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

15th Report.

Two Contrary Effects of "Yakritisation"; and Antibacterial
and Balance-keeping Effects of Yakriton.

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The administration of yakriton, the detoxicating hormone of the liver, has, as far as our experimental and clinical experience are concerned, two effects, which may seem contrary to each other. The present paper is only the preliminary report concerning these effects, yet a brief description of them will be necessary for any further comprehension of the effect of yakriton.

1. Two Contrary Effects of Yakritisation.

The "yakritisation" has two effects, which have been already mentioned in a preceding paper¹⁾ of these studies as the *pro*- and *con*-effects of yakriton (Fig. 1).

* "Yakritisation" used for (subcutaneous, rectal, intravenous or peroral) administration of yakriton as well as the state after the administration.

1) K. Suzuki, Tohoku J. Exp. Med. 1928, 11, 291.

The curve o...p...q represents the con-effect and is called the "Anti-anaphylactic Curve or Line," while the curve r...s...t representing the pro-effect of yakriton, is called the "Liver-strengthening Curve or Line."

Fig. 1.

The Con-effect of Yakritisation.

The name "con-effect" may indeed be taken to mean "undesirable effect," but the fact is different. It is indeed by this con-effect that ammonium is detoxicated. This con-effect detoxicates, as far as our experience is hitherto concerned, the injurious effects of the ammonium chloride,²⁾ commercial ammonium carbonate,³⁾ and urea.⁴⁾ The name "antianaphylactic curve" is selected, because it is by this curve that yakriton saves sensitive animals from fatal anaphylactic shock. Thus this effect may be considered as weakening in a measure the reactivity of the liver, though apparently acting to detoxicate the fatal effect of anaphylaxis. Further explanation will follow later.

The maximum of this effect seems, as drawn in Fig. 1., to pass away rather rapidly, while its late effect will still be seen even after the pro-effect is over. This latter fact will be recognized from Table VII of the 9th report of these studies.

The Pro-effect of Yakriton.

This "Liver-strengthening effect" is only weak at the time of yakriton injection, while its maximum will occur much later, after the maximum of the antianaphylactic curve is over (Fig. I). This pro-effect will be seen most distinctly from the works of Suzuki (Table VI of the 9th¹⁾ report).

It is suspected that the antihyperglycemic action of yakriton as reported by Asakura and Sakurada,⁵⁾ is rather the result of the pro-effect than of the con-effect.

2) A. Sato, Tohoku J. Exp. Med., 1928, 11, 273.

3) Paper of H. Morishita, to be published in this Journal (16th Report of Yakriton).

4) H. Sakurada and A. Sato, Tohoku J. Exp. Med., 1927, 9, 66.

5) Ky. Asakura and H. Sakurada, Tohoku J. Exp. Med., 1929, 13, 450.

*How to Magnify the Pro-effect without Magnification
of the Con-effect.*

It is, as will be understood from the foregoing, impossible to utilize the pro-effect alone of yakritisation without the previous accompaniment of the con-effect. But one will be able to magnify the pro-effect alone, while keeping down the con-effect. If one "yakritises" an animal with small amounts of yakriton repeatedly (once a day for instance), then the con-effects as well as the pro-effects of this repeated yakritisation will be piled up. But the con-effects, each of which manifests itself most strongly at the time of injection and leaves only a moderate effect thereafter, will be piled to a slight height as will be seen from Fig. 2. (see $o \dots o' \dots o'' \dots o''' \dots$). As to the pro-

effects, each of which will become much stronger only later, will be piled up to a considerable height, if the following injection is performed not too late (Fig. 2. $r \dots r' \dots r'' \dots r'''$). And one can thus expect a strong pro-effect of yakritisation with accompaniment of only a more or less negligible con-effect. Here, however, it should be noted that the (maximum of) accumulated pro-effect will pass away

Fig. 2.

rather soon, as will be suspected from the declivity represented in Fig. 2, while at this time the con-effect still exists, though weak in strength, and will last some time longer.

The relation of these different effects of yakritisation will be seen most distinctly in the experiment of Suzuki⁶⁾ on anaphylaxis.

2. Antibacterial Effects of Yakriton.

Investigations concerning antibacterial effects of yakriton are being carried on in our laboratory. Here will be published only my preliminary

6) K. Suzuki, Tohoku J. Exp. Med., 1928, II, 282.

work, which was published already as a discussion⁷⁾ and is based on the following result (Table).

TABLE.
Effect of yakriton on pneumococcus infection.

No. of mouse	Coarse yakriton, subcutaneously injected	Pneumococcus emulsion	Result		
			The next day	The third day	Later
No. 1	0.1 c.c.	1.0 c.c.	Death	Death	Survival
No. 2	"	"			"
No. 3	"	"			"
No. 4	"	"			"
No. 5	"	"			"
No. 6	No yakriton	"			"
No. 7	"	"			"
No. 8	"	"			"
No. 9	"	"			Survival
No. 10	"	"			"

This work was done very early when very coarse yakriton was prepared in only small amounts. The amount of yakriton used is, though 0.1 of the sample used at that experiment was meant to contain 1/10 R. A. U., most probably less than 1/20 R. A. U. in 0.1 cc. so that only 1/20 R. A. U. per 10–15 grms of body weight (or only 5 R. A. U. per kilo) was used. This early work was attempted, when nothing was known about the two effects of yakritisation, under the assumption that yakriton itself might represent the antibacterial power of the liver.

The work had to be suspended later for some time, but my explanation at that time was that yakriton saved those animals from pneumococcus infection in the same sense, as this hormone would prevent animals from ammoniac poisoning, and I thought that the larger the amount (=more units) of yakriton used, the better the result would be. My later explanation is that in the above experiment the amount of yakriton was rather too much than too small, and that it should have been used in a much smaller amount. According to the result found in our laboratory it is almost certain that the antibacterial effect of yakriton will not be found in the (maximum) con-effect of yakritisation, while it is too premature to conclude that the antibacterial effect will be found in the pro-effect; concerning this, further experiments will be necessary.

7) A. Sato, Discussion following the paper of I. Fukuda: The Antibacterial Function of the Liver, read at the 32nd General Meeting of the Japanese Pediatric Society, 1928, April, Kyoto.

3. *Blood Ingredient Balacing Effect of Yakriton.*

It was through its ammonium detoxicating property that I was able to isolate the detoxicating hormone of the liver. As to the blood finding⁸⁾ I knew at that early time only the fact that in yakritized animals the blood ammonium was not augmented in spite of the injection of ammonium chloride. Later it was found that yakriton would detoxicate the injurious effect of urea injection,⁹⁾ though the mechanism was not then known.

It was only through the chemical study of Sakurada¹⁰⁾ that the detoxicating mechanism of yakriton was revealed, at least part of it. Though yakriton removes the harmful effects of ammonium salt, it owes the ammonium-detoxicating function not to its blood ammonia-decreasing property, because even a considerable amount of yakriton will not make the normal blood ammonia content lower. Only 10 R. A. U. of yakriton will save rabbits from the injurious effects of 3% ammonium chloride solution in an amount of 10 c.c. per kilogram of body weight, but 1000 R. A. U. of the same hormone will never lower the normal blood ammonia content. Yakriton again can save rabbits from fatal convulsions caused by urea injection. But it is not because the hormone has the property to decrease the blood urea content, but because of its property to keep constant the normal blood urea content. Such a large amount of yakriton as 1000 R. A. U. will, if injected into a normal animal, never cause the blood urea to disappear, but will keep constant the normal blood urea content, as if no yakriton were introduced into the system.

Asakura and Sakurada¹¹⁾ saw that yakriton was also effectual for the detoxication of artificial hyperglycemia, and that it would cure the hyperglycemia. But it will according to Asada, Asakura and Niitsu¹²⁾ never lower the normal level of blood sugar, even if injected in such a large amount as 2500 R. A. U. It keeps the normal blood sugar content; this is the reason why Niitsu failed to see any effect of yakriton on the blood sugar in early times, because he then experimented only on normal rabbits.

It will thus be seen that yakriton will strive to keep constant the content of a normal blood constituent or to keep the normal level of a blood ingredient. Yakriton keeps the normal level of blood ammonia, blood urea

8) Sh. Yoshimatsu and A. Sato, *Tohoku J. Exp. Med.*, 1926, 8, 236.

9) H. Sakurada and A. Sato, *Tohoku J. Exp. Med.*, 1927, 9, 69.

10) Sakurada, *Tohoku J. Exp. Med.*, 1929, 13, 481.

11) Ky. Asakura and H. Sakurada, *Tohoku J. Exp. Med.*, 1929, 13, 450.

12) Y. Asada, Ky. Asakura and R. Niitsu, *Tohoku J. Exp. Med.*, 1929, 13, 456.

and blood sugar. And it is most probably through this blood-ingredient-balancing property of yakriton that the blood chloride¹³⁾ will remain constant in yakritized animals in spite of the injection of ammonium chloride, and that the amount of the blood CO_2 ¹³⁾ will remain constant in yakritized animals in spite of the injection of ammonium carbonate, while in control animals a remarkable decrease of it will occur. This property of yakriton to keep constant the normal level of a blood ingredient may be called—"blood ingredient balancing property of yakriton."

4. Appendix.

a) *Effect of Yakriton on Another Hormone.*

It is still very premature to say anything of the relation of yakriton to other hormones. Here, however, one word will be necessary about this relation for the prevention of misapprehension. If yakriton is, as stated in the above paragraph, the hormone which keeps the blood ingredients normally constant, then what will be the relation between yakriton and insulin, for instance?

Two possibilities will be thought of. First, yakriton which will keep the normal level of blood sugar, may fight against (injected) insulin, the blood sugar lowering hormone, and strive to keep the normal blood sugar constant. Second, if we take into account the normal life of an animal, the normal chemical constituents of the blood are held on their normal level, not only through yakriton, but through a number of different other hormones, insulin among them. And if now into such a normal organism insulin is artificially injected, yakriton will, as it were, make no discernment between the naturally secreted "insulin" and the artificially injected "insulin" and not prevent the lowering of sugar content through insulin. The outcome of this second thought will be: insulin will protest itself whether or not yakriton is injected. The result of Asada's¹⁴⁾ experiment with yakriton and insulin has shown that (injected) yakriton will allow (injected) insulin to lower the blood sugar almost as if no yakriton were injected.

The plausibility of the second idea above mentioned, made probable by the real investigation of Asada, will lead us to the following presumption: "As yakriton not only does not interfere with another hormone, but also—so to speak—lets it have its own way, so will in depancreatized

13) Papers of Morishita, 25th and 28th Reports (of Yakriton), to be published in this Journal.

14) Paper of Y. Asada, to be published in this Journal.

animals (dogs, for instance) the blood remain hyperglycemic (with the other changes secondary to the want of insulin) in spite of the use of yakriton." The effect of yakriton injected in such a case will be made an object of study in our laboratory.

b) Effect of Yakriton on Foreign Poisons.

It is wonderful to see how yakriton—one and the same substance—will fight against a number of different poisons and that in a specific way. Yakriton will, as previously explained, exert such a detoxicating action on different poisons with different numbers of units or with different phases of yakritisation. We shall not go into details here about this fact.

Here only the behavior of yakriton toward a foreign poison will be mentioned. It is not difficult to suspect that yakriton may detoxicate phosphorus, this well-known liver poison. If one undertakes a preparatory experiment concerning the preventive yakritisation against phosphorus intoxication, it is very natural that one will inject a very large amount of yakriton previous to the administration of a lethal dosis of phosphorus. A very large amount of yakriton indeed, because one will think that phosphorus is a drastic poison and that even the prevention of (not fatal) ammonia convulsion requires 10 R. A. U. of yakriton. But the fact is quite different. Asakura and T. Sato¹⁵⁾ tried the experiment of subacute phosphorus poisoning and found that $\frac{1}{2}$ R. A. U. of yakriton, subcutaneously injected 20 minutes previous to the peroral administration of phosphorus, was more effectual than 5 or 1 R. A. U. and made almost all those yakritized rabbits survive the phosphorus poisoning and remain in perfect health. The details will be seen from their paper, but such a fact is to be explained only by taking into account a combination of different effects or phases of yakritisation already mentioned (cf. Paragraph 1).

*c) Clinical Remarks Concerning the Alleged
Effects of Yakriton.*

As this is no place for clinical communications, only a few remarks will be made here. Our clinical experience with yakriton began as early as the very year that yakriton was first published in 1926. Those diseases in which yakriton has been repeatedly used are : grave bronchopneumonia, grave empyema, toxic typhoid and grave measles. But the disease in which

15) K. Asakura and T. Sato, 18th Report (of Yakriton), to be published in this Journal.

yakriton was most frequently used was severe infantile diarrhea of acute and chronic types¹⁶⁾ (or severe dyspeptic and dystrophic forms of infantile disorders of nutrition). Infantile diarrhea, especially its acute form, is the disease in which the effect of yakriton has been most distinctly seen. If the hormone is injected in too many units in severe cases of the disease, the con-effect (cf. Paragraph 1) will occur immediately with such an undesirable effect as restlessness. But if it is injected in a small amount, then there is no symptom at the time of injection, as if quite an indifferent injection were performed; the favorable effect, corresponding to the pro-effect (cf. Paragraph 1), will occur only later,—half a day later or the next day. And it is very interesting to note here that this effect was clinically recognized long before the experiment concerning the effect of yakriton on anaphylaxis was made by Suzuki. The clinical experience of the use of yakriton in cases of hepatic insufficiency and other diseases—dysentery, pertussis, convulsive states, scarlet fever,¹⁷⁾ nephritis etc.—will be reported in another journal.

Conclusions.

According to the results of the investigations hitherto made in our laboratory,—

1. Yakritisation has two apparently contrary effects,—the pro- and the con-effects. The con-effect may be called the antianaphylactic effect, and the pro-effect, the liver-strengthening effect. A third effect will arise from a combination of these two effects and is entirely new in its action.

2. If chemically observed,—

- a. the con-effect will detoxicate ammonium chloride, commercial ammonium carbonate and urea;
- b. the pro-effect will detoxicate hyperglycemia; and—
- c. phosphorus will be detoxicated by the third effect above mentioned.

3. The antibacterial effect of yakritisation seems to belong rather to the pro-effect.

4. Yakriton has the blood ingredient balancing property.

16) The effect of Yakriton on severe infantile diarrhea was reported by me in the 33rd General Meeting of the Japanese Pediatric Society, 1928, April 5, Sendai.

17) The effect of Yakriton on the prevention of scarlatina nephritis was reported by A. Sato, Yamagishi, Abe and Yoshida in the 17th Meeting of the Sendai Branch of the Japanese Pediatric Society, 1929, June.