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BOSTON

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STUDY XXI: THE IMMEDIATE EFFECT OF REPEATED DOSES OF THEOBROMIN SODIUM SALICYLATE AND THEOCIN ON RENAL FUNCTION IN ACUTE EXPERIMENTAL NEPHRITIS *

R. FITZ, M.D.
BOSTON

Such authorities as Senator,[1] Osler,[2] Bradford,[3] Herrick[4] and Forschheimer[5] agree that in the treatment of acute nephritis a cautious trial with the use of diuretics may be made with safety, but that such drugs should not be given persistently unless a distinct effect is produced, since large doses or the continued effect of small doses may lead to scanty excretion of urine with retention of urinary products. The experimental evidence for this contention is slight.

Of the diuretics in clinical use, purin derivatives are given most extensively. The exact mechanism by which they produce diuresis is not altogether certain. Munk[6] and Schwartz,[7] from perfusion experiments on the isolated dog's kidney injected with caffein and allied drugs, found a marked diuresis without any evidence of increased flow of blood through the kidney, and concluded that these substances had a specific effect on renal secretory functions. Von Schroeder[8] and Loewi[9] confirmed these observations in normal animals, finding after injections of

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* This is one of a series of studies on experimental cardiorenal disease: Study I, Smith: Boston Med. and Surg. Jour., 1908, clviii, 696; Study II, Christian: Boston Med. and Surg. Jour., 1908, clix, 8; Study III, Christian: Jour. Am. Med. Assn., 1909, liii, 1792; Studies IV-XV, Christian, Smith and Walker: The Archives Int. Med., 1911, viii, 468-551; Study XVI, Christian and O'Hare: The Archives Int. Med., 1913, xi, 517; Studies XVII and XVIII, O'Hare: The Archives Int. Med., 1913, xii, 49, 61; Study XIX, Christian and O'Hare; Jour. Med. Research, 1913, xxviii, 227; Study XX, Walker and Dawson: The Archives Int. Med., 1913, xii, 171.

1. Senator: Nothnagel's Specielle Pathologie und Therapie, 1896, xix, (1), p. 64.
2. Osler: Practice of Medicine, 1909, p. 691.
3. Bradford: Allbutt and Rolleston's System of Medicine, 1908, iv, 607.
4. Herrick: Osler's Modern Medicine, 1908, vi, 143.
5. Forchheimer: Therapeusis of Internal Diseases, 1913, iv, 58.
6. Munk: Centralbl. f. die med. Wissensch., 1886, xxiv, 481.
7. Schwartz: Arch. f. exper. Path. u. Pharmakol., 1899, xliii, 1.
8. Von Schroeder: Arch. f. exper. Path. u. Pharmakol., 1887, xxii, 39.
9. Loewi: Arch. f. exper. path. u. Pharmakol., 1902, xlviii, 410.

caffein and other purin bodies an increased outflow of urine, salts and urea which they considered to be due to direct stimulation of the epithelium. Phillips and Bradford,[10] and Gottlieb and Magnus[11] supplemented these experiments by oncometer studies. They found usually after injection of diuretics of this group dilatation of the renal blood-vessels which was independent of changes in the aortic blood-pressure and which was accompanied by a marked diuresis; but occasionally diuresis occurred with little vascular dilatation or marked vascular dilatation without any additional outflow of urine. Therefore they believed that while the vasomotor phenomena were important in producing diuresis, more complex processes must be present to explain the effect of purin bodies. Fletcher, Henderson and Loewi[12] made parallel observations and drew identical conclusions. Frey,[13] however, using the oncometer, and Beco and Plumier,[14] working with a perfusion apparatus, found that the amount of urine following the injection of these diuretics was directly related to the quantity of blood going through the kidney in a given unit of time. Hence the evidence on the pharmacological action of the purin diuretics is conflicting. By the use of these drugs, however, in normal animals an increased outflow of urine and its solids occurs whether due to a specific dilating action on the blood-vessels of the kidney or to a stimulation of the renal epithelium or to a combination of both these effects.

Under pathological conditions the kidney's reaction to these drugs is varied. Hellin and Spiro[15] studied the action of caffein in rabbits poisoned with arsenic, aloin, chromium and cantharidin. Diuresis could be obtained in those nephritides in which tubular lesions predominated, but did not occur when the glomeruli were chiefly affected. Weber,[16] working on dogs, found that in chromium nephritis the kidneys were unable to excrete a concentrated urine, so that although sodium chlorid and theophyllin produced an increased outflow of fluid except in most advanced cases, yet there was no increase in the output of the solids of the urine, and in certain animals a retention. Hedinger attacked the problem from a different point of view. Schlayer and Hedinger,[17] and Schlayer and Takayasu[18] showed in experimental nephritis in rabbits that the renal vessels as tested in an oncometer were hypersensitive or hyposensitive to physiological stimuli at different stages of the disease.

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10. Phillips and Bradford: Jour. Physiol., 1887, viii, 117.
11. Gottlieb and Magnus: Arch. f. exper. Path. u. Pharmakol., 1901, xlv, 223.
12. Fletcher, Henderson and Loewi: Arch. f. exper. Path. u. Pharmakol., 1905, liii, 15.
13. Frey: Arch. f. d. ges. Physiol. (Pfluger's), 1906, cxv, 175.
14. Beco and Plumier: Jour. de phys. et de path. gén., 1906, viii, 10.
15. Hellin and Spiro: Arch. f. exper. Path. u. Pharmakol., 1896, xxxviii, 368.
16. Weber: Arch. f. exper. Path. u. Pharmakol., 1906, liv, 1.
17. Schlayer and Hedinger: Deutsch. Arch. f. klin. Med., 1907, xc, 1.
18. Schlayer and Takayasu: Deutsch. Arch. f. klin. Med., 1910, xcviii, 17.

While hypersensitive the vessels dilated abnormally with a marked diuresis, while hyposensitive they no longer reacted and oliguria resulted. Hedinger[19] applied this method to animals injected with different renal irritants, using as vascular stimuli theophyllin, digalen and digipuratum in small doses. Diuresis occurred only when the renal vessels were physiologically intact. MacNider[20] was unable to confirm these results entirely. He observed the renal vascular response to caffein, theobromin, digitalen and saline solutions in dogs with uranium nephritis. His animals were divided into two main groups, those anuric or practically anuric with a normal blood-pressure and normal renal vascular system which showed no diuretic reaction to the various drugs, and those with an identical blood-pressure and renal vascular response which, however, had a definite diuresis. In the anuric group, the histological examination showed marked epithelial desquamation which produced an encroachment on the tubular lumen. In the second group this was less distinct. He concluded that mechanical obstruction to the lumen of the tubules played a part in determining the amount of urine. Mosenthal and Schlayer[21] studied the effect of repeated doses of sodium chlorid and caffein on the amount of urine and chlorid excretion and on renal volume as recorded by an oncometer in uranium and chromate nephritis in rabbits. In most advanced cases of each type of lesion neither diuretic was active; but in the early stage of chromate nephritis, sodium chlorid produced an increased outflow of urine and chlorid with renal dilatation, while caffein in repeated doses caused a diminishing amount of these substances with vascular contraction. In the early stage of uranium nephritis directly opposite results were obtained. These findings were explained on the assumption that in one type of lesion the functional condition was hypersensitive to fatigue by caffein, and in the other to fatigue by chlorid. Finally, Christian and O'Hare[22] gave theobromin sodium salicylate, and Walker and Dawson[23] gave theocin, caffein, potassium acetate and spartein sulphate from day to day to rabbits poisoned with uranium nitrate. In most severe cases all these drugs seemed to shorten the animals' lives, but in the less severe cases theobromin sodium salicylate, at least, apparently had a beneficial action. Therefore, from the literature it appears that in mild cases of acute experimental nephritis various diuretics cause an increased output of urine unless repeated rapidly enough to cause renal fatigue, and they are of possible therapeutic benefit. In severe cases, however, they are not pharmacologically active and are even injurious.

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19. Hedinger: Deutsch. Arch. f. klin. Med., 1910, c, 305.
20. MacNider: Jour. Pharm. and Exper. Therap., 1912, iii, 423.
21. Mosenthal and Schlayer: Deutsch. Arch. f. klin. Med., 1913, cxi, 217.
22. Christian and O'Hare: The Archives Int. Med., 1913, xi, 517.
23. Walker and Dawson: The Archives Int. Med., 1913, xii, 171.

Except for investigations regarding the total amount of urine and its constituents, no systematic studies have been reported as to the influence of diuretics on renal excretory functions under pathological conditions. This paper describes a series of experiments which were made to determine the immediate effect of repeated doses of theobromin sodium salicylate and theocin on the amount of water, nitrogen, sodium chlorid and phenolsulphonephthalein eliminated during different stages of acute experimental nephritis.

Rabbits were injected subcutaneously with toxic amounts of potassium bichromate or uranium nitrate in sufficient quantity to produce definite changes in renal function without rendering the animals anuric. These drugs were chosen because chromium produces marked tubular destruction in the kidney, leaving the glomeruli practically intact, while uranium nitrate produces lesions in both glomeruli and tubules. Thus renal function was tested under diverse pathological conditions. To obtain different degrees of severity of the same type of nephritis, animals were selected at varying times after injection and renal excretion was studied in the following manner: The animal to be observed was anesthetized by a subcutaneous injection of urethane (ethyl carbamate) in dosage of from 1.25 to 1.50 gm. per kilogram of body-weight. At the same time 2 gm. of urea and 2 gm. of sodium chlorid were administered in 50 c.c. of water by stomach-tube to insure a flow of salt and nitrogen containing fluid. It was realized that these three substances in themselves were powerful diuretics, but it was believed that after their rate of excretion was once established, any marked subsequent variation during the time of these experiments was due to changes in renal function brought about by the drugs introduced. Cannulas were inserted into the bladder and jugular vein according to the usual technic and the elimination of phenolsulphonephthalein, water, salt and nitrogen was followed.

The phenolsulphonephthalein test was slightly modified, but was made on the whole according to Rowntree and Geraghty's[24] method for obtaining constant output of the drug. At the beginning of the experiment, depending on the severity of the clinical condition of the animal, from 0.0015 to 0.006 gm. of the dye in 1 c.c. of saline solution was injected intravenously. After the color appeared, the urine during the next thirty minutes was measured in drops and diluted to 10 or 20 c.c. with distilled water, and the amount of phenolsulphonephthalein in an aliquot part estimated by Rowntree and Geraghty's modification of the Autenrieth-Königsberger colorimeter. Except when only traces were recovered, an amount of phenolsulphonephthalein equal to 10 per cent.

24. Rowntree and Geraghty: The Archives Int. Med., 1912, ix, 284.

more than the total amount recovered at this time was reinjected into the vein, to be excreted during the following interval, thus allowing for the loss between observations. In the few animals which were unable to excrete appreciable amounts of the drug, no further injections were made. In this way the phenolsulphonephthalein concentration in the blood and tissues was kept as nearly constant as possible, and any distinct increase or decrease in the excretion was assumed to be due to changes in renal function. At the end of every half hour the total amount of urine, nitrogen and salt excretion for the period was recorded. The nitrogen was quantitated by Kjeldahl's method, and the chlorids by the Lütke-Martius method. From these figures the concentration of nitrogen and salt in one hundred drops of urine was found. After the flow of water and phenolsulphonephthalein was approximately constant for two half-hour periods, theobromin sodium salicylate and theocin in increasing dosage were injected intravenously. As Hedinger[25] had found clinically that the repeated use of small amounts of diuretics often produces greater effect than single large doses, it seemed advisable to determine experimentally the action of repeated small injections of such drugs on renal function. Therefore, solutions of theobromin sodium salicylate[26] and theocin sodium acetate were made containing 10 mg. to the cubic centimeter of the former drug, and 5 mg. to the cubic centimeter of the latter drug (corresponding to 0.3 gm. of theobromin sodium salicylate and 0.15 gm. of theocin if given to a man weighing 150 pounds). At first 1 c.c. of theobromin sodium salicylate solution was given, followed in fifteen minutes by 2 c.c., yielding a total of 30 mg. of the drug. Then 1 c.c. of theocin solution was injected, and at fifteen-minute intervals 2 c.c., 3 c.c. and 4 c.c., making in all 50 mg. of the drug. Finally, the animal was killed and the kidneys were examined histologically after Zenker fixation and eosin-methylene blue staining. The drugs were given in this order and amount for arbitrary reasons. No effort was made to determine their relative efficacy of action. The experiments were conducted solely to discover the immediate effect on renal function in different kinds of acute experimental nephritis of the repeated injection of two typical purin diuretics.

The results have been grouped into three tables, each table representing the mean of eight experiments. While each observation in general showed the same features, by averaging them in this way, any exceptional finding due to individual peculiarity of the animal was ruled out.

Table 1 shows that under the conditions stated for the time observed, the excretion of fluid in normal animals diminished slightly but con-

25. Hedinger: München. med. Wchnschr., 1912, lix, 1098.

26. The substance used in these experiments was the brand of theobromin sodium salicylate made by Knoll & Co., and sold under the proprietary name "Diuretin." The theocin sodium acetate was made by Bayer & Co.

TABLE 1.—Experiments on Normal Animals

PART I. NORMAL ANIMALS

Average of Rabbits I, II, III, 737:* Average weight, 1,750 gm. Histological findings
Urethane narcosis. At the beginning of the experiment each animal was given 2 gm. of urea a
of sodium chlorid in 50 c.c. of water by stomach-tube. Injected intravenously with phenol
phthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	180	43	24	55	31	48	
35	...	..	..	..	..	..	Reinjected with phth
35–65	175	54	31	48	27	46	
70	...	..	..	..	..	..	Reinjected with phth
70–100	164	72	44	40	24	49	Killed.

* The numbers of these animals correspond to those recorded in the laboratory of The
Practice, Harvard Medical School.

PART II. NORMAL ANIMALS WITH DIURETICS

Average of Rabbits III, IV, 731, 737: Average weight, 1,750 gm. Histological findings
Urethane narcosis. At the beginning of the experiment each animal was given 2 gm. of u
2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected intravenously with
sulphonephthalein.

Time Minutes from First Collected Urine	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
1–30	96	47	49	45	46	52	
35	...	...	..	..	..	..	Reinjected with phth 1 c.c. of theobromin salicylate.
50	...	...	..	..	..	..	2 c.c. of theobromin salicylate.
35–65	150	62	41	52	34	58	
70	...	...	..	..	..	..	Reinjected with phth 1 c.c. of theocin solut
85	...	...	..	..	..	..	2 c.c. of theocin solut
70–100	584	198	34	70	12	66	
105	...	...	..	..	..	..	Reinjected with phth 3 c.c. of theocin solut
120	...	...	..	..	..	..	4 c.c. of theocin solut
105–135	572	188	32	61	10	64	Killed.

TABLE 2.—URANIUM EXPERIMENTS

PART I. ANIMALS WITHOUT DIRUETICS

of Rabbit 754: 5 mg. of uranium nitrate subcutaneously; 48-hour nephritis histologically showing marked tubular lesions.

of Rabbit 755: 3 mg. of uranium nitrate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

of Rabbit 756: 5 mg. of uranium nitrate subcutaneously; 72-hour nephritis histologically showing mild tubular lesions.

of Rabbit 757: 6 mg. of uranium nitrate subcutaneously in divided doses; 48-hour nephritis histologically showing advanced tubular lesions and slight glomerular lesions.

rage weight, 2,000 gm. Urethane narcosis. At the beginning of the experiment each animal n 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected ously with phenolsulphonephthalein.

es rst ed	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
	213	59	28	30	14	21	
	...	...	..	..	..	..	Reinjected with phthalein.
	184	44	24	32	17	21	
	...	..	..	..	..	..	Reinjected with phthalein.
)	137	29	21	27	20	18	
	...	..	..	..	..	..	Reinjected with phthalein.
5	138	23	17	25	18	20	Killed.

PART II. ANIMALS WITH DIURETICS

of Rabbit 741: 3.5 mg. of uranium nitrate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

of Rabbit 730: 9 mg. of uranium nitrate subcutaneously in divided doses; 120-hour nephritis, histologically showing advanced tubular lesions, and slight glomerular lesions.

of Rabbit 728: 4 mg. of uranium nitrate subcutaneously; 48-hour nephritis histologically showing marked tubular lesions.

of Rabbit 729: 5 mg. of uranium nitrate subcutaneously in divided doses; 96-hour nephritis, histologically showing marked tubular lesions.

age weight 1,900 gm. Urethane narcosis. At the beginning of the experiment each animal n 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected ously with phenolsulphonephthalein.

s rst ed	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
	176	68	39	18	10	16	
	...	...	..	..	..	..	Reinjected with phthalein.
							1 c.c. of theobromin sodium salicylate solution.
	...	...	..	..	..	..	2 c.c. of theobromin sodium salicylate solution.
	332	91	28	32	10	17	
	...	...	..	..	..	..	Reinjected with phthalein.
							1 c.c. of theocin solution.
	...	...	..	..	..	..	2 c.c. of theocin solution.
	496	137	28	38	07	18	
	...	...	..	..	..	..	Reinjected with phthalein.
							3 c.c. of theocin solution.
	...	...	..	..	..	..	4 c.c. of theocin solution.
5	369	97	26	39	11	18	Killed.

stantly, while chlorid and nitrogen excretion varied somewhat both in amount and in concentration without bearing direct relation to the amount of urine. The phenolsulphonephthalein excretion remained almost unchanged. When the diuretics were injected there was a pronounced increase in the amount of urine passed, paralleled by that of sodium chlorid. The concentration of chlorid became lower, suggesting that the excess of salt was carried through the kidney by water. The output of nitrogen was less affected by the diuresis, but increased as did that of the phenolsulphonephthalein, agreeing with Rowntree and Geraghty's[24] observations. On the whole, in normal animals the immediate effect on renal function of repeated injections of theobromin sodium salicylate and theocin was beneficial. This was shown by an increased output of water, chlorid, nitrogen and phenolsulphonephthalein; but by repeated dosage there was evidence of beginning renal fatigue, since the excretion of all these substances diminished during the last period of observation.

As in the first part of Table 1, animals with uranium nephritis which had not received diuretics (Table 2) showed a constant diminution in the amount of urine. In this series the chlorid and nitrogen decreased both in amount and in concentration. The phenolsulphonephthalein remained unchanged. The theobromin sodium salicylate and theocin produced a definite reaction. There was a marked increase in the amount of urine paralleled by that of nitrogen and chlorid without any increase in concentration. The amount of phenolsulphonephthalein, however, did not vary to an appreciable degree. In the last period the evidence of renal fatigue was exaggerated. The total amount of urine and salt diminished to a greater extent than in normal animals, though remaining above the initial level, while the nitrogen and phenolsulphonephthalein were unaffected. Therefore, in uranium animals the immediate effect on renal function of repeated injections of theobromin sodium salicylate and theocin was not harmful. There was an increased output of water, chlorid and nitrogen with an unchanged excretion of phenolsulphonephthalein. The kidney was fatigued more easily than under normal conditions, as shown by the diminishing output of salt and water under the influence of repeated injections of the drugs.

Table 3 shows the effect on animals poisoned with potasium bichromate and treated in similar fashion. As in the previous control experiments, animals without diuretics showed a constant falling off in their salt and water excretions, although the excretion of nitrogen increased without relation to the total amount of urine. The elimination of phenolsulphonephthalein was nearly constant. The action of the diuretics was less marked. While both salt and water were excreted in increased amounts they were proportionately less well put out than in the previous

TABLE 3.—Bichromate Experiments

PART I. ANIMALS WITHOUT DIURETICS

of Rabbit 762: 20 mg. of potassium bichromate subcutaneously; 72-hour nephritis histologically showing mild tubular lesions.

of Rabbit 763: 20 mg. of potassium bichromate subcutaneously; 72-hour nephritis histologically showing mild tubular lesions.

of Rabbit 764: 40 mg. of potassium bichromate subcutaneously; 96-hour nephritis histologically showing mild tubular lesions.

of Rabbit 765: 40 mg. of potassium bichromate subcutaneously; 96-hour nephritis histologically showing well-marked tubular lesions.

age weight 2,500 gm. Urethane narcosis. At the beginning of the experiment each animal n 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected usly with phenolsulphonephthalein.

s st d	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
	221	56	25	35	16	45	
	...	..	..	..	..	..	Reinjected with phthalein.
	219	64	29	38	17	45	
	...	..	..	..	..	..	Reinjected with phthalein.
	180	54	30	40	22	43	
	...	..	..	..	..	..	Reinjected with phthalein.*
	180	49	27	41	23	40*	Killed.

presents average of three animals. In one animal part of injection was lost.

PART II. ANIMALS WITH DIURETICS

of rabbit 732: 20 mg. of potassium bichromate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

of rabbit 734: 20 mg. of potassium bichromate subcutaneously; 72-hour nephritis histologically showing no lesions, but functionally abnormal.

of rabbit 735: 20 mg. of potassium bichromate subcutaneously; 96-hour nephritis histologically showing marked tubular lesions.

of rabbit 743: 20 mg. of potassium bichromate subcutaneously; 24-hour nephritis histologically showing mild tubular lesions.

age weight 1,800 gm. Urethane narcosis. At the beginning of the experiment each animal n 2 gm. of urea and 2 gm. of sodium chlorid in 50 c.c. of water by stomach-tube. Injected usly with phenolsulphonephthalein.

s st d	Urine Drops	Sodium Chlorid		Nitrogen		Phthalein % of Amt. Injected	Remarks
		Total No. Mg.	Mg. Per 100 Drops	Total No. Mg.	Mg. Per 100 Drops		
	192	64	33	40	21	33	
	...	..	..	..	..	..	Reinjected with phthalein.
							1 c.c. of theobromin sodium salicylate solution.
	...	..	..	..	..	..	2 c.c. of theobromin sodium salicylate solution.
	224	57	25	40	18	28	
	...	..	..	..	..	..	Reinjected with phthalein.
							1 c.c. of theocin solution.
	...	..	..	..	..	..	2 c.c. of theocin solution.
	351	96	27	45	13	24	
	...	..	..	..	..	..	Reinjected with phthalein.
							3 c.c. of theocin solution.
	...	..	..	..	..	..	4 c.c. of theocin solution.
5	260	64	25	30	11	18	Killed.

series. There was no definite increase in nitrogen excretion, and during the last period a diminution. The most striking feature, however, was the steady decrease in phenolsulphonephthalein elimination during the entire time of observation. In chromate nephritis, therefore, the immediate effect of purin diuretics was to produce a slight diuresis of water and salt, to have little effect on the excretion of nitrogen and to hinder that of phenolsulphonephthalein. If a large enough amount of drugs were given, the kidney was more easily fatigued than in normal or uranium animals, as shown by a greater lessening in the excretion of all the substances studied.

In addition a series of experiments with cantharidin nephritis was attempted. When sufficient amount of the poison was given to produce outspoken lesions, it was found that the animals became anuric and failed to react to the diuretics, confirming the observations of Hellin and Spiro,[15] Schlayer and Hedinger[17] and Schlayer and Takayasu.[18] If lesser amounts were injected, the anatomical and functional conditions of the kidney were so little changed as to make the observations of no value. These experiments, therefore, have been discarded.

On the whole, in normal animals the immediate effect of injections of theobromin sodium salicylate and theocin was to produce an increased outflow of urine, sodium chlorid and to a less extent of nitrogen and phenolsulphonephthalein. After repeated small doses of the drug were given the kidney became fatigued and excreted these substances in lesser amounts.

In animals suffering from uranium nephritis of varying intensity a similar immediate response to these diuretics was obtained except that the kidney became more easily fatigued. In chromium nephritis, on the other hand, while the kidney responded to the theobromin sodium salicylate and theocin by increasing the output of water and chlorid, yet the excretion of nitrogen remained almost constant and that of phenolsulphonephthalein diminished. After large amounts of the drugs had been injected, the signs of renal fatigue were more pronounced than in uranium nephritis or normal animals as the water, chlorid, nitrogen and phenolsulphonephthalein excretions diminished with greater rapidity.

Mosenthal and Schlayer[21] have demonstrated differences in renal fatigability to repeated injections of caffein and sodium chlorid in uranium and chromate nephritis. In these experiments following repeated injections of purin diuretics the kidneys became more easily fatigued in relation to excretion of the substances studied in chromate nephritis than in uranium nephritis or normally. Thus these observations are to a certain extent confirmatory of previous work.

Folin, Karsner and Denis[27] have shown that the non-protein nitrogen of the blood of animals having acute toxic nephritis accumulated in proportion to the severity of the disease. It was most pronounced in uranium and cantharidin nephritis and least marked in chromate nephritis. Clinically, it has long been recognized as a grave prognostic sign in kidney disease. Frothingham, Fitz, Folin and Denis,[28] working with rabbits poisoned with uranium nitrate, showed that the curve of nitrogen accumulation in the blood and of the excretion of phenolsulphonephthalein in the urine correspond closely. Therefore, it seems reasonable to conclude that in uranium nephritis the immediate effect of theobromin sodium salicylate and theocin was beneficial, for by the use of these drugs the outflow of water, sodium chlorid and nitrogen was increased, thereby tending to prevent nitrogenous accumulation in the blood. In chromate nephritis, however, the immediate effect of these diuretics was harmful, since, although they increased the outflow of water and chlorid, the nitrogen excretion was unaffected and the phenolsulphonephthalein elimination was diminished. In each nephritis repeated injections of theobromin sodium salicylate and theocin to the point of fatigue of the kidney was harmful to the renal function by producing a diminution in the total amount of urine, chlorid, and to a less degree, of phenolsulphonephthalein and nitrogen excreted.

CONCLUSIONS

1. The immediate effect of repeated small doses of theobromin sodium salicylate and theocin on renal function in acute experimental uranium nephritis of different degrees of severity is beneficial since they cause an increased output of urine, chlorid and nitrogen and do not diminish the excretion of phenolsulphonephthalein.

2. The immediate effect of repeated small doses of theobromin sodium salicylate and theocin on renal function in acute experimental bichromate nephritis of different degrees of intensity is harmful, since although an increased output of urine and chlorid occurs, the excretion of nitrogen is unaffected and that of phenolsulphonephthalein is diminished.

3. The repeated injection of small doses of theobromin sodium salicylate and theocin in sufficient amount produces a condition of renal fatigue in which the kidney is no longer able to react. This is most easily obtained in bichromate nephritis.

4. Various types of acute experimental nephritis respond differently to repeated injections of theobromin sodium salicylate and theocin both in regard to immediate changes in the excretion of chlorid, nitrogen and

27. Folin, Karsner and Denis: Jour. Exper. Med., 1912, xvi, 789.
28. Frothingham, Fitz, Folin and Denis: The Archives Int. Med., 1913, xii, 245.

phenolsulphonephthalein and in regard to the degree of renal fatigue which is induced.

5. These experiments do not include observations on nephritis of the most extreme grade of severity. In the few studies made on animals which had the different kinds of lesions and were anuric, the diuretics were not active in provoking an increased output of either water, chlorid, nitrogen or phenolsulphonephthalein.

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