On the Effect of Cold upon the Pupil, Deprived of the Upper Cervical Sympathetic Ganglion, and upon the Blood Sugar Content of Dogs, Normal and Deprived of the Suprarenal Medulla.

By

Kazuo Itikawa.

(市川 肇)

(From the Physiological Laboratory of Prof. Y. Satake,
Tohoku Imperial University, Sendai.)

The pupil, deprived of its innervation, either incompletely or completely, has been used by several investigators for assaying the discharge of epinephrine from the suprarenals.

Hartman¹⁾ studied with his co-workers the effect of cold upon cats with the pupil so operated on. When chilled by a cold bath, the denervated pupil dilated so long as the mechanism of epinephrine liberation remained intact. In a cat, which possessed a single but denervated suprarenal, the dilatation did not occur. The same held true when the suprarenals were removed per laparotomiam and 3 to 5 hours later the cats were subjected to cold. Shivering occurred, but there was sometimes a decrease of the size of the pupil, instead of paradoxical dilatation.

In the next paper of Hartman,²⁾ in which he came to recognize the outstanding rôle of peripheral stimulation in causing the paradoxical pupil dilation on subjecting cats to cold, an attempt was made to occlude both suprarenal veins by traction on ligatures placed under each suprarenal vein after tying the vein from the lumbar muscles. Cold was applied by soaking the animal's back in water and using an electric fan. Then the completely denervated pupil became larger; when the ligatures were tightened a-new the pupil became smaller. Incomplete occluding of the suprarenal veins because of movements

1) Hartman, McCordock and Loder, *Am. J. of Physiol.*, 1923, **64**, 19-25.

2) Hartman and Hartman. *Ibid.*, 1923, **65**, 614 ff.

of the animal should, according to these writers, account for this dilatation.

Cold is capable of increasing the output rate of epinephrine from the suprarenal capsules provided it is extensive. While a mild cooling, such as to occasion a fall of the body temperature by 1.5–1.7°, does not alter the epinephrine output rate^{3,4)} from the suprarenals of dogs, a conspicuous increase is brought about in the rate by an excessive cooling, so as to bring the body temperature below 30°. ⁴⁾

It is then apparently reasonable to assume that the excessively liberated epinephrine accounts solely or partly for the paradoxical pupil dilatation, which becomes manifest when animals are sufficiently cooled. This question is however quantitative in nature, and on the other hand there are some definite evidences that the denervated organs cannot be utilized with safety as indicators of the epinephrine liberation.⁵⁾ A paper of F. Watanabe, published in this number of this journal affords such evidence too.⁶⁾

We thought it thus worth while to re-investigate the paradoxical pupil reaction in dogs by applying extensive cooling and studying its relation to the function of the suprarenal medulla, since it may be too hasty to take a fact detected in one species of animals as applicable to another species and that of one organ as applicable to another organ without any direct examination.

The dogs deprived of the left upper cervical ganglion were immersed in cold water; the pupil width of the deganglionated side and of the control was measured. This measurement was carried out also in dogs, whose suprarenal medulla was removed. The blood sugar content was also estimated from time to time.

The cold hyperglycaemia is classical.⁷⁾

Further, Freund and Marchand⁸⁾ were able to see the cold

3) Saito, Tohoku J. of Exp. Med., 1928, 11, 544.

4) Wada, Seo and Abe, Ibid., 1935, 26, 381.

5) Wada, Ibid., 546.

6) F. Watanabe, Ibid., 1935, 27, 556.

7) Rather complete bibliography re the cold diabetes is to be found in Morita, Tohoku J. of Exp. Med., 1921, 2, 403 and Wada, Seo and Abe (4). In completing the bibliography the following may be added: Schwarz and Kospar, Biol. Gen., 1927, 3, 689 (Dogs, 2–4 hours at 0–3°, a slight hyperglycaemia, the mean excess of 6 cases being 18%); Moracci and Trifilio, Fisiol. e Med., 1932, 3, 491–510: Cit. in Ber. üb. ges. Physiol., 1933, 70, 90 (Pigeons, 3–12 minutes (Cit. in p. 516) in water of 4–8°, after the bath, a transitory hyperglycaemia in 8 cases out of 20, a hypoglycaemia in 2, and no change in the remainder.—Perhaps not so essentially different from a paper in Boll. Soc. Ital. Biol. Sper., 1931, 6, 903–907.

8) Freund and Marchand, Arch. f. exp. Path. u. Pharm., 1913, 72, 73.

hyperglycaemia in a rabbit, surviving the double suprarenalectomy over one month, and Ciaccio⁹⁾ obtained also cold diabetes in dogs, in which one suprarenal body was removed and the other demedullated or partly removed, or both bodies demedullated. Some contradictory results were reported by Britton¹⁰⁾ in insulinized cats, and in rats Hartman¹¹⁾ failed to find any definite relation between low body temperature and low blood sugar, when the doubly suprarenal-ectomized rats were exposed to cold. Bilateral splanchnicotomy abolishes the ability of rabbits to increase the blood sugar content against the low temperature of environmental air¹²⁾ or cold bath.¹³⁾ The same is the fate of cold-puncture hyperglycaemia of rabbits, which makes its appearance first if the body temperature falls below about 30° (Morita).⁷⁾

DATA.

Removal of the left upper cervical ganglion and of the suprarenal medulla, collection of blood samples and determination of the blood sugar concentration were done as described in my previous paper.¹⁴⁾ Ten dogs were employed for the present experiments; five of them were utilized in the previous experiment also,¹⁴⁾ the intra-ocular pressure having been measured.

Cold was applied to dogs by immersing them in cold water at 0.5 to 6° for from 15 to 27 minutes; for doing this, the forelimbs and the hindlimbs were tied together by each and the whole body except the head was immersed in water by an assistant, the limbs being held by his hands, and the head by the present writer. Sometimes the dogs struggled and cried but only at the beginning of the immersion, and they soon became calm. And some dogs became depressed.

When about five minutes had elapsed after immersing shivering became manifest with gradual intensifying.

Now the measurements in each dog will be mentioned.

Dog 1, Kuma, a young female.

Three weeks after removal of the left cervical sympathetic gan-

9) Ciaccio, Boll. Soc. Ital. Biol. Sper., 1930, **5**, 997.

10) Britton, Am. J. of Physiol., 1928, **84**, 119.

11) Hartman, Brownell and Crosby, Ibid., 1931, **98**, 679.

12) Freund and Marchand, Arch. f. exp. Path. u. Pharm., 1913, **73**, 289.

13) Geiger, Ibid., 1927, **121**, 67.

14) Itikawa, Tohoku J. of Exp. Med., 1935, **28**, 550.

gion, it was immersed in cold water at 5° for 17 minutes. The dog soon struggled slightly, and two minutes after immersion shiverings began. The left ganglionectomized pupil dilated but rather slowly, so that its diameter reached 8 mms. 17 minutes after immersion from 2 mms. before the immersion, while the control pupil dilated from 8 mms. to 9 mms. at once on immersion, but it soon became narrower, so that 2 mms. was recorded 12 minutes after the immersion and this diameter was held thereafter in the bath, and 2-3 mms. was the diameter observed one and one half hours after withdrawal from the bath. The denervated pupil became also narrow with the lapse of time after the withdrawal, and 2 mms. was noted about twenty minutes after the withdrawal and held during one hour.

The blood sugar concentration increased largely, as from 0.098% to 0.165%, the latter being the first determination after the withdrawal. During the immersion no collection of blood was made. Afterwards the sugar concentration was apt to decrease and the initial value was recovered about forty minutes after the withdrawal. The body temperature reached the bottom, 32.5°, also soon after the withdrawal and recovered the initial one hour thereafter.

The pulse rate increased and the respiratory rate decreased on immersion in the cold bath, and after the withdrawal they tended to recover.

About one month later the left suprarenal medulla was removed, and two weeks later the right. One week still later, i.e. about ten weeks after the removal of the left cervical sympathetic ganglion the dog was cooled in the same manner as before. The cold water bath was 3°. Before the immersion the transversal diameter of the denervated pupil was 2 mms. On immersion the dog slightly struggled and whined, the pupil started to dilate about two minutes after the dipping and 4 mms. was recorded five minutes after the dipping. This was the acme, and the diameter had a tendency to become a little narrower, and 3 mms. was the value in the later period of immersion, the whole period having been 17 minutes. After withdrawal from the bath the pupil became still narrower, as to 2 mms. The opposite side normal pupil dilated at once on dipping into cold water, 2 minutes later 10 mms. was recorded, and then it became narrow gradually, so that 13 minutes later 4 mms. was measured. After withdrawal 2 mms. was the diameter of the normal pupil.

The blood sugar concentration was found to be largely increased (0.177%) when examined a few minutes after the withdrawal of the dog from the bath; it was then apt to decrease and recovered the

initial about one hour later. 32.5° was the lowest body temperature which was estimated at the end of 17 minutes immersion and a few minutes after the withdrawal. The initial value recovered one hour and twenty minutes after the withdrawal, that is a little later than the complete recovery of the blood sugar concentration.

The heart rate increased, and the respiratory rate decreased, but this time the greatest variation became manifest some minutes after the withdrawal from the cold bath.

The demedullation of the suprarenals did effect largely the paradoxical pupil reaction against cooling; but it did not entirely disappear. The determination was made respectively three and ten weeks after the removal of the upper cervical ganglion. On the contrary the blood sugar variation due to cooling was just the same in both experiments, that is before and after the demedullation. The body temperature fell too.

Dog 2, Shiro, a young male.

About three weeks after the extirpation of the upper cervical ganglion the cooling experiment was made. When the dog was immersed in cold water at 5° it struggled slightly; the denervated pupil began to dilate soon from 2 mms., after 3 minutes in the bath 5 mms., 6 minutes, 7 mms., 11 and 14 minutes, 8 mms. When the dog was taken out of the bath, the pupil was 7 mms. wide. Later the width of the pupil diminished gradually, so that half an hour after the withdrawal it was measured as 2 mms. The normal pupil also dilated from 3 mms. to 6 mms. a few minutes after dipping and had recovered the pre-cooling value already when the dog was taken out of the bath.

The blood sugar level was 0.151% soon after withdrawal of the dog from the bath, it further increased and 0.171% was recorded about thirty minutes after the withdrawal, and afterwards it was inclined to decrease, so that one hour later the initial value was recovered. The body temperature was the lowest (29.8°) when the dog was taken out of the bath; about two hours were not sufficient to see a complete recovery of the anal temperature (38° against 38.5°).

The respiration was largely accelerated in dipping, such as 42 a minute against 18 before dipping. The pulse rate more or less increased on dipping, but it decreased remarkably while the dog was still remaining in the bath; after the withdrawal the pulse rate recovered gradually and again reached above the initial value with a gradual recovery.

One month later the suprarenal medulla was interfered with on both sides, and two weeks later the cooling experiment was again

carried out. The temperature of bath 5° , and duration of immersion 17 minutes. The dog struggled slightly and 3 minutes later shivering commenced with gradual exaggeration. The left pupil, which was partly denervated by extirpating the upper cervical ganglion just three months before, was measured a little dilated throughout the whole period of cooling, such as 3 mms. against 2 mms. before cooling, and the initial value was regained soon after withdrawal from the cold bath. The normal pupil dilated from 4 mms. to 8 mms. soon after immersion with a gradual recovery, so that it was of 5 mms. width when the animal was taken out of the bath, and afterwards it became narrower, as 3 mms.

The cold hyperglycaemia occurred with the acme 0.154% 13 minutes after withdrawal of the dog from the bath, and disappeared about one hour after the withdrawal. The magnitude of hyperglycaemia was thus somewhat smaller than before the demedullation, but there was no material difference in its duration between those before and after the demedullation.

The greatest body temperature fall (30.5°) was measured 5 minutes after the removal of the dog from the bath, and one hour later the initial value was recovered.

The respiration rate decreased a little in the bath, but the recovery on withdrawal was followed again by a long continued decrease. The pulse rate increased on cooling, the maximum acceleration being counted as about 40 beats a minute.

Dog 3, Kuro, a young female.

Eleven days after removal of the upper cervical ganglion, the dog was dipped into a cold bath at 3° . On dipping the dog struggled a little. The denervated pupil dilated from 2.5 mms. to 4 mms. The dog struggled again and began to shiver a few minutes later. The diameter was 7 mms. 7 minutes after the immersion; shivering became marked. After ten minutes bath the dog was taken out; the pupil was then 5 mms. wide with a very gradual recovery, so that 3 mms. was the diameter one hour after the withdrawal. The pupil with the intact innervation dilated from 6 mms. to 7 mms. soon after dipping, but soon it became narrower, 4 mms. 7 minutes after dipping, and 3 mms. just on withdrawal. Afterwards 4 mms. continued for a long time.

The blood sugar concentration reached its acme 12 minutes after the withdrawal, and one hour was needed thereafter to see a complete recovery of the concentration. The maximal body temperature

fall (32.8°) was detected 5 minutes after the withdrawal, and one and one half hours after the withdrawal it was still subnormal (38.5 against 39.2°).

The respiration rate decreased in the bath and the heart rate increased; after the withdrawal they recovered slowly.

About ten days later the suprarenal medulla was removed bilaterally. Another ten days later the dog was put into cold water at 5° for 21 minutes. The left pupil, which had been denervated about one month earlier remained practically unaltered in its width; 2.5 mms. was the only one measured 5 minutes after immersion against 2 mms. At this moment the dog was struggling and crying. A few minutes later the dog whined, but the pupil width remained as 2 mms. In the other eye, a dilatation occurred; it widened at once on dipping the animal, afterwards the width fluctuated between 3 mms. and 7 mms., in a wave like manner. 2 mms. was measured after the withdrawal from the bath.

Hyperglycaemia was also detected, but its magnitude was of a lesser degree, compared with other cases. 0.136% was the acme, noted ten minutes after the withdrawal from the bath. Thirty minutes later a blood sugar content lower than the initial was noted, and afterwards it lowered still further, but never below than 0.08%. The lowest body temperature was 32.6° ten minutes after withdrawal from the bath, and about two hours later the initial value was scarcely recovered.

The respiration rate rather increased in the cold bath, but it was small (18 per minute against 36 of the initial), when the blood sugar concentration became somewhat lower. The pulse rate was accelerated, and the initial rate was again noted about two hours after the withdrawal.

This case is similar to the findings of Hartman,¹³ and the hyperglycaemia was far less in comparison with the other instances. It must also be noted that there was a tendency of developing the hyperglycaemia though only slightly, and a considerable decrease of the breathing simultaneously occurred.

Dog 4, Poti, a young male dog.

One week after extirpating the left cervical sympathetic ganglion, the dog was cooled by means of a cold bath at 5° . The dog slightly struggled for a while, shivering commenced 6 minutes after dipping. With struggling the denervated pupil began to dilate, so that the maximum, 8 mms. against 2 mms. of the initial, was reached

11 minutes after the beginning of cooling. 5 minutes later the width was 4 mms. A few minutes after discontinuance of cooling the initial value was recovered and continued so till the end of the experiment. The right pupil on the contrary largely dilated at once on dipping the animal into cold water. Before the cooling the diameter was 4 mms., 1 minute after dipping 10 mms., 3 minutes later 11 mms., later it soon diminished to the initial width.

The cold hyperglycaemia was of a small magnitude in this dog, 0.123% 7 minutes after cold application of 19 minutes and 0.133% 15 minutes later being noted. 15 minutes still later there was no hyperglycaemia any more. The body temperature was lowest (32.9°) 7 minutes after stopping the bath. One hour was never sufficiently long to see the recovery of the body temperature.

The respiration rate became a little smaller, and continued so till the end of the experiment, i.e. one hour after withdrawal of the dog from the bath. The pulse rate increased from 130 per minute to 200 at the end of the bathing. Afterwards some greater frequency was noted, but towards the end of the experiment it was apt to recover the initial rate.

About one week later the right suprarenal capsule was deprived of the medullary portion, and also about one week still later the same was conducted on the other side. One week later a cold bath was again applied to the dog for 17 minutes. 5° was the temperature of the bath. On dipping the dog struggled slightly but transitorily. 4 minutes later the shivering began. The denervated pupil with the initial width of 2-1.5 mms. dilated at once to 3 mms., but a few minutes later 2 mms. was resumed. 9 minutes later it dilated to 3 mms., and in the following minutes 3.5 mms. was the width, when the dog was whining. Then the dog became depressed with the pupil width of 3 mms. After withdrawal from the bath the width soon became 2.5 mms. and later decreased to 2 mms. and further to 1.5 mms. A long continued dilatation occurred in the other pupil, as from 3 mms. to 7-8-9-9-7-6-8-9-9-7 mms. in 17 minutes immersion. After the withdrawal it diminished soon to 3-2.5 mms.

The hyperglycaemia was a little larger and continued a little longer than before the demedullation of the suprarenal capsules, 0.141% being the acme, estimated 13 minutes after the withdrawal, and about one hour was the time required to see the normal level, reckoned from the stopping of the bath.

Such figures re the paradoxical pupil reaction and the blood sugar concentration on applying a cold bath are common.

In regard to the respiratory frequency and the heart beat rate this experiment yielded similar figures with those of before the demedullation.

Dog 5, Kazu, a young female.

Two weeks after removing the left cervical sympathetic ganglion, the dog was immersed in cold water at 6°. The dog made no struggle though it whined for a short time. The denervated pupil dilated on cooling, but only slowly. Before immersing it was 2 mms., 15 minutes after the beginning of the cooling it fluctuated between 2.5 mms. and 4 mms. When shivering became exaggerated and the dog was whining, it dilated distinctly, that is to 5 mms.; a few minutes later the dog struggled and had a further dilated pupil (7-8 mms.). After stopping the bath the pupil became narrow, as to 3 mms. and 15 minutes later to 2 mms. The diameter of the normal pupil was 4 mms. before cold, and when the dog was exposed to cold, it became enlarged with some fluctuations as 9-7-8-5-5-5-7-7-8-4-5-3 (shivering and whining)-4-3-6-7 (struggling)-10-7. On discontinuing the cooling, it narrowed to 4 mms. and finally to 2 mms.

The blood sugar content increased considerably, 0.197% being estimated 20 minutes after the withdrawal of the dog from the bath. Afterwards it was apt to decrease and 40 minutes later the preliminary value was recovered. The body temperature fell only by 4°; 35.1° being the actual degree. This was measured 20 minutes after withdrawal. About one and one half hours later the initial value was regained.

The respiratory rate increased during the cold bath, but some minutes after withdrawal it decreased. The heart rate increased during the bath, and further accelerated after withdrawal from the bath, but a half hour after withdrawal it tended to decrease and one and one half hours later the initial value was recovered.

This dog died before attempting the last series of experiments.

Dog 6, Jone, a young female.

One week after removing the left cervical sympathetic ganglion, the dog was chilled in cold water at 3°. Soon it struggled slightly, and then shivering began. The left, denervated pupil dilated soon, and rather slowly its maximum, 7 mms. 8 minutes from the beginning of chilling. 2 mms. was the initial width. The maximal width (6-7 mms.) continued seven minutes till 15 minutes after withdrawal of the dog from the bath. Afterwards it became much narrower, a little narrower than 3 mms. The right, normal pupil widened suddenly on immersing the animal in cold water, afterwards the width fluctu-

ated between 5-3-7-5 mms., and after withdrawal from the bath it became a little narrower; 5 mms. before the immersion and 4 mms. towards the end of the experiment 1-2 hours after the withdrawal.

The blood sugar concentration was found to be increasing after the withdrawal, and it continued to increase further till 0.188% 35 minutes after the withdrawal, and then decreased gradually, so that the hyperglycaemia period lasted for about two hours after the withdrawal. The lowest body temperature 28.9° was measured 15 minutes after the withdrawal, and one and one half hours later it was found to have nearly recovered the preliminary value.

The respiratory rate was somewhat diminished in general, during and after the cooling. The pulse rate increased during the cooling, after stopping it, it diminished, but afterwards a large acceleration was noted.

On the next day the right suprarenal gland was demedullated and one week later the left gland was operated on. 6 days later, that is three weeks after extirpation of the left cervical sympathetic ganglion, the dog was again cooled by dipping it into cold water at 3° for 13 minutes. The dog struggled soon for a while, and afterwards shivering commenced, finally the animal became depressed. The left, denervated pupil was 2 mms. wide before cooling, and dilated to 3 mms. 2 minutes after the beginning of the cooling, but soon, i.e. 3 minutes later the former size was resumed; afterwards the width remained wholly constant throughout the whole experimental course. The normal pupil first increased a little in diameter on cooling, but later it was apt to decrease, and after stopping the cooling it went further to decrease.

In this experiment the hyperglycaemia was of somewhat small magnitude, with 0.152% as the acme, 45 minutes after the withdrawal. The hyperglycaemic period covered about two hours after the withdrawal. The lowest body temperature was 27.8° , more or less lower than the experiment before the demedullation. Two hours after the withdrawal the body temperature was still lower than the initial.

The respiratory rate first decreased after the withdrawal of the animal from the water; the behaviour of the pulse rate was very similar to that before the demedullation.

In the foregoing 5 experiments the removal of the suprarenal medulla was proved to interfere largely with paradoxical pupil re-action due to cooling, while the cold hyperglycaemia was either never notably or not at all affected by the removal. But the time which was allowed to elapse from the removal of the superior cervical gan-

gion to the cooling experiment was always in favour of the control experiment, i. e. the cooling experiment before the demedullation. That is, the control experiment was made while the pupil is most sensitive to adrenaline. In the last experiment (Exp. 6) the second cooling was carried out three weeks after the extirpation of the superior cervical ganglion. The results were the same as the others.

In the next experiments no control experiments were run; only the animals were first deprived of the suprarenal medulla, followed by the ganglionectomy and cooled one to three weeks after the last operation.

Dog 7, a young male.

First the right suprarenal gland was demedullated, and later the left. Then the upper cervical sympathetic ganglion was removed, followed by a cooling experiment with an interval of one week. Each operation was carried out with about one week's interval.

The dog was immersed in cold water at 5° for 19 minutes. At first the dog was excited and struggled for a while. 12 minutes after the onset of the cooling shivering began. The left, denervated pupil, with an initial diameter of 1.5 mms., soon dilated to 2 mms., and further to 2.5 mms. almost simultaneously with the onset of the shivering, but seven minutes later it returned to 2 mms., which was held for about fifty minutes after the withdrawal of the animal from water. The dog became depressant soon after the withdrawal, and shivering became more violent, about half an hour later they weakened. The normal pupil dilated on dipping the dog into cold water, with some fluctuations during the cold bath, as from 4 mms. to 5-7-8-5-6-5-7-8, and nearly returned to the initial when the dog was taken out from the bath.

The blood sugar concentration was already increased when the dog was taken out of the cold water, but it continued to increase till 0.154% about fifty minutes after the withdrawal; 45 minutes later the initial value (0.096%) was again found. The body temperature was lowest (27°) a few minutes after the withdrawal, and about two hours later a complete recovery occurred in the body temperature.

The respiratory rate was accelerated in the bath, but became less after the withdrawal of the animal therefrom. The pulse rate increased in the bath, and decreased after the withdrawal, while the body temperature was low. And it was distinctly accelerated when the body temperature was ascending, but still subnormal (35-37°), but later it tended to descend.

One week later another cooling experiment was carried out. A

water bath at 5° was given for 18 minutes. Immediately the dog struggled for a while. 5 minutes later shiverings started. 3 minutes still later the dog whined, 6 minutes still later it became depressed and the shivering was violent.

The denervated pupil, with an initial width of 1.5 mms., dilated at once to 3 mms., a few minutes later to 2.5 mms., which continued for only 5 minutes. Later it was reduced to 2 mms., but dilated again to 2.5 mms., while the dog was shivering violently and incessantly, after the withdrawal from the bath. The normal pupil dilated at once on applying cold, to 10 mms. from 3 mms., after a short period of immersion it was 5–6 mms.; after the withdrawal it fluctuated for three hours between 6–9 mms.

The blood sugar concentration was highest (0.143%) 15 minutes after the withdrawal, and fifty minutes later complete recovery was noted. The lowest body temperature (30°) appeared at the same time with the acme of hyperglycaemia. Of the respiratory and pulse frequency almost the same as of the foregoing experiment may be said.

Dog 8, a young female.

On 18. XI. 33 right demedullation, on 25. left demedullation. On 2. XII. L. Ganglion cervicale superius removed, n. auricularis cut. On 12. XII. first cooling experiment, in cold water at 5° for 30 minutes. At first the dog struggled, 12 minutes later shivering commenced, 12 minutes still later shivering became violent, the dog whined. About 25 minutes after the onset of the cooling the dog was depressed. After withdrawal shivering was violent, about half an hour later they nearly died away.

The denervated pupil dilated on cooling to 1.5 mms. from 1 mms., and continued so still 5 minutes after withdrawal from the bath. The control pupil dilated too, with a diameter of 3–6 mms., during the cooling. The blood sugar level increased only to 0.123% 15 minutes after the withdrawal. Thirty minutes later the hyperglycaemia disappeared. 30.4° was the lowest body temperature, noted 5 minutes after the withdrawal.

The respiration was accelerated during the bath and about one hour after the withdrawal. Of the heart rate only it may be added that the reduction during the low body temperature after the withdrawal was very small.

On 23. XII. the dog was again cooled, three weeks from the ganglionectomy. 35 minutes in cold water at 3°. This time the paradoxical pupil reaction was of somewhat shorter duration (2 mms. for 7 minutes from 20 minutes after the beginning of the cold bath, against

1 mm. of initial width). The limits of blood sugar and the body temperature were 0.135% and 28.8° respectively. They appeared 15 minutes after the withdrawal. One and half hours later 0.08% was noted of the blood sugar content.

Dog 9, a young male.

The cold experiment was performed on 17. I. 1934; three weeks before both suprarenals were deprived of the medullary tissue, and 3 days before the left cervical sympathetic ganglion was extirpated.

The temperature of the bath was 0.5°. The dog was excited and struggled, 5 minutes later shivering set in, then it whined. The cooling was continued for only 10 minutes; when the dog was taken out from the bath, it lay down, and shivered violently.

The denervated pupil dilated to 3 mms. from 2 mms., and continued so one hour after withdrawal from the bath. The right, nor-

EXAMPLE I.

Dog 9, (♂). Exp. II.

26. XII. 1933. 3.59 kilos. Bilateral demedullation of suprarenal glands.
13. I. 1934. 3.78 kilos. Extirpation of l. sup. cerv. gangl. and section of auricular nerve.
17. I. 1934. 3.86 kilos.

Time (hour: min.)	Blood sugar (%)	Body tempera- ture (°C.)	Frequen- cy of re- spiration (per min.)	Rate of heart beat (per min.)	Initial width of pupil (mms.)		Room temperature (°C.)
					r.	l.	
1:00 p.m.	0.100	37.9	24	144	6	2	17.5
1:8-20	Dog was dipped in cold water at 0.°5C for 12 minutes				8	3	R. pupil dilated at once, Animal began to shiver.
1:10					8	3	
1:11					7	3	
1:12					8	3	
1:13					8	4	
1:15					8	3	Dog was depressed, and whined.
1:17		33.0			8	3	
1:18					9	4	
1:20		31.0			8	4	Dog was taken from cold bath.
1:25	0.170	30.2	24	150	3	2	
1:35	0.189	30.5	30	204	4	2	Dog lay down, shivered markedly.
1:45	0.214	32.5	30	198	4	2	
1:55	0.189	34.9	24	210	5	2	Dog was unable to stand. 20
2:10	0.155	37.0	18	216	4	2	
2:25	0.116	37.5	18	186	4	2	Dog stood up, walked about. Recovery set in.
2:40	0.109	37.9	18	146	4	2	
3:00	0.109	37.9	12	146	4	2	21.5 Dog appeared normal.
3:15	0.105	38.1	18	"	4	2	
4:00	0.100	38.2	18	"	3	2	

mal pupil dilated at once in cold water; the width varied from 7–8–6 mms. in the bath, and became narrow after leaving the bath, and the initial value was regained at the same time with the denervated pupil.

The hyperglycaemia was considerable, with 0.217% twenty minutes after the withdrawal. One hour after the withdrawal there was a high blood sugar content, such as 0.118%; half an hour later the content was still higher than the initial, though insignificantly so. The lowest body temperature (29.9°) appeared 10 minutes after the withdrawal; two hours later it was nearly normal.

On the next day the dog was again cooled in a similar manner in a quantitative sense, and similar results were yielded, as the accompanying protocol shows, as an example.

10 days later the dog was immersed into cold water at 0° for 20 minutes, but this time no paradoxical pupil reaction occurred, though there appeared a moderate hyperglycaemia as 0.182% and a body temperature fall to 30.2°. The normal pupil dilated, and the heart rate varied in the usual manner.

Dog 10, a young male.

A severe colling, such as was applied to Dog 9, was tried with this dog as the control, one week after removal of the upper cervical sympathetic ganglion. The dog was dipped into cold water at 0.5° for 15 minutes, the paradoxical pupil reaction, the hyperglycaemia and the body temperature fall were considerable and lasted a long time. The protocol, reproduced here, speaks for itself. The reduction of pulse and breathing rate was also very remarkable.

The general outcome, quoted above, is summarized in the accompanying table in order to show it rather concisely.

In comparing the figures in both series of experiments, that is, with and without the suprarenal medulla, it is clear that the body temperature fell in quite the same magnitude in both sets, and further the blood sugar content increased also considerably on cooling. It is not fair to say with definiteness that there was some inferiority in the group of the dogs with the demedullated suprarenals. In respect to the blood sugar problem the present results harmonize with those of Wada, Seo and Abe, and also with those of Freund and Marchand, and of Ciaccio, in contrast with some recent observations in America.

The pupils of the dogs in which the upper cervical ganglion was extirpated, reacted with some dilatation in most cases when the dogs were cooled after the bilateral demedullation of the suprarenals, but

it was of definitely smaller scale in comparison to that in the dogs with intact suprarenal capsules. It was so in every case, without exception. The loss of the suprarenal medulla, namely, of the epinephrine secretion must be taken as responsible for this decided decrease in the paradoxical pupil reaction, as Hartman assumes. Hartman was unable to find any trace of the paradoxical pupil reaction on cooling cats after removing the suprarenal bodies. The ciliary ganglion also was removed in the work of Hartman.

These present findings are of more significance in that we were now able to see at the same time the blood sugar concentration hav-

EXAMPLE II.

Dog 10 (♂).

30. I. 1934. 3.6 kilos. Exstirpation of l. sup. cerv. ganglion and section of auricular nerve.

5. II. 1934. 3.55 kilos.

Time (hour: min.)	Blood sugar (%)	Body tempera- ture (°C.)	Frequen- cy of re- spiration (per min.)	Rate of heart beat (per min.)	Initial width of pupil (mms.)		Room temperature (°C.)
					r.	l.	
1:10 p.m.	0.107	38.5	12	114	3	2	16
1:30	Dog was immersed in cold water at $\frac{1}{2}$ C°.				5	5	Both pupils dilated immediately.
1:32					5	7	L. pupil became larger.
1:33					4	7	
1:35					3	7	Shivering started.
1:36					4	8	Dog was whining.
1:37					4	7	
1:38					5	8	
1:40		33			4	8	
1:42					4	8	Shivering increased.
1:43					4	9	
1:45		29 Dog was taken from cold bath.			4	9	
1:50	0.170	24.3	18	24	4	10	16
2:5	0.221	23.5	6	24	4	10	Dog lay down, the body temperature of dog decreased markedly, therefore it was placed near the steam heater. Continuous, vigorous shivering occurred.
2:15	0.211	25.3	12	54	4	10	
2:30	0.213	26.7	24	108	4	9	
2:45	0.207	28.2	24	108	4	9	
3:00	0.207	31.0	24	160	2	5	
3:15	0.207	33.6	18	180	2	3	Dog lay down, moved its head.
3:30	0.204	35.1	18	192	2	3	Stood up, walked about.
3:45	0.202	36.0	24	144	4	2	Recovery set in.
4:10	0.175	37.4	24	168	4	2	17
4:30	0.152	37.5	24	168	4	2	
5:00	0.120	38.0	24	144	4	2	
5:30	0.108	38.4	24	144	4	2	

ing been increased just as in the dogs with intact glands in accordance with the experimentalists in this Laboratory, who were able, on the other hand, to find the same reaction in the denervated organ, such as the heart, as before demedullation. It must then be a question in the first place, whether or not such a difference is to be attributable to different kinds of organs; further investigations are required in this respect.

In respect to the divergency between the paradoxical pupil reaction and the blood sugar concentration on cooling in the dogs with demedullated suprarenals, we remember the results of asphyxia experiments of Kellaway,¹⁵⁾ noting that the blood sugar was more sensitive than the pupil paradox after the suprarenal glands were extirpated, while the two phenomena appeared, or failed to appear, together so long as the glands were intact.

SUMMARY.

The upper cervical sympathetic ganglion was removed unilaterally in a number of dogs. They were cooled by means of cold water; the body temperature fell commonly to 30° or beneath. The pupil width and the blood sugar concentration were determined. Paradoxical pupil reaction and hyperglycaemia invariably occurred. Then the suprarenal glands were bilaterally deprived of their medullary tissues. On cooling the paradoxical pupil reaction still occurred, but only on a largely diminished scale, while hyperglycaemia of sufficient strength was brought about simultaneously. Then, the relation between the time elapsed after the ganglionectomy and the sensibility of the denervated pupil being taken into consideration, the removal of the suprarenal medulla was carried out before that of the upper cervical ganglion, and cooling was carried out from a few days to three weeks after the latter operation. The results were similar.

It may be therefore concluded that removal of the suprarenal medulla or abolishing the epinephrine secretion from the suprarenal glands, interferes largely with the paradoxical pupil dilatation due to cold stimulations to dogs, while it never significantly influences the hyperglycaemia.

15) Kellaway, J. of Physiol., 1919(-20), 53, 225-230.

On proof-reading: In a recent paper (Am. J. of Physiol., 1935 (October), 113, 251) Cannon and Rosenblueth mentioned that when adrenaline and sympathins evoked nearly equal responses of the nictitating membrane of cats, in which the upper cervical ganglion had been removed, sympathins caused only a slight dilatation of the pupil while adrenaline provoked a marked dilatation.