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

78th Report.

**Possibility of Judging Individual Liver Power of Ammonia-Detoxication
by Adrenalin; Classification of Liver Power by Use of Yakriton
and Adrenalin. The Yakriton-Adrenalin Method.**

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Introduction.

Literature as to function tests of the liver is already abundant. Prof. A. Sato and H. Sakurada¹⁾ reported in 1927 that rabbits can be divided into several groups, Classes a, b, c, d, e, f, etc. according to their individual liver power of detoxicating ammonia. Recently I have studied the influence of yakriton on the hyperglycemic action of adrenalin. This adrenalin-inhibiting effect of yakriton, however, depends, as I have found, on the ammonia-detoxicating liver power of animals, and normal rabbits may, thus, be divided into at least three groups in consideration of the effect yakriton exerts on adrenalin. The present paper treats of this problem.

There is, as is well known, a wide range of individual susceptibility to a poison, so that the same amount of the same substance may prove fatal to one individual, while another may be quite safe from it. Such a difference depends to a large extent, as has been shown by a number of experiments with yakriton, on individual liver power of ammonia detoxication. A paper on the determination of the individual liver power of ammonia detoxication was first published by Sato and Sakurada in 1927, the next year of the isolation of yakriton by

1) A. Sato and H. Sakurada, Tohoku J. Exp. Med., 1927, 8, 347.

Prof. Sato²⁾ himself. Below the classification according to Sato-Sakurada's liver function test will be shown.

Classification of detoxicating power of animals.

3% ammonium chloride, freshly prepared, intra-peritoneally injected in an amount of 10 c.c. per kilo gram of body weight	Class of detoxicating power
1) Convulsion within 5 minutes after the injection	a*
2) Convulsion within 15 minutes after the injection	b*
3) 1. Convulsion more than 15 minutes after the injection.....	} c
2. Lose of consciousness within 15 minutes after the injection (with or without convulsion more than 15 minutes after the injection).....	
4) Apparently unaffected during the first 10-15 minutes after the injection, then gradual loss of consciousness	d
5) Almost unaffected, only with no appetite for the first 10-15 minutes	e
6) Utterly unaffected, with no impaired appetite (apparently quite healthy)	f
* Animals of this class may frequently die during the convulsion attacks.	
* Animals of this class may sometimes die during the convulsion attacks.	

Only a few examples may be cited here. T. Sato³⁾ found that the same amount of uranyl acetate invariably caused death in *b*-classed rabbits, while *f*-classed ones were, as he found, able to outlive the fatal nephritis. He⁴⁾ again found that the same amount of heparin, the anti-coagulant remedy, caused a remarkable prolongation of blood coagulation time in *b*-classed rabbits, whereas in the case of *f*-classed ones, as he reported, no prolongation would occur. Also Asakura's⁵⁾ experiment on phosphorus poisoning showed a difference of susceptibility to the poison according as the animals were *f*- or *b*-classed.

It has been my desire for a long time to apply this liver test to human cases, because, if individual liver power in human cases were known, then it could, as I believe, lead to a more reasonable dosage of remedies in daily practice. Of course, there is no direct application of the above method to clinical medicine, for we of course can not use so much ammonium chloride in the case of human beings as to cause convulsions. In the present paper, however, I am able to report on a possibility that the individual ammonia detoxicating power may be

2) A. Sato, Tohoku J. Exp. Med., 1926, 8, 232, and 1928, 11, 272.

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

4) T. Sato, Tohoku J. Exp. Med., 1932, 19, 15.

5) K. Asakura, Tohoku J. Exp. Med., 1931, 17, 512.

determined very roughly, on the basis of my animal experiment reported in this work. Below I shall relate my experiment.

Method of Experiment.

The experiments were performed on normal healthy rabbits, which had been fasted about 24 hours before the proper experiment. Blood sugar was estimated before each experiment and at definite times following the administration of yakriton and adrenalin. Blood samples were taken from ear veins. The Hagedorn and Jensen method was used for blood sugar estimation. In each experiment adrenalin* was used subcutaneously in an amount of 0.1 c. c. per kilo and the blood sugar was determined. Then after one week adrenalin was used in the same way as above mentioned with the difference that 4 hours previous to the use of adrenalin yakriton was injected subcutaneously, and again the blood sugar was determined.

Schedule of Experiment.

Result of Experiment.

Before examining the accompanying tables (Tables I, II and III) an explanation should be made about β -, γ -, and ζ -classed rabbits. These are of course different from b- c-, and f-classed ones respectively. The b-, c- and f-classed animals are classified on the basis of Sato and Sakurada's¹⁾ ammonium-test, while the β -, γ - and ζ -classed are named according to the result of my yakriton-adrenalin test.

1. ζ -classed rabbits—animals in which adrenalin hyperglycemia will be mitigated by a previous use of yakriton.
2. β -classed rabbits—animals in which adrenalin hyperglycemia will be aggravated by a previous use of yakriton.

* Adrenalin "Sankyo" (1:1000) was used.

TABLE I.
Classification of liver power by use of yakriton and adrenalin. Experiment performed in summer.

No. of rabbits	Body weight in kilograms	Amount (c.c.) of yakriton (1 R.A.U. in 1 c.c.)	Amount (c.c.) of adrenalin (1:1000)	Before yakriton	Blood sugar in per cent						Class of liver function		Coincidence between the two tests	
					Before adrenalin	Time after the injection of adrenalin in hours					Chemical test (Own method)	NH ₄ Cl-test (Sato-Sakurada's method)		
						½ hour	1 hour	2 hours	3 hours	4 hours				5 hours
No. 1 (No. 4437)	1.97		0.19	0.093	0.205	0.254	0.231	0.183	0.136	0.105	R-ζ	R-f (bff)	+	
No. 2 (No. 4438)	1.94	1.9	0.19	0.095	0.093	0.147	0.154	0.175	0.129	0.121		R-β	R-b (bbe)	+
No. 3 (No. 4439)	2.75	2.7	0.27	0.115	0.102	0.193	0.221	0.201	0.170	0.132	0.101			+
No. 4 (No. 4440)	2.26	2.2	0.22	0.093	0.114	0.144	0.189	0.198	0.184	0.135	0.093	R-γ	R-c (bcc)	+
No. 5 (No. 4441)	2.25	2.2	0.22	0.093	0.095	0.171	0.193	0.208	0.171	0.130	0.112	R-ζ	R-c (ebc)	+
No. 6 (No. 4442)	1.88	1.9	0.19	0.093	0.088	0.152	0.218	0.283	0.230	0.140	0.107	R-ζ	R-f (fff)	+
No. 7 (No. 4443)	1.92	2.1	0.21	0.114	0.101	0.200	0.254	0.241	0.204	0.154	0.116	R-β	R-b (bbb)	+
No. 8 (No. 4444)	2.12	3.2	0.32	0.109	0.104	0.189	0.206	0.199	0.157	0.121	0.098	R-ζ	R-b (bbb)	+
No. 9 (No. 4445)	3.00	2.25	0.25	0.109	0.112	0.174	0.206	0.248	0.231	0.200	0.170	R-ζ	R-b (bbb)	+
No. 10 (No. 4446)	2.25	2.3	0.23	0.106	0.099	0.187	0.240	0.220	0.201	0.138	0.107	R-β	R-f (fbf)	+
No. 11 (No. 4447)	2.36	2.3	0.23	0.103	0.104	0.140	0.172	0.171	0.154	0.120	0.121	R-γ	R-e (fbc)	+
No. 12 (No. 4448)	2.18	2.2	0.22	0.111	0.113	0.121	0.140	0.126	0.121	0.114	0.100	R-ζ	R-f (cfff)	+
No. 13 (No. 4449)	2.25	2.2	0.22	0.103	0.104	0.130	0.154	0.163	0.136	0.116	0.102	R-ζ	R-b (bbb)	+
No. 14 (No. 4450)	3.00	3.0	0.30	0.111	0.091	0.186	0.243	0.259	0.198	0.190	0.149	R-β	R-b (bbb)	+
No. 15 (No. 4451)	3.05	3.0	0.30	0.111	0.108	0.135	0.160	0.184	0.170	0.132	0.122	R-ζ	R-f (cfff)	+
No. 16 (No. 4452)	2.48	2.4	0.24	0.098	0.098	0.113	0.141	0.150	0.148	0.121	0.116	R-γ	R-e (fbc)	+
No. 17 (No. 4453)	2.38	1.7	0.18	0.102	0.096	0.167	0.230	0.282	0.280	0.250	0.180	R-β	R-b (bbb)	+
No. 18 (No. 4454)	1.77	1.7	0.18	0.102	0.096	0.185	0.249	0.247	0.211	0.178	0.160	R-β	R-b (bbb)	+
No. 19 (No. 4455)	2.06	2.0	0.20	0.094	0.110	0.151	0.172	0.222	0.190	0.142	0.134	R-β	R-b (bbb)	+
No. 20 (No. 4456)	2.07	2.0	0.20	0.094	0.103	0.176	0.145	0.238	0.202	0.147	0.134	R-β	R-b (bbb)	+

10 (83.3%) out of 12 animals

TABLE II.
Classification of liver power by use of yakriton and adrenalin. Experiment performed in autumn.

No. of rabbits	Body weight in kilos	Amount (c.c.) of yakriton (1 R.A.U. in 1 c.c.)	Amount (c.c.) of adren- alin (1:1000)	Blood sugar in per cent						Class of liver function (Chemical test (Own Sakurada's method))	Coin- cidence between the two tests			
				Before yakri- ton	Before adre- nalin	Time after the injection of adrenalin in hours								
						1/2 hour	1 hour	2 hours	3 hours			4 hours	5 hours	
No. 1 (No. 4437)	2.00		0.20	0.091	0.190	0.280	0.271	0.233	0.167	0.122	R-ζ	R-f (ffe)	9 (51.8%) out of 11 animals + + + + + + + + + +	
	1.88	1.9	0.19	0.096	0.099	0.164	0.196	0.188	0.175	0.152	0.113	R-ζ		
No. 2 (No. 4438)	2.23		0.22	0.105	0.195	0.272	0.270	0.216	0.118	0.110	0.110	R-ζ		R-f (bff)
	2.92	2.9	0.29	0.098	0.100	0.182	0.234	0.249	0.196	0.126	0.103	R-γ		R-c (cbc)
No. 3 (No. 4439)	2.23		0.22	0.109	0.209	0.256	0.232	0.181	0.108	0.096	0.096	R-ζ		R-f (fcf)
	2.19	2.1	0.21	0.096	0.106	0.154	0.193	0.233	0.198	0.133	0.120	R-β		R-b (bbb)
No. 4 (No. 4440)	2.01		0.20	0.122	0.211	0.314	0.288	0.268	0.209	0.144	0.144	R-β		R-b (bbb)
	2.15	2.1	0.21	0.100	0.111	0.162	0.223	0.263	0.232	0.148	0.124	R-ζ		R-c (cef)
No. 5 (No. 4441)	2.10		0.21	0.112	0.119	0.226	0.221	0.222	0.181	0.108	0.105	R-ζ		R-c (cef)
	2.20	2.2	0.22	0.105	0.107	0.140	0.241	0.252	0.260	0.149	0.115	R-ζ		R-f (ffe)
No. 6 (No. 4442)	3.46		0.34	0.111	0.171	0.228	0.224	0.192	0.147	0.119	0.119	R-ζ		R-f (fff)
	3.50	3.5	0.35	0.103	0.098	0.151	0.234	0.270	0.266	0.224	0.180	R-ζ	R-f (bff)	
No. 7 (No. 4443)	2.60		0.26	0.104	0.140	0.154	0.165	0.165	0.145	0.136	0.131	R-ζ	R-c (cef)	
	2.50	2.5	0.25	0.083	0.091	0.101	0.122	0.132	0.118	0.106	0.103	R-ζ	R-c (cef)	
No. 8 (No. 4444)	2.44		0.24	0.119	0.149	0.167	0.155	0.159	0.154	0.127	0.127	R-ζ	R-f (ffe)	
	2.55	2.5	0.25	0.104	0.112	0.124	0.132	0.159	0.123	0.111	0.101	R-ζ	R-f (fff)	
No. 9 (No. 4445)	2.57		0.25	0.095	0.190	0.245	0.246	0.167	0.121	0.100	0.100	R-ζ	R-f (bff)	
	2.50	2.5	0.25	0.097	0.099	0.156	0.212	0.174	0.134	0.117	0.102	R-ζ		
No. 10 (No. 4447)	1.82		0.18	0.097	0.178	0.211	0.260	0.228	0.190	0.189	0.189	R-ζ		
	1.90	1.9	0.19	0.104	0.092	0.172	0.204	0.235	0.227	0.183	0.160	R-ζ		
No. 11 (No. 4448)	2.45		0.25	0.097	0.187	0.294	0.276	0.234	0.194	0.167	0.167	R-ζ		
	2.50	2.5	0.25	0.098	0.094	0.165	0.224	0.249	0.218	0.220	0.149	R-ζ		

3. γ -classified rabbits—animals in which adrenalin hyperglycemia will not be influenced by a previous use of yakriton, or, if at all, to a slight degree only.

Comparison between the Result of Sato-Sakurada's Liver Function Test and the Yakriton-Adrenalin Test.

The present trial, which may be called the yakriton-adrenalin test has divided all the rabbits used for the experiment into three kinds; β -, γ - and ζ -classified animals, as above explained. Now I want to find out the relation between these differences due to the yakriton-adrenalin test and the ammonia detoxicating ability of the liver.

Assumption: Before proceeding further let us assume that a ζ -classified animal corresponds to an f -classified, and a γ -classified to a c -classified, and a β -classified to a b -classified.

Table I shows the first series of animal experiments of the yakriton-adrenalin test. This experiment was made mostly during the hot season. The result shown in Table I justifies the above mentioned assumption in ten animals out of a total of 12 or with about 80% accuracy. Table II shows the second series of animal experiments, which was performed mostly during the autumn. And the result given in Table II again justifies the above mentioned assumption in 9 animals out of 11, thus which about 80% accuracy. Table III shows the third and last series of animal experiments, which was performed mostly during the winter time. The result shown in this table again justifies the above mentioned accuracy in 8 animals out 10 or with 80% accuracy.

It will be seen from these series of experiments that no striking difference of adrenalin hyperglycemia was seen between f -classified (high-classed) and b -classified (low-classed) animals, or between rabbits with high-classed ammonia detoxication and those with low-classed. But if yakriton was used 4 hours previous to the use of adrenalin, the resulting hyperglycemia was in most cases different according as the rabbits were of the high-classed liver power or of the low-classed. In the high classed animals, the resulting hyperglycemia was not so remarkable as that occurring on adrenalin alone, while in the low classed rabbits, the resulting hyperglycemia was more pronounced than that occurring on adrenalin alone.

Summary.

Sato-Sakurada's liver function test based on the individual

liver power of ammonia detoxication in the case of rabbits of course cannot be applied to human beings, because the method aims at the development of severe convulsions. It has been my intention to apply the principle of the method to clinical medicine. In the present paper I tried a yakriton-adrenalin method of my own device in the case of rabbits to test whether a direct relation would exist between the Sato-Sakurada's liver function test and my own method. And a rather close relation was found between the two methods, so that β -, γ - and ζ -classed rabbits in my own method corresponded in most cases to b-, c- and f-classed ones in Sato-Sakurada's method. During this experiment, it was found that the ammonia detoxicating liver power was weakest in summer and strongest in autumn. Though the experiment did not happen to be performed in spring, yet the result of the experiment in this season would, as it may be easily imagined, have been almost the same as in autumn.

Conclusion.

This new liver function test—the-Yakriton-Adrenalin Method—coincides in most cases with the liver function method of Sato and Sakurada.