Effect of Muscular Exercise upon the Epinephrine Secretion from the Suprarenal Gland.§

By

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In the literature regarding the epinephrine output on muscular work there have been found two important evidences which yield considerable support to the view that muscular exercise is accompanied by an increase of the epinephrine secretion from the suprarenal glands. In 1922 Hartman and his collaborators\(^1\) reported that the pupil of cats with the superior cervical ganglion removed usually dilated larger than the control, on walking in a treadmill for a short time and that this dilation increased as the work proceeded. After extirpating both suprarensals or cutting the nervous connection with a single remaining suprarenal, this “fatigue” dilatation was greatly reduced or entirely eliminated. From this they inferred that such a phenomenon of dilatation might be due to increased discharge of epinephrine, thus agreeing with the view of the previous investigators that the activity of the suprarenal medullae has an important relation to the muscular efficiency of animals.

This work was however criticized sometimes, for the reason that the eye thus operated on could not be regarded as completely denervated, since there remained the third cranial nerve undisturbed. In a further investigation\(^2\) Hart-

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2) Hartman, McCordock and M. M. Loder, Ibid., 1923, 64, 1.
man was able to note a good dilatation of a pupil disconnected from central influence by extirpation of the superior cervical ganglion and the ciliary ganglion, during muscular work. However, unfortunately there was no further report of the event after the exclusion of the activity of the suprarenal medullae.

The view of Hartman was upheld soon afterward by Cannon and Britton. The latter investigators used as an indicator of the circulating epinephrine a lasting preparation of the cat's heart which was isolated in situ from the nervous system by section of the right vagus below the recurrent branch, by severance of all the cardiac connections of the left vagus and by removal of the upper thoracic sympathetic strands. With the suprarenal glands intact, minor movements such as extending the legs, turning the body or walking about for two minutes was followed by marked quickening of the heart beat, the average cardiac acceleration being noted as 15 beats per minute. After the glands were rendered inactive, the right gland being removed and the left denervated, such acceleration failed to occur or was small; the increase averaged only 1 beat per minute under the same experimental conditions. These findings led them to conclude that such a faster rate of the denervated heart might be due to increased activity of the suprarenal medullae.

All this testimony is based on the consideration, that since in the lasting preparation of the denervated heart the liver and the thyroid gland are denervated, the medullisuprarenal secretion alone remains to produce a faster heart rate.

However, the reaction of these denervated organs is known to be not specific for determining the increased output of epinephrine as the above writers themselves pointed out later.

In order to observe the influence of any one of the accelerators on the denervated heart, it is necessary to exclude all the others, leaving only that one; the suprarenals, thyroid, liver and all the sympathetic endings have been pointed out as such by the Boston physiologists. Some years ago the significance of the sympathetic endings was not yet known; the conditions seemed rather simple.

That the denervated eye of the cat is sensitive not only to epinephrine, but also to the rise of the temperature of blood and even to some substance probably produced outside of the suprarenal gland under certain condition is Hartman's statement. With regard to the denervated heart also, it has been recently shown that this preparation is influenced by the epinephrine-like sub-

stance, "sympathin," which is poured out from the smooth muscles as a circulating chemical mediator of the sympathetic impulses, in just such cases as when an augmented secretion of epinephrine is suggested to occur. 6)

The diminution of the epinephrine store in the suprarenal gland can not nowadays be taken as a cogent proof of the abundant output of epinephrine, but its occurrence gives rise to a doubt of an excessive secretion of epinephrine. About thirty years ago Battelli and Boatta 5) detected a considerable reduction of the epinephrine content (colorimetric) in the glands of dogs which were run until exhausted. In these animals the epinephrine store could be decreased to one third of the minimal amount which was determined in normal animals. In a single case where a travel extending ten hours did not exhaust the animals the suprarenals exhibited no change in the epinephrine store. The exhaustion of the epinephrine (enucleated eye of frog) or the disappearance of the chromaffine reaction of the suprarenal medulla was noted by Schur and Wiesel 6) in dogs subjected to prolonged exercise. The experiments of these investigators were soon afterward repeated and seriously criticized by Kahn 7). Opposed to the former investigators, Kahn failed to find, using the Meltzer-Ehrmann's method, any evidence of hyperepinephrinaemia in dogs exhausted by six to twelve hours' running. The suprarenal glands and paraganglia were rich in epinephrine and its chromaffine reaction was found to be not reduced. These results led him to suppose that the activity of the suprarenals has no special bearing on the muscular exertion. In cats subjected to vigorous exertion for four hours, Crile 8) found diminution of the epinephrine content in the suprrenal gland. Stewart and Rogoff 9) working with cats, demonstrated that after severe muscular work the epinephrine store (colorimetric) of the gland with intact innervation underwent a definite, although not a very great depletion, as compared with its denervated fellow. But no depletion was found even in considerable muscular exertion falling short of great fatigue. According to Vincent 10) the prolonged exercise at room temperature lowered the body temperature and reduced remarkably the chromaffine reaction of the suprarenals of white rats; but if they were exercised at higher temperature the body temperature increased and the reaction did not diminish. From these results the effect of muscular effort on the chromaffine reaction seems, according to him to be not direct, but secondary to the fall of the animal's temperature.

The view of the favourable influence of epinephrine secretion on the efficiency of muscle in the body has obviously been based on the evidence that adrenaline has beneficial action on the muscular con-

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7) Kahn, Pflüger's Arch., 1909, 128, 519.
9) Stewart and Rogoff, J. Pharm. Exp. Ther., 1922, 19, 87.
10) Vincent, Quart. J. Exp. Physiol., 1925, 15, 319.
tration or muscular work, although it has been confronted by the negative results reported by several authors. Is the epinephrine secreted favourable for the betterment of the performance of the organism during the muscular exertion?

Stewart and Rogoff subjected normal cats and those which survived removal of a large portion of the suprarenal tissue on each side, and those with one gland removed and with the other denervated to prolonged and repeated spells of muscular exercise and found no difference between the normal and those operated on, in resistance to, recovery from fatigue or change in body temperature, heart rate and respiratory frequency. Recently a paper published from the Cannon's laboratory showed that inactivation of the suprarenal medullae of dogs by extirpation of one and denervation or demedullation of the other did not exhibit any decrease in the capacity for prolonged muscular work. The same was noted in the experiments with suprarenal-ectomized rabbits. Cannon and his co-workers explained the little difference in the working capacity between the normal animals

11) Oliver and Schäfer, J. Physiol., 1895, 18, 283 f. (suprarenal extract; frog). D ess y and Grandis, Arch. ital. Biol., 1904, 41, 225 (suprarenal extract; frog). P anella, Arch. ital. Biol., 1907, 48, 430 (suprarenal extract; frog, toad, guinea pig & rabbit). J o t e y k o, La fonction musculaire, 1909 Paris, p. 164 (adrenaline, suprarenal extract; frog & toad). R ad w a n s k a, Bull. intern. de l'Acad. d. Sci. Cracovie, 1910, 738 (adenaline, suprarenal extract; frog). G r u b e r, Am. J. Physiol., 1913, 32, 221 & 438; 1914, 33, 33; 1914, 34, 89; 1917, 42, 610 (Proc.); 1917, 43, 530; 1918, 47, 185; 1922, 61, 475; E ndocrinol., 1919, 3, 145; G r u b e r and K r e t s c h m e r, Am. J. Physiol., 1918, 47, 178 (adrenaline; cat & frog). C annon and N i c e, Am. J. Physiol., 1913, 32, 44 (adrenaline; cat). L u c i e n and P a r i s o t, Les glandes à sécrétion interne. Glandes surrénales et organes chromaffines, 1913 Paris, p. 210 (suprarenal extract; frog & dog). F o n s e e a, Arch. bras. de Méd., 1919, 9, 149 (Cit. in Physiol. Abstr., 1920, 4, 340) (adrenaline; frog). G u g l i e l m e t t i, Quart. J. Exp. Physiol., 1919, 12, 139 (adrenaline; frog & toad). H a r t m a n, Endocrinol., 1922, 6, 514 f. (adrenaline; cat—treadmill). E d d y, Am. J. Physiol., 1924, 69, 432 (suprarenal extract; frog). F e r re i r a d e M i r a, C. R. Soc. Biol., 1926, 95, 1284 (adrenaline, suprarenal extract; frog). D o m i n g u e z and S o l o m j a n, C. R. Soc. Biol., 1926, 95, 1083 (adrenaline; frog). M a i b a c h, Ztschr. f. Biol., 1928, 88, 207 (adrenaline; frog). F e r re i r a d e M i r a and F o n t e s, Arch. portug. des Sci. Biol., 1929, 2, 221 (adrenaline; frog & rabbit). H u n t, Cit. in Am. J. Physiol., 19 (28-29, 87, 699. C a m p o s, C a n n o n, L u n d in and W a l k e r, Am. J. Physiol., 1929, 87, 680 (adrenaline; dog—running). K u s c h i n s k y and V i a u d, Schmiedeberg's Arch., 1933, 170, 492 (adrenaline; guinea pig). W a c h h o l d e r and M o r g e n s t e r n, Pflüger's Arch., 1933, 232, 444 (adrenaline 1:500 000; frog).


13) C a m p o s, C a n n o n, L u n d in and W a l k e r, Am. J. Physiol., 1929, 87, 680.

14) F e r re i r a d e M i r a and F o n t e s; C. R. Soc. Biol., 1931, 107, 1167.
and those with the suprarenal medullae inactivated, as due to the fact that the normal animal does not use that apparatus to any noteworthy degree in routine running.

It must be added here that earlier appearance of exhaustion from the muscular work in the suprarenalectomized animal, of course, did not necessarily suggest favourably action of epinephrine, if secreted, on the muscular efficiency.

The question arises as to what significance an increased secretion of epinephrine, if it be true, in relation to the muscular efficiency of the organism has. In order to settle this question it is necessary at first to have direct information, which is absent in the previous experiments described above, on the rate of the epinephrine secretion on muscular exercise. The purpose of the present research is to contribute something towards this question by the observations in non-anaesthetized, non-fastened dogs.

**Methods.**

Non-anaesthetized, de-afferented dogs with the lumbar route preparation were experimented on. Since the posterior spinal roots corresponding to the operation area were severed about four to twenty weeks prior to the experiment proper, the procedure for collecting the suprarenal vein blood was performed, under possibly the normal state of the animals, that is without their being fastened or without their giving any evidence of pain.

Epinephrine concentration was determined mainly by means of the rabbit intestine segment method and in a single instance together with the paradoxical eye reaction of a cat. For finer measurement of the transverse diameter of the pupil a reading microscope of magnification 9 was adopted instead of a millimeter rule, as described elsewhere. The increase of the diameter can be read with accuracy to 1/8th of one millimeter by means of an eyepiece micrometer. By this small modification the paradoxical eye reaction has become satisfactorily available for the estima-


17) Sugawara, Watanabe and Saito, Ibid., 1926, 7, 3 f.
18) Sugawara, Ibid., 1927, 8, 357.
tion of a small amount of epinephrine in the blood, just as by the rabbit intestine segment method.

The animal was let run usually, being led by an assistant riding a bicycle, over a course of known length at an average speed of 105 to 190 meters per minute. In some cases the animal was exercised in a revolving wooden cage of 1.8 meters in inner diameter and 0.4 meters in inner width which was driven by hands at a speed averaging 14 to 16 revolutions per minute. As the sign of exhaustion, we have taken for convenience the state of the animal such as was described by Campos et al.,133 the state in which the animal lies down stretching its four legs, with heavy panting, and refuses to rise and run farther even by any manipulations.

The suprarenal vein blood was taken before, soon after, and at intervals after the muscular exertion. It should be noted here that during running and at the time of sampling the suprarenal vein blood through the lumbar approach, the animals thus prepared showed no departure from the normal ones in their behaviour.

In parallel with the determination of the epinephrine output rate, blood sugar percentage in the arterial blood, obtained simultaneously, was estimated by the method of Hagedorn and Jensen.

Results.

The results brought about from nine experiments on eight dogs ranging in weight from 8.2 to 17.7 kilograms are given in Table I, in which the data obtained are roughly arranged according to the condition of each animal at the end of the muscular exercise.

The rate of the epinephrine secretion.

For clearness the results obtained may be described separately for each instance as follows

In Exp. I the dog travelled about 770 meters in a revolving cage for a period of five minutes (154 meters per minute) without refusal; at the end of the exercise it was tired slightly, but preserved well the capacity to run farther. Panting did not appear. The heart was accelerated 45 beats per minute when estimated soon after cessation of running; the respiration became faster, before exercise 25 and soon after it 37 per minute. The blood was successively sampled from the suprarenal vein at the end of 2, 14, 21, 36, 54 and 91 minutes after
TABLE I.

Effect of muscular exercise upon the epinephrine secretion and the blood sugar content in non-anaesthetized dogs.

<table>
<thead>
<tr>
<th>Time of procedure (hour : min.)</th>
<th>No. of specimen</th>
<th>Blood flow (c.c.)</th>
<th>Epinephrine output (mgrm.)</th>
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<tr>
<td></td>
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<td>Quantity</td>
<td>Epinephrine output</td>
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<td>Duration of</td>
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<td>collection (sec.)</td>
<td>per animal</td>
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<td>Quantity</td>
<td>per minute</td>
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<td></td>
<td></td>
<td>contained in 1 c.c.</td>
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<td></td>
<td></td>
<td>Epinephrine output</td>
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<td></td>
<td></td>
<td>% heart beat per minute</td>
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<td></td>
<td></td>
<td>Rate of respiration per minute</td>
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<td>Body temperature (°C)</td>
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<td>Room temperature</td>
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Experiment I.

Dog 2. 8.7 kilos. ♀ 17. VI. 1931.

9:30-11:30 a.m. The right lumbar route preparation completed. The right femoral artery laid bare and cannula inserted for taking blood samples.

1:15 p.m. Hind legs not ataxic.

2:00 Pupils dilated slightly. Dog very quiet on the table.

2:41 Very quiet on the table.  

3:29 Very quiet on the table.

3:30 Moved about on the table.

3:55 Moved about on the table.
Experiment II.

Dog 3. 11.5 kilos. ♀ 14. X. 1931.

10:10 a.m.-12:15 p.m. The left lumbar route preparation completed. The right femoral artery laid bare and cannula inserted for taking blood samples.

1:48 p.m. Hind legs not ataxic. Quiet on the table. 94 12 38.7 25

1:53
1:55
2:15
2:18
2:20
2:30-2:40 p.m. The animal ran 1045 meters in 10 minutes (105 meters per minute): Refused several times to continue to run. At the end of running pupils dilated markedly. Tired slightly. No panting appeared.

2:41 Lying down quietly. Heart beat irregular. 0.114/93(?) 32 39.7 25

2:42
2:55
3:00
3:07
3:09
3:10
3:40
3:43
3:45
3:48
4:10
4:13
4:15
4:45
4:48

Experiment III.

Dog 4. 11.8 kilos. ♂ 4. XI. 1931.


10:30 a.m.-12:30 p.m. The left lumbar route preparation completed. The right femoral artery laid bare and cannula inserted for taking blood samples.
Effect of Muscular Exercise upon Epinephrine Secretion

2:51-3:02 p.m. The animal ran 1425 meters in 11 minutes (130 meters per minute). Refused several times to continue to run. Tired slightly. Pupils dilated markedly.

2:51-3:02 p.m. The animal ran 1425 meters in 11 minutes (130 meters per minute). Refused several times to continue to run. Tired slightly. Pupils dilated markedly.

Experiment IV.

Dog 4. 11.4 kilos. 9. XII. 1931.

[16. IX. 1931. 13.6 kilos. D_{10}-L_{3} dorsal spinal roots severed under morphine-ether anaesthesia.

4. XI. 1931. 11.8 kilos. The running experiment carried out.

10:10-11:40 a.m. The right lumbar route preparation completed. The left femoral artery laid bare and cannula inserted for taking blood samples.

1:59 p.m. Hind legs not ataxic. Moved about on the table.

2:03

2:05

2:15

2:20

2:25
2:40–2:45 p.m. The animal ran 760 meters in 4 1/2 minutes (169 meters per minute): Refused once to continue to run. Seemed to retain the ability to continue running. No panting. Pupils dilated slightly.

2:46

V 1.4 60 1.4 0.12 (V+ VI)
VI 0.8 30 1.5 0.14 0.00005 0.00008 0.00007

2:50 Moved about on the table. Pupils not dilated.

2:52 1.000 3

3:00 177 16 39.6 21

3:03 0.103

3:05 VII 0.7 30 1.4 0.12 0.00005 0.00008 0.00007

3:05 VIII 1.5 60 1.5 0.14 0.00005 0.00008 0.00007

3:25 Moved about on the table. Blood clotted in the suprarenal vein. 160 16 39.3 21

Experiment V.

Dog 7. 17.7 kilos. ♀ 12. V. 1932.

10:05 a.m.–12:40 p.m. The left lumbar route preparation completed. The right femoral artery laid bare and cannula inserted for taking blood samples.

2:38 p.m. Hind legs not ataxic. Quiet on the table.

2:43 116 16 39.0 16

2:45 I 2.0 20 6.0 0.34 0.00005- 0.00030- 0.000017-

3:00 Quiet on the table.

3:03 114 16 39.0 16

3:05 II 2.5 20 7.5 0.42 0.00005- 0.00038- 0.000021-

3:05 III 1.6 20 4.8 0.27 0.00005- 0.00024- 0.00014-

3:13–3:16 p.m. The animal ran 380 meters in 3 minutes (127 meters per minute): No signs of fatigue appeared. Pupils dilated slightly.

3:17

3:18 V 2.4 20 7.2 0.41 0.00005- 0.00036- 0.000020-

3:20 VI 2.3 20 6.9 0.39 0.00005- 0.00038- 0.000017-

3:26–4:03 p.m. The animal ran 6840 meters in 37 minutes (185 meters per minute): Refused several times to continue running. Panting appeared at times. At the end of running seemed to be tired, but not exhausted.

4:04 Lying down very quietly. Pupils dilated markedly.

4:04 No panting.

4:05 VII 1.6 20 4.8 0.27 0.00001 0.00048 0.000027

4:08 VIII 2.7 30 5.4 0.31 0.00005 0.00027 0.000015


4:22 IX

4:25 X 1.6 20 4.8 0.27 0.00015 0.00072 0.000041

4:42 XI 2.2 30 4.4 0.25 0.000075 0.00033 0.000019

5:00 XII 2.1 30 4.2 0.24 0.000075 0.00032 0.000018

5:10 Moved about on the table.

5:12 111 14 38.8 17
### Effect of Muscular Exercise upon Epinephrine Secretion

#### Experiment VI.

**Dog 8. 8.2 kilos. 3. V. VII. 1932.**

9 IV. 1932. 9.3 kilos. D110-L9 dorsal spinal roots severed under morphine-ether anaesthesia.

9:40-11:07 a.m. The left lumbar route preparation completed. The left femoral artery laid bare and cannula inserted for taking blood samples.

<table>
<thead>
<tr>
<th>Time of procedure (hour : min)</th>
<th>No. of specimen</th>
<th>Blood flow (c.c.)</th>
<th>Epinephrine output (mgram.)</th>
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<tbody>
<tr>
<td>9:40 a.m.</td>
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<td>2:27-2:30 p.m.</td>
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<td>2:32 p.m.</td>
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<td>2:40-2:59 p.m.</td>
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<td>3:00 p.m.</td>
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<td>3:15 p.m.</td>
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<td>3:45 p.m.</td>
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<tr>
<td>4:13 p.m.</td>
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</tbody>
</table>

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**Blood sugar (g%)**  
**Rate of heart beat per minute**  
**Rate of respiration per minute**  
**Body temperature (°C)**  
**Room temperature (°C)**

---

**Marked widening of pupils appeared.**

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**Experiment VI.**

**Dog 8. 8.2 kilos. 3. V. VII. 1932.**

9 IV. 1932. 9.3 kilos. D110-L9 dorsal spinal roots severed under morphine-ether anaesthesia.

9:40-11:07 a.m. The left lumbar route preparation completed. The left femoral artery laid bare and cannula inserted for taking blood samples.

1:45 p.m. Hind legs not ataxic. Quiet on the table.

2:05 p.m. Quiet on the table.

2:27-2:30 p.m. The animal ran 360 meters in 3 minutes (120 meters per minute): No signs of fatigue developed.

2:31 p.m. Moved about on the table.

2:32 p.m. Moved about on the table.

2:40-2:59 p.m. The animal ran 3040 meters in 19 minutes (160 meters per minute): Refused several times to continue running. At the end of 8 minutes panting appeared. At the later stage of running lay down three times. Marked widening of pupils appeared.

3:00 p.m. Lying down.

3:17 p.m. Panting disappeared. Lying down still.

3:45 p.m. Very quiet on the table.

3:47 p.m. Moved about on the table.

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*Estimated by the cat paradoxical pupil reaction.
Experiment VII.

**Dog 1. 8.5 kilos. ♀ 3. VI. 1931.**

11:00 a.m.-1:03 p.m. The left lumbar route preparation completed. The left femoral artery laid bare and cannula inserted for taking blood samples.

2:28 p.m. Hind legs somewhat ataxic. Quiet on the table.  

3:00-3:15 p.m. The animal travelled 880 meters in the treadmill in 5 minutes (176 meters per minute): At the end of running lay down in the treadmill with stretching the legs. Severe panting and marked dilatation of pupils appeared. Urination occurred.


3:17 Blood clotted easily.  

3:40 Very quiet on the table. Somewhat depressed.  

4:00 Very quiet on the table.  

4:15 Moved about on the table.  

4:45 Moved about on the table.

Experiment VIII.

**Dog 5. 12.5 kilos. ♀ 25. XI. 1931.**

10:15 a.m.-12:02 p.m. The right lumbar route preparation completed. The left femoral artery laid bare and cannula inserted for taking blood samples.
Effect of Muscular Exercise upon Epinephrine Secretion

Experiment IX.


[28. X. 1931. 16.0 kilos. D_{19}L_{2} dorsal spinal roots severed under morphine-ether anaesthesia.]

10:15 a.m.-12:45 p.m. The left lumbar route preparation completed. The left femoral artery laid bare and cannula inserted.

3:09-3:25 p.m. The animal ran 5655 meters in 16 minutes (160 meters per minute): Refused several times to continue running. At the end of running lay down exhaustedly with stretching the four legs. Pupils dilated. Panting heavily.

3:26 Lying down exhaustedly on the table. Vigorous panting appearing.

3:27 V 3.2 30 6.4 0.40 0.0001 0.000040

3:31 III 3.0 30 6.0 0.37

3:35 Lying down quietly. Panting appeared at times.

3:36 40.8 29.5

3:38 129 20 39.8 20

3:39 0.096

3:40 141 53 40.8 29.5
it stopped running. After this muscular exertion the blood flow through the suprarenal gland was increased to some degree and the epinephrine concentration remained almost unchanged, accordingly the rate of the epinephrine secretion being changed from the quiet value of 0.000015 mgm. per kilo per minute to 0.00003 mgm. In this experiment the rise of the body temperature was insignificantly small, 0.3°C.

In Exp. II the animal ran 1045 meters in ten minutes (105 meters per minute). During running the animal refused several times to run and was slightly tired. Pupils dilated markedly, but no panting appeared. The heart beat became irregular and the respiration was accelerated, 21 before running and 32 per minute soon after running. The blood was taken successively at the end of 2, 20, 30, 65, 95 and 130 minutes after it stopped running. The blood flow through the gland was increased slightly. The epinephrine concentration was determined to be unaltered by running (0.00005 mgm. in 1 c.c. The epinephrine output rate was therefore estimated as nearly unaltered; it was roughly 0.00003 mgm. per kilo per minute before as well as after running. The body temperature rose 1°C.

In Exp. III the animal ran 1425 meters in eleven minutes (130 meters per minute). During running the animal refused frequently to continue to run, but was found slightly tired at the end of this muscular work. Pupils dilated. The heart rate was found increased, that is 51 beats per minute above the initial when determined at the end of

<table>
<thead>
<tr>
<th>Time of procedure (hour: min.)</th>
<th>No. of specimen</th>
<th>Blood flow (c.c.)</th>
<th>Epinephrine output (mgm.)</th>
<th>Blood sugar</th>
<th>Rate of heart beat per minute</th>
<th>Rate of respiration per minute</th>
<th>Body temperature (°C)</th>
<th>Room temperature (°C)</th>
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<tr>
<td>3:38 p.m.</td>
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<tr>
<td>3:40</td>
<td>VII</td>
<td>2.3 30</td>
<td>4.6 0.28</td>
<td>0.00015</td>
<td>0.00075</td>
<td>0.000046</td>
<td>0.091</td>
<td>105</td>
</tr>
<tr>
<td>3:50</td>
<td>VIII</td>
<td>2.5 30</td>
<td>5.0 0.31</td>
<td>0.00015</td>
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<td>0.089</td>
<td>102</td>
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<tr>
<td>4:10</td>
<td>Very quiet on the table</td>
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<tr>
<td>4:25</td>
<td>IX</td>
<td>2.3 30</td>
<td>4.6 0.28</td>
<td>0.0001</td>
<td>0.00052</td>
<td>0.000032</td>
<td>0.096</td>
<td>108</td>
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<tr>
<td>4:30</td>
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six minutes after stopping running. The frequency of respiration was augmented transitorily, but soon became slow. The blood flow through the gland was increased slightly, while the epinephrine concentration was unchanged or a little reduced. The rate of the epinephrine output increased from 0.00002 mgrm. per kilo and per minute to 0.00003 mgrm.; only for a while, later a rather small rate was noted. The rectal temperature showed a rise of 1°C.

In Exp. IV the dog was subjected to a run of 760 meters in 4½ minutes (169 meters per minute). At the end of the running the animal was still active and showed no signs of fatigue. The cardiac acceleration of 42 beats per minute was determined at the end of five minutes after stopping the running. No panting occurred. Pupils dilated slightly. Soon after running the blood flow through the gland was found somewhat decreased, while the epinephrine concentration remained unaltered. The rate of the epinephrine secretion fluctuated between 0.00001 and 0.000007 mgrm. per kilo and per minute through the whole experimental course. The rise of the body temperature at the end of 5 minutes was 0.8°C.

In Exp. V two attempts were made. The dog was run at the first time 380 meters in three minutes (127 meters per minute). At the end of the running the animal remained active. A cardiac acceleration of 56 beats per minute was found when tested at the end of 4 minutes. The respiration also became faster. The running was followed by a slight increase in the blood flow through the gland, if compared with that just before starting to run, but almost the same as that estimated about a half hour before it; the epinephrine concentration was unchanged. The rate of the epinephrine output fluctuated between 0.000015 and 0.00002 mgrm. per kilo and per minute. The body temperature increased as slightly as 0.4°C. The second trial was made ten minutes after the discontinuation of the first running. The dog was run 6840 meters in thirty seven minutes (185 meters per minute). After the muscular effort the animal panted vigorously and refused to continue to run farther even by urging. The heart was markedly accelerated and the respiration also became faster. On this trial, the epinephrine concentration was increased to a slight degree, while the blood flow decreased only insignificantly. Accordingly there was a tendency to increase the rate of the epinephrine output, but only slightly (0.00004 mgrm. per kilo per minute). The rectal temperature determined five minutes after discontinuing the running was 40.6°, that is a rise of 1.2°C.
In Exp. VI also two trials were made. At first the dog was run 360 meters in three minutes (120 meters per minute). At the end of the running the animal was still active and showed no signs of fatigue from the muscular work. The heart rate was raised 48 beats per minute and the respiration was quickened, 16 before running and 36 per minute at the end of the running. The body temperature rose from 39°C. to 39.5°C. Such an amount of muscular work resulted in no noteworthy alteration either in the blood flow through the gland or in the epinephrine concentration. About ten minutes after the first muscular work, the second running of 3040 meters in nineteen minutes (160 meters per minute) was attempted. During this running, the animal lay down three times on the pavement with vigorous panting, but seemed to reserve well the power to continue to run. Pupils dilated markedly. The heart rate showed a considerable increase as much as 201 beats per minute soon after running. The blood flow through the gland was reduced by the muscular exercise, while the epinephrine concentration was magnified about four times; the increased rate of the secretion being determined as more than two times the original rate, from 0.00002 mgrm. per kilo per minute to 0.00005 mgrm. This increased rate was noted in the samples collected a few minutes after the end of the running. The samples taken 15 minutes later already indicated a wholly normal value.

In Exp. VII the animal travelled 880 meters in the revolving cage in five minutes (176 meters per minute). At the end of this work the animal, the hind legs of which had been somewhat ataxic, lay down in the cage with four legs spasmodically stretched out and with vigorous panting. On taking the animal out of the cage a slight struggling and urination followed. Pupils were dilated conspicuously. The rate of the heart beat was increased, 78 beats per minute being estimated at the end of the running. In this experiment the blood flow through the gland was reduced a little soon after running, but later was increased; the epinephrine concentration of the sample taken soon after the discontinuance of working was about two times the initial, but about a half hour later it was found definitely magnified as about five times that before running. The rate of the epinephrine liberations was noted in this spell as increased more than three times, that is from 0.000025 mgrm. per kilo and per minute to 0.0001 mgrm. at the end of thirty minutes. Later an increased rate, though small, was noted one after another. The body temperature showed a rise of 1.5°C.
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 the "numeral" by the indifferent blood solution to which a certain quantity of adrenaline 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 1/2000" shows "0.1 c.c. of adrenaline solution with the concentration of 1/2000 mgm. in 1 c.c." i.e. 0.00005 mgm. adrenaline.

To show the I specimen, we used the numeral "I".

In all tracings, time intervals are 30 seconds.

Fig. 1 a. I: Stronger than 0.000025 mgm., almost as strong as 0.00005 mgm.
III: Stronger than 0.000025 mgm. (Obs. 6), almost as strong as 0.00005 mgm.
Fig. 1 b. V: Far stronger than 0.000025 mgm., a little stronger than 0.0001 mgm., and a little weaker than 0.00015 mgm.
Fig. 1 c. VI: Weaker than 0.000125 mgm. and 0.0001 mgm., almost as strong as 0.000075 mgm. (Obs. 16).
Fig. 1 d. VIII: Weaker than 0.0002 mgm., a little stronger than 0.00015 mgm.
Fig. 1 e. X: Weaker than 0.000075 mgm., almost as strong as 0.00005 mgm.

To sum up: Specimen I is estimated as 0.0001 mgm. in 1 c.c. Specimen III, 0.0001 mgm. in 1 c.c. Specimen V, 0.00025 mgm. in 1 c.c. Specimen VI, 0.000175 mgm. in 1 c.c. Specimen VIII, 0.0003 mgm. in 1 c.c. Specimen X, 0.0001 mgm. in 1 c.c.
In Exp. VIII the animal ran 760 meters in five minutes (152 meters per minute). At the end of the running the animal lay down exhaustedly on the pavement, with vigorous panting. The muscular exertion was followed by an acceleration of the heart beat of 36 beats per minute. Pupils dilated ad maximum. The rise of the body temperature was determined as 0.8°C. In this exhausted animal the concentration of epinephrine was increased to as much as three times the initial value, while the blood flow through the suprarenal gland also was a little increased. The greatest increased rate of the epinephrine secretion, such as about five times the original rate, was detected in the blood samples taken at the end of thirty minutes, namely from 0.000017 mgram per kilo and per minute to 0.00008 mgram. The sample collected soon after the running showed a rate of about half of that; one hour after the running the output rate returned to nearly the initial.

In Exp. IX the animal was exhausted by a run of 2565 meters in sixteen minutes (160 meters per minute). The animal refused several times to continue running during the course of the muscular exercise and finally lay down rigidly extending its four legs. Panting was very vigorous and continued a long time. Pupils dilated markedly. The heart was accelerated to a remarkable degree. A rise of the rectal temperature of 0.5°C. was found when measured six minutes after end of the running. In this animal the blood flow through the gland was double the initial rate on the muscular work, and the epinephrine percentage in the suprarenal vein blood slightly increased fifteen minutes after the end of the running. Accordingly, the greatest increase in the rate of the epinephrine output was determined as small as only twice the original rate, namely from 0.00002 mgram per kilo and per minute to 0.00005 mgram at the end of fifteen minutes. A few minutes after the end of the running it was only a little smaller compared with the peak, and after reaching the peak it decreased slowly.

Taking the data, above described, altogether, in the cases where the animals did not show any fatigue at all or only a slight one, no augmentation occurred in the output rate of epinephrine from the suprarenal gland regardless of the length of the run, such as 360 to 1425 meters or of the speed, such as 105 to 170 meters per minute, (Exps. II; III; IV; V & VI, the first run), while an augmentation took place, though small in general, when the animal betrayed some signs of fatigue. The excess was 0.00002 mgram to 0.000075 mgram per kilo per
minute from the one gland tested; the maximum increase was therefore 0.000075 mgrm. from one gland, that is 0.00015 mgrm. per kilo per minute from both the glands. In two cases where the augmentation of epinephrine discharge took place, the distance of running or travelling the revolving cage was not so large; it was in fact 760 meters (Exp. VIII) and 880 meters (Exp. VII) respectively. But in the two others it was long, 3040 (Exp. VI, the second run) and 2565 meters (Exp. IX), respectively. The longest distance run in the present sets of experiment was 6840 meters (Exp. V, the second run), and the speed was also the quickest there; this dog showed a slight degree of fatigue, and a small increase of the epinephrine discharge rate, the maximal excess being 0.00002 mgrm. per kilo per minute; about a similar figure was yielded in Exp. I, where the dog traveled 770 meters on a treadmill in 5 minutes and showed a slight degree of fatigue.

It is thus noted, that muscular work is capable of accelerating the rate of the epinephrine output only if it causes the animal to become fatigued, and the degree of the acceleration is distinctly small. That is, if compared with agencies, such as sensory stimulation (maximum 0.006 mgrm. from both the glands per kilo per minute), haemorrhage (maximum, 0.001 mgrm.), pique (maximum, 0.001 mgrm.), asphyxia (maximum, 0.003 mgrm.), the difference was too distinct. The maximum acceleration in the cooling experiments was 0.0004 mgrm. from both the glands per kilo per minute. The highest rate detectable in the present exercise experiments was 0.0002 mgrm. per kilo per minute from both the glands, and the excess 0.00015 mgrm.

The distance run by the animal as well as the speed of running have apparently no direct influence upon the rate of the epinephrine discharge, though it is readily comprehensible that they have some bearing upon bringing about fatigue in the animal.

The present facts harmonize well with the previous findings on cats, in which one suprarenal body was removed and the other denervated, of Stewart and Rogoff and of Campos, Cannon, Lundin and Walker, and also with the data that the epinephrine store in the suprarenal gland is not influenced merely by the muscular exercise, if the animal is not exhausted therefrom. On the other hand the present outcome does not correspond to the observations made on

20) Saito, Ibid., 1928, 11, 73.
21) Yen, Kaiwa and Wada, Ibid., 1931, 17, 345.
22) Sato, T. Inaba and Takahashi, Ibid., 1932, 19, 421.
23) Wada, Seo and Abe, Ibid., 1935, 26, 381.
cats with a denervated organ, such as the pupil and the heart, by Hartman and by Cannon and Britton. The latter noted a marked acceleration of the denervated heart by minor movements such as, extending the legs, turning the body or walking about for two minutes. Inactivation of the suprarenal medullae abolished the acceleration wholly or nearly entirely. After this publication, Cannon with his co-workers witnessed another influential factor upon the rate of denervated heart in addition to the hormones from the suprarenals, thyroid and liver, namely sympathin. It is open to question whether the above quoted results of Cannon and Britton will be affirmed again if renewed.

In this connection, our interest has been aroused towards the experiments of Cannon, Campos and others, demonstrating that small doses of adrenaline (0.02 mgrm. per kilo) subcutaneously administered were capable of improving the ability of dogs to run to a striking degree when applied in the state of exhaustion, while no favourable action was seen when applied before running. If it is assumable, from the view point of the emergency theory, that the epinephrine is liberated for the self-protection of the organism, it may be reasonable to suppose on the ground of the beneficial effect of adrenaline on the muscular activity, that epinephrine is discharged abundantly during strenous muscular exercise and at least before the appearance of some very great fatigue. When fatigue becomes profound, the epinephrine discharge might be supposed as going conspicuously or already rather insufficiently owing to exhaustion of its storage. Such is however a mere speculation; the data in our hands never correspond to it. When the animal was exhausted, the epinephrine discharge was accelerated, and in reality only on a small scale, while the central mechanism of the epinephrine secretion has an ability to discharge it abundantly in response to some agents, as haemorrhage, asphyxiation, etc., and no acceleration was ever witnessed when the dog was active, not tired or only slightly tired, notwithstanding the fact that the animal ran a very long distance with great speed, as much as 6840 meters with an average speed of 185 meters per minute.

The present fact should not be taken out of consideration in delving in general the significance of the accelerated output of epinephrine upon the organism.

The blood sugar level.

Survey of a great deal of the literature shows that the change
in the glycaemic level following muscular exertion is not invariably in the same direction. In the present experiments a run of 360 to 6840 meters resulted in no alteration, or a fluctuation of only a small magnitude, in the glycaemic level. In six cases where the animals presented no signs of exhaustion, the blood from the femoral artery taken soon after cessation of the muscular exertion exhibited a slight rise of the glycaemic level or no change. The level before running 0.101% (Exp. I), 0.098% (Exp. II), 0.099% (Exp. III), 0.098% (Exp. IV), 0.117% (Exp. V) and 0.100% (Exp. VI), and that soon after running being determined respectively 0.107%, 0.114%, 0.114%, 0.100%, 0.115% and 0.109 (-0.136)%.

The hyperglycaemic spell was short as from a few minutes to a half hour. In the remaining three cases where the animals were exhausted, the glycaemic percentage showed a tendency to decrease sooner or later. The initial value was 0.102% (Exp. VII), 0.109% (Exp. VIII) and 0.101% (Exp. IX), the respective value after running being estimated 0.120-0.077%, 0.090-0.109% and 0.096-0.089%. Occurrence of the hypoglycaemia in exhausted animals, though not profound, may be considered as associated with the beneficial effect of glucose or adrenaline in improving the ability to work when administered in the stage of exhaustion.

It is also noteworthy that the variation of the epinephrine output rate and that of blood sugar concentration following muscular exercise do not run parallel with each other, though the magnitude of both variations was rather insignificant, in contrast to the common occurrence in the diabetes of the central mechanism.

**Summary.**

Dogs, in which the operation area was previously de-afferented, were experimented on. The procedure for collecting the suprarenal vein blood through the lumbar approach was performed, namely without their being fastened or without their giving any evidence of pain. The dogs were compelled to run on a paved road or in a revolving wheel.

(1) When the animals presented no signs of fatigue or were tired slightly after a run of 360 to 6840 meters, the rate of the epinephrine secretion remained almost unaltered, while in the animals which were much fatigued or exhausted, by running 760 to 2565 meters, the rate was increased from the quiet value of 0.000015-0.000025 mg/m. from one suprarenal capsule per kilo and per minute to 0.00003-0.0001
mgrm.: This peak being noted a few minutes or about a half hour after running. The magnitude of acceleration was thus very small and its duration was short, ad maximum about one hour after running. Whether the epinephrine discharge will be accelerated, though only a little, depends directly upon the condition of the animal, whether exhausted or not, and not directly upon the magnitude of the work.

(2) In cases where the animals presented no signs of exhaustion, the blood from the femoral artery, taken soon after cessation of the muscular exertion, exhibited only a slight rise of the glycaemic level or no change. In cases where the animals were exhausted from the muscular effort, the glycaemic percentage showed a tendency to decrease, though slightly, sooner or later.