

STUDY XXIV: THE EFFECT OF THEOBROMIN SODIUM SALICYLATE IN ACUTE CHROMATE NEPHRITIS *

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The effect of diuretics in acute nephritis has been the subject of much theorization and of some experimental work, especially during the past few years. The meager literature on the experimental work has been so recently reviewed by Fitz¹ in his article on the "Immediate Effect of Repeated Doses of Theobromin Sodium Salicylate and Theocin in Acute Experimental Nephritis" that it does not seem worth while repeating it here. In 1913 with Dr. Christian² I reported the results of our experiments on the effect of theobromin sodium salicylate on the duration of life of rabbits with acute uranium nephritis, and Walker and Dawson³ reported in the same way the effects of theocin, caffein, potassium acetate, spartein sulphate and water. More recently Dr. Christian⁴ has reported the effect of theobromin sodium salicylate on renal function as measured by the excretion of phenol-sulphonaphthalein in acute uranium nephritis. It seemed, therefore, desirable to supplement this work of a year ago by making a study of the effect of this same diuretic in other types of acute experimental nephritis. Following the theories of Schlayer and his coworkers in the attempt to produce a vascular nephritis, arsenic acid was selected. After

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* This is one of a series of studies on experimental cardio-renal disease. Study I, Smith: *Boston Med. and Surg. Jour.*, 1908, clviii, 696; Study II, Christian: *Boston Med. and Surg. Jour.*, 1908, clx, 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; Study XXI, Fitz: *THE ARCHIVES INT. MED.*, 1914, xiii, 945; Study XXII, Christian: *THE ARCHIVES INT. MED.*, 1914, xiv, 827; Study XXIII, Fitz: *THE ARCHIVES INT. MED.*, 1915, xv, 524.

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* The theobromin sodium salicylate used was purchased under the trade name of Diuretin.

1. Fitz: *THE ARCHIVES INT. MED.*, 1914, xiii, 945.

2. Christian and O'Hare: *THE ARCHIVES INT. MED.*, 1913, xi, 517.

3. Walker and Dawson: *THE ARCHIVES INT. MED.*, 1913, xii, 171.

4. Christian: *THE ARCHIVES INT. MED.*, 1914, xiv, 827.

TABLE SHOWING EFFECT OF THEOBROMIN SODIUM SALICYLATE ON LIFE OF RABBITS WITH POTASSIUM BICHROMATE NEPHRITIS

	Rabbit No.	Weight gm.	Duration of Life After First Bichrom- ate Injection (Days)	Average Life of Those that Died (Days)	Number Dead
<i>Series 1—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	846 862 864	2,100 2,060 2,260	6 4 17 *	5	2
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobro- min sodium sali- cylate, daily; 0.014 gm. per kg.	866 865 877	2,250 2,100 2,060	3 6 7	5½	3
<i>Series 2—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	881 882 885	2,070 2,360 1,780	3 39 * 3	3	2
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobro- min sodium sali- cylate, daily; 0.028 gm. per kg.	878 879 884	2,100 2,030 1,840	39 * 6 3	4½	2
<i>Series 3—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	883 886 889	1,900 2,230 2,060	7 25 * 25 *	7	1
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobro- min sodium sali- cylate, daily; 0.056 gm. per kg.	888 890 891	2,050 2,230 2,080	3 5 25 *	4	2
<i>Series 4—</i>					
Potassium bichromate, 2 doses; 0.015 gm. per kg.	893 894 895	1,790 2,020 2,730	21 27 * 26 *	21	1
Potassium bichromate, 2 doses; 0.015 gm. per kg. Theobro- min sodium sali- cylate, daily; 0.56 gm. per kg.	896 901 902	2,350 2,040 1,880	19 18 27 *	18½	2

* Experiment discontinued.

TABLE SHOWING EFFECT OF THEOBROMIN SODIUM SALICYLATE ON LIFE OF RABBITS WITH POTASSIUM BICHROMATE NEPHRITIS—(Continued)

	Rabbit No.	Weight gm.	Duration of Life After First Bichromate Injection (Days)	Average Life of Those that Died (Days)	Number Dead
Series 5—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	899	2,500	5	5	1
	909	2,200	15 *		
	915	1,750	15 *		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.056 gm. per kg.	911	1,900	4	4½	3
	913	2,270	6		
	914	2,450	4		
Series 6					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	910	1,800	18 *	6	1
	917	2,000	18 *		
	923	2,100	6		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.014 gm. per kg.	916	1,850	18 *	5½	2
	921	1,950	7		
	920	2,050	4		
Series 7—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg.	925	1,920	18 *	6	1
	930	2,820	18 *		
	924	1,800	6		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg.	926	2,450	2	3	2
	927	1,980	18 *		
	929	1,550	4		
Series 8—					
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Urea and salt daily	934	2,210	4	4	1
	949	2,000	10 *		
	952	1,940	10 *		
Potassium bichromate, 2 doses; 0.0175 gm. per kg. Theobromin sodium salicylate, daily; 0.028 gm. per kg. Urea and salt daily.	944	2,070	10 *	3	2
	947	2,240	2		
	951	2,110	4		

* Experiment discontinued.

Average duration of life after first bichromate injection:

Bichromate only 7 $\frac{1}{8}$ days

Bichromate and theobromin sodium salicylate..... 6 $\frac{1}{16}$ days

Number dead:

Bichromate only 10

Bichromate and theobromin sodium salicylate..... 18

much work with this drug, however, I came to the same conclusion arrived at by Fitz and others working with it, that it was not possible to control the action of arsenic so as to produce regularly a uniform, workable nephritis, and so the plan of studying the effect of diuretics on a vascular type of nephritis was given up. For the study of a tubular type of nephritis potassium bichromate, which produces lesions confined almost exclusively to the tubules, was selected as the kidney irritant.

Forty-eight normal adult rabbits, on a known diet of carrot, oats and water, were divided into eight groups of six each. These, in turn, were subdivided into "controls," which received potassium bichromate only, and so-called "diuretic" rabbits which were given, in addition, theobromin sodium salicylate. The controls and diuretic animals were paired off in each group so as to be of approximately parallel weights.

The potassium bichromate was given subcutaneously on two successive days in body weight doses. The diuretic was given in a similar manner except that it was begun on the day of the second bichromate injection and was repeated daily until the animal died or until the experiment was discontinued. The dose of the two drugs was varied in each group so as to get the effect of different dosage of the diuretic in nephritides of varying degrees of severity. (For doses used, see table.)

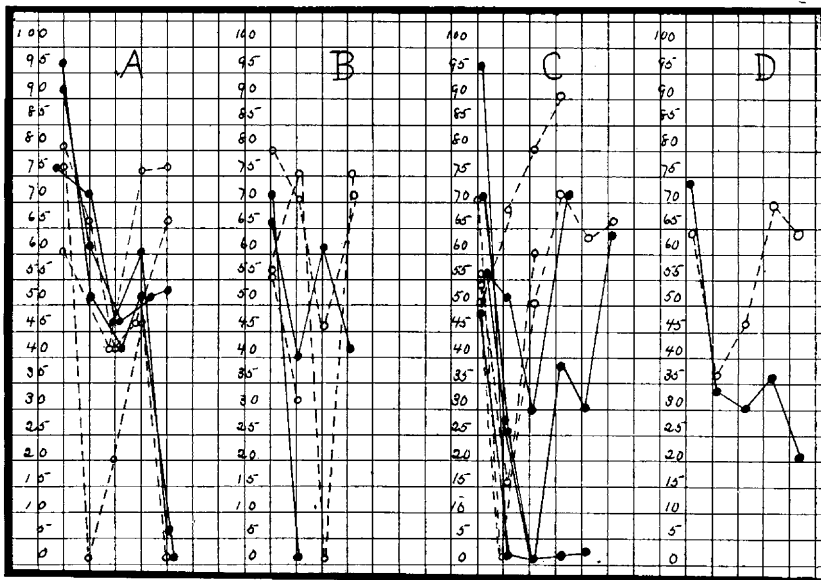
In these eight groups observations were made on the comparative length of life of control and diuretic rabbits; their comparative pathology and their comparative water excretion. In a smaller number of these rabbits a comparative study was made on the output of phenol-sulphonephthalein, nitrogen and sodium chlorid.

The primary object of the work was to determine whether or not theobromin sodium salicylate affected in any way the length of life of rabbits with acute chromate nephritis. Not all of the forty-eight rabbits died, but, as the table shows, of the twenty-eight that died only ten were controls, whereas eighteen, almost twice as many, had been treated with theobromin sodium salicylate. This is, I think, a rather striking result, more striking even than our results in uranium nephritis.

The average duration of life after the first dose of potassium bichromate was $6\frac{1}{16}$ days for the diuretic rabbits, and $7\frac{1}{8}$ for the controls. This too, though not so striking, is in favor of those not treated with the diuretic. These two results show rather conclusively that in this type of nephritis, as has already been shown for uranium nephritis, theobromin sodium salicylate is usually distinctly harmful. It must be said, however, that in Series 1 and 2, where small doses of bichromate and a small and medium dose, respectively, of theobromin sodium

salicylate were used, those diuretic animals that died lasted somewhat longer than the corresponding controls. This is in keeping with the results obtained previously in uranium nephritis, namely, that in mild types of nephritis small doses of theobromin sodium salicylate occasionally seem to prolong life.

No attempt was made to study the question of comparative pathology very accurately. Careful studies were made, however, of the kidneys of those rabbits that died, and the pathological picture of the controls was set off against that of the diuretic animals in the same



Dotted lines show excretion of phenolsulphonephthalein in rabbits which received potassium bichromate. Solid lines show phenolsulphonephthalein excretion in rabbits which received both potassium bichromate and theobromin sodium salicylate. *A* gives the results for rabbits 893, 894, 895, 896, 901 and 902; *B*, rabbits 924, 925, 930, 927 and 929; *C*, rabbits 931, 938, 933, 944, 939, 934, 949 and 952. (In the accompanying table is shown the dosage of drugs used and other details in regard to these rabbits.) In *D* is shown by the dotted line the average phenolsulphonephthalein excretion for all rabbits that received potassium bichromate but no diuretic, while by the solid line is shown the average excretion of those rabbits that received potassium bichromate followed by theobromin sodium salicylate.

group. This is scarcely a fair comparison. It was found, however, that the rabbits treated with the diuretic did seem to show slightly more pronounced tubular lesions.

The majority of the rabbits showed edema when examined post mortem; but, of those that did not, six were rabbits which had received the diuretic while three had not. As to the rest the amount of fluid was about the same in both divisions.

The question of change in the outflow of urine following the production of the nephritis was studied in carefully prepared intake and output charts. These showed on the whole that theobromin sodium salicylate not only did not produce any increase of water excretion, but seemed often to have caused an inhibition.

The phenolsulphonephthalein function test was performed in twenty-one animals. The results (see Chart A, B and C), though not at all uniform, show that the control rabbits (those that received the chromate but no diuretic) were less severely affected in the majority of cases, and that when they did get back to a normal output of phenol-sulphonethalein they did so more quickly than the diuretic rabbits. This agrees with the results obtained by Dr. Christian. The harmful action of the diuretic drug is shown more clearly by charting the averages of the phenolsulphonephthalein output in the two groups of rabbits (see chart, D).

The nitrogen and sodium chlorid metabolism was studied in eight cases. No definite conclusions, of course, can be drawn from such a small number of cases, especially in view of the fact that the results are far from uniform. This last is true even when a fairly large amount of urea and salt was added to the daily diet to render the output more stable. Making three day averages of the output of the nitrogen and salt helps somewhat, but not greatly. The nitrogen output was measured by the Kjeldahl method, the sodium chlorid by Goodall's modification of the Volhard method. Charts of these eight cases show that in the diuretic rabbits there is usually a falling off rather than an increase in the nitrogen elimination immediately following the treatment with theobromin sodium salicylate. In the controls, on the other hand, there is, in some cases, an increase. As to the salt excretion the results are so variable that they indicate nothing.

CONCLUSIONS

In conclusion we may say that in an experimental tubular nephritis caused by potassium bichromate of a severe or moderately severe type theobromin sodium salicylate usually shortens the life of the animals; in mild cases it sometimes seems to prolong it.

On the whole, it seems to increase the lesion in the kidney and to hinder the excretion of water, phenolsulphonephthalein and possibly nitrogen.

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