Studies on the Detoxicating Hormone of the Liver (Yakriton).

77th Report.[§]

Effect of Yakriton* upon Urobilinuria and Third Report on Clinical
Experiment to Prevent Scarlatinal Nephritis by Yakriton.

By

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Introduction.

In the 71st Report on Yakriton,¹⁾ Prof. Sato, Yamagishi, Abe and Yoshida reported on a tentative experiment to prevent scarlatinal nephritis by yakriton in 10 cases of typical scarlatina. And in the 75th Report on Yakriton,²⁾ Prof. Sato, Yoshida, Chiba and Kimura widened the same experiment on 25 further cases of typical scarlatina and made a summarizing report on all the 35 cases, including the 10 cases above mentioned. The present paper is the third report on the prophylactic effect of yakriton against scarlatinal nephritis in my 20 cases, but the most important thing I wanted to study in these cases was the effect of yakriton upon urobilinuria.

PART I.

EFFECT OF YAKRITON UPON UROBILINURIA.

Method of Experiment.

1. Materials. Typical cases of scarlet fever admitted to our Pediatric Department.

§ Paper read at the 39th General Meeting of the Japan Pediatric Society held in Tokyo, April, 1934.

* Throughout the experiment emulsified yakriton was used.

1) A. Sato, M. Yamagishi, J. Abe and M. Yoshida, Tohoku J. Exp. Med., 1936,

2) A. Sato, M. Yoshida, M. Chiba and J. Kimura, Tohoku J. Exp. Med., 1936.

2. Yakriton. Yakriton was subcutaneously injected in the amount of $\frac{1}{2}$ or 1 R.A.U., not every day, but every second or third day in the morning after the last collection of urine. The nephritis-prophylactic effect of yakriton used on every second or third day had not been known, but I wanted to know the amount of urobilin which might change according as yakriton was or was not used on the previous day.

3. Identification of urobilin in urine. The determination was made on a sample of the urine collected for 24 hours from one morning to the next. The method for urobilin was that of Adler's,³⁾ but 95% alcohol instead of absolute alcohol was used in consideration of the criticism of Opitz and Brehme.⁴⁾ The fluorescence of the urobilin was examined by means of an electric light in a dark room.

Result of Experiment.

The result of the effect of yakriton upon urobilinuria will be shown in Table I (No. 1—No. 18) and Charts 1 and 2.

If one gives even a glance at these tables, especially at the charts (Cf. Chart 1, for instance), one will see that an injection of yakriton always acted to decrease the excretion of urobilin or to counteract an increase of its excretion, so that in Chart I each arrow showing yakri-

TABLE I.
Cases of scarlatina.
No. 1. T.C., aged 8 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	—	0.85	12.8	1500	15	0	17	$\frac{1}{2}$ R.A.U.	0.85	14.5	1700	10	1
6	$\frac{1}{2}$ R.A.U.	0.85	8.5	1000	15	1	18	—	0.85	15.7	1850	10	0
7	—	1.375	11.5	900	16	1	19	$\frac{1}{2}$ R.A.U.	1.7	21.3	1250	15	1
8	—	8.5	51.0	600	22	0	20	—	1.7	32.3	1900	7	0
9	$\frac{1}{2}$ R.A.U.	6.8	40.8	600	22	0	21	$\frac{1}{2}$ R.A.U.	0.68	10.2	1500	17	1
10	—	11.0	77.0	700	15	0	22	—	0.31	5.3	1700	10	0
11	$\frac{1}{2}$ R.A.U.	6.8	61.2	900	10	1	23	$\frac{1}{2}$ R.A.U.	0.34	7.1	2100	10	0
12	—	5.95	47.6	800	11	0	24	—	1.1	18.7	1700	12	1
13	$\frac{1}{2}$ R.A.U.	5.95	47.6	800	10	0	25	$\frac{1}{2}$ R.A.U.	0.34	5.8	1700	15	0
14	—	4.25	42.5	1000	12	1	26	—	0.85	21.3	2500	10	0
15	$\frac{1}{2}$ R.A.U.	3.4	34.0	1000	10	0	27	$\frac{1}{2}$ R.A.U.	0.85	14.5	1700	15	1
16	—	2.55	24.5	960	10	0							

3) A. Adler, Deutsch. Arch. f. klin. Med., 1922, 138, 309.

4) Opitz and Brehme, Klin. Wochenschr., 1923, 1269.

No. 2. S.M., aged 8 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
6	—	3.40	7.5	220	25	0	17	1 R.A.U.	0.34	1.	300	18	1
7	—	8.5	25.5	300	20	0	18	—	0.34	1.4	400	18	0
8	1 R.A.U.	1.7	6.	350	16	1	19	—	0.34	2.	600	14	1
9	—	4.25	10.6	250	22	0	20	1 R.A.U.	0.34	1.7	500	15	0
10	—	1.7	6.	350	20	0	21	—	0.68	2.7	400	18	1
11	1 R.A.U.	0.68	3.	450	15	1	22	—	0.34	2.	600	10	1
12	—	0.85	3.4	400	17	1	23	1 R.A.U.	0.31	1.4	450	18	0
13	—	0.425	2.1	500	15	2	24	—	0.31	2.	650	12	0
14	1 R.A.U.	0.34	1.7	500	15	0	25	—	0.425	1.7	400	18	1
15	—	0.425	2.1	500	13	1	26	1 R.A.U.	0.17	0.9	550	15	1
16	—	0.425	1.3	300	17	1							

No. 3. S.S., aged 13 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	—	12.75	44.6	350	30	1	16	—	2.125	10.5	400	30	0
6	1 R.A.U.	11.0	38.5	350	30	0	17	—	2.53	12.8	500	24	1
7	—	17.05	144.9	850	15	1	18	1 R.A.U.	5.95	23.8	400	26	0
8	—	17.05	76.7	450	25	1	19	—	5.95	35.8	600	18	1
9	1 R.A.U.	11.0	71.5	650	18	2	20	—	5.95	32.7	550	20	1
10	—	8.5	80.8	950	14	1	21	1 R.A.U.	3.4	23.8	700	20	1
11	—	5.95	59.5	1000	14	1	22	—	2.55	12.8	500	24	1
12	1 R.A.U.	1.7	20.4	1200	11	1	23	—	2.125	15.9	750	14	1
13	—	3.4	37.4	1100	14	1	24	1 R.A.U.	1.1	9.9	900	14	1
14	—	2.125	12.8	600	18	1	25	—	0.85	9.4	1100	12	0
15	1 R.A.U.	1.275	4.5	350	30	1							

Myosalvarsan
0.02 in.

No. 4. K.N., aged 3 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
7	—	5.10	20.4	400	7	2	19	1 R.A.U.	5.10	7.7	150	22	1
8	1 R.A.U.	2.55	17.9	700	5	4							
9	—	2.125	14.9	700	9	1	20	$\frac{1}{2}$ R.A.U.	6.80	17.0	250	19	2
10	—	2.55	17.9	700	7	2							
11	1 R.A.U.	2.55	15.3	600	10	3	21	—	5.95	23.8	400	15	1
12	—	5.95	11.9	200	16	1	22	$\frac{1}{2}$ R.A.U.	2.125	8.5	400	11	3
13	$\frac{1}{2}$ R.A.U.	4.25	6.4	150	25	1							
14	—	5.95	10.1	170	15	2	23	—	17.05	25.6	150	21	5
15	—	11.0	22.0	200	22	1	24	$\frac{1}{2}$ R.A.U.	6.8	9.5	140	20	4
16	1 R.A.U.	8.50	17.0	200	20	0	25	—	5.10	?	90	20	4
17	—	8.50	21.3	250	25	1							
18	—	17.05	34.1	200	21	1	26	$\frac{1}{2}$ R.A.U.	1.70	?	130	20	4
							27	—	1.275	1.9	150	22	5

Isravlin
3.5 c.c. in.

Isravlin
4.0 c.c. in.

No. 5. Y.H., aged 10 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	1 R.A.U.	5.95	29.8	500	22	0	12	—	2.125	27.6	1300	10	0
6	—	1.7	22.1	1300	13	1	13	—	2.55	23	900	12	1
7	—	5.95	51.	1000	10	1	14	$\frac{1}{2}$ R.A.U.	0.85	3.9	450	10	1
8	1 R.A.U.	3.4	37.4	1100	11	1	15	$\frac{1}{2}$ R.A.U.	0.425	1.9	350	10	1
9	—	4.25	57.4	1350	10	1	16	$\frac{1}{2}$ R.A.U.	1.1	3.9	350	16	1
10	—	5.1	71.4	1400	10	1	17	$\frac{1}{2}$ R.A.U.	2.55	7.7	300	20	1
11	1 R.A.U.	2.55	25.5	1000	9	1	18	$\frac{1}{2}$ R.A.U.	2.55	8.9	350	20	1

No. 6. M.A., aged 6 y. 7 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
6	1 R.A.U.	11.0	22.0	200	27	0	14	—	2.125	14.9	700	10	0
7	—	21.25	21.3	100	21	0	15	1 R.A.U.	0.31	1.6	500	15	0
8	—	12.75	25.5	200	21	1	16	—	2.125	8.5	400	16	0
9	1 R.A.U.	5.1	15.3	300	13	0	17	—	2.125	12.8	600	10	1
10	—	2.125	6.8	300	20	0	18	1 R.A.U.	0.425	2.6	610	15	0
11	—	4.25	21.3	500	7	0	19	—	0.31	2.5	800	10	0
12	1 R.A.U.	3.4	17.0	500	10	0	20	—	0.31	1.9	600	10	1
13	—	—	—	—	—	1							

No. 7. A.W., aged 3 y. 11 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
2	—	5.95	17.9	300	25	0	9	—	0.425	5.1	1200	8	0
3	1 R.A.U.	4.25	17.0	400	20	1	10	1 R.A.U.	0.34	4.1	1200	10	1
4	—	4.25	13.6	320	25	0	11	—	0.34	3.4	1000	10	1
5	—	4.25	14.9	350	25	1	12	—	0.31	4.0	1300	10	1
6	—	2.125	20.1	1000	13	0	13	1 R.A.U.	0.17	2.7	1600	10	0
7	1 R.A.U.	0.68	8.8	1300	6	0	14	—	0.34	2.4	700	20	0
8	—	0.425	5.5	1300	5	1							

No. 8. K.N., aged 7 y. 3 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
3	$\frac{1}{2}$ R.A.U.	1.275	7.7	600	31	1	9	$\frac{1}{2}$ R.A.U.	0.85	6.0	700	12	1
4	—	4.25	17.0	400	25	1	10	—	1.275	8.9	700	11	2
5	$\frac{1}{2}$ R.A.U.	2.125	5.3	250	27	1	11	$\frac{1}{2}$ R.A.U.	0.31	1.9	600	10	2
6	—	2.55	10.2	400	30	1	12	—	0.31	2.8	900	11	2
7	$\frac{1}{2}$ R.A.U.	2.55	8.9	350	20	1	13	$\frac{1}{2}$ R.A.U.	0.34	2.2	650	14	2
8	—	5.95	29.8	500	22	1	14	—	0.34	3.4	1000	15	2

No. 9. A.T., aged 3 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
3	—	0.34	1.7	500	13	2	9	$\frac{1}{2}$ R.A.U.	1.275	2.6	200	10	1
4	—	1.1	2.2	200	25	1	10	—	5.1	10.2	200	27	0
5	$\frac{1}{2}$ R.A.U.	1.1	2.2	200	16	0	11	$\frac{1}{2}$ R.A.U.	1.1	2.2	200	20	0
6	—	2.55	5.1	200	10	0	12	—	1.275	2.6	200	20	1
7	$\frac{1}{2}$ R.A.U.	5.1	10.2	150	21	1	13	$\frac{1}{2}$ R.A.U.	1.275	2.6	200	15	0
8	—	6.8	13.6	200	13	0	14	—	1.275	3.2	250	25	1

No. 10. F.H., aged 4 y. 2 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	—	21.25	63.8	300	18	0	11	—	0.425	1.	250	11	2
6	$\frac{1}{2}$ R.A.U.	6.8	27.2	400	12	2	12	$\frac{1}{2}$ R.A.U.	0.425	2.1	500	15	3
7	—	2.55	10.2	400	10	2	13	—	0.425	1.1	250	20	1
8	—	1.1	5.5	500	11	1	14	—	0.425	1.7	400	20	3
9	$\frac{1}{2}$ R.A.U.	0.68	3.4	500	11	3	15	$\frac{1}{2}$ R.A.U.	0.34	1.0	300	24	2
10	—	0.425	1.7	400	18	2	16	—	0.425	1.1	250	28	2

No. 11. H.S., aged 6 y. 3 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
4	—	2.55	10.2	400	22	1	8	—	0.68	3.4	500	15	1
5	$\frac{1}{2}$ R.A.U.	0.425	2.1	500	22	1	9	$\frac{1}{2}$ R.A.U.	0.34	2.0	600	15	1
6	—	0.68	3.4	500	20	1	10	—	0.34	1.4	400	25	2
7	$\frac{1}{2}$ R.A.U.	0.68	4.4	600	16	1	11	$\frac{1}{2}$ R.A.U.	0.34	1.0	300	30	1

No. 12. T.Y., aged 2 y. 5 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
4	$\frac{1}{2}$ R.A.U.	2.125	2.1	100	18	2	9	—	0.425	1.3	300	25	2
5	—	0.68	1.4	200	18	2	10	$\frac{1}{2}$ R.Y.U.	0.425	0.6	150	25	5
6	$\frac{1}{2}$ R.A.U.	0.17	0.9	500	11	1	11	—	0.34	0.3	100	24	3
7	—	0.34	1.7	500	15	3	12	$\frac{1}{2}$ R.Y.U.	0.31	0.6	200	25	3
8	$\frac{1}{2}$ R.A.U.	0.425	1.7	400	8	1							

No. 13. Y.T., aged 6 y. 11 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	—	1.1	3.3	300	10	0	10	1 R.Y.U.	0.17	3.1	1800	7	1
6	—	1.275	3.8	300	15	2	11	—	0.31	5.3	1700	4	2
7	1 R.Y.U.	1.1	11.0	1000	6	1	12	—	0.17	3.2	1900	8	1
8	—	0.85	12.8	1500	5	1	13	1 R.Y.U.	0.17	3.5	2050	8	0
9	—	0.425	8.5	2000	4	1	14	—	0.17	2.9	1700	6	2

No. 14. T.S., aged 8 y. 5 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
4	1 R.Y.U.	4.25	29.8	700	15	1	9	1 R.Y.U.	0.34	2.7	800	12	1
5	—	1.7	20.4	1200	10	1	10	—	0.425	2.1	500	20	1
6	—	0.425	2.1	500	15	2	11	1 R.Y.U.	0.34	1.7	500	18	0
7	1 R.Y.U.	0.425	4.3	1000	10	0	12	—	0.34	1.4	400	20	1
8	—	0.425	3.7	900	10	1	13	1 R.Y.U.	0.17	1.1	650	15	1

No. 15. S.A., aged 7 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	—	11.0	22.0	200	32	0	14	½ R.Y.U.	8.5	25.5	300	20	0
6	½ R.Y.U.	8.5	21.3	250	30	1	15	—	8.5	21.3	250	30	0
7	—	8.5	42.5	500	20	1	16	1 R.Y.U.	1.7	9.4	550	21	1
8	½ R.Y.U.	8.5	34.0	400	17	0	17	—	0.85	3.4	400	21	0
9	—	21.25	85.0	400	25	0	18	1 R.Y.U.	0.425	1.9	450	20	1
10	½ R.Y.U.	12.75	70.1	550	15	0	19	—	0.425	3.4	800	17	1
11	—	8.5	34.0	400	15	1	20	1 R.Y.U.	0.31	1.7	550	18	1
12	½ R.Y.U.	5.95	26.8	450	20	0	21	—	0.31	2.2	700	18	0
13	—	11.0	27.5	250	20	0							

No. 16. N.H., aged 5 y. 1 m.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
3	—	2.125	8.5	400	15	1	8	½ R.Y.U.	0.34	1.7	500	15	1
4	½ R.Y.U.	1.10	5.0	450	15	0	9	—	0.68	3.4	500	15	0
5	—	0.68	2.7	400	13	1	10	½ R.Y.U.	0.34	1.0	300	20	2
6	½ R.Y.U.	0.68	2.4	350	18	1	11	—	0.34	0.9	250	20	1
7	—	0.68	3.7	550	18	1							

No. 17. T.A., aged 9 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
9	—	2.55	10.2	400	20	1	12	$\frac{1}{2}$ R.Y.U.	0.17	1.4	800	6	1
10	$\frac{1}{2}$ R.Y.U.	0.68	6.8	1000	12	0	13	—	0.17	1.7	1000	12	1
11	—	0.425	4.3	1000	11	1	14	$\frac{1}{2}$ R.Y.U.	0.17	1.5	900	15	1

No. 18. K.A., aged 12 years.

Days	Yakriton	Urobilin		Urine		Stool	Days	Yakriton	Urobilin		Urine		Stool
		mgr. %	daily amount	daily amount	specific gravity				mgr. %	daily amount	daily amount	specific gravity	
5	—	6.8	68.0	1000	10	3	9	—	0.85	12.8	1500	15	2
6	$\frac{1}{2}$ R.Y.U.	2.125	23.4	1100	12	2	10	$\frac{1}{2}$ R.Y.U.	0.31	3.1	1000	12	3
7	—	0.68	8.2	1200	7	2	11	—	0.34	4.8	1400	12	1
8	$\frac{1}{2}$ R.Y.U.	0.68	10.2	1500	17	2	12	$\frac{1}{2}$ R.Y.U.	0.31	4.7	1500	12	2

Chart 1.
(Cf. Tab. I. No. 1.)

ton administration lay over the bottom of the valley or over the valley of the curve, but not over the summit. The same state of things will be seen from Chart 2, representing No. 8. on Table I.

But a closer inspection of all the tables above shown (Cf. Table I) will reveal that the arrow of yakriton injection, if represented in a chart, would come over the summit of a urobilinuric curve in 5 cases [Cf. Table I, No. 10 (on the 12th day of the disease), Table I, No. 11 (on the 7th day of the disease), Table I, No. 12 (on the 12th day of the disease), Table I, No. 13 (on the 13th day of the disease) and Table I, No. 14 (on the 7th day of the disease)], though such occurred only once in each case. The reason will be explained below (Cf. Table II).

In Table II the whole amount of urobilin excreted in each case on the day on which the arrow showing the yakriton injection came over the summit of the urobilinuric curve was shown with the whole amount of urine on that day. The whole amount of urobilin in all the 5 cases ranged from 0.6 mgrm. (the minimum) to 4.4 mgrms. (the maximum), so that the amount in each case was far below 20-25 mgrms.,

TABLE II.

Apparently exceptional instances in some cases.

Case (Tab. I)	Urobilin		Urine (Daily amount)	Days
	mgrm. %	Daily amount		
No. 10. F.H., aged 4 years	0.425 (not increased)	2.1	500 (250 increased)	12th.
No. 11. H.S., aged 6 years	0.68 (not increased)	4.4	650 (150 increased)	7th.
No. 12. T.Y., aged 2 years	0.31 (decreased)	0.6	200 (100 increased)	12th.
No. 13. Y.T., aged 6 years	0.17 (not increased)	3.5	2050 (150 increased)	13th.
No. 14. T.S., aged 8 years	0.425 (not increased)	4.3	1000 (500 increased)	7th.

which figures are according to Adler⁵⁾ the upper limit of one day's physiological amount of urobilin. Besides, as was shown in Table II, the amount of urine on that day was much larger than on the previous day, which caused the whole amount of the excreted urobilin to be naturally larger. And it has thus been shown that yakriton acts to decrease the amount of urobilin in the urine. Of course this effect of the hormone will not come to light if it is used in normal cases or in cases in which the excretion of urobilin is within physiological limits.

The Explanation of Yakriton Effect upon Urobilinuria.

The origin of urobilin is still an open question, but authors⁶⁾ agree on the point of a close relation between the functional disorders of the liver and the increase of urobilin formation. And the functional disorder of the liver in the case of scarlatina was reported by Hildebrandt,⁷⁾ Bingel⁸⁾ and others. Mishima⁹⁾ also saw the hepatic disorder in scarlatina from the standpoint of *crise hémoclasique*. Tachau¹⁰⁾ attributes an increased excretion of urobilin in the urine to the hepatic disorder and Kiyokawa¹¹⁾ states that scarlatinal virus or toxin plays a causative rôle in the pathological urobilinuria.

Rach and Reuss¹²⁾ accept, besides the primary, a secondary factor for the origin of the pathological urobilinuria in scarlatina, in which disease skin capillaries are prone to hemorrhage, resulting in an increase of destruction of red cells leading, as they state, to the secondary disorder of the liver and to pathological urobilinuria.

Yakriton, the detoxicating hormone of the liver, acts of course favorably upon a hepatic insufficiency which, even excepting our daily clinical experience, will be seen from the work of Asakura¹³⁾ for instance. Besides it counteracts different poisons, as phenol,¹⁴⁾ chloro-

5) A. Adler, Deutsch. Arch. f. klin. Med., 1922, **140**, 302.

6) A. Adler, Deutsch. Arch. f. klin. Med., 1922, **138**, 309.

Th. Brugsch, Folia haematologica, II, Teil, 1911, **10**, 385.

M. Oshima, Nihon Naika Gk. Z., 1931, **18**, 1004.

7) W. Hildebrandt, Münch. med. Wochenschr., 1910, 2512.

8) A. Bingel, Jahrb. f. Kinderheilk., 1907, **65**, 393.

9) H. Mishima, Nihon Densenbyo Gk. Z., 1928, **3**, 126.

10) P. Tachau, Jahrb. f. Kinderheilk., 1913, **77**, 534.

11) Y. Kiyokawa, Rinsho Shonika Z., 1932, **7**, 25.

12) E. Rach and A. Reuss, Jahrb. f. Kinderheilk., 1910, **72**, 422.

13) K. Asakura, Tohoku J. Exp. Med., 1933, **22**, 346.

14) Y. Asada, Tohoku J. Exp. Med., 1930, **15**, 507.

form,¹⁵⁾ salvarsan,¹⁶⁾ toluylendiamine,¹⁷⁾ methyl alcohol,¹⁸⁾ etc., so that it is not difficult to suppose that it will act directly on the scarlatinal toxin. Besides, according to our daily clinical experience, yakriton seems to decrease hemorrhage on the skin in infantile cases of nutritional disorders. So yakriton acts to decrease urobilinuria either through its effect on the insufficient liver or through its combined effect as above explained.

PART II.

THIRD REPORT ON CLINICAL EXPERIMENT TO PREVENT SCARLATINAL NEPHRITIS BY YAKRITON.

In treating these 20 cases a very strict regimen was not followed. Yakriton was used on every second or third day, because I wanted to know the amount of urobilin which might change according as yakriton was or was not used on the previous day. This method—the use of yakriton on every second or third day—had not yet been known to be efficacious in the prevention of scarlatinal nephritis. But according to the present experiment only one case out of my own twenty cases developed scarlatinal nephritis (Cf. Table I, No. 5). Observing this result from the point of the different intervals of injections, no case of complicated nephritis occurred in 13 cases, in which yakriton was used on every second day, whereas nephritis occurred in one out of 7 cases, in which yakriton was used on every third day.

According to the conclusion of the 75th Report on Yakriton,²⁾ the use of yakriton is effectual for the prevention of scarlatinal nephritis, if it is given early in the first week of the disease. This conclusion will hold true in my experiment. Here I desire to present a small statistical study of the results of all the 55 typical scarlatinal cases including 35 cases, reported in the 71st¹⁾ and the 75th²⁾ Reports on Yakriton, and divide all the cases into 3 groups according to the time of beginning yakriton therapy as will be seen from Table III.

As is clear from Table III, 19 cases in which yakriton therapy began not later than on the 4th day of the disease did not develop nephritis, while, of the 20 cases in which it began in the first week later

15) A. Sato, and S. Yanagawa, *Tohoku J. Exp. Med.*, 1933, 22, 342

16) M. Yoshida, *Tohoku J. Exp. Med.*, 1933, 22, 371.

17) M. Yoshida, *Tohoku J. Med.*, 1934, 22, 379.

18) M. Yoshida, *Tohoku J. Exp. Med.*, 1934, 23, 434.

TABLE III.

Relation between the date of the first use of yakriton and the frequency of nephritic complication.

Groups	Commencement of yakriton therapy			Nephritis complicated		
	up to and on the 4th day	up to and on the 7th day	up to and on the 12th day	Cases	%	As total
Group 1	19 cases			0	0	0 %
Group 2		20 cases		2	10	3.6 %
Group 3			16 cases	3	18.8	5.5 %
Total		55		5	9.1	9.1 %

TABLE IV.

Frequency of nephritic complication according to different authors.

Author	Scarlatina	Nephritis complicated
Hirschberg. (Moskau)	845	19.75 %
Hase. (St. Petersburg)	2453	14.7 %
I. Mitsutake (Tokio)	164	18.3 %
S. Sato (Tokio)	196	15.3 %
K. Ohwaki (Nagoya)	54	17.2 %
C. Kozima (Kyoto)	177	14.6 %
T. Narabayashi (Kokura)	48	33.3 %
K. Tanaka (Keijo)	33	12.1 %
T. Miyake (Taihoku)	95	8.4 %
I. Shimada (Taihoku)	83	14.5 %
Our cases (Sendai)	55	<div style="display: flex; align-items: center;"> <div style="margin-right: 10px;"> $\left\{ \begin{array}{l} 19 \\ 20 \\ 16 \end{array} \right.$ </div> <div> <div style="display: flex; align-items: center;"> <div style="margin-right: 5px;"> $\left\{ \begin{array}{l} 0 \\ 10.0 \\ 18.8 \end{array} \right.$ </div> <div> % different according to the time of commencing yakriton therapy. </div> </div> </div> </div>

than the 4th day of the disease, 2 cases or about 10% (i. e. 3.6% of all the 55 cases) developed nephritis. And of the 16 cases in which yakriton therapy began between the 8th and 12nd day of the disease, nephritis occurred in 18.8% (i. e. 5.5% of all the 55 cases) (Cf. Table III).

About the frequency of nephritic complication in scarlatina, there will be a wide difference according to epidemics, races etc. Here I give the frequency of nephritic complication in children's cases of scarlatina (Cf. Table IV).

Comment.

The tentative effect of yakriton to prevent nephritic complication in scarlet fever was reported by Prof. Sato, Yamagishi, Abe and Yoshida,¹⁾ and then as to how and when yakriton should be used to

prevent the nephritic complication it was reported by Prof. Sato, Yoshida, Chiba and Kimura.²⁾ They all used yakriton every day, while in the present work I used it not every day, but on every second or third day.

The favorable effect of yakriton for the prevention of scarlatinal nephritis is not an accidental result. Its antinephritic effect has already been proven by way of animal experimentation by T. Sato,¹⁹⁾ who was able to rescue by means of yakriton low-classed rabbits from the fatal outcome due to uranyl nephritis. But he did not use it at random, because an indiscriminate use of it would not give a favourable result, as will be seen from the following table (Cf. Tab. V). Furthermore, the number of units of yakriton favourable for rescuing rabbits from fatal nephritis is different according to the difference of the poisons causing nephritis. So, Asano²⁰⁾ saw a less favourable effect of yakriton, when he experimented on nephritis produced by mercury bichloride; this fact was without doubt due to the fact that mercury bichloride was more poisonous than uranyl acetate. His result is shown in Table VI.

TABLE V.

Experiment of T. Sato on the effect of yakriton to save rabbits from uranyl nephritis.

Groups	Daily use of yakriton	Survival
1	$\frac{1}{2}$ R.A.U. (per kilogram of body weight)	80%
2	$\frac{1}{4}$ " "	ca. 67%
3	1 " "	ca. 57%
4	$\frac{1}{10}$ " "	50%
5	10 " "	ca. 30%

TABLE VI.

Experiment of Asano on the effect of yakriton to save rabbits from mercuric nephritis.

Groups	Daily use of yakriton	Survival
1	$\frac{1}{2}$ R.A.U. (per kilogram of body weight)	0%
2	$\frac{1}{4}$ " "	0%
3	$\frac{1}{10}$ " "	50%

19) T. Sato, Tohoku J. Exp. Med., 1933, 408.

20) J. Asano, Tohoku J. Exp. Med., 1935, 27, 99.

It is evident from their results with yakriton that the number of units of the hormone to be used for the prevention of nephritis must differ to a more or less remarkable degree according to the severity of each scarlatinal case. But it is of course difficult to determine an optimum amount of it for a given case. From my own actual clinical experiments the amount of from $\frac{1}{2}$ to 1 R.A.U. of yakriton for a single dose may be sufficient. The most important thing is an early commencement of yakriton therapy; it should be instituted as soon as a case is diagnosed as scarlatina. As to the interval, the hormone may be used daily or every other day, although its use on every second day may not be so favourable.

Very eloquent evidence of the close relation between the liver and the kidney was given from our Laboratory in 1933 by T. Sato,²¹⁾ and in 1935 by Asano and Hasegawa.²²⁾ It is evident then that yakriton, the detoxicating hormone of the liver, will act favorably upon scarlatinal nephritis—so to speak by “using the influence of the liver upon the kidney.”—And we may well use the term “Hepatogenous nephritis”²³⁾ suggested by Prof. A. Sato in the case of scarlatinal nephritis.

So much for the antinephritic action of yakriton. As to its effect to counteract urobilinuria or to decrease urobilin excretion of which I have made a point in the present work, no animal experiment has been published hitherto. But the work is going on and I expect to be able to publish it in the near future. It is of course imaginable that even in the case of “hepatogenous nephritis,” if the nephritic affection has gone too far and is too severe, then yakriton may not be able to counteract it any longer with sufficient potency.

Summary.

A preliminary report on the prophylactic treatment of scarlatinal nephritis was published in 1929 by Prof. Sato, Yamagishi, Abe and Yoshida.¹⁾ And then a summarizing report on 35 scarlatinal cases was published in 1931 by Prof. Sato, Yoshida, Chiba and Kimura.²⁾ The most important point in the report was that yakriton therapy should be commenced as early as possible in the first week of

21) T. Sato, *Tohoku J. Exp. Med.*, 1933, **20**, 399.

22) J. Asano and M. Hasegawa, *Tohoku J. Exp. Med.*, 1935, **27**, 95.

23) A. Sato, *Tohoku J. Exp. Med.*, 1933, **20**, 419.

the disease in order to prevent nephritic complications. It is very clear that their favorable result was not an accidental one, which may well be inferred also from T. Sato's¹⁹⁾ paper concerning antinephritic effect of yakriton.

In the present work I tried to use yakriton not daily, but every second or third day to see whether such a usage would likewise act to prevent nephritic complication. And I found that, if yakriton therapy is begun early in the first week of scarlatina, then its use on every other day will be able to prevent the complication. Besides I made it a point of investigation, whether yakriton would act favorably upon scarlatinal hepatitis or scarlatinal disorder of the liver and counter-act urobilinuria, and I found that it would act to decrease urobilin excretion.

Conclusions.

1. Yakriton, the detoxicating hormone of the liver, acts to decrease urobilin excretion in scarlatinal cases.
 2. The use of yakriton, even if it is used on only every other day, is effectual for the prevention of scarlatinal nephritis, if the administration of yakriton is begun early in the first week of the disease.
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