On the action of some diuretica and other drugs upon the glomeruli.

By

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Substances which, when they enter the blood stream, increase the amount of urine formed by the kidneys are called diuretics and their diuretic action is produced by the increase of filtration in the glomeruli, or prevention of absorption in the tubules, or cooperation of these two processes. The increase of filtration in the glomeruli is caused by the following three cases.

1. Rise of blood pressure in the renal arterial system.
2. Velocity of blood flow in the kidney.
3. Hydraemia.

Diuretics are to have some one of these actions.

Since a long time, the experiments about the action of drugs upon the kidney have been performed by means of perfusion experiment or with oncometer. But in these experimental methods it can not be decided whether the action of drugs is upon the renal arteries or upon glomerular capillaries.

Hill and McQueen described experiments on glomerular capillary pressure in which they took direct observation of the frog's kidney.

Richards and Schmidt observed the state of glomerular circulation in the frog's kidney and the action of various drugs upon it.

Method of illumination and observation used by the latter two, was such as had been used by Krogh in his study of capillaries in muscles.

They reported that, when the experiment was conducted with minimal or no blood loss, a considerable increase in the number of glomeruli which received blood could be brought about by injection of urea, caffeine, glucose, and sodium sulphate, but on the other hand, decrease in the number of glomeruli which received blood could be effected by large doses of pituitrin and adrenalin.

I made the following experiments to examine the increase and decrease of the number of glomeruli and variation of the state of circulation in the glomerular capillaries through which blood flows, applying directly each solution of some diuretics and of other drugs to the exposed kidney of frog under observation with the microscope.

Method.

As I have mentioned in my previous papers, *Rana nigromaculata* was used in the majority of experiments. The animal was narcotized weakly with curara and then brain was destroyed. The kidney was exposed by longitudinal abdominal incision.

Illumination of the kidney was best secured by means of an arc-lamp. The rays were condensed and then were cooled by passing through a layer of water tinged with methylen blue.

A drop of solution of some diuretics and of other drugs were placed by means of a fine glass capillary which has been made as fine as possible, on the glomeruli in the kidney under observation with the microscope or a solution of these drugs was injected into the anterior abdominal vein in amounts of 0.05—0.1 cc and the following results were obtained.

1. Caffeine.

It has been known for a long time that caffeine causes dilatation of the blood vessels, and as I have mentioned in my previous papers, the blood capillaries are also dilated by it.

Douglass Cow found that caffeine, whilst moderately dilating the renal artery, produced an equal amount of dilatation in the case of the splenic artery but had no appreciable effect on the carotid artery.

When a drop of a solution stronger than 0.2 p. c. was placed on the glomeruli, the glomerular capillaries were dilated and accordingly the quantity of blood which flows

The following table shows the results of these experiments.

Case.	Concentration. %	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of circulation in the glomeruli.
			Before application	After applicat	
1	0.2	} dilated slightly.	3	5	} became more rapid.
2	"		3	4	
3	"		5	7	
4	"		4	4	
5	"		5	7	
1	0.5	} dilated.	4	7	} became more rapid.
2	"		6	8	
3	"		5	8	
4	"		6	7	
5	"		8	10	
1	1.0	} dilated extremely.	3	6	} became much more rapid.
2	"		4	7	
3	"		7	10	
4	"		5	9	
5	"		7	11	

through the glomerular capillaries was increased and the circulation in the glomerular capillaries became much more rapid. The glomeruli which had hitherto been stationary, became active and were congested and swollen.

A number of glomeruli unobserved until then became visible.

When a solution of caffeine stronger than 0.1 p. c. was injected into the anterior abdominal vein in amounts of 0.05—0.1 cc, the same results were obtained.

2. Caffeine sodio-benzoate.

When Caffeine sodio-benzoate was dropped on the glomeruli or injected into the anterior abdominal vein in amounts of 0.05—0.1 cc the same results were obtained as caffeine.

But the dilator effect produced by caffeine was generally more marked than that produced by caffeine sodio-benzoate.

3. Theocin and glucose (isotonic with 0.6% Ringer's solution).

These drugs had no effect upon the glomeruli when each drop of these drugs was placed on the exposed kidney surface or injected into the anterior abdominal vein.

4. Diuretin.

A solution stronger than 0.1 p. c. caused dilatation of glomerular capillaries, when it was dropped on the glomeruli or injected into the anterior abdominal vein and the circulation in the glomerular capillarie became more rapid. The quantity of blood which flows through the glomerular capillaries increased and accordingly the glomeruli got congested and swollen. The number of glomeruli increased.

The results of this experiment are shown in the following table.

Case.	Concentration. %	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of the state of circulation in the glomeruli.
			Before application	After applicat.	
1	0.1	} Dilated slightly.	7	8	} became more rapid.
2	"		3	5	
3	"		6	6	
4	"		4	5	
5	"		4	6	

1	0.3	} dilated.	3	5	} became more rapid.
2	"		5	7	
3	"		5	6	
4	"		3	5	
5	"		4	7	
1	0.5	} dilated remarkably.	6	8	} became much more rapid.
2	"		3	6	
3	"		5	10	
4	"		6	7	
5	"		3	4	
1	1.0	}	4	7	}
2	"		6	10	
3	"		4	6	
4	"		5	8	
5	"		7	11	

5. Liquor kalii acetici (Solution of potassium acetate).

When a solution stronger than 0.1 p. c. was applied in drops to the exposed kidney, the glomerular capillaries contracted and also the efferent- and afferent vessels contracted. The blood flow in the glomerular capillaries became remarkably slow and the quantity of blood which flows through them decreased. The glomeruli, hitherto active, became stationary and a number of glomeruli diminished.

The following table shows the results of this experiment.

Case.	Concentration. %	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of circulation in the glomeruli.
			Before application	After applicat	
1	0.1	} contracted.	5	3	} became slow remarkably.
2	"		4	1	
3	"		3	1	
4	"		4	0	
5	"		5	1	
1	0.3	} contracted remarkably.	3	0	} stopped in all cases.
2	"		5	1	
3	"		6	0	
1	0.5		5	0	
2	"		3	0	
3	"		7	1	

6. Kreatin.

A solution stronger than 0.2 p. c. caused dilatation of glomerular capillaries and the circulation in them became more rapid.

The quantity of blood flowing through them increased and accordingly the glomeruli got congested and swollen.

A number of glomeruli, hitherto unobserved, became visible.

7. Guanidin.

When a drop of solution weaker than 0.4 p. c. was applied to the exposed kidney, the glomerular capillaries were dilated and the circulation in them became more rapid. The glomeruli were congested and swollen, their number increasing in number. But on the contrary, a solution stronger than 0.5 p. c., when it was dropped on the kidney, caused contraction of glomerular capillaries and the quantity of blood which flows through them decreased.

The glomeruli, hitherto observed, became invisible.

When a 0.5 p. c. solution was injected in amount of 0.05 cc into the anterior abdominal vein, the circulation in the glomerular capillaries at first became more rapid and the quantity of blood flowing through them increased. But in no time the glomerular capillaries began to contract and the circulation in them stopped.

The following table shows the action of guanidin in various concentrations.

Case.	Concentration. %	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of the state of circulation in the glomeruli.
			Before application.	After applicat.	
1	0.3	} dilated.	5	6	} became more rapid.
2	"		4	7	
3	"		3	3	
4	"		4	6	
5	"		3	4	
1	0.5	} contracted.	6	4	} became remarkably slow or stopped.
2	"		3	1	
3	"		5	4	
4	"		3	2	
5	"		7	5	
1	0.8	} contracted remarkably !	3	0	} stopped in all cases.
2	"		7	3	
3	"		4	1	
4	"		6	2	
5	"		5	1	

The glomeruli, hitherto active, became stationary and at the same time a number of them became invisible.

During these experiments, when the convulsion occurred, the glomerular capillaries contracted without exception.

8. Sodium salts and potassium salts.

Various sodium salts and potassium salts which are isotonic with 0.6 p. c. Ringer's solution, were used.

It has been known for many years that the nitrites produce vaso dilatation.

Brunton, as long ago as in 1870, concluded that the lowering of blood pressure caused by nitrites, is due not to weakening of the heart's action, but to a dilatation of the vessels, and that this dilatation is due to the direct action of the drug upon the walls of vessels.

NaNO_3 , NaNO_2 and Na_2HPO_4 caused slight dilatation of the glomerular capillaries and the circulation in them became more rapid.

The quantity of blood flowing through them slightly increased.

Other sodium salts had no effect upon the glomeruli.

On the other hand, all the potassium salts caused a remarkable constriction of glomerular capillaries without exception. And the quantity of blood which flows through them decreased remarkably.

All of the glomeruli, hitherto active, became stationary and at last became invisible.

The following table shows the results of this experiment.

Drugs.	Concentration. %	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of the state of circulation in the glomeruli.
			Before application.	After applicat.	
NaBr	1.3	no change.	5	5	no change.
NaNO_3	1.0		4	5	
NaNO_2	0.8		3	5	
Na_2HPO_4	2.4	dilated slightly.	6	7	became more rapid.
NaJ	1.8		4	4	
Na_2SO_4	1.5		3	3	
NaHCO_3	0.9	no change.	8	8	no change.
KBr	1.5		7	1	
KNO_3	1.2		3	0	
KCl	0.9	contracted remarkably.	4	0	stopped completely.
KJ	1.4		8	1	
K_2CO_3	1.2		5	0	
KClO_3	1.2		6	1	
KS_2O_4	1.5		3	0	
KClO	0.9		7	0	

A drop of 0.1 p. c. solution of these potassium salts was applied to the kidney surface or injected into the anterior abdominal vein in amounts of 0.05—0.1 cc and the same results were obtained.

9. Calcium salts and Magnesium salts.

Hans Meyer has shown that the administration of calcium salts inhibits inflammatory exsudation, and that withdrawal of the normal calcium salts produce a hyperirritability of the sympathetic system towards adrenalin and other drugs. Douglas Cow found that when the arterial ring was placed in calcium free saline solution, and adrenalin and pituitrin instilled, a greater reaction occurred than followed by equal doses of these drugs when the experiment was performed in saline solution containing an excess of calcium salts.

1.0% CaCl_2 , 1.5% Ca_2NO_3 , 2.1% $\text{CaH}_4(\text{PO}_4)_2$, 1.5% MgCl_2 and 4.5% MgSO_4 were used and they are isotonic with 0.6% Ringer's solution.

All of these calcium salts and magnesium salts caused dilatation of glomerular capillaries and the circulation in them became much more rapid.

The glomeruli were congested and swollen and the number of them increased.

A 0.5 p. c. solution of these salts was dropped on the kidney or injected into the anterior abdominal vein and the same results were obtained.

In these experiments it seems that the effect of calcium salts is weaker than that of magnesium salts.

These results are shown in the following table.

Drugs.	Concentration. %	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of the state of circulation in the glomeruli.
			Before application.	After applicat.	
CaCl_2	1.0	} dilated remarkably.	4	6	} became much more rapid.
"	"		3	5	
Ca_2NO_3	1.5		3	4	
"	"		5	7	
$\text{CaH}_4(\text{PO}_4)_2$	2.1		4	6	
"	"		6	8	
MgCl_2	1.5		3	6	
"	"		5	8	
MgSO_4	4.5		4	9	
"	"		3	7	

10. Some organic substances.

A solution stronger than $\frac{m}{100}$ in density of these substances always produced a remarkable dilatation of glomerular capillaries and accordingly the circulation in them became much more rapid with the increase of the quantity of blood which flows through them.

The glomeruli, hitherto stationary, became active and the number of them increased. When a drop of 0.1 p. c. solution of potassium salts was dropped on the kidney surface, the glomeruli observed till then, became invisible and as soon as a drop of $\frac{m}{100}$ solution of hydrochinon was applied to that kidney, the glomeruli remaining unobserved became visible and active.

The following table shows the results of this experiment.

Drugs.	Concentration.	Variation of diameter of glomerular capillaries.	Variation of the number of glomeruli.		Variation of the state of circulation in the glomeruli.
			Before applicat.	After applicat.	
Hydrochinon.	$\frac{m}{100}$	} dilated remarkably.	4	6	} became much more rapid.
"	"		4	7	
"	$\frac{m}{10}$		3	5	
"	"		5	11	
Phrologultin.	$\frac{m}{100}$		3	4	
"	"		6	7	
"	$\frac{m}{10}$		5	7	
"	"		3	5	
Pyrogallol.	$\frac{m}{100}$		7	9	
"	"		3	5	
"	$\frac{m}{10}$		6	10	
"	"		4	8	

Summary.

From the results of my experiments the conclusion may be summarized as follows.

1. Caffeine, caffeine sodio-benzoate and diuretin have dilator effect upon the glomerular capillaries and the circulation in them becomes more rapid. The quantity of blood which flows through them increases and a number of glomeruli, hitherto unobserved, become visible.

On the other hand, theocin and glucose have no effect upon the glomeruli.

2. Solution of potassium acetate causes a remarkable contraction and at the same time the glomeruli till then observed, become invisible.

3. Kreatin produces a dilatation of glomerular capillaries and accordingly the circulation in them becomes more rapid and also the number of glomeruli increased.

Guanidin in a solution weaker than 0.4 p. c. causes dilatation of glomerular capillaries and increase of the quantity of blood which flows through them and also it causes the increase of verocity of blood flow in the glomerular capillaries. The glomeruli, hitherto stationary, become active and the number of them increases.

On the contrary, a solution stronger than 0.5 p. c. always causes contraction of glomerular capillaries and the number of glomeruli are decreased.

4. Isotonic solution (with 0.6% Ringer's solution) of NaNO_2 , NaNO_3 and Na_2HPO_4 causes a slight dilatation of glomerular capillaries and accordingly the increase of verocity of blood flow in them and of quantity of blood flowing through them are produced.

But other sodium salts have no effect upon the glomeruli.

All of potassium salts, on the contrary, have an opposite effect upon the glomeruli to that of sodium salts.

5. Calcium salts and magnesium salts (isotonic with 0.6% Ringer's solution) and some organic substances ($\frac{m}{100}$ in density) have a remarkable dilator effect upon the glomerular capillaries and cause the increase of verocity of blood flow in them and of quantity of blood which flows through them. Glomeruli are increased in number und are remarkably congested and swollen.

In conclusion, allow me to give my hearty thanks for my indebtedness to Prof. S. Oinuma.

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内 容 大 意

利尿劑並ニ其他ノ藥劑ノ腎臟絲絨體ニ及ボス作用ニ就テ

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利尿劑ノ利尿作用ハ絲絨體ニ於ケル濾過作用ヲ亢進スルカ細尿管ノ吸收ヲ抑制スルカ或ハ此兩者ヲ兼スルニ在リ、而シテ血管絨(絲絨體)ノ濾過ヲ亢進スルモノハ腎動脈系ノ血壓上騰、腎臟ニ於ケル血液灌流ノ速度及ビ血液中水分ノ増大即チ水血症ナリ果シテ利尿劑ハ絲絨體ニ對シ如何ナル影響ヲ及ボスモノナルヤヲ見ント欲シ次ノ實驗ヲ行ヘリ。

古來腎臟ニ對スル藥品ノ作用ハ灌流試験又ハ Oncometer ヲ以テ行ハルルヲ常トスルモ此場合カカル方法ニテハ腎絲絨體ニ作用スル結果ナルヤ又腎臟動脈ニ作用スルモノナルヤヲ判別スル事難キヲ以テ予ハ腎臟ヲ露出セシメ絲絨體ノ狀態ヲ顯微鏡下ニ觀察シツツ豫メ造リタル硝子毛細管ヲ用ヒ各種利尿劑及ビ其他ノ藥液ヲ滴下シツツ絲絨體ノ變化ヲ觀察セリ而シテ次ノ成績ヲ得タリ。

「カフエイン」、安息香酸「ナトリウムカフエイン」「ヂウレチン」及ビ「クレアチン」ハ絲絨體毛細血管ヲ擴大セシメ爲ニ絲絨體內ノ血流ハ早クナリ血量ハ増加シ絲絨體ハ充血且膨大ス今迄見エザリシ絲絨體ハ出現シ活動盛トナル。之ニ反シ醋剥液ハ 0.1%ニ於テ既ニ絲絨體毛細血管ヲ收縮セシメ活動セル絲絨體ハ靜止シ漸次其數ヲ減ズ。

「テオチン」「葡萄糖」ハ何等ノ影響ヲ及ボサズ。

Guanidin ハ稀薄液ニ於テハ絲絨體毛細血管ヲ擴大シ其數ヲ増加セシムルモ濃厚液ニ於テハ毛細管ハ收縮シ絲絨體ハ消失ス。「ナトリウム」鹽類中 (0.6%ノ Ringer 氏液ト等滲透性液ニ於テ) NaNO_2 , NaNO_3 及ビ Na_2HPO_4 ハ輕度ニ毛細管ヲ(絲絨ノ)擴大セシムルモ其他ハ何等ノ影響ナシ。「カリウム」鹽類ハ 0.1%ノ稀薄液ニ於テ絲絨體毛細血管ヲ收縮セシメ絲絨體ハ活動ヲ停止シ遂ニ全ク消失スルニ至ル。

「カルチウム」鹽類「マグネシウム」鹽類並ニ二三有機酸ハ共ニ絲絨體毛細血管ヲ擴大セシム絲絨體ハ充血大ス靜止ノ狀態ニ在リシ絲絨體ハ活動ヲ初メ其數ヲ増加ス。