Action of Morphine on the Epinephrine Output, Blood Sugar Content and Blood Pressure in Dogs.*

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Nearly all the experiments attacking the question relating to the action of morphine on the epinephrine liberation have brought about affirmative evidence, although there are some data betraying shortcomings in the techniques employed. Only Stewart and Rogoff who were successful in finding an augmenting effect of this drug in cats failed to do so when dogs were tested by means of one and the same method as employed for cats.

The Cleveland physiologists¹⁾ collected the blood by means of the cava pocket method from the suprarenals of cats and dogs, anaesthetized with ether or urethane, and estimated the epinephrine in the blood by the rabbit intestine segment method. After the administration of morphine sulphate, subcutaneously or intravenously, ether was given only a little from time to time. In all the cats, four in number, the output rate of epinephrine was invariably increased; as much as 10 times the initial rate was observed. But no dogs indicated on the other hand any remarkable increase in the output rate, when they received morphine sulphate in subcutaneous doses of about 20–14 mgrms. per kilo of body weight or in intravenous doses of about 4–6 mgrms. per kilo. The difference in the action of morphine upon the cat and the dog is therefore, they noted, as striking in this particular as in its other effects.

To the donor dog with the suprarenal-jugular anastomosis Houssay and his co-adjustors²⁾ gave morphine in a dose of 0.03 mgrm. per

* The essentials of this paper were read before the XI. Annual Meeting of the Japan Physiological Society, held at Niigata, 1932, April.

1) Stewart and Rogoff, Jour. of Pharm. and Exp. Ther., 1922, 19, 59.

2) Houssay, Lewis and Molinelli, C. R. Soc. Biol., 1924, 91, 1013.

kilo hypodermically, then in 4 out of 7 cases hyperglycaemia was elicited in both the donor and recipient. Double splanchnicotomy prevented the occurrence of hyperglycaemia in the recipient. Molinelli³⁾ came to see further an augmented secretion of epinephrine due to morphine in the dogs provided with the suprarenal-jugular anastomosis, the blood pressure and pulse-rate in the recipient being measured this time as the indicators of the epinephrine hypersecretion in the donor. Hayama was able to abolish nearly or wholly the sedative action of the morphine injection upon the intestine movements of rabbits *in situ* by either tying the suprarenal veins or removing the glands themselves or by interfering with the splanchnic nerves bilaterally,⁴⁾ and further noted an increase of the epinephrine concentration of the carotid blood in rabbits 5 and 15 minutes after an intravenous injection of morphine, the citrate blood according to Trendelenburg and Yagi being applied to the rabbit ear vessels. The increase was annulled by the double removal of the glands or by double splanchnicotomy.⁵⁾ Hayashi⁶⁾ fastened rabbits and collected the jugular vein blood, the serum of which was tested for epinephrine according to the method of Chikano. 0.032–0.06 mgrm. in 1 c.c. was the epinephrine value before morphine—an astonishingly large concentration, and that 2.5–3 hours after morphine was 0.046–0.132 mgrm. in 1 c.c.

Harmon and McFall,⁷⁾ cut in cats, anaesthetized with ether, the vagosympathetic nerves, removed the stellate ganglia, and the thoracic sympathetic chains to the level of 6 or 7 ribs, and some endeavours were paid to hold the body temperature as uniform as possible by an electric heating pad. When the suprarenals were tied and in most cases the nerves strands on the duodeno-hepatic artery cut, morphine sulphate, given subcutaneously or intravenously, had little or no effect upon the rate of the denervated heart, but when the suprarenal glands were not tied and the liver not denervated, the denervated heart was accelerated in the rhythm by morphine in 8 cases out of 14. They further related that the suprarenals are only responsible for this acceleration because no acceleration occurred on morphine intoxication when the suprarenals only were tied, but the liver not denervated. In all the experiments no food was given for 24 hours before the operation. It is rather interesting to see in respect to this drug that the accelerating action was

3) Molinelli, *La secrecion de adrenalina*, Buenos Aires 1926, 257.

4) Hayama, *Folia Jap. Pharmacol.*, 1928, 7, 128 (Jap.), German abstract p. 10.

5) Hayama, *Ibid.*, 1928, 7, 137 (Jap.), German abstract p. 10.

6) Hayashi, *Jour. of Orient. Med.*, 1928, 9, 681 (Jap.), English abstract p. 62.

7) Harmon and McFall, *Jour. of Pharm. and Exp. Ther.*, 1929, 37, 147.

invariably noted in Cleveland and some negative cases were noted in Boston, on working with the same kind of animal. London and Kotschneff⁸⁾ injected into white mice the blood from the suprarenal gland of the dog and decapitated them 2 hours later and estimated the blood sugar. According to London and Kotschneff morphine is the most effective stimulant of the epinephrine secretion.

It is a well established fact that double splanchnicotomy or suprarenalectomy largely diminishes the intensity of the hyperglycaemia due to morphine.⁹⁾ From such findings some writers deduced an accelerating effect of the drug upon the epinephrine discharge. It is also unquestionable that morphine intoxication reduces the epinephrine load of the suprarenal gland.⁹⁾

Now in order to know quantitatively the accelerating influence of morphine upon the epinephrine liberation rate of the normal animal, undisturbed by any other complicating factors, the following investigations were carried out.

METHODS :

The D₁₀-L₃ dorsal spinal roots of dogs were severed under ether-chloroform narcosis but not as a rule by morphine. Three weeks or later the morphine experiment was carried out. The suprarenal vein blood was collected, the vein exposed through the lumbar route without anaesthesia¹⁰⁾ and the epinephrine was estimated by means of the rabbit intestine segment, adrenalin hydrochloride of Sankyo Co. being taken as the standard.¹¹⁾

Morphine has a certain effect upon the intestine movement, as described by Uhlmann and Abelin¹²⁾ with a complete review of that matter and also by some subsequent writers.¹³⁾ In estimating the epinephrine we have paid some care to this matter; as the indifferent blood or the control blood we have taken the blood sample from the jugular or saphena vein at the same time with the corresponding sample from the suprarenal vein.

As is to be seen from the intestine tracings no visible influence upon the intestine movement and tone was produced by morphine in such an amount existing in the general blood. The doses applied in the present researches were

8) London and Kotschneff, *Proc. Soc. Exp. Biol. and Med.*, 19(30-31), 28, 1003.

9) Tada, *Tohoku Jour. of Exp. Med.*, 1932, 19, 405. A rather complete review re this question is given in the paper of Tada. This may be supplemented by a recent paper of MacKay, *Jour. of Pharm. and Exp. Ther.*, 1931, 43, 51.

10) Satake, Sugawara and Watanabe, *Tohoku Jour. of Exp. Med.*, 1927, 8, 501.

11) Sugawara, Watanabe and Saito, *Ibid.*, 1926, 7, 6-9.

12) Uhlmann and Abelin, *Ztschr. f. exp. Path. u. Ther.*, 1920, 21, 58.

13) Tachikawa, *Jour. of Orient. Med.*, 1932, 17, 521 (Jap.), English abstract p. 37.

really less than the threshold value found by the previous experimentalists as capable of interfering with the intestine movements, provided the amount injected be uniformly distributed in the total blood of the animal. Even when 40 mgrms. morphine per kilo were subcutaneously injected (Dog No. 3), practically no modification occurred in the intestine movements by applying the blood from the general circulation.

To determine the sugar concentration by Hagedorn and Jensen, blood samples were taken from the lumbar, jugular or saphena vein. The arterial blood pressure was registered from the femoral artery connected with the Hg-manometer throughout the whole observation period.

Morphine hydrochloride was injected as a 2 or 4 per cent solution in the physiological saline solution under the skin in the deafferented area or into the jugular or saphena vein. Intravenously 2, 4 or 8 mgrms. per kilo body weight were dosaged, and hypodermically 10, 20 or 40 mgrms.

The general symptoms, heart rate, respiratory frequency, anal temperature and room temperature were noted from time to time.

RESULTS :

Three dogs received the drug subcutaneously and the other three intravenously.

A. Subcutaneous cases.

10 mgrms. morphine hydrochloride per kilo body weight. This dose was given to Dog 1, weighing 15 kilos, and the epinephrine output rate was remarkably augmented thereby. The rate before morphine was about 0.000006-7 mgrm. per kilo per minute, 11 minutes after morphine it increased to 0.000032 mgrm. per kilo per minute, and about a half hour after morphine 0.00016 mgrm. And the rate measured after further lapse of 30 minutes was nearly the same. 30 minutes later the rate was halved, but further one hour later the rate was found only a little decreased, that is a velocity about ten folds the initial was recorded. These increases in the liberation rate are due in fact largely to the increase in the epinephrine concentration; the rate of the blood flowing through the gland only being nearly doubled after the morphine administration.

The blood sugar, which was 0.11% before morphine, became a little lower 10 minutes after the injection, and 20 minutes later it was apt to recover, when the rate of the epinephrine liberation was found largely accelerated as to attain the peak in this case. 30 and 60 mi-

minutes later 0.14% was estimated; at the latter estimation the epinephrine liberation rate already showed a tendency to descend from the acme. One hour later the initial value of the blood sugar was regained, but at this moment an augmented liberation of epinephrine was still going.

The blood pressure rose but only slowly on injecting morphine, about four minutes after morphine there were recorded the waves of Traube and Hering, the period of which was measured as 10 to 15 seconds and also were visible for about 4 minutes, and the peak of the pressure (180 mms. Hg.) was reached 6 minutes after the injection, then it tended to decrease but only very slowly. At the time when the mean blood pressure reached the peak, the rate of the epinephrine liberation was probably at the beginning of the ascending limb. In the descending limb no abrupt change occurred.

The heart beat rate also showed a tendency to increase at first on morphine, the initial and that 3–8 minutes after the injection being recorded as 126 beats per minute and 216 beats respectively, but later the rate decreased, and in fact a half hour after the administration the slow rate as 84 beats per minute was established, and remained nearly so throughout the whole experimental course.

The respiratory frequency increased remarkably on the injection but only for some minutes, the anal temperature fell gradually, 1 degree in the lapse of 2.5 hours. Vomiting occurred 6 minutes after the injection when the blood pressure reached the peak, and about fifty minutes elapsed before the narcotic effect of the drug became prominent and it progressed further.

In this case the rate of the epinephrine secretion was ad maximum about thirty times accelerated, and the blood sugar concentration increased from 0.09% to 0.14%. And the variation of the former always preceded that of the latter. The blood pressure rise occurred very early, and when the acceleration of the epinephrine output reached the acme the arterial pressure had already resumed nearly the initial height, and the heart rate was also slow.

20 mgrms. morphine per kilo. This dose was tried on Dog 2 with 11.6 kilos body weight. On cutting the dorsal roots about five months before morphine was applied as narcosis in addition to ether and chloroform.

15, 30, 60, 90 and 150 minutes after morphine the blood samples were taken. In the suprarenal venous blood the epinephrine content was found always increased, as 3.5–5 times the initial value, and consequently the rate of the epinephrine liberation was calculated as increased about 2–5 times the initial rate. The sample taken 30 minutes after morphine showed only a relatively small increase in the rate because of a remarkable diminution in the outflow rate of the blood from

the gland. No notable change was recorded re the mean arterial blood pressure height; the heart beat became very slow, and in a rather early stage of the intoxication sometimes 4–8 beats were followed by a pause in the beating.

The blood sugar estimated 15 minutes after morphine was 0.193 %, the highest of the determinations, and thereafter the concentration decreased slowly, but at the end of 2.5 hours of the poisoning it was still higher than the initial. The body temperature fell as usual, 35.4° being noted 2.5 hours after morphine against 38.1° before it.

40 mgrms. morphine per kilo were given to Dog 3, of 18 kilos. The data are given as Example 1, and the epinephrine matter in the Table.

Example I.

Dog 3. 18. III. 1931. 18.0 kilos ♂.

[D₁₀-L₃ dorsal spinal roots excised under ether-chloroform anaesthesia]
[about a month prior to the morphine experiment (13. II. 1931, 21.8 kilos).]

- 10:10–11:20 a.m. The left lumbar route preparation, and the mercury manometer connected with the left femoral artery.
- 1:30 p.m. I suprarenal specimen, 2.3 c.c. in 40 seconds (3.4 c.c. per minute). Lying down, quiet.
- 1:31 II specimen, 1.6 c.c. in 30 seconds (3.2 c.c. per minute). Blood pressure 96 mms. Hg. Blood sugar content 0.089%. Body temperature 38.7°. Pulse 90 per minute. Respiration 15 per minute. Room temperature 22°.
- 1:40 Hypodermic injection of 18 c.c. 4% morphine hydrochloride (40 mgrms. per kilo body weight.) in the denervated area. Occupied 15 seconds. Blood pressure 100 mms. Hg.; no change immediately after injection.
- 1:50 III specimen, 3.0 c.c. in 30 seconds (6.0 c.c. per minute). Blood pressure 78 mms. Hg., blood sugar 0.081%.
- 1:51 IV specimen, 2.1 c.c. in 20 seconds (6.3 c.c. per minute). Condition about the same. Room temperature 21°, body temperature 38.0°, pulse 108, respiration 15.
- 2: 3 Reflexes increased, but dog lay quietly. Both pupils small.
- 2:10 V specimen, 2.6 c.c. in 30 seconds (5.2 c.c. per minute). Blood pressure 90 mms. Hg., blood sugar 0.113%.
- 2:11 VI specimen, 1.7 c.c. in 20 seconds (5.1 c.c. per minute).
- 2:14 Room temperature 21.5°, body temperature 37.7°, pulse 102, respiration 18. Condition of animal as before.
- 2:40 VII specimen, 2.3 c.c. in 30 seconds (4.6 c.c. per minute). Blood pressure 94 mms. Hg., blood sugar 0.122%.
- 2:41 VIII specimen, 1.6 c.c. in 20 seconds (4.8 c.c. per minute). More sleepy, reflexes increased.
- 2:43 Room temperature 21°, anal temperature 37.2°, heart rate 108, respiration 18, pupils small, eye reflexes present.
- 3:10 IX specimen, 2.3 c.c. in 30 seconds (4.6 c.c. per minute). Blood pressure 94 mms. Hg., blood sugar 0.131%.
- 3:11 X specimen, 1.6 c.c. in 20 seconds (4.8 c.c. per minute).

- 3:14 p.m. Room temperature 21°, body temperature 37.3°, heart rate 126, respiration 15, less sleepy.
- 3:40 XI and XII specimens, 2.0 c.c. in 30 seconds and 1.2 c.c. in 20 seconds (4.0 c.c. and 3.6 c.c. per minute). Blood pressure 90 mms. Hg., blood sugar 0.154%. Room temperature 21°, anal temperature 36.9°, heart rate 114, respiration 15, condition about the same.
- 4:10 XIII and XIV specimens, 2.0 c.c. in 30 seconds and 1.3 c.c. in 20 seconds (4.0 c.c. and 3.9 c.c. per minute) respectively. Blood pressure 90 mms. Hg., blood sugar 0.136%.
- 4:13 Room temperature 20°, anal temperature 36.9°, heart rate 114, respiration 15, reflexes slightly increased, but dog lay quietly.
- 5:10 XV and XVI specimens, 3.7 c.c. in 60 seconds and 2.0 c.c. in 30 seconds (3.7 c.c. and 4.0 c.c. per minute) respectively, blood pressure 92 mms. Hg., blood sugar 0.129%.
- 5:14 Room temperature 17.5°, anal temperature 36.8°, heart rate 114, respiration 15, behavior about the same as before the injection.
- 5:30 The wound sewed up. About 50 c.c. indifferent blood shed from the femoral artery.

Fig. 1 a (Reduced to $\frac{1}{2}$). Fig. 1 b (Reduced to $\frac{1}{2}$).

Intestine tracings* (Reduced to $\frac{2}{3}$).

Fig. 2 a. I: Quite similar to 0.00025 mgrm. and II.

II: Almost as strong as I; decidedly weaker than 0.0005 mgrm.

XV: Far stronger than 0.0005 mgrm. and far weaker than 0.00015 mgrm.

Fig. 2 b. XV: About the same with 0.0001 mgrm. (Obs. 7 and 8).

XIII: Stronger than 0.0001 mgrm. and weaker than 0.00015 mgrm.

XI: Weaker than 0.00015 mgrm., almost as strong as 0.0001 mgrm. (Obs. 11, 12 and 13).

A very little weaker than IX.

IX: A little stronger than XI.

Fig. 2 c. IX: About as strong as VII (Obs. 14 and 15).

VII: Almost as strong as IX and far weaker than 0.0002 mgrm.

V: Decidedly weaker than 0.0002 mgrm., almost as strong as or a very little weaker than 0.00015 mgrm. and a little weaker than VII.

VII: A little stronger than V and decidedly stronger than 0.0001 mgrm.

* 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 blood solution.

All the blood solutions were prepared by diluting with 4 volumes of Tyrode's solution and the quantity of blood employed for one assay was 0.5 c.c. Time intervals 30 seconds.

"0.05 1/2000" shows "0.05 c.c. of adrenalin chloride solution with the concentration of 1/2000 mgrm. in 1 c.c." i. e. 0.000025 mgrm. adrenalin chloride.

Fig. 2. d. III: Far weaker than 0.0001 mgrm. (Obs. 21 and 22). Weaker than 0.00005 mgrm. and almost as strong as 0.000025 mgrm.

To sum up:

I: Quite similar to 0.000025 mgrm. and II. It was taken as 0.00005 mgrm. in 1 c.c.

II: Almost as strong as I (0.000025 mgrm.); decidedly weaker than 0.00005 mgrm. It was assayed at 0.00005 mgrm. in 1 c.c.

III: Far weaker than 0.0001 mgrm. Weaker than 0.00005 mgrm. and almost as strong as 0.000025 mgrm. It was taken as 0.00005 mgrm. per 1 c.c.

V: Decidedly weaker than 0.0002 mgrm., almost as strong as or a very little weaker than 0.00015 mgrm. and a little weaker than VII (0.000175). It was assayed at 0.0003 mgrm. per 1 c.c.

VII: Almost as strong as IX (0.000175) and far weaker than 0.0002 mgrm. A little stronger than V (0.00015 mgrm.), and decidedly stronger than 0.0001 mgrm. It was taken as 0.00035 mgrm. in 1 c.c.

IX: A little stronger than XI (0.0001). About as strong as VII (0.000175 mgrm.). It was taken as 0.00035 mgrm. in 1 c.c.

XI: Weaker than 0.00015 mgrm., almost as strong as 0.0001 mgrm. A very little weaker than IX. It was assayed at 0.0002 mgrm. per 1 c.c.

XIII: Stronger than 0.0001 mgrm. and weaker than 0.00015 mgrm. It was assayed at 0.00025 mgrm. in 1 c.c.

XV: Far stronger than 0.00005 mgrm. and far weaker than 0.00015 mgrm. About the same with 0.0001 mgrm. It was assayed at 0.0002 mgrm. in 1 c.c.

The epinephrine output rate in the normal state of the dog was a little less than 0.00001 mgrm. per kilo per minute. On receiving this dose of morphine the sample taken 10 minutes thereafter indicated the rate about doubled, but at this moment the blood sugar content was found rather decreased, just as in Experiment 1, but in this case the blood pressure curve underwent no noticeable alteration as the accompanying figure, Fig. 1 shows, in contrast to Exp. 1. Then both the epinephrine discharge velocity and the blood sugar content increased step by step, and the former reached the acme 60–90 minutes after the injection, about 0.00009 mgrm. per kilo per minute, viz. about 10 times the initial, and the latter the peak of 0.154% 30–60 minutes later. At the end of 3.5 hours of the intoxication both values were still definitely larger than the initial. The increase in the output rate was in fact largely the result of the epinephrine concentration in the suprarenal vein blood, the outflow rate of which was also clearly increased at

once and showed a tendency to recover to the initial but only slowly. When the third sample which showed a better outflow from the gland was taken, the arterial pressure was a little low; afterwards the blood pressure nearly recovered the initial and remained so throughout the rest of the experimental course. It is thus impossible to find any definite relationship between the blood pressure variation and the change of the epinephrine output rate.

A half hour after the injection the respiration rate became a little decreased, but when another half hour had passed and the animal became more somnolent, it was somewhat accelerated, but later the initial rate was recovered. The pulse rate accelerated a little and the body temperature decreased.

B. Intravenous cases.

About 2 mgrms. morphine hydrochloride per kilo body weight were intravenously given into Dog 4, 9.8 kilos. This dog received morphine in an intravenous dose 8 mgrms. per kilo about one month before and showed a large augmentation of the epinephrine liberation.

This time the liberation rate was also accelerated, and was found about five times as large one 18 minutes after the injection; at this time the outflow rate of the blood from the gland was doubled and the epinephrine concentration trebled. 7 minutes after the injection both the estimations, liberation and sugar, were already increased, the latter reached its peak later than the former. The peak exceeded the initial by 0.047%. About one hundred minutes later both values were clearly larger than the initial.

The injection was followed by a small immediate rise of the arterial pressure, which was soon replaced by a small transitory fall. Afterwards there were some variations, rather irregular, in the blood pressure curve, but they were on a small scale and had nothing to do with those in the epinephrine output rate. No increase occurred in the pulse rate, but only a reduction. Tachypnoea set in soon after the injection and lasted about a half hour. The respiration rate which was 24 per minute before the injection, increased to 258 per minute soon after the injection. Then it decreased but gradually. The body temperature fell from 38.1° to 36.6° in two hours.

The animal became uneasy 20 minutes after the injection and further 10 minutes elapsed before drowsiness appeared, but it was never very deep.

4 mgrms. morphine per kilo to Dog No. 5, weighing 16.1 kilos. This experiment is reproduced in Example II. When the injection

Example II.

Dog 5. 4. III. 1931. 16.1 kilos ♂.

[D₁₀-L₃ dorsal spinal roots severed under ether-
chloroform anaesthesia (10. XII. 1930, 19.5 kilos).]

- 10: 0-11:10 a.m. The left lumbar route preparation. Lumbar region bent, but the gait nearly normal.
- 11:15 The mercury manometer connected with the right femoral artery, and the left saphena vein prepared for injection.
- 1:30 p.m. I suprarenal specimen, 3.0 c.c. in 30 seconds (6.0 c.c. per minute). Blood pressure 104 mms. Hg., blood sugar 0.119%.
- 1:31 II specimen, 2.9 c.c. in 30 seconds (5.8 c.c. per minute).
- 1:33 Room temperature 19°, body temperature 38.0°, heart beat 90 per minute, respiration 15 per minute.
- 1:40 Intravenous injection of 3.25 c.c. 2% morphine hydrochloride into L saphena vein (4 mgrms. per kilo of body weight). Immediately after the injection, agony, defecation, laboured breathing. Some minutes later the animal spastic and then very weak, pulse feeble.
- 1:46 III and IV specimens 2.9 c.c. and 3.1 c.c. in 30 seconds (5.8 c.c. and 6.2 c.c. per minute). Blood pressure 78 mms. Hg., blood sugar 0.126%, room temperature 19°, anal temperature 38.0°, heart rate 114, not so weak, respiration 18.
- 2: 0 V and VI specimens, 2.6 c.c. in 30 seconds and 1.8 c.c. in 20 seconds (5.2 c.c. and 5.4 c.c. per minute). Lay quietly as if asleep, reflexes slightly increased, pupils small, blood pressure 76 mms. Hg., blood sugar 0.128%.
- 2: 4 Room temperature 19°, body temperature 37.5°, heart beat 66, respiration 18.
- 2:30 VII and VIII specimens, 2.5 c.c. in 30 seconds and 1.9 c.c. in 20 seconds (5.0 c.c. and 5.7 c.c. per minute). Blood pressure 80 mms. Hg., blood sugar 0.132%.
- 2:33 Room temperature 19°, body temperature 37.3°, heart beat 60, respiration 18.
- 3: 0 IX and X specimens, 2.6 c.c. in 30 seconds and 1.5 c.c. in 15 seconds (5.2 c.c. and 6.0 c.c. per minute). Conditions about same. Blood pressure 76 mms. Hg., blood sugar 0.141%.
- 3: 4 Room temperature 9.5°, body temperature 36.6°, heart beat 54, respiration 12.
- 3:40 XI and XII specimens, 2.5 c.c. in 40 seconds and 1.3 c.c. in 20 seconds (3.8 c.c. and 3.9 c.c. per minute). Blood pressure 86 mms. Hg., blood sugar 0.137%, lips dry, pupils small, palpebral fissures wide, reflexes increased, lifted the head from time to time.
- 3:44 Room temperature 20°, body temperature 36.3°, heart beat 54, respiration 12.
- 4:40 XIII and XIV specimens, 2.3 c.c. in 40 seconds and 1.3 c.c. in 20 seconds (3.4 c.c. and 3.9 c.c. per minute). Blood pressure 94 mms. Hg., blood sugar 0.091%.
- 4:44 Room temperature 19°, body temperature 35.3°, heart rate 48, respiration 12. Dog lay quietly, less active, eyes same as before.
- 5:35 XV and XVI specimens, 2.8 c.c. in 40 seconds and 1.5 c.c. in 20 seconds (4.2 c.c. and 4.5 c.c. per minute). Blood pressure 96 mms. Hg., blood sugar 0.088%.
- 5:37 Room temperature 19°, body temperature 35.2°, heart beat 54, respiration 12. Behavior about the same as before the injection.
- 5:45 Shed about 100 c.c. indifferent blood from the femoral artery.
- 6: 0 The wound sewed up.

Fig. 3 a (Reduced to $\frac{1}{2}$). Fig. 3 b (Reduced to $\frac{1}{2}$).Intestine tracings (Reduced to $\frac{1}{2}$).

Fig. 4 a. I: Weaker than 0.00005 mgrm., about the same with 0.000025 mgrm (Obs. 2, 3 and 4) and about the same with II.

II: As strong as I and a very little weaker than 0.000025 mgrm.

XV: Stronger than 0.000025 mgrm.

Fig. 4 b. XV: Weaker than 0.00005 mgrm. (Obs. 7 & 8).

XIII: As strong as 0.00005 mgrm. and weaker than XI.

XI: Stronger than XIII, as strong as 0.0001 mgrm. and about the same with IX.

IX: About the same with XI and weaker than 0.00015 mgrm.

Fig. 4 c. VII: A little weaker than 0.00015 mgrm. (Obs. 14 and 15) and a little stronger than V.

V: A little weaker than VII and almost as strong as 0.0001 mgrm.

III: Far stronger than 0.0001 mgrm., stronger than 0.0002 mgrm. and about the same with 0.0003 mgrm.

To sum up:

I: Weaker than 0.00005 mgrm., about the same with 0.000025 mgrm. and about the same with II. It was assayed at 0.00005 mgrm. per 1 c.c.

II: As strong as I (0.000025 mgrm.) and a very little weaker than 0.000025 mgrm. It was taken as 0.00005 mgrm. in 1 c.c.

III: Far stronger than 0.0001 mgrm., stronger than 0.0002 mgrm. and about the same with 0.0003 mgrm. It was assayed at 0.0006 mgrm. in 1 c.c.

V: A little weaker than VII (0.000125 mgrm.) and almost as strong as 0.0001 mgrm. It was taken as 0.0002 mgrm. per 1 c.c.

VII: A little weaker than 0.00015 mgrm. and a little stronger than V. It was assumed as 0.00025 mgrm. per 1 c.c.

IX: About the same with XI (0.0001 mgrm.) and weaker than 0.00015 mgrm. It was assayed at 0.0002 mgrm. in 1 c.c.

XI: Stronger than XIII (0.00005 mgrm.), as strong as 0.0001 mgrm. and about the same with IX. It was assayed at 0.0002 mgrm. per 1 c.c.

XIII: As strong as 0.00005 mgrm. and weaker than XI. It was taken as 0.0001 mgrm. in 1 c.c.

XV: Stronger than 0.000025 mgrm. Weaker than 0.00005 mgrm. It was assayed at 0.000075 mgrm. in 1 c.c.

was performed the mean blood pressure ascended from about 100 mms. Hg. to about 140 mms. Hg. at once, then pretty rapidly decreased to about 30 mms. Hg. which was recorded 2 minutes after the injection, and then a gradual recovery occurred so that it was about 80 mms. Hg. 4 minutes later when the third suprarenal vein blood specimen

was collected. Afterwards the recovery progressed only slowly, but 3 hours after the injection the initial value was nearly resumed, as the accompanying figure, Fig. 3 shows. The morphine slow pulse was also evident in the advanced stage of intoxication. The pulse rate began to increase on the injection, on the ascending limb of the blood pressure the increase was clear, and on the descending limb the large rhythm as 228 beats per minute was noted, and at the bottom of the pressure, that is about 2 minutes after the injection, the rate was still large as about 180 per minute, and then apt to decrease gradually, so that 5 minutes after the injection 150 per minute was the rate. Six minutes elapsed from the injection to the first collection of the suprarenal vein blood sample under influence of morphine, and this sample showed an increase in the epinephrine discharge rate, about ten times the initial, which is due solely to the increase of epinephrine in the blood. At this time the blood sugar content was found also increased, but the epinephrine output rate was found by the subsequent collections to decrease gradually, so that the initial rate was regained at the end of about two hundred minutes of poisoning, while the blood sugar tended to increase and reached its acme 0.140% 80 minutes after morphine injection. By this case it is also plainly shown that the acceleration of the epinephrine secretion precedes by far the increase of the blood sugar content. When there was an exaggerated liberation of epinephrine the blood pressure was low, but when the latter was the case, the former was not so certain.

The breathing became laboured soon after the injection, but later the frequency was restored to the usual value; the body temperature fell from 38.0° to 35.2° during 3.5 hours of intoxication.

8 mgrms. morphine per kilo was the dose for Dog 6, with the body weight of just 10 kilos. As to the blood pressure the similar figure with the foregoing case was observed, that is the pressure rose on beginning the injection but only transitorily, and before ending it the pressure began to decrease and in a few seconds thereafter the bottom was reached, and only very gradually it tended to recover, but at the end of 2.5 hours of the poisoning the pressure had not yet wholly recovered. The pulse rate decreased at once, then once recovered the initial, but it decreased again by degrees. No increase above the initial was ever recorded.

5 minutes after the injection when the blood pressure was low as 55 mms. Hg. the first sample under morphine was tested with a definite increase of the output velocity of epinephrine, as about twenty times the initial. For this increase that of epinephrine content in the blood was responsible. Simultaneously the blood sugar concentration increased too, as from 0.11% to 0.15%. The epinephrine output

rate tended then to diminish, but about two hours after the injection it was five times the initial; on the contrary the blood sugar increased further, about 1.5 hours after the injection it was measured as 0.165%. One hour later it descended to 0.14%. A mutual relationship between the variations of the three items, the epinephrine output rate the blood sugar and the blood pressure, was thus similar to that in Dog No. 5. Tachypnoea followed the injection, similarly also to Dog No. 5; it lasted only for a while. The body temperature fell from 38.6° to 37.7° only.

In every experiment an acceleration was produced in the epinephrine output rate on giving morphine; hyperglycaemia also occurred. When it was given hypodermically in doses 10, 20 or 40 mgrms. per kilo body weight the maximum liberation rate was estimated respectively as 0.00017 mgrm. per kilo per minute, 0.00053 mgrm. and 0.00009 mgrm. at the end of about 1 to 1.5 hours of intoxication. Otherwise expressed, 25, 5 or 10 times the initial rate were found as the peak of acceleration. In three cases of intravenous application the figures were 0.00007 mgrm. per kilo per minute, 0.00022 mgrm. and 0.00058 mgrm., and they were estimated a few minutes after the injection. About 5, 10 or 20 times the initial rate were thus seen. The peak of the accelerated secretion appeared about one hour after the subcutaneous application and within ten minutes after the intravenous.

To Dogs 2 and 4 morphine was once given prior to the present experiment, but many days before, as 150 days and 23 days respectively, too long a spell to think of the effect of the first administration, were allowed to elapse between the two injections. The acceleration in the epinephrine output rate and the fall in the arterial pressure in Dog 4 can be taken as somewhat smaller compared with the scale in Dogs 5 and 6, provided the effects be taken nearly proportional to the doses, but the blood sugar increased more largely in Dog 4, than in Dog 5 receiving double the dose of Dog 4. Only it may be noted in passing that Tachikawa¹⁴⁾ was able to see a decrease in the blood sugar content and also the epinephrine content of the blood in the general circulation on giving morphine to dogs in a condition of tolerance against morphine. The latter was estimated from the arterial blood treated with sodium citrate by means of the rabbit ear perfusion.

The doses of morphine, here applied, were similar to those of Stewart and Rogoff for dogs. Their failure to detect an increase in the epinephrine output rate thereby may be explained by the inadequateness of their experimental conditions. In interpreting the difference in the outcome in both Laboratories, Cleveland and Sendai, in this manner, we do not wish to question the value of their findings, viz:- that there is a striking difference in the action of morphine upon the cat and dog in respect to the epinephrine liberation as in its other pharmacological effects.

It may be added that in the present experiments morphine, given in the above doses, never occasioned respiratory failure and reflex excitability usually increased—a commonly known symptom, while in a dog of Stewart and Rogoff (Dog 620), which received an intravenous injection of 6.2 mgrms. morphine sulphate per kilo, a similar dose as with us, respiration ceased so that artificial respiration was employed for a while and no increase of reflex excitability was observed.

The blood sugar concentration increased on morphine as usual. The time elapsing before the peak was reached was usually one to one and half or two hours for both kinds of application, subcutaneous and intravenous, and it was rather uniform in cases of the intravenous injection. Only 15 minutes were needed in a single case of subcutaneous injection (No. 2). And the maximum concentration was 0.14–0.19% in the subcutaneous cases and 0.14–0.16% in the intravenous.

In two instances of the former group, a transient decrease preceded development of the hyperglycaemia phase.

At any rate the increase in the blood sugar concentration set in as a rule later than that in the epinephrine output rate; both peaks were separated by one hour or more. The latter developed abruptly, especially in the intravenous cases, while the former rather slowly, as illustrated in the Figure 5. The blood sugar figures are no different

Fig. 5. Epinephrine output rate per kilo per minute (solid lines) and blood sugar content (dotted lines) are given here, the initials being schematically as 0.00001 and 0.1 respectively. The values in Dog 3, which received 40 mgrms. morphine per kilo subcutaneously are expressed with solid circles and there in Dog 5, poisoned with 4 mgrms. per kilo intravenously with light circles. Thus solid circles with solid lines indicate the epinephrine output rate in mgrm. per kilo per minute in Dog 3; light circles with solid lines that in Dog 5; solid circles with dotted lines the blood sugar content in Dog 3 and light circles with dotted lines that in Dog 5.

in both application modi, subcutaneous or intravenous, as above related. The descending limb of both estimations shows a rough parallelism. Only Dog No. 2 betrayed strange features, the blood sugar

increased abruptly contrary to the rest of the cases, and the epinephrine output curve showed two summits.

The magnitude and the time course of the epinephrine secretion during the morphine poisoning in Dogs 5 and 6 find some similarities in the average pattern of Kaiwa¹⁴⁾ for the acceleration of the epinephrine discharge on peptone. According to that pattern Kaiwa gave intravenously adrenaline hydrochloride to a number of dogs, and measured the blood sugar concentration. If now such data of Kaiwa and those in our Dogs 5 and 6 be compared with each other, one can readily a striking difference in the duration of the hyperglycaemia, that is in the morphine experiments the high level of the sugar content lasted incomparably longer than in the adrenaline experiment of Kaiwa. It is scarcely necessary to say that in order to acknowledge the rôle of the augmented secretion of epinephrine due to morphine for the blood sugar increase simultaneously occurring a special trial must be made such as to introduce adrenaline hydrochloride solution with the velocity with which epinephrine is liberated on morphine poisoning with simultaneous injection of morphine into the dog rendered incapable of secreting epinephrine but suffering no other disturbing manipulations.

On subcutaneous application the blood pressure did not show any definite change, in one case (No. 1, 10 mgrms. per kilo) it ascended but slowly, in another (Dog 3, 40 mgrms. per kilo) it fell in the later stage, and in the third it fell a little for some time. On intravenous application a transient, small elevation occurred at once, but was replaced by a long-lasting, severe depression, which finally but slowly tended to disappear. In Dog 4, receiving 2 mgrms. morphine per kilo, the variation was of a small magnitude.

The finding in Dogs 1 and 2 in which nausea and vomiting occurred 4-6 minutes after the injection with accompanying accelerated pulse (for example, initial 126 beats per minute and 216 beats immediately before this vomiting in Dog 1.) coincides well with the view of Egmond,¹⁵⁾ but it must be remembered that in the other instances of the accelerated pulsation we were not able to see the nausea or vomiting. The case of Dog 3, in which the heart rate was 90 beats per minute before the injection and always found as increased on intoxicating, may possibly find its analogy in a patient suffering from spinal progressive muscle atrophy of Hoesslin.¹⁶⁾

In three dogs (Nos. 1, 4 & 6) tachypnoea occurred on the morphine administration for a while, and in the rest no material alteration occurred in the breathing frequency.

14) Kaiwa, *Tohoku Jour. of Exp. Med.*, 1933, **20**, 401.

15) Egmond, *Arch. f. exp. Path. u. Pharm.*, 1911, **65**, 199-200.

16) Hoesslin, *Kl. W.*, 1928, **7**, 2401.

TABLE.

*The epinephrine output, blood sugar content, blood pressure, etc.
after administration of morphine.*

Number of specimen	Time of collection (min.)	Blood flow (c.c.)				Epinephrine output (mgrm.)			Blood pressure (mms. Hg.)	Blood sugar (%)	Body temperature (°C.)	Heart beat (per min.)	Frequency of respiration (per min.)	
		Quantity	Duration (sec.)	Quantity per minute	Quantity per kilo per minute	in 1 c.c. blood	per minute	per kilo per minute						
Dog 1. 15.0 kilos ♂ 4. II. 1931. Both hind legs somewhat ataxic. (22. XI. 1930. 14.7 kilos. L ₃ -D ₁₀ dorsal spinal roots severed under ether-chloroform narcosis.) 10: 5 a.m.-11:20 Left lumbar route preparation. 1:45 p.m. Experimented on as follows:—(Room temperature 19°)														
I	before	5	2.0	60	2.0	0.13	0.00005	0.00010	0.0000067	130	0.111			
II		4	1.8	60	1.8	0.12	0.00005	0.00009	0.0000060			37.8	126	18
1:50 p.m. Injection: 7.5 c.c. of 2% morphine (10 mgrms. per kilo) subcutaneously in 10 sec.														
III	after	10	2.7	60	2.7	0.18				147	0.089			
IV		11	1.6	30	3.2	0.21	0.00015	0.00048	0.000032			37.8	126	108
V		30	2.3	40	3.4	0.23				144	0.105			
VI		31	2.3	40	3.4	0.23	0.00070	0.0024	0.00016			37.7	84	15
VII		60	2.3	40	3.4	0.23				132	0.141			
VIII		61	2.4	40	3.6	0.24	0.00070	0.0025	0.00017			37.3	78	18
IX		90	2.0	40	3.0	0.20				138	0.41			
X		91	1.8	30	3.6	0.24	0.00035	0.0013	0.000087			37.3	84	15
XI		150	1.8	40	2.7	0.18				143	0.110			
XII		151	1.6	30	3.2	0.21	0.00030	0.00096	0.000064			36.8	78	12
5:0 The wound sewed up. Vomiting 6 minutes after the injection. Respiration frequent and irregular about 10 minutes after the injection. 2:40 Getting sleepy, but aroused with ease. 3:30 More drowsy. 4:20 Condition about the same, but less sleepy.														
Dog 2. 11.6 kilos ♀ 28. I. 1931. Both hind limbs normal. (3. IX. 1930. 14.5 kilos. L ₃ -D ₁₀ dorsal spinal roots severed under ether-chloroform and morphine (about 7 c.c. of 2% solution) narcosis. 5. XI. 1930. 11.25 kilos. Chloralose experiment on the left suprarenal gland.) 10:30 a.m.-11:20 Right lumbar route preparation. 2:20 p.m. Experimented on as follows:—(Room temp. 18-20°)														
I	before	10	2.8	15	11.2	0.97	0.0001	0.0011	0.000095	130	0.104			
II		9	3.0	15	12.0	1.03	0.0001	0.0012	0.00010			38.1	102	15
2:30 p.m. Hypodermic injection of 11.6 c.c. 2% morphine hydrochloride (20 mgrms. per kilo).														
III	after	15	2.6	15	10.4	0.90	0.0005	0.0052	0.00045	142	0.193			
IV		16	2.1	15	8.4	0.72						37.1	84	18
V		30	2.1	20	6.3	0.54	0.0004	0.0025	0.00022	123	0.182			
VI		31	1.0	20	3.0	0.26						37.0	84	11
VII		60	2.8	15	11.2	0.97	0.00035	0.0039	0.00034	123	0.152			
VIII		61	2.6	15	10.4	0.90						36.7	84	12

Number of specimen	Time of collection (min.)	Blood flow (c.c.)				Epinephrine output (mgrm.)			Blood pressure (mms. Hg.)	Blood sugar (%)	Body temperature (°C.)	Heart beat (per min.)	Frequency of respiration (per min.)
		Quantity	Duration (sec.)	Quantity per minute	Quantity per kilo per minute	in 1 c.c. blood	per minute	per kilo per minute					
	after												
IX	90	2.8	15	11.2	0.97	0.00055	0.0062	0.00053	135	0.140			
X	91	2.8	15	11.2	0.97						36.1	78	12
XI	150	2.3	15	9.2	0.97	0.00045	0.0041	0.00035	131	0.116			
XII	151	2.3	15	9.2	0.79						35.4	62	15
	170	Final bleeding.											
		About 4 minutes after injection, nausea & vomiting. 2:40 p.m. Dog lay quietly, thereafter getting sleepy, but reflexes slightly increased.											
		3:5 Increase of reflex excitability; pupils small. 5:0 Animal appears to be normal just as before injection.											
		Dog 3. 18.0 kilos ♂ 18. III. 1931. Both hind legs ataxic.											
		(13. II. 1931. 21.8 kilos. L ₃ -D ₁₀ dorsal spinal roots severed under ether-chloroform narcosis.)											
		10:10-11:20 a.m. Left lumbar route preparation.											
		1:30 p.m. Experimented on as follows:—(Room temp. 17.5-22°)											
I	before												
II	10	2.3	40	3.4	0.19	0.00005	0.00017	0.0000094	96	0.089			
	9	1.6	30	3.2	0.18	0.00005	0.00016	0.0000089			38.7	90	15
		1:40 p.m. Hypodermic injection of 18 c.c. 4% morphine hydrochloricum. (40 mgrms. per kilo) in 15 sec.											
	after												
III	10	3.0	30	6.0	0.33	0.00005	0.00030	0.000017	78	0.081			
IV	11	2.1	20	6.3	0.35						38.0	108	15
V	30	2.6	30	5.2	0.29	0.0003	0.00156	0.000087	90	0.113			
VI	31	1.7	20	5.1	0.28						37.7	102	18
VII	60	2.3	30	4.6	0.26	0.00035	0.00161	0.000089	94	0.122			
VIII	61	1.6	20	4.8	0.27						37.2	108	18
IX	90	2.3	30	4.6	0.26	0.00035	0.00161	0.000089	94	0.131			
X	91	1.6	20	4.8	0.27						37.3	126	15
XI	120	2.0	30	4.0	0.22	0.0002	0.00080	0.000044	90	0.154			
XII	121	1.2	20	3.6	0.20						36.9	114	15
XIII	150	2.0	30	4.0	0.22	0.00025	0.0010	0.000056	90	0.136			
XIV	151	1.3	20	3.9	0.22						36.9	114	15
XV	210	3.7	60	3.7	0.21	0.0002	0.00074	0.000041	92	0.129			
XVI	211	2.0	30	4.0	0.22						36.8	114	15
	230	The wound sewed up.											
		The protocol of this experiment is reproduced in full as Example I.											
		Dog 4. 9.8 kilos ♂ 13. III. 1931. Both hind limbs normal.											
		(9. XII. 1930. 13.2 kilos. L ₃ -D ₁₀ dorsal spinal roots severed under ether-chloroform anaesthesia. 18. II. 1931. 10.0 kilos. Morphine experiment (Dog 6.) on left suprarenal gland.)											
		10:30 a.m.-12:0 m. Right lumbar route preparation.											
		1:40 p.m. Experimented on as follows:—(Room temperature 21-22°)											
I	before												
II	7	2.8	60	2.8	0.29	0.00005	0.00014	0.000014	160	0.100			
	6	2.5	60	2.5	0.26	0.00005	0.00012	0.000012			38.1	210	24
		1:47 p.m. Intravenous injection of 1 c.c. 2% morphine (ca. 2 mgrms. per kilo). Occupied about 10 seconds.											
III	after												
	7	2.2	60	2.2	0.22	0.0003	0.00066	0.000067	130	0.120			

Number of specimen	Time of collection (min.)	Blood flow (c.c.)				Epinephrine output (mgrm.)			Blood pressure (mms. Hg.)	Blood sugar (%)	Body temperature (°C.)	Heart beat (per min.)	Frequency of respiration (per min.)
		Quantity	Duration (sec.)	Quantity per minute	Quantity per kilo per minute	in 1 c.c. blood	per minute	per kilo per minute					
IV	after 8	2.0	60	2.0	0.20								
V	18	2.3	30	4.6	0.47	0.00015	0.00069	0.00007	133	0.130	38.1	180	210
VI	19	2.3	30	4.6	0.47								
VII	60	0.8	30	1.6	0.16	0.00025	0.00040	0.000041	142	0.147	37.0	126	168
VIII	61	1.5	60	1.5	0.15								
IX	98	2.1	60	2.1	0.21	0.0002	0.00042	0.000043	136	0.139	37.2	138	66
X	99	1.4	60	1.4	0.14								
	134	2:4 p.m. Slight salivation. Respiration 258 per minute, heart rate 210: Uneasy. 2:15 Slept, but waked with ease.											
		2:30 Less sleepy, reflexes slightly increased. 2:55 Nearly recovered, the conditions as before the injection.											
		Dog 5. 16.1 kilos ♂ 4. III. 1931. Both hind legs nearly normal.											
		(10. XII. 1930. 19.5 kilos. L ₃ -D ₁₀ dorsal spinal roots severed under ether-chloroform narcosis.)											
		10: 0-11:10 a.m. Left lumbar route prepared.											
		1:30 p.m. Experimented on as follows:—(Room temp. 19-20°)											
I	before	3.0	30	6.0	0.37	0.00005	0.00030	0.000019	104	0.119			
II	9	2.9	30	5.8	0.36	0.00005	0.00029	0.000018			38.0	90	15
		1:40 p.m. Intravenous injection of 3.2 c.c. 2% morphine (ca. 4 mgrms. per kilo).											
	after												
III	6	2.9	30	5.8	0.36	0.0006	0.0035	0.00022	78	0.126			
IV	7	3.1	30	6.2	0.38						38.0	114	18
V	20	2.6	30	5.2	0.32	0.0002	0.0010	0.000062	76	0.128			
VI	21	1.8	20	5.4	0.34						37.5	66	18
VII	50	2.5	30	5.0	0.31	0.00025	0.0012	0.000074	80	0.132			
VIII	51	1.9	20	5.7	0.35						37.3	60	18
IX	80	2.6	30	5.2	0.32	0.0002	0.0010	0.000062	76	0.141			
X	81	1.5	15	6.0	0.37						36.6	54	12
XI	120	2.5	40	3.8	0.24	0.0002	0.00076	0.000047	86	0.137			
XII	121	1.3	20	3.9	0.24						36.3	54	12
XIII	150	2.3	40	3.4	0.22	0.0001	0.00035	0.000022	94	0.091			
XIV	151	1.3	20	3.9	0.24						35.3	48	12
XV	205	2.8	40	4.2	0.26	0.000075	0.00031	0.000019	96	0.088			
XVI	206	1.5	20	4.5	0.28						35.2	54	12
		6:0 p.m. The wound sewed up.											
		The details of the experiment is shown in Example II.											
		Dog 6. 10.0 kilos ♂ 18. II. 1931. Both hind limbs normal.											
		(9. XII. 1930. 13.2 kilos. L ₃ -D ₁₀ dorsal spinal roots severed under ether-chloroform anaesthesia.)											
		11: 0 a.m.-12:0 m. Left lumbar route preparation.											
		2:35 p.m. Experimented on as follows:—(Room temp. 19°)											
I	before												
II	10	2.4	60	2.4	0.24	0.0001	0.00024	0.000024	114	0.115			
	9	1.5	30	3.0	0.30	0.0001	0.00030	0.000030		0.112	38.6	186	24
		2:45 p.m. Intravenous injection of 4 c.c. 2% morphine (8 mgrms. per kilo).											
		The injection occupied about 30 seconds.											

Number of specimen	Time of collection (min.)	Blood flow (c.c.)			Epinephrine output (mgrm.)			Blood pressure (mms. Hg.)	Blood sugar (%)	Body temperature (°C.)	Heart beat (per min.)	Frequency of respiration (per min.)
		Quantity	Duration (sec.)	Quantity per kilo per minute	in 1 c.c. blood	per minute	per kilo per minute					
	after											
III	5	1.8	30	3.6 0.36	0.0016	0.0058	0.00058	55	0.151			
IV	6	2.1	30	4.2 0.42						38.5	132	150
V	20	1.9	30	3.8 0.38	0.0010	0.0038	0.00038	55	0.158			
VI	21	2.0	30	4.0 0.40						38.3	180	90
VII	45	1.9	30	3.8 0.38	0.0010	0.0038	0.00038	82	0.111			
VIII	46	2.0	30	4.0 0.40						38.0	174	42
IX	80	2.8	30	5.6 0.56	0.0004	0.0022	0.00022	90	0.165			
X	81	2.0	20	6.0 0.60						37.9	168	36
XI	135	2.7	40	4.0 0.40	0.0004	0.0016	0.00016	102	0.138			
XII	136	1.4	20	4.2 0.42						37.7	132	15
	165	The wound sewed up.										

Soon after the injection, uneasiness, urination, salivation occurred, lay down and then appeared weak. The blood pressure rose a little (from 116 to 170 mms. Hg.) and then fell rapidly to 36 mms. which was recorded a few seconds after the end of injection. Some minutes after the injection, tachypnoea, set in and lasted about 15 minutes.

3:30 Lay quietly, drowsy, but wakend with ease. 4:30 Conditions same.

5: 0 The dog appeared somewhat weak.

SUMMARY.

Morphine hydrochloride was administered to the dogs, non-anaesthetized, non-fasted, but provided with the lumbar route preparation for collecting the suprarenal vein blood. Before and after morphine the velocity with which epinephrine is secreted from the suprarenal body was estimated. Epinephrine was determined by means of the rabbit intestine segment method. Blood sugar was simultaneously determined by Hagedorn and Jensen, the mean arterial pressure was also measured.

Morphine hydrochloride was applied subcutaneously in doses varying from 10 to 40 mgrms. per kilo of body weight, intravenously in those of 2 to 8 mgrms. Every application caused an accelerated secretion of epinephrine.

The epinephrine discharge rate increased in every case, its maximum rate being measured as 0.00007-0.00058 mgrm. per kilo per minute, that is about as much as 5 to 25 times the initial rate. The peak was attained about half an hour after the injection in the subcutaneous cases and within 10 minutes in the intravenous. In contrast to the epinephrine output rate the blood sugar concentration reached its acme rather slowly, viz. about one to two hours after the injection, and the

modi of application have apparently no significant influence upon the length of time needed for arriving at the acme.

Simultaneous recording of the mean arterial pressure did not yield any close relationship between its variation and that of the epinephrine output rate.