Epinephrine Discharge, Blood Sugar and Blood Pressure in Anaphylactic Shock of Dogs, Non-Anaesthetized, Non-Fastened.

By

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That the anaphylaxis is capable of considerably accelerating the epinephrine liberation in animals, provided no anaesthesia is resorted to, is readily conceivable from analogy of allied experimental conditions such as peptone poisoning,\textsuperscript{1)} excessive bleeding,\textsuperscript{2)} and it has been realized in facts in the investigations given in the following pages.

This problem was investigated by Houssay and Molinelli\textsuperscript{3)} with some positive results in dogs under chloralose, the method of the suprarenal-jugular anastomosis being employed, but the acceleration was of quite a small degree, and of no constant occurrence. When the serum was injected into the suprarenal gland of the sensitized donor dog, a slight reaction was sometimes visible in the recipient. A similar experiment was carried out by La Barre\textsuperscript{4)} who failed to find an accelerating action of the anaphylaxis upon the epinephrine secretion. The same outcome was obtained in the experiment where the suprarenal vein blood was estimated for epinephrine by means of the rabbit intestine segment method. An acceleration took place only when the asphyxiation set in.

Tournade and Hermann\textsuperscript{5)} reported some similar observation with Houssay and Molinelli.

Of the epinephrine content of the suprarenal body in the anaphylactic shock,

\textsuperscript{1)} Watanabe, Tohoku J. of Exp. Med., 1927, 9, 412; etc.
\textsuperscript{2)} Saito, Ibid., 1928, 11, 79; Saito, Kamei and Tachi, Ibid., 205.
\textsuperscript{3)} Houssay and Molinelli, C. r. Soc. Biol., 1925, 93, 1638; Am. J. of Physiol., 1926, 77, 181.
\textsuperscript{4)} La Barre, Arch. intern. de méd. exp., 1927, 3, 62 ff.
\textsuperscript{5)} Tournade and Hermann, C. r. Soc. Biol., 1927, 96, 931.
some details with the previous references may be found in a recent paper of Kanowokas.\(^6\)

Removal of the suprarenals, complete or incomplete, reduces the resistance of animals against the anaphylactic shock.\(^7\)

In order to elucidate the rôle of the augmented epinephrine discharge in the variations of the blood sugar concentration, and the arterial blood pressure simultaneously occurring in the anaphylactic shock, the latter two alternatives have been determined in the same manner as the previous, in addition to measuring the epinephrine output rate. Needless to say, no anaesthesia was used at all in the present researches. The particular region of the body was previously deafferented, as usual in this laboratory, for collecting the suprarenal vein blood without fastening, narcotizing, and opening the abdominal cavity. The epinephrine in the suprarenal vein blood was assayed against adrenaline hydrochloride solution of Sankyo Co., by means of the rabbit intestine segment method. All the other methods are fully given in our previous papers.\(^1,2,8\)

25–34 days after the second injection of serum, the serum of the same specimen was slowly introduced into the saphena vein until the blood pressure started to decrease. The femoral artery was used for connecting with a mercury manometer, and the suprarenal vein blood was utilized to determine the blood sugar concentration too.

**RESULTS.**

Dog 1, weighing 7.4 kilos, had the mean arterial blood pressure of 92 mms. Hg., the blood sugar of 0.09% and the epinephrine output rate of 0.00003 mgm. per kilo per minute.

Anaphylaxis was produced by introducing 3.4 c.c. horse serum in about two minutes into a saphena vein; it was of moderate strength. The blood pressure fell to 30 mms. Hg. in a minute after the start of serum injection. This low pressure continued for a few minutes and some recovery occurred, but at the end of one hour the pressure was

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\(^6\) Z. Kanowoka and Sh. Kanowoka, Tohoku J. of Exp. Med., 1935, 25, 249. In order to make complete the bibliography in this paper two articles may be added here: Oltbrächt and Ramult, Deut. Ztschr. f. ges. ger. Med., 1924, 3, 401 (Guinea-pigs, rabbits, dogs: The epinephrine load, determined by Comessati, was reduced by anaphylactic shock brought about slowly, but not by an acute one.); Mourigaud, Leullier and Se dallian, C. r. Soc. Biol., 1929, 100, 682 (Anaphylactic shock did not reduce the epinephrine content of suprarenals.)

\(^7\) Képinow, C. r. Soc. Biol., 1922, 87, 327 (Guinea-pigs; incomplete removal.); Flashman, J. of Infect. Dis., 1926, 38, 461 (Albino rats); Wyman, Am. J. of Physiol., 1929, 99, 586 (Coloured varieties of the albino rat.).

\(^8\) Ohguri, Ibid., 1935, 25, 437.
TABLE.
Epinephrine output, blood sugar content and blood pressure in non-anaesthetized and non-fastened dogs, during anaphylactic shock.

<table>
<thead>
<tr>
<th>Time</th>
<th>No. of specimen</th>
<th>Blood flow (c.c.)</th>
<th>Epinephrine output (mgram.)</th>
<th>Blood pressure (mm Hg)</th>
<th>Blood sugar (%)</th>
<th>Rate of heart beat (per min)</th>
<th>Frequency of respiration (per min)</th>
<th>Temperature (°C)</th>
<th>Room temperature (°C)</th>
<th>Colour of the saphena vein blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>quantity</td>
<td>duration (sec)</td>
<td>output per minute</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>of collection (sec) per animal per kilo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>quantity contained in 1 c.c.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>per animal</td>
<td>per kilo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Dog 1. 7.4 kilos 18. I. 1930.
18. I. 1930. 7.2 kilos. D_{50-59} dorsal spinal roots severed.
24. I. 1930. 7.2 kilos. 3.6 c.c. of horse serum injected subcutaneously.
25. I. 1930. 7.2 kilos. 3.6 c.c. of the same serum was injected intravenously.

10:42 a.m.-12:10 p.m. Left lumbar route preparation. Hind legs somewhat ataxic.

2:10 Right femoral artery was prepared and connected with mercury manometer.

2:45 I 2.4 30 4.8 0.65 0.00082 0.00024 0.000032 92 0.088 156 21 39.2 21 normal

2:56 II 2.5 30 5.0 0.68 0.00005 0.00020 0.00027 92 0.091 132 18 39.2 21

3:38-3:10 In about 2 minutes, 3.4 c.c. of the serum injected into the left saphena vein.

Symptoms: Pupils dilated ad maximum, complete flabbiness, urination and defecation occurred soon after the injection. Corneal reflex +. About 20 minutes after the injection, pupils recovered, the animal moved the head spontaneously. About 30 minutes after the injection, the dog seemed almost normal. The animal died the next morning.

Blood pressure and intestine tracings are given on pp. 510 & 511.

Dog 2. 7.5 kilos 6. III. 1930.
30. I. 1930. 7.0 kilos. D_{50-59} dorsal spinal roots severed.
6. II. 1930. 7.0 kilos. 3.6 c.c. of horse serum injected subcutaneously.
7. II. 1930. 3.6 c.c. of the same serum was injected intravenously.

9:50-11:0 a.m. Left lumbar route operation. Hind limbs somewhat paretic.

12:38 p.m. Mercury manometer connected with the right femoral artery.

1:11-1:15 In about 3 minutes, 10.3 c.c. of the serum injected into saphena vein.

Symptoms: Pupils dilated ad maximum, complete flabbiness, urination and defecation occurred soon after the injection. Corneal reflex +. About 20 minutes after the injection, pupils recovered, the animal moved the head spontaneously. About 30 minutes after the injection, the dog seemed almost normal. The animal died the next morning.

Blood pressure and intestine tracings are given on pp. 510 & 511.
<table>
<thead>
<tr>
<th>Time</th>
<th>No. of specimen</th>
<th>Blood flow (c.c.)</th>
<th>Epinephrine (mgram.)</th>
<th>Blood pressure (mm Hg)</th>
<th>Blood sugar (mg%)</th>
<th>Rate of heart beat (per min.)</th>
<th>Frequency of respiration (per min.)</th>
<th>Anaerobic temperature (°C)</th>
<th>Room temperature (°C)</th>
<th>Colour of the spinal fluid with blood</th>
</tr>
</thead>
<tbody>
<tr>
<td>3:15</td>
<td>XV</td>
<td>2.5</td>
<td>60</td>
<td>0.33</td>
<td>0.0001</td>
<td>0.00025</td>
<td>0.000033</td>
<td>114</td>
<td>0.086</td>
<td>180 30 38.8 18</td>
</tr>
<tr>
<td>3:16</td>
<td>XVI</td>
<td>1.2</td>
<td>30</td>
<td>2.4</td>
<td>0.32</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:30-3:45</td>
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<td>3:50</td>
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</tr>
</tbody>
</table>

**Dog 3.** 17.0 kilos 27. III. 1930.
21. II. 1930. 15.3 kilos. D_{19}-L_{3} dorsal spinal roots severed.
27. III. 1930. Subcutaneous injection of horse serum (7.6 c.c.).
28. III. 1930. Intravenous injection of the same serum (7.6 c.c.).
10:10-11:20 a.m. L. lumbar route preparation. Manometer connected with r. femoral artery.

<table>
<thead>
<tr>
<th>p.m.</th>
<th>I</th>
<th>5.0</th>
<th>50</th>
<th>6.0</th>
<th>0.35</th>
<th>0.00005</th>
<th>0.000030</th>
<th>0.00018</th>
<th>80</th>
<th>0.092</th>
<th>108 30 38.4 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:50</td>
<td>II</td>
<td>3.0</td>
<td>30</td>
<td>6.0</td>
<td>0.35</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>dark</td>
<td></td>
</tr>
<tr>
<td>1:0</td>
<td>III</td>
<td>3.4</td>
<td>30</td>
<td>6.8</td>
<td>0.40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:30</td>
<td>IV</td>
<td>2.9</td>
<td>30</td>
<td>5.8</td>
<td>0.34</td>
<td>0.00005</td>
<td>0.000029</td>
<td>0.000017</td>
<td>94</td>
<td>0.092</td>
<td>114 33 38.4 18</td>
</tr>
<tr>
<td>1:20</td>
<td>XV</td>
<td>3.2</td>
<td>30</td>
<td>4.3</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>a little</td>
<td></td>
</tr>
</tbody>
</table>

**Symptoms:** The clog was very quiet before as well as after the injection. The blood pressure did not so significantly fall after the injection and the state of the animal was not so much altered too, except a reduced heart rate. At about 30 minutes after the injection the animal seemed as quite normal.

**Dog 4.** 14.0 kilos 18. IV. 1930.
14. III. 1930. 10.2 kilos. D_{19}-L_{3} dorsal spinal roots severed.
24. III. 1930. 17.0 kilos. 8.5 c.c. of horse serum injected subcutaneously.
25. III. 1930. 8.5 c.c. of the same serum injected intravenously.
0:50-10:45 a.m. Left lumbar route preparation. Manometer connected.

<table>
<thead>
<tr>
<th>p.m.</th>
<th>I</th>
<th>5.0</th>
<th>40</th>
<th>6.0</th>
<th>0.30</th>
<th>0.00005</th>
<th>0.000025</th>
<th>0.000018</th>
<th>100</th>
<th>0.094</th>
<th>156 21 39.4 22.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:11</td>
<td>II</td>
<td>3.2</td>
<td>45</td>
<td>3.3</td>
<td>0.24</td>
<td>0.000075</td>
<td>0.000025</td>
<td>0.000018</td>
<td>100</td>
<td>0.094</td>
<td>156 21 39.4 22.5</td>
</tr>
<tr>
<td>1:25</td>
<td>III</td>
<td>2.2</td>
<td>30</td>
<td>4.4</td>
<td>0.31</td>
<td>0.00005</td>
<td>0.000022</td>
<td>0.000016</td>
<td>102</td>
<td>0.101</td>
<td>156 24 39.4 22</td>
</tr>
<tr>
<td>4:30</td>
<td>XX</td>
<td>1.2</td>
<td>30</td>
<td>2.4</td>
<td>0.14</td>
<td>0.000045</td>
<td>0.00011</td>
<td>0.00006</td>
<td>95</td>
<td>0.089</td>
<td>168 36 38.8 18</td>
</tr>
</tbody>
</table>

**Symptoms:** Respiration deep and slow after the injection, but some minutes later, it recovered. Pupils not altered. Prostration, urination and defecation. Breathing became faster during the collection VII and VIII samples. 3:00 The animal became quite normal.
Symptoms: Pupils dilated ad maximum, prostration, urination, salivation and defecation occurred after the injection. The anus relaxed. 2:02 cramp-like movements, nausea, vomiting (yellowish, brown, slimy mass). Pupils narrow. Rigidity increased on extremities. 2:07 Respiration 60 per minute, deep. Defecation several times.

Dog 5. 19.0 kilos ♀ 24. IV. 1930.
15. III. 1930. 23.5 kilos. D10-L3 dorsal spinal roots severed.
24. III. 1930. 21.7 kilos. 11 c.c. of horse serum injected subcutaneously.
25. III. 1930. 20.5 kilos. 11 c.c. of the same serum injected intravenously.

Symptoms: Pupils dilated ad maximum, prostration, urination, salivation and defecation occurred after the injection. The anus relaxed. 2:02 cramp-like movements, nausea, vomiting (yellowish, brown, slimy mass). Pupils narrow. Rigidity increased on extremities. 2:07 Respiration 60 per minute, deep. Defecation several times.

Dog 6. 18.8 kilos ♂ 1. V. 1930.
4. IV. 1930. 18.8 kilos. 9.4 c.c. of horse serum injected subcutaneously.
5. IV. 1930. 18.7 kilos. 9.4 c.c. of the same serum injected intravenously.

Symptoms: Nausea, vomiting, urination (3 times) and defecation after the injection. Respiration irregular. 2:17 Respiration stopped. 2:19 Heart beat stopped.
**Epinephrine Discharge in Anaphylactic Shock**

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood flow (c.c.)</th>
<th>Epinephrine (mgrm.)</th>
<th>Blood Pressure (mms. Hg.)</th>
<th>Blood Sugar (%)</th>
<th>Rate of Heart Beat (per min.)</th>
<th>Respiration (per min.)</th>
<th>Anal Temperature (°C)</th>
<th>Room Temperature (°C)</th>
<th>Colour of the superficial vein blood</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of specimen</td>
<td>quantity per kilo</td>
<td>output per minute</td>
<td>per animal</td>
<td>per kilo</td>
<td>per animal</td>
<td>per kilo</td>
<td>per kilo</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>duration of collection (sec)</td>
<td></td>
<td>per animal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:33-2:34</td>
<td>In 52%, 5 c.c. serum injected intravenously.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:39</td>
<td>V 0.5</td>
<td>60 0.5 0.03 0.015</td>
<td>0.0075 0.00040</td>
<td>25 0.107</td>
<td>quite</td>
<td>dark</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:40</td>
<td>VI 0.7</td>
<td>60 0.7 0.04</td>
<td>0.0069 0.00039</td>
<td>132 33 40.2 17.5</td>
<td>almost</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:46</td>
<td>VII 0.9</td>
<td>60 0.9 0.05</td>
<td>0.0090 0.00043</td>
<td>144 24 40.0 18</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:1</td>
<td>VIII 2.0</td>
<td>40 3.0 0.16</td>
<td>0.0022 0.00035</td>
<td>94 0.166</td>
<td>dark</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3:33</td>
<td>IX 1.4</td>
<td>30 4.2 0.22</td>
<td>0.0051 0.00027</td>
<td>95 0.124</td>
<td>almost</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4:11</td>
<td>XI 1.2</td>
<td>30 4.5 0.38</td>
<td>0.0040 0.00021</td>
<td>103 0.096</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:3</td>
<td>XII 1.2</td>
<td>30 4.5 0.28</td>
<td>0.0004 0.000096</td>
<td>109 0.091</td>
<td>dark</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5:40</td>
<td>XIV 1.2</td>
<td>15 4.8 0.28</td>
<td>0.0004 0.000096</td>
<td>162 23 40.7 17</td>
<td>normal</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Remarks:** Blood samples for estimation of sugar were collected also from the saphena vein. The results as follows:

- 2:01, 0.108%; 2:21, 0.133%; 2:43, 0.152%; 3:03, 0.142%; 3:36, 0.123%; 4:14, 0.098% and 5:04, 0.090%.

10 c.c. indifferent blood taken at 2:21 and 3:03 from the saphena vein. And the former was used for estimation of I and III samples, and the latter for V, VII, VIII and X. For XII and XIV, the blood, collected at 5:10 from the femoral artery, was used.

**Symptoms:** After the injection; urination, pulse feeble (22 per minute), prostration, pupils almost unaltered, defecation. The animal almost normal at 3:00.

**Dog 7.** 8.3 kilos 8. V. 1930.

30. III. 1930. 7.0 kilos. D₁₋₅ dorsal spinal roots severed.

6. III. 1930. 7.5 kilos. L lumbar route preparation for anaphylaxis experiment (Dog 2).

4. IV. 1930. 8.5 kilos. 4 c.c. of horse serum injected subcutaneously.

5. IV. 1930. 7.5 kilos. 4 c.c. of the same serum injected intravenously.

10:10-11:00 a.m. Right lumbar route preparation. Mercury manometer connected with l. carotid artery.

### Symptoms:
- Shock was very slight. The condition of the animal almost unaltered, except very slight flabbiness. 1:41 Defecation.
- * estimated on the blood samples collected from l. femoral artery.

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The table above summarizes the blood flow and epinephrine discharge in an anaphylactic shock experiment. The blood samples were collected from various sites and used for estimating sugar and other physiological parameters. The results show a significant decrease in blood pressure and a rise in blood sugar levels, indicating a marked response to the epinephrine injection. The animal's symptoms, such as urination and pulse feebleness, also reflect the anaphylactic shock response. The table highlights the importance of monitoring key physiological parameters during such experiments.
Intestine tracings (Reduced to $\frac{1}{2}$) of the Dog 1.

In all the intestine tracings, at the mark "x" atropine-Tyrode's solution, in which the rabbit intestine segment was beating rhythmically, was replaced by indifferent blood solution, and at the "numeral" by the indifferent blood solution to which a certain quantity of adrenalin-chloride of Sankyo Co. was added, or by the specimen solution. All the blood solution were prepared by diluting with 4 volumes of Tyrode's solution, and the quantity of the blood employed for one assay was 0.5 c.c.

The numeral of specimen and the quantity of adrenaline solution, which is showed in c.c. and in concentration, were added to each observation. For example, "0.1/2000" shows "0.1 c.c. of adrenaline solution with the concentration of 1/2000 mgrrn. in 1 c.c. i.e. 0.0005 mgrrn. adrenaline. To show the 1 specimen, we used the numeral "1".

In all tracings, time intervals are 30 seconds.

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Fig. 1 a. I: Almost as strong as 0.000025 mgrrn. and stronger than the indifferent blood. Weaker than 0.00005 mgrrn. (Obs. 6.)

Fig. 1 b. III: Weaker than 0.00005 mgrrn. and almost as strong as 0.000025 mgrrn. IX: Far stronger than III. A little stronger than (V×8).

Fig. 1 c. V (diluted 24 times): A little stronger than 0.00006 mgrrn. and weaker than 0.000025 mgrrn.

Fig. 1 d. V (diluted 24 times): Quite alike with, or a very little weaker than, 0.0001 mgrrn. VI (diluted 10 times): Far stronger than (V×24), and 0.00025 mgrrn.

Fig. 1 e. VI (diluted 10 times): Stronger than 0.0004 mgrrn. and weaker than 0.0007 mgrrn. Almost as strong as 0.0006 mgrrn. (VII+VIII)×3: Stronger than (VI×10).

Fig. 1 f. (VII+VIII)×6: Stronger than 0.0005 mgrrn., and weaker than 0.0007 mgrrn. (IX+X)×2: Weaker than 0.0007 mgrrn., a little stronger than 0.0004 mgrrn., and almost as strong as 0.0005 mgrrn. (Obs. 32.)

Fig. 1 g. (XI+XII)×2: Stronger than 0.0008 mgrrn. Weaker than 0.0012 mgrrn.
still somewhat low, viz. 60–70 mms. Hg. A few minutes after the injection the blood sugar concentration showed a tendency to increase, and about 15 minutes after, 0.235% was measured, which was the highest in this experiment. Then the sugar concentration decreased, but only slowly, so that a rather considerable hyperglycaemia continued for a long time.

During the anaphylaxis, the blood flow through the suprarenal capsule reduced considerably, and suddenly, from 0.5–0.7 c.c. per kilo per minute to 0.01 c.c., afterwards it showed a tendency to recover, but only partially. Meanwhile the epinephrine content of the suprarenal vein blood increased very remarkably, 0.012 mgrm. in 1 c.c. being the greatest. In consequence the epinephrine output rate increased but with a short latency. One minute after the end of the serum injection, when the arterial pressure was at its lowest, the epinephrine output rate increased insignificantly, but two minutes later a rate of 0.00065 mgrm. per kilo per minute, viz. about twenty times the preliminary rate, was obtained, and at 13–14 minutes the same rate was again recorded. Afterwards the rate diminished but slowly. In this experiment the hyperglycaemia and the hyperepinephrinaemia both of significant magnitude thus continued for a long period, and at the same time the blood pressure was far from complete recovery. In the time relation, the blood pressure fall preceded, then the acceleration of the epinephrine liberation, and lastly the increase of the blood sugar followed.

The heart rate did not alter significantly, while the respiration increased largely for a few minutes just after the injection. The body temperature remained nearly constant.

Dog 2, with body weight of 7.5 kilos on the day of the shock, had the normal values re the mean blood pressure, the blood sugar and
the epinephrine output rate (105 mms. Hg., 0.09% and 0.000037 mgrm. per kilo per minute respectively). When about 10 c.c. of the horse serum was introduced intravenously, the blood pressure began to fall; then the injection was discontinued. The shock was of a very slight degree. Neither irritation nor depression appeared; the animal looked nearly normal throughout the whole course of experiment. The blood pressure fall was also of a small scale, and of a short duration, so that the preliminary level was again recorded about ten minutes after the end of the injection. In accordance with the smallness of the blood pressure fall, the outflow rate from the lumbo-suprarenal vein decreased only a little, but the epinephrine output rate increased about five times the initial rate, by virtue of an increased concentration of epinephrine. The augmentation was only transitorily, and the blood samples collected ten minutes later showed a wholly normal rate of liberation. The blood content determined 2 minutes after the end of the injection showed a tendency of increasing, that obtained one minute later the acme (0.124%), and that taken a further ten minutes later showed still the hyperglycaemia.

The heart rate became very slow immediately after the injection, but ten minutes later it almost recovered the initial rate, and afterwards a somewhat frequent rhythm was recorded. Half an hour after the injection the Traube-Hering's wave with a rhythm of 12 a minute appeared for about twenty minutes. No abnormity was noted of the respiration and the anal temperature.

Dog 3, 17 kilos; the preliminary values: 94 mms. Hg., 0.09% and 0.000017 mgrm. per kilo per minute. On receiving 7 c.c. horse serum, the anaphylactic shock occurred; the mean pressure fell to 22 mms. Hg. at once, and the low pressure continued for about half an hour. Then the recovery went on gradually and at the end of three hours the preliminary level was completely recovered with an appearance of the Traube-Hering's wave of a rhythm of about six a minute. The respiration became deep and slow after the injection, but some minutes after, it recovered the preliminary state. Prostration, urination and defecation occurred. The shock was of a moderate strength.

A few minutes after the injection, the blood flow through the suprarenal body was as slow as 0.06 or 0.18 c.c. per kilo per minute against 0.35 c.c. before the injection, but afterwards some recovery took place. The epinephrine content of the suprarenal vein blood increased considerably during the shock. One minute after the end of the serum injection, the epinephrine liberation increased to six times the initial, and a minute later a rate of 0.00066 mgrm. per kilo per
minute was discovered, which corresponds to forty times the initial. This augmented velocity continued for at least ten minutes, and afterwards the rate decreased, but only a little, viz. 0.0003–0.0002 mgm. per kilo per minute and continued for one hour at least. Two hours after the injection the rate diminished considerably, when the blood pressure almost recovered and the animal looked normal.

The blood sugar content increased also, but the velocity with which the concentration altered was smaller than the epinephrine output rate. A minute after the end of the injection the content was wholly unaltered. One minute further later it was found already hyperglycaemic, but the acme was reached about fifty minutes after the injection, when the epinephrine output rate began to decline from its peak. One and half hours later the normal value was regained for the first time.

Twelve minutes after the injection when the blood samples (VII & VIII) indicated a largely accelerated discharge of epinephrine, viz. 0.00066 mgm. per kilo per minute, the breathing was faster and correspondingly the blood was dark. The blood taken before and after it was a little dark.

The heart rate diminished a little transitorily after the injection, and one and a half hours after it, a little accelerated rhythm was common. The respiration set in to increase half an hour after the injection, but another half hour later the acceleration disappeared. The body temperature decreased slightly for a while, beginning from half an hour and ending one and a half hours after the injection.

Dog 4, 14 kilos; the preliminary determinations gave the figures within the normal limits. The serum injection caused a severe anaphylactic shock with the lethal outcome in three hours and a quarter. The pupils dilated ad maximum, prostration, salivation, urination and defecation occurred soon after the injection; the anus relaxed. The blood pressure fell to about 20 mms. Hg. and the low pressure continued for approximately twenty minutes; and the blood flow through the suprarenal capsule underwent a great reduction, about one tenth of the preliminary rate. By virtue of a considerable increase of the epinephrine content, the epinephrine discharge accelerated to 0.00063 mgm. per kilo per minute, roughly forty times the preliminary value about twenty minutes after the injection and 4 minutes after the end of the injection it was already large, so it may be said that a rate of about 0.0006 mgm. per kilo per minute continued fifteen minutes at least. Subsequently the rate was apt to decrease as time went on, but two hours later still an increased rate was noted.

The blood sugar content reduced at once in the beginning of the
shock, as from 0.10% to 0.085%, 1 minute later 0.095% was measured, and then it tended to increase with the peak, 0.213%, about forty minutes after the injection; one hour later the hyperglycaemia had not yet disappeared. Afterwards it was replaced by the hypoglycaemic spell, followed by death. When the blood pressure fall was excessive and the epinephrine output rate reached already a remarkable height a few minutes after the injection, the blood sugar was still small, and when the peak of the hyperglycaemia appeared, the blood pressure recovered somewhat as did the epinephrine liberation rate also.

The heart rate decreased appreciably in the beginning of the shock, but afterwards it increased, while the respiration became frequent and deep about one hour after the injection. The anal temperature ascended towards the verge of death.

About half an hour after the serum injection, when the blood sugar content almost reached the peak, convulsions and vomiting occurred with narrowing of the pupils.

The blood samples taken twenty minutes after the injection and showing the great output rate, were very dark, but the next samples indicating a somewhat smaller rate were not so dark.

Dog 5, weighing 19 kilos, died of shock in a few minutes after the serum injection. Nausea, vomiting, urination and defecation occurred, the respiration was irregular and finally stopped ten minutes after the injection. No abnormalities were found in the values of the alternatives under question. The blood pressure fell instantly, and the blood flow through the suprarenal gland diminished considerably too, but the epinephrine output rate was very accelerated, being about ninety times the preliminary 6 minutes after the end of the injection. The blood was very dark, the blood sugar remained practically unaltered, and the heart rate decreased on shock.

Dog 6, weighing 18.8 kilos; on receiving the horse serum, a shock of a not severe degree occurred; the pulse became slow, viz. 22 beats a minute, and feebleness, prostration, urination, and defecation ensued. As low a pressure as 15 mms. Hg., due to shock continued for a fair while, but some complete recovery took place before half an hour had elapsed following the injection. In parallel with the low arterial pressure, the blood outflow from the cannula inserted into the lumbo-suprarenal vein diminished, and the blood samples collected during this period were very dark and contained much epinephrine, which resulted in an accelerated liberation of epinephrine, viz. 0.0004 mgm. per kilo per minute, equal to twenty times the preliminary velocity. About twenty minutes later the animal looked wholly normal, and the blood samples taken were brightly red and indicated also an accelerat-
Epinephrine Discharge in Anaphylactic Shock

ed epinephrine secretion, though a little inferior to the previous. The rate then diminished but slowly, so that two hours later an augmented secretion was still observable. The latency with which the hyperglycaemic period became manifest was also a little longer than the epinephrine discharge; 0.176% was the highest among all the samples taken, and some reduction compared with the initial was noted two hours after the injection, when the blood pressure already recovered the initial height, but the epinephrine discharge continued still somewhat abnormal.

Excepting a transitory decrease occurring at the onset of the anaphylaxis, the heart rate remained almost unchanged, and the respiration rate also. The body temperature ascended a little, 2 hours after the injection. The Traube-Hering's wave was recorded at intervals, as half an hour and one and a half hours after the injection.

Dog 7, weighing 8.3 kilos. A slight anaphylactic shock was brought about again in this small dog by injecting the horse serum very slowly. During the injection some variations occurred in the blood pressure level and the heart rate. A few minutes elapsed from the end until the onset of the blood pressure fall; the lowest level was 60 mms. Hg., and the recovery progressed somewhat slowly till the preliminary level was regained two hours after the injection. The outflow rate of the suprarenal vein blood became small for a while. Three minutes after the end of the injection the epinephrine output rate was somewhat accelerated, and a further one minute later about sixteen times the initial was estimated. These blood samples were dark. Afterwards the rate gradually diminished, and two hours after the injection quite an insignificant acceleration was witnessed only. The blood collected 3 minutes after the end of the injection, or quite shortly after the blood pressure fall, contained 0.118%, and about twenty minutes later a slightly greater content was estimated. Two hours after the injection the hyperglycaemic period passed.

The heart rate increased for a while during the anaphylaxis, the respiratory frequency temporarily increased soon after the injection, the Traube-Hering's wave appeared twenty minutes after the injection, and the body temperature ascended a little, two hours after the injection.

In summarizing the data given in the Table and described above, the present cases may be classified into three groups according to the severity of the shock symptoms.

In two experiments (Dogs 2 & 7) which were carried out on one and the same dog, the anaphylaxis was of a minor degree, and the mean arterial pressure fell to 50–60 mms. Hg. only with a quick re-
covery. The blood sugar concentration increased also slightly, the excess being 0.02–0.03%. The epinephrine output rate increased but it was small in Exp. 2 as expressed in the maximum rate 0.00017 mgrm. per kilo per minute, about five times the initial, while in Exp. 7 0.0006 mgrm. per kilo per minute, fifteen times the initial, was the maximum rate. In the latter cases, however, the acceleration was likewise only transitory.

A moderate shock was brought about in Dogs 1, 3, 4 & 6. The blood pressure fell also to 20–30 mms. Hg., and the blood sugar increased to 0.18%–0.23%. The epinephrine liberation rate reached to 0.0004–0.0007 mgrm. per kilo per minute, viz. 20–40 times the preliminary, normal value.

Dog 5 soon died on a heavy shock, the epinephrine output rate, measured 6 minutes after the end of the injection, registered at 0.0015 mgrm. per kilo per minute, about one hundred times the initial value, but until the death, which took place about ten minutes after the injection, no hyperglycaemia measured. Such a great velocity of the epinephrine discharge is obtainable in the peptone poisoning of dogs9) under similar experimental conditions as ours, and is in fact an example of the greater rate achievable in dogs, non-anaesthetized. On the whole, similar results with the peptone experiments of Watanabe9) were yielded in the present anaphylaxis experiments, as is to be reasonably expected.

Now the time relation between these alternatives will be discussed. In every case the blood pressure fall and the acceleration of the epinephrine discharge occurred definitely earlier than the onset of hyperglycaemia, and reached their peak earlier also.

There are cases in which the peak of the epinephrine output rate became manifest later than the bottom of the blood pressure, even though the interval was only one minute, as shown in Dogs 1, 3 & 7. It is almost impossible to determine this time interval from the technical point of view. If the epinephrine output rate be determinable at each moment, it might always be possible to detect the existence of the time interval between the bottom of the blood pressure and the peak of the epinephrine discharge. On an average, however, the fluctuations of the both alternatives went exactly hand in hand, as shown in Fig. 3.

The blood sample, collected 1–2 minutes after the end of the serum

injection indicated invariably an accelerated secretion of epinephrine. The haemorrhage exceeding a certain limit effects an acceleration of the epinephrine discharge, but we are not sure at present whether or not it is to be expected to see the blood pressure fall as the cause of an accelerated epinephrine discharge from the time relation between both the phenomena in the present investigations. The data of Saito on the haemorrhage hyperepinephrinaemia seemingly give us no suggestion in regard to this question, because some minutes were usually needed to draw out a sufficient quantity of blood to effect the hyperepinephrinaemia.

In several experiments the blood samples which were taken shortly after the serum injection and in fact flowed out very slowly, such as V, VI, VII & VIII of Dog 1, VII & VIII of Dog 3, VII, VIII, IX & X of Dog 4, V & VI of Dog 5, V, VI & VII of Dog 6 and V & VI of Dog 7, were very dark and found containing much epinephrine indicating an accelerating epinephrine discharge. They may be then taken as proving a view that the hyperepinephrinaemia during the anaphylaxis is nothing other than an asphyctic in nature. In the anaphylaxis experiments on dogs, La Barre noted a slight augmentation of the epinephrine discharge at a moment when asphyctic symptoms became manifest, while he generally failed otherwise to see an augmentation. But we hesitate to adhere to this view, on the grounds that it was difficult to assume an occurrence of asphyxiation from the conditions of the animal in that period. The darkness might be accounted for by the smallness of the blood flow through the suprarenal gland, and an exaggerated consumption of oxygen gas in the gland functioning vividly. The augmented effect of asphyxia upon the epinephrine discharge is wholly of the central origin.

The peak of the epinephrine discharge was noted as a rule a few minutes after the serum injection, and that of the hyperglycaemia, some three to ten minutes after the injection. In a single case of a severe anaphylaxis the output rate considerably augmented, but the animal died before the blood sugar content could increase. In most cases the epinephrine discharge rate remained still high, though slightly so, at the end of about two hours after the injection, while the blood pressure almost regained or completely recovered as did the blood sugar too. In a single case the hypoglycaemia was noted in this period.

10) La Barre (4), 65.
In order to show the time course of the fluctuation in the blood pressure, the epinephrine output, and the blood sugar content and their mutual relationship, a figure is composed from the data of four dogs (Dogs 1, 3, 4 & 6), moderately attacked by the anaphylactic shock. The average figures tell us that the blood pressure fall and the augmented epinephrine secretion precede definitely the onset of the hyperglycaemia. Further, the histographic figure of the epinephrine liberations during the anaphylactic shock is added, which may serve to acknowledge the significance of the epinephrine secretion upon the fluctuations of the blood pressure and sugar. These amounts are for only one gland, and expressed as: Before injection 0.00002 mgrm. per kilo per minute; during first 10 minutes of shock 0.00045 mgrm. per kilo per minute, next 10 minutes 0.00053 mgrm. per kilo per minute, next 20 minutes 0.00039 mgrm. per kilo per minute, next 40 minutes 0.00026 mgrm. per kilo per minute, next 40 minutes 0.00015 mgrm. per kilo per minute; and last 40 minutes 0.0001 mgrm. per kilo per minute.

That the previous investigators failed to note the accelerating epinephrine output during an anaphylactic shock or were able to detect
only a small acceleration is due, most probably, to the shortcoming of the experimental conditions in obtaining the suprarenal vein blood, as clearly shown in the paper of Watanabe re the peptone poisoning, who attempted to collect the suprarenal vein blood both with and without anaesthesia.

**Summary.**

The epinephrine secretion rate was measured in dogs, non-anaesthetized, non-fastened, non-laparotomized, during the anaphylactic shock. Epinephrine was assayed by means of the rabbit intestine segment.

As in the peptone experiments of Watanabe, the epinephrine secretion rate was copiously accelerated. In moderate shock, a rate as 0.0006 mgm. epinephrine per kilo per minute, about twenty to thirty times the preliminary normal rate, was noted a few minutes to a quarter of an hour, and when a very severe shock occasioned, a rate 0.0015 mgm. epinephrine per kilo per minute, about one hundred times the normal value, was observed. About two hours were needed until the preliminary velocity of epinephrine liberation regained.

The blood pressure fall and acceleration of the epinephrine output rate as well, precede definitely the outset of the hyperglycaemia by from one or two to some ten minutes. In a dog which died early by a very heavy shock, the hyperglycaemia could not be determined before the death, while the epinephrine output rate was very remarkably increased.

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§§) That Rogoff, with co-workers failed recently to see an accelerating epinephrine discharge in dogs during an anaphylactic shock is undoubtedly explainable by their experimental conditions, which have been amply proved here as seriously interfering with the acceleration of epinephrine discharge. Cohen, Rudolf, Wasserman and Rogoff, Am. J. of Physiol., 1933, 106, 414; J. of Allergy, 1934, 5, 221.