The Dependence of the Nature of Caffeine Diuresis upon the Dose used.

I.

Renal Oxygen Consumption and Blood Flow during Caffeine Diuresis.

By

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The dispute on the mechanism of the diuretic action of caffeine and its allies, an important pharmacological and also clinical question, is not yet settled. Besides the three well known theories, (1) that caffeine causes diuresis acting as a stimulant to the secretory kidney cells, (2) that it acts as a vasodilator to the blood vessels supplying the kidney and (3) that the caffeine diuresis is based upon the inhibition of the tubular reabsorption, Cushny's¹⁾ recent assertion, in which he attributes its diuresis to the reduced resistance of the glomerular capsule to filtration, is also noteworthy. Barcroft and Straub²⁾ measured directly the blood flow and oxygen consumption of the kidney under caffeine diuresis and found a very slight increase in the rate of blood flow, which seems to be insufficient to account for the diuresis and augmentation in the oxygen-intake during the diuretic period followed by a subsequent depression of the gaseous metabolism. Since the increase in the demand of an organ for oxygen indicates its raised activity, they concluded from this finding that caffeine acts as a diuretic not by its vasodilating effects, but by stimulating the renal secretory cells, whereby an accompanying of increased oxygen absorption is necessary.

1) Cushny, The secretion of urine, London 1917, 180.

2) Barcroft & Straub, Journ. Physiol., 1910-1911, 41, 145.

Conversely Miwa and Tamura,¹⁾ employing similar experimental methods observed no significant increase in the oxygen-intake during diuresis from caffeine and its allies, except diuretine which augments the oxygen consumption owing to its content of salicylate, nor was the blood flow through the kidney changed or even often decreased during the diuretic period. They suggested that the action of purine diuretics is based on the increase in active physiological permeability of the kidney cells.

Led by the divergence of these experimental results we have undertaken the present investigation repeating similar experiments, because it seemed very interesting to find out the source of the controversy and to add some contribution to the much vexed question about purine diuresis. As the alkaloids may act as renal poisons in quite different ways according to the amount used (which will later be fully discussed), in our experiments attention was especially devoted to the dose.

Experimental method: Our experiments were all performed on rabbits weighing 1.5-3 kilos, anaesthetized, with about 1 grm. urethane per kilo body weight. In each experiment determinations of (1) the rate of urine flow, (2) the blood pressure, (3) the rate of urine flow, (2) the blood flow through the renal vessels and (4) the oxygen consumption of the kidney per minute before and during the purine diuresis were made.

The general experimental method did not differ essentially from that introduced by Barcroft and Brodie,²⁾ except in some insignificant modifications. Cannulae were first inserted in an external jugular vein and the femoral artery, the arteria iliaca communis of the other side being ligated, and the carotid was as usual prepared to measure the blood pressure. After the abdomen had been opened, the rectum, both inferior and superior mesenteric arteries, the lowest end of oesophagus and the portal vein were, in the order here mentioned, doubly ligated and divided, and then the mesentery being tied *en masse*, all the digestive organs in the abdomen were removed, only the liver being left *in situ*. Almost all the veins entering the inferior vena cava, except both the renal veins and the left suprarenal vein, were ligated and loops were passed under this latter vein and the cava just above the point of entrance of the right renal vein respectively. Then a cannula for collecting the urine was inserted in the bladder, the inferior cava cramped at the the lowest point,

1) Miwa & Tamura, Mitteil. aus d. med. Fakultät d. kais. Univ. zu Tokio, 1920, 23, 350.

2) Barcroft & Brodie, Journ. Physiol., 1905, 32, 18.

cut, and a larger cannula inserted into its central end. For the measurement of the rate of the venous blood from the kidney, a 2 c.c. pipette with a bore sufficiently wide to prevent the venous congestion and specially marked at each point of 0.4 c.c., was connected to the cannula in the cava and held in a nearly horizontal position at the level of the cava. Both loops were raised until the veins were occluded, then releasing the clip on the cava, the blood which came from both kidneys was allowed to flow into the pipette and every moment where the meniscus of the blood column passed the marks, was marked on a kymograph moving at a uniform rate, which was expressed with Jaquet's time marker. 1 c.c. of this blood was taken for analysis of the blood gas which was performed with Barcroft's differential blood gas apparatus, and the remainder of the blood column was returned to the circulation by raising the pipette. A sample of arterial blood (1 c.c.) was collected from the femoral artery. The rate of the urine was measured by counting the urine drops per minute coming out of the cannula in the bladder.

The purine diuretics used in our experiments were caffeine, caffeine sodium benzoate, diuretine and agurine.

I. *Caffeine*. Caffeine purified by resublimation was dissolved in various doses in 5 c.c. Ringer's solution and injected into the jugular vein. The larger dose varied between 0.01-0.02 grm., the smaller one between 0.001-0.002 grm. A few examples of the experiments are described below:

Experiment 1 (0.001 grm caffeine).

Rabbit ♂ 1.6 kilos. Sep. 10, 1919.

- 135 7 c.c. 25% urethane subcutaneously injected.
- 200 Dissection commenced.
- 245 Dissection completed.
- 246-50 Urine flow: 7 drops (in 5 mins.).
- 251-60 Urine flow: 16 drops (in 10 mins.). Blood pressure: 96 mm. Hg.
- 300 Blood flow from both kidneys: 13 c.c. per min. 1 c.c. venous blood sample from kidney taken.
- 301 1 c.c. arterial blood sample taken. Renal oxygen consumption: 1450 c.mm. per min.
- 304 Blood pressure: 84 mm. Hg.
- 306-15 Urine flow: 2 drops (in 10 mins.).
- 315 0.001 grm. caffeine in 5 c.c. Ringer's solution intravenously injected.
- 316-20 Urine flow: 63 drops; 319-20 12 drops.
- 320 1 c.c. venous blood sample collected. Renal blood flow: 12 c.c.
- 321 Arterial blood sample collected. Oxygen consumption: 2245 c.mm. per min.

Experiment 2 (0.002 gm. caffeine, Fig. 1 a).

Rabbit ♂ 2.5 kilos. Sept. 1, 1919.

0⁵⁵ 3 grms. urethane hypodermically administered.2³⁵ Dissection completed.2⁴⁵ Blood pressure: 110 mm. Hg. Rate of urine flow: $\frac{1}{2}$ drops per min.2⁴⁶ Rate of blood flow through both kidneys: 12 c.c. Oxygen consumption of both kidneys: 1509 c.mm. per min.3¹⁰ Blood pressure: 100 mm. Hg. Rate of urine flow: $\frac{1}{2}$ drop per min.3¹¹ 0.002 gm. caffeine, dissolved in 5 c.c. Ringer's solution, injected in

right jugular vein.

- 314 Blood pressure: 100 mm. Hg. Rate of urine flow: 2 drops per min.
 315 Rate of renal blood flow: 13.5 c.c. per min.
 316 Oxygen consumption: 2560 c.mm. per min.
 325 Bled.

Experiment 3 (0.01 caffeine, Fig. 1 b).

Rabbit ♂ 2.1 kilos. Aug. 11, 1919.

- 11³⁵ 9 c.c. 25% urethane subcutaneously injected.
 11⁵⁰ Operation commenced.
 0⁵⁵ Operation completed.
 1³⁰ Blood pressure: 82 mm. Hg.
 1³¹⁻⁴⁰ Rate of urine flow: 6 drops (in 10 mins.).
 1⁴⁰ Venous blood sample taken. Rate of renal blood flow: 14 c.c. per min.
 1⁴¹ Arterial blood sample taken. Renal oxygen consumption: 940 c.mm. per min.
 1⁴¹⁻⁴⁵ No urine.
 1⁴⁶⁻⁵⁰ 3 drops of urine. Blood pressure: 70 mm. Hg.
 1⁵⁰ 0.01 gm. caffeine in 5 c.c. Ringer intravenously injected.
 1⁵¹⁻⁵⁴ Urine flow: 5 drops per min.
 1⁵⁵⁻⁵⁷ Urine flow: 18 drops per min.
 1⁵⁷ Blood pressure: 70 mm. Hg. Venous blood sample collected. Rate of blood flow: 12 c.c. per min.
 1⁵⁸ Arterial blood sample collected. Oxygen consumption: 804 c.mm. per min.

Experiment 4 (0.02 gm. caffeine).

Rabbit ♂ 2 kilos. Sept. 18, 1919.

Urethane. Operation.

- 3¹⁰ Operation completed.
 3⁵¹ Rate of urine flow: $\frac{2}{3}$ drops per min. Blood pressure: 104 mm. Hg.
 Rate of renal blood flow: 10 c.c. per min. Venous blood sample taken
 3⁵⁵ Arterial blood sample taken. Oxygen consumption of kidneys: 1569 c.mm. per min.
 4¹² Blood pressure: 88 mm. Hg. Rate of urine flow: $\frac{1}{3}$ drop per min.
 4¹³ 0.02 gm. caffeine in 5 c.c. Ringer intravenously injected.
 4¹⁶ Urine flow: 6 drops per min.
 4²² Blood pressure: 94 mm. Hg. Urine flow: 6 drops per min. Venous blood sample taken. Rate of renal blood flow: 2.0 c.c. per min.
 4²³ Arterial blood sample taken. Oxygen consumption: 576 c.mm. per min.
 Bled.

4 other experiments, in which two small and two large doses of caffeine were respectively injected yielded similar results.

II. *Caffeine sodium benzoate*. This double salt of caffeine purified before using and given into the jugular vein dissolved in 5 c.c. warm Ringer's solution, as a small dose 0.002-0.005 gm., as a large dose 0.03-0.05 gm., sometimes 0.1-0.2 gm. was administered.

Experiment 5 (0.002 grm. caffeine sodium benzoate).

Rabbit ♂ 1.7 kilos. Sept. 28, 1919.

Anaesthetic, dissection etc. as usual.

4¹⁰ Urine flow: 3 drops.4¹¹⁻²⁰ Urine flow: 1 drop.4²¹⁻³⁰ Urine flow: 2 drops.4³¹ Venous sample taken. Rate of renal blood flow: 13.3 c.c. per min.
Blood pressure: 130 mm. Hg.4³³ Arterial sample taken. Oxygen consumption of kidneys: 1048 c.mm. per min.4³¹⁻⁴⁰ Urine flow: none.4⁴¹⁻⁵⁰ Urine flow: 1 drop.4⁵² 0.002 grm. caffeine sodium benzoate injected.4⁵¹⁻⁶⁰ Urine flow: 9 drops.5⁰⁰ Blood pressure: 123 mm. Hg. Venous sample taken. Rate of blood flow: 15 c.c. per min.5⁰² Arterial sample taken. Oxygen used up: 1141 c.mm. per min.

Experiment 6 (0.005 grm. caffeine sodium benzoate).

Rabbit ♂ 2.2 kilos. Oct. 9, 1919.

2⁵⁰ Urethane.3⁵⁵ Operation finished.4¹⁰ No urine.4¹¹⁻¹⁵ Urine flow: 3 drops (in 5 mins.).4¹⁶⁻²⁵ Urine flow: 8 drops (in 10 mins.).4²⁵ Blood pressure: 105 mm. Hg. Venous blood sample taken. Rate of blood flow: 7.5 c.c. per min.4²⁶ 1 c.c. arterial blood taken. Oxygen consumption: 1560 c.mm. per min.4²⁶⁻³³ No urine flow.4³⁵ 0.005 grm. caffeine sodium benzoate in 5 c.c. Ringer administered.4³⁵⁻³⁷ Urine flow: 3 drops (in 2 mins.).4³⁸ Urine flow: 3 drops (in 1 min.).4³⁷⁻⁴⁰ Urine flow: 5 drops (in 2 mins.). Blood pressure: 100 mm. Hg.4⁴⁰ Venous blood sample taken. Rate of blood flow: 10 c.c. per min.4⁴¹ Arterial blood sample taken. Oxygen used up 1999 c.mm. per min.

Experiment 7 (0.03 grm. caffeine sodium benzoate).

Rabbit ♂ 1.8 kilos. Nov. 19, 1919.

Urethanized and operated as usual.

2⁴⁰ Operation finished.2⁴⁸ Rate of urine flow: 0.6 drop per min. Blood pressure: 106 mm. Hg.

Rate of blood flow: 12 c.c. per min. Venous blood sample collected.

2⁴⁹ Arterial blood sample collected. Oxygen consumption 2955 c.mm. per min.2⁴⁹⁻⁵⁸ Rate of urine flow: 0.6 drop per min. Blood pressure: 100 mm. Hg.3⁰⁰ 0.03 grm. caffeine sodium benzoate in 5 c.c. in Ringer's solution intravenously injected. The blood pressure rose after preliminary slight

fall to 103 mm. Hg. and the diuresis was affected immediately after the injection.

- 302-05 Rate of urine flow: 17-19 drops per min.
 305 Rate of renal blood flow: 11 c.c. per min. Venous blood sample taken.
 306 Arterial blood sample taken. Oxygen consumption 1786 c.mm. per min.
 310 Bled.

Experiment 8 (0.1 gm. caffeine sodium benzoate).

Rabbit ♂ 1.9 kilos. Febr. 2, 1920.

- 130 Urethanized.
 330 Operation completed.
 341-45 Urine flow: 4 drops.
 446-50 Urine flow: 2 drops.
 351-55 Urine flow: 5 drops. Blood pressure: 120 mm. Hg.
 356-60 Urine flow: 3 drops
 401-05 Urine flow: 1 drop.
 401 1 c.c. venous blood taken. Rate of blood flow: 12 c.c. per min.
 403 1 c.c. arterial blood taken. Oxygen consumed 576 c.mm. per min.
 406-10 No urine flow.
 411-15 Urine flow: 1 drop.
 416-25 No urine flow.
 424 Blood pressure: 110 mm. Hg.
 425 0.1 gm. caffeine sodium benzoate in 5 c.c. Ringer intravenously injected.
 426-27 No urine flow. Blood pressure: 95 mm. Hg.
 428-30 Urine flow: 16 drops.
 431-35 Urine flow: 35 drops.
 436-40 Urine flow: 17 drops.
 437 1 c.c. venous blood sample taken. Rate of blood flow 9 c.c. per min.
 438 1 c.c. arterial blood taken. Oxygen consumption 412 c.mm. per min.
 441-45 Urine flow: 3 drops.

Experiment 9 (0.2 gm. caffeine sodium benzoate).

Rabbit ♂ 1.8 kilos. Febr. 14, 1920.

Urethane and operation as usual.

- 240 Dissection completed.
 301-05 Urine flow: 7 drops.
 306-10 Urine flow: 6 drops.
 311-16 Urine flow: 10 drops.
 317 Venous blood sample taken. Rate of blood flow: 24 c.c. per min.
 319 Arterial blood sample taken. Oxygen consumed: 2223 c.mm. per min.
 316-20 Urine flow: 6 drops.
 321-25 Urine flow: 6 drops.
 326-30 Urine flow 5 drops.
 331-35 Urine flow: 3 drops. Blood pressure: 100 mm. Hg.
 336-40 Urine flow: 4 drops.
 341-45 Urine flow: 4 drops.

- 3⁴⁴ 0.2 gm. caffeine sodium benzoate in 5 c.c. Ringer's solution administered.
- 4⁴⁶⁻⁵⁰ Urine flow: 6 drops.
- 3⁵¹⁻⁵⁵ Urine flow: 14 drops. Blood pressure: 75 mm. Hg.
- 3⁵⁶⁻⁶⁰ Urine flow: 17 drops. Blood pressure: 80 mm. Hg.
- 4⁰¹⁻⁰³ Urine flow: 9 drops.
- 4⁰³ Venous blood sample taken. Rate of blood flow: 17 c.c. per min.
- 5⁰⁴ Arterial blood sample taken. Oxygen consumed 1554 c.mm. per min.

The protocols of 5 other experiments similarly performed with small and large doses of caffeine sodium benzoate are here omitted.

III. *Diuretine*. As representative of theobromine diuretics diuretine and agurine were used. 0.002-0.05 gm. diuretine (Knoll) dissolved in 5 c.c. Ringer's solution was intravenously injected and 12 experiments with smaller and larger doses varying from 0.002 and 0.05 gm. were performed. A few examples are given.

Experiment 10 (0.005 diuretine).

Rabbit ♂ 2 kilos. Febr. 1, 1920.

Urethanized and operated as usual.

- 0²¹⁻³⁰ Urine flow: 3 drops. Blood pressure: 180 mm. Hg.
- 0³¹⁻⁴⁰ Urine flow: 1 drop.
- 0⁴⁰ Venous blood sample collected. Rate of blood flow: 12.6 c.c.
- 0⁴² Arterial blood sample collected. Oxygen consumed: 768 c.mm. per min.
- 0⁴¹⁻⁵⁰ No urine flow.
- 0⁵¹⁻⁶⁰ 2 drops of urine.
- 1⁰¹⁻⁰² 0.005 gm. diuretine in 5 c.c. Ringer's solution intravenously injected.
- 1⁰²⁻¹⁰ 8 drops of urine.
- 1¹⁰ Venous blood sample collected. Rate of blood flow: 12 c.c. per min.
- 1¹² Arterial blood sample collected. Oxygen consumed: 1045 c.mm. per min.
- 1²⁹ No urine flow.

Experiment 11 (0.05 gm. diuretine).

Rabbit ♂ 1.9 kilos. June 9, 1919.

Urethane and operation as usual.

- 3²⁵ Operation finished.
- 4³⁰ Blood pressure: 140 mm. Hg. Rate of urine flow: 1.5 drops per min.
- 4³² Venous sample taken. Rate of renal blood flow: 20 c.c. per min.
- 4³³ Arterial sample taken. Oxygen consumption of both kidneys: 1285 c.mm. per min.
- 4⁴⁷ Blood pressure: 130 mm. Hg.
- 4⁴⁸ 0.05 gm. diuretine in 5 c.c. Ringer injected.
- 4⁵³ Rate of urine flow: 15 drops per min.
- 4⁵⁵ Blood pressure: 130 mm. Hg. Urine flow unchanged. Venous sample taken. Rate of blood flow: 15 c.c. per min.
- 4⁵⁶ Arterial sample taken. Oxygen consumed: 1005 c.mm. per min.

IV. *Agurine*. Agurine (Bayer) also dissolved in 5 c.c. Ringer's solution was injected in a dose of 0.005-0.05 gm., and 7 experiments in all, with various doses of the drug (2 with 0.005 gm., 2 others with 0.01 gm., 1 with 0.015 gm. and 2 more with 0.05 gm.) were performed. Examples of experiments :

Experiment 12 (0.005 gm. agurine).

Rabbit ♂ 2.4 kilos. Oct. 30, 1919.

Urethanized and operation ended at 4 o'clock.

- 4⁰¹⁻¹⁰ 2 drops of urine. Blood pressure : 110 mm. Hg.
- 4¹¹⁻¹⁵ 3 drops of urine.
- 4¹⁶ 1 c.c. venous blood taken. Rate of blood flow : 5.4 c.c. per min.
- 4¹⁸ 1 c.c. arterial blood taken. Oxygen consumed by the kidneys : 541 c.mm. per min.
- 4¹⁶⁻²⁵ No urine flow.
- 4²⁶⁻³⁰ 1 drop of urine. Blood pressure : 110 mm. Hg.
- 4³¹⁻⁴⁰ 3 drops of urine.
- 4⁴⁰ 0.005 gm. agurine in 5 c.c. Ringer's solution intravenously injected.
- 4⁴¹⁻⁴² 7 drops of urine.
- 4⁴³ 15 drops of urine.
- 4⁴⁴ 18 drops of urine.
- 4⁴⁵ 18 drops of urine.
- 4⁴⁵ 1 c.c. venous blood taken. Rate of blood flow : 5.8 c.c. per min.
- 4⁴⁷ 1 c.c. arterial blood taken. Oxygen consumption : 876 c.mm. per min.

Experiment 13 (0.05 gm. agurine).

Rabbit ♂ 2.1 kilos. Febr. 20, 1920.

Urethane. Operation.

- 11⁴⁰ Operation completed.
- 0⁰⁰ Commenced to collect urine.
- 0⁰¹⁻⁰⁵ No urine.
- 0⁰⁶⁻¹⁰ Urine flow : 1 drop.
- 0¹¹⁻¹⁵ Urine flow : 1 drop.
- 0¹⁶⁻²⁰ No urine. Blood pressure : 110 mm. Hg.
- 0²¹⁻²⁵ No urine.
- 0²⁶ Venous blood sample taken. Rate of blood flow : 17 c.c. per min.
- 0²⁸ Arterial blood sample taken. Oxygen consumption of the kidneys : 1087 c.mm. per min.
- 0²⁶⁻⁴⁰ No urine flow. Blood pressure : 100 mm. Hg.
- 0⁴⁰ 0.05 gm. agurine in 5 c.c. Ringer intravenously injected.
- 0⁴⁴ Diuresis commenced.
- 0⁴⁴⁻⁴⁵ Urine flow : 2 drops.
- 0⁴⁶⁻⁵⁰ Urine flow : 8 drops. Blood pressure : 85 mm. Hg.
- 0⁵¹⁻⁵⁴ Urine flow : 5 drops.
- 0⁵⁴ Venous sample taken. Rate of blood flow : 15 c.c. per min.
- 0⁵⁵ Arterial sample taken. Oxygen consumption : 953 c.mm. per min.

The result of these experiments and others which are not described above all agree in that a small amount of caffeine or its allies increases more or less the oxygen consumption and also often the blood flow of the kidneys, whilst a large dose acts in a contrary manner upon both the renal gaseous metabolism and blood flow. Our particular attention has been given to the choice of the dosage of drugs used. Since in our experiments the circulation of the blood was restricted in the upper half of the animal body upwards from the left kidney, most of the abdominal organs being eviscerated, there is a difficulty in comparing the dosage of the drugs employed in our experiments with that in many other researches made on similar question. With the same experimental method Barcroft and Straub¹⁾ injected 0.1 grm., and Miwa and Tamura²⁾ 0.2-0.4 grm. caffeine sodium benzoate, an amount corresponding to the large dose in our experiments. In Miwa and Tamura's experiments caffeine was administered in the dose of 0.15 grm., diuretine in the dose of 0.15-0.2-0.3 grm., and agurine in that of 0.2 grm. We tested varying quantities of the purine diuretics and injected as small dosage of caffeine 0.001-0.002 grm., and of caffeine sodium benzoate, diuretine or agurine 0.002-0.005 grm., and as large dosage 0.01-0.02 grm. of caffeine, and 0.05 grm. of the latter three drugs; sometimes 0.1-0.2 grm. caffeine sodium benzoate was examined as in the experiments of the authors above mentioned.

In most cases in our experiments the diuresis was interrupted or greatly depressed immediately after the collection of venous and arterial blood samples for gas analysis which amounted to only 2 or at most 3 c.c., so that we could not follow up the course of changes in the renal oxygen consumption and blood flow, the determination of which requires, repeated drawings of blood.

The measurement of the rate of blood flow from the kidney was made after the dissection when the flow of urine became uniform, and that after the injection of the drug, when the diuresis under caffeine reached its maximum. The diuresis sets in after a large dosage of the alkaloid later than after a small dosage, on an average 3-5 minutes after the injection, while the injection of a small dose is followed by immediate diuresis, which often begins during the injection. Sometimes the first effect of a large amount of caffeine is an oliguria of short duration followed

1) Barcroft & Straub, l. c.

2) Miwa & Tamura, l. c.

by a rapid flow of urine, as Phillips and Bradford¹⁾ observed. This checking action is the more marked, the larger the dose. In both cases it attains its maximum usually in a few minutes. Because of this difference of both dosages in relation to the time elapsing until the maximal diuresis occurs, we could not measure the renal blood flow in uniform time after the injection of the drugs at each dosage. After repeated injections of large doses the urine flow decreased or ceased, as has already been pointed out by many authors, owing to its poisonous action on the kidney.

The injection of caffeine and its allies into the jugular vein is often followed by an insignificant rise of the carotid pressure, but there is sometimes a preliminary short depression, which is, according to Phillips and Bradford, cardiac in origin. This preliminary fall of pressure is very frequently found after a large dosage of caffeine; for example see Exp. 9 and 10.

DISCUSSION AND SUMMARY.

A number of investigators ascribe the caffeine diuresis to the changes in the renal circulation. They observed with the oncometer or perfusion method dilatation of the kidney vessels under caffeine diuresis, but the fallacy of the conclusion made upon the change of the kidney vessels by means of the oncometer has already been pointed out (Loewi²⁾ and others). In perfusion experiments Munk³⁾ and others found dilatation of the renal vessels when caffeine was added to the perfusion fluid, but no diuresis followed. The same is also true of Richard and Plant's⁴⁾ recent experiments, in which the kidneys were kept alive by a special method of perfusion. Direct measurement of the renal blood supply also did not confirm a causal relation between caffeine diuresis and the increased circulation of the kidneys. Thus, in Landergren and Tigerstedt's⁵⁾ experiments which were made with the "Stromuhr" inserted in the renal artery, there was an augmented flow of renal blood, but it was accompanied by no diuresis. Schwarz⁶⁾ who measured with Pick's⁷⁾ method the outflow from the renal veins under

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- 1) Phillips & Bradford, *Journ. Physiol.*, 1887, **8**, 117.
 - 2) Loewi, Fletcher & Henderson, *Arch. f. exp. Path. u. Pharm.*, 1905, **53**, 15.
 - 3) Munk, *Virchow's Arch.*, 1887, **107**, 291.
 - 4) Richard & Plant, *Journ. Pharmacol. & Exp. Therap.*, 1915, **7**, 485.
 - 5) Landergren & Tigerstedt, *Skand. Arch. f. Physiol.*, 1893, **4**, 241.
 - 6) Schwarz, *Arch. f. exp. Path. u. Pharm.*, 1899, **43**, 1.
 - 7) Pick, *Arch. f. exp. Path. u. Pharm.*, 1899, **42**, 399.

positive caffeine diuresis found no significant increase of the blood flow. Also Barcroft and Straub¹⁾ ascertained after the injection of caffeine only a slight increase of the renal blood flow which was not to be accounted for the diuresis. Miwa and Tamura²⁾ demonstrated that sometimes even a depressed blood supply occurred during caffeine diuresis.*

In our experiments in which the venous blood flow from the kidneys was measured by the method introduced by Barcroft and Brodie,³⁾ as in Barcroft and Straub's and Miwa and Tamura's experiments, it has been noticed as the following table (Table I) shows, that in the cases of a small dosage of caffeine the rate of renal blood flow is often though not always, slightly augmented, whereas the effect of a large dose shows a tendency to depress the blood supply to the kidneys.

TABLE I.

1. Changes in the Renal Blood Flow and Blood Pressure after Injection of Caffeine in various dosages.					
No. of exp.	Blood pressure (mm. Hg.)	Renal blood flow, c.c. per min.	Dose injected (gram.)	Blood pressure (gram.)	Renal blood flow, c.c. per min.
1	96	13.2	0.001	96	12.0
2	80	4.4	0.002	70	7.2
3	110	8.0	0.002	96	9.6
4	110	12.0	0.002	100	13.5
5	124	6.0	0.01	110	6.0
6	82	10.2	0.01	72	9.6
7	104	10.0	0.02	94	2.0
2. Do. after Injection of Caffeine Sodium Benzoate.					
8	130	13.3	0.002	123	15.0
9	95	20.0	0.002	80	18.0
10	112	10.0	0.004	110	8.6
11	104	7.5	0.005	104	10.0
12	104	5.2	0.01	110	9.0
13	106	12.0	0.03	106	11.0
14	90	8.4	0.03	90	8.0
15	114	12.0	0.05	110	9.2
16	110	17.1	0.05	100	15.0
17	110	12.0	0.1	110	9.2
18	120	24.0	0.2	80	17.0

1) Barcroft & Straub, l.c.

2) Miwa & Tamura, l.c.

3) Barcroft & Brodie, l.c.

* In Cushny and Lambie's recent paper (Journ. Physiol., 1921, 55, 276) which has been published after the manuscript of our paper was completed, they observed an accelerated blood flow immediately after an injection of 0.02 gram. caffeine, but the diuresis began earlier and continued longer than it.

At any rate, these changes in the blood supply under caffeine diuresis either towards augmentation or decrement seem to be insufficient to account for the increased flow of urine.

The main sequel of our experiments is the fact that caffeine and its allies influence the gas metabolism of the kidneys in different ways according to the amount administered. A small dose augments, in most cases, more or less the oxygen-intake of the kidney, whilst the use of a large dose depresses it. So far as Barcroft's statement is true, that there is no instance in which it can be proved that an organ increases its activity under physiological conditions without increasing its demand for oxygen, this increase, though not very considerable, in the renal oxygen consumption during the resulting diuresis due to a small amount of caffeine may be of important significance for the interpretation of its diuretic action, if we think that only some parts of the kidneys are concerned in the secretion of urine and in all tissues of the kidney oxygen consumption is indispensable. This will be again discussed in our second paper.