proof to that problem.

Vogt and Pickford11) (1951) found later that the epinephrine secretion from the isolated perfused adrenal by the blood obtained from the hypophysectomized dog still continued its cortical hormone secretion and that the adrenal venous blood of the hypophysectomized dog frequently assumed towards the adrenalectomized rats toxic properties, which disappeared when epinephrine was being infused. She had said "whether this phenomenon is the expression of a secretion of cortical hormone produced by the adrenaline cannot at present be decided. Nevertheless, it favours the view that adrenaline, besides releasing ACTH, can also act on the adrenal cortex by some other means." Speiers12) (1949) also reported that the secretion from the adrenal cortex did not entirely dis-
appear still after the hypophysectomy, and Deane and Greep\(^4\) (1946) had an opinion that the mineralo-corticoid might be secreted automatically, independently from the ACTH-control.

Vogt suggested, in respect to the mechanism of the adrenocortical hormonal secretion through the epinephrine, that the possibility of direct stimulation of the adrenal cortex through the epinephrine might exist to some extent, besides the indirect stimulation through the ACTH mobilization from the hypophysis.

Independently from Vogt, Hungerford\(^12\) (1949) found the decrease of peripheral circulating lymphocytes after the epinephrine-injection either in the normal, demedullated or hypophysectomized rat, while he could’nt observe any decrease of lymphocytes in the total adrenalectomized rat. And he pointed out the possibility that the epinephrine might have partly a direct influence without the aid of hypophysis on the adrenal cortex. Kessel\(^14\) (1936) and Crile\(^15\) (1937) had reported suggestive clinical cases: both cases of Cushing’s disease (pituitary basophil adenoma) observed in females aged 17 and 18 had improved remarkably after the section of the N. splanchnicus on both sides.

We could confirm in these series of experiments that the stimulation of the N. splanchnicus caused a remarkable increase of chemocorticoid substance in the adrenal venous blood only on the stimulated side and further made sure that this increase of the chemocorticoid through the stimulation of the splanchnic nerve could be found still in the hypophysectomized dog. We could obtain also histological findings supporting the above view.

The finding that the small amount of epinephrine injected intravenously caused an increase of chemocorticoid in the adrenal venous blood, even in the hypophysectomized animal, also offers an important contribution to this problem. It favours the view that the epinephrine or the splanchnic nerve may act on the adrenal cortex by some peripheral mechanisms, besides releasing ACTH. The detail of the secretory mechanism by the splanchnic nerve must be inquired more closely, but it may be said, at least, that the adreno-cortical secretion is regulated not exclusively through the ACTH from the anterior pituitary gland, but it is controlled directly through the N. splanchnicus or through some other peripheral mechanism. Whether the epinephrine stimulates adreno-cortical cell directly, or it acts on the cell through the excitation of the splanchnic nerve or through other ways, it is not easily decided. But, at any rate, we think it may be an undeniable fact that the secretion of the cortical hormone is regulated, besides ACTH action from the hypophysis, through some peripheral mechanism, i. e. by the direct or indirect nerve control, by the epinephrine influence, or by the co-operation of both.
There have been two great hypotheses in respect to the defense mechanism of the body against the stress, namely, the emergency function of the sympathico-adrenomedullar system of Cannon and the function of adaptation of the pituitary-adrenocortical system of Selye. As to the defense mechanism of the body, Cannon layed emphasis on the autonomic nervous system, particularly on the sympathetic system, while Selye attached importance to the hormonal system, above all, to the pituitary-adrenal system. According to Sayers, the sympathico-adrenal system of Cannon plays the role of ignition to the defense function of the organism in emergency, and the pituitary-adrenal system promotes the universal defense activity of the organism by mobilization of the hormonal system.

At any rate it is certain that the autonomic nervous system and the hormonal system work in co-operation with each other in respect to the defense activity of the body against stress.

We believe that the autonomic nervous system and the hormonal system have much more close connection than they are generally considered, and we offer a new concept through our studies, suggesting a close relation between the N. splanchnicus and the adrenocortical system, which has not been supposed hitherto generally. We propose here that the N. splanchnicus-adrenocortical system may play an important role in the defense mechanism of the body.

We want to continue our study in order to confirm in different methods whether the mobilized chemocorticoid substance in the adrenal venous blood through the stimulation of the N. splanchnicus is a real hormone substance secreted from the adrenal cortex or not. We have already demonstrated that the secreted chemocorticoid substance in the adrenal venous blood is not epinephrine itself.

These findings revealed that the theoretical basis for the interpretation of the so-called Thorn's test using epinephrine must be sceptically reexamined, because there are no reliable proof that the epinephrine promotes the secretion of ACTH from the anterior pituitary, and because we demonstrated that the epinephrine-injection resulted in the mobilization of chemocorticoid in the adrenal venous blood even in the hypophysectomized animal. On the other hand, Thorn's test using epinephrine seems to get a new theoretical basis, because it was demonstrated in our experiment that the chemocorticoid substance in the adrenal venous blood is obviously increased after the epinephrine-injection. But, the true mechanism of the transient reduction of blood eosinophils after the epinephrine-injection in the Thorn's test remains still unsolved. The role of the adrenal cortex in reducing blood eosinophils in Thorn's test is not yet settled, because it has been reported that the decrease of eosinophils after the epinephrine-injection was sometimes observed even in
the adrenalectomized persons or in Addison's disease. The diagnostic value of Thorn's test in determining the function of the pituitary adrenal system and its theoretical basis demands further investigation.

CONCLUSION

1. The stimulation of the N. splanchnicus causes a remarkable increase of chemocorticoid in the adrenal venous blood on the stimulated side and this phenomenon is similarly observed in the hypophysectomized animal.

2. The histological investigation of the adrenal cortex after the stimulation of the splanchnic nerve reveals the hyperactivity of cells in the cortical layers, just in accordance with the increased chemocorticoid in the adrenal venous blood.

3. The adrenocortical layers after the section of the splanchnic nerve show the histological features, indicating reduced secretory activity.

4. The intravenous injection or infusion of a small amount of epinephrine causes a marked increase of chemocorticoid in the adrenal venous blood and this is also observed in the hypophysectomized animal.

5. In respect to the secretory mechanism of the adrenocortical hormone, we presume there might be a direct neural control on the adrenal cortex through the N. splanchnicus or some other peripheral mechanism without the aid of the pituitary gland, besides the pure humoral control through ACTH. Namely, the fact that the chemocorticoid substance is mobilized in the hypophysectomized animal either by the stimulation of the N. splanchnicus or by the epinephrine-injection, suggests the possibility that the secretory mechanism of adrenal cortex may be under the control of the peripheral neurohumoral mechanism, besides under the ACTH through the anterior pituitary gland.

6. The theoretical basis for the so-called Thorn's test using epinephrine instead of original ACTH must be reexamined, because there is a new fact that the epinephrine injection produces an increased chemocorticoid in the adrenal venous blood in the hypophysectomized animal and that the reduction of circulating eosinophils after epinephrine-injection may occur through some other mechanism.

References

306 S. Okinaka, K. Nakao, M. Nishikawa, H. Ibayashi and C. Ishibashi

12) Speiers, et al., Endocrinology, 1949, 45, 403.