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

21st Report.

What is the Difference between a Strong Individual and an Individual with a Strong Liver? Problem of Constitution from the Standpoint of the Theory of Yakritisation.

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I. Definition of a Strong Individual.

A strong individual is surely an individual that is strong,—'strong in the sense understood by laymen. He who is strong must not only remain healthy, but also outlive any affection which may attack him. This

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definition, commonplace as it may seem, ought of course to hold true in the medical world.

On the other hand it seems to be a somewhat popular idea among laymen that they want a 'strong liver'; this is interesting when we remember that the liver is the most important organ of metabolism. Here I want to discuss the relation between a 'strong individual' and an 'individual with a strong liver' from an experimental point of view,—from that of the experimental results already published from my laboratory concerning yakriton and yakritisation.

Is an individual with a 'strong liver' 'strong'? Is, *ceteris paribus*, Individual A with a 'strong liver' stronger than Individual B with a 'weak liver'? The question can be freely answered in the affirmative, as it seems, because one with a normal liver must certainly be stronger than another with liver insufficiency. But the answer cannot, as I deem it, be so simple, because it is not clear what is meant by a 'strong liver.'

An Individual with a 'Strong Liver.'

What is a strong liver? The question is a difficult one. I shall start with the ammonia detoxicating power of the liver. The detoxicating function of the liver is at least one of the most important functions of the organ.

A rabbit, which remains quite unaffected in spite of an intraperitoneal injection of ammonium chloride—an animal of class *f*—is stronger than one, which develops severe convulsions with the same amount of the ammonium salt—one of class *b* or *c*. The former is certainly stronger than the latter; there can be no doubt about it. Yakriton,[1] the detoxicating hormone of the liver isolated by myself, raises the latter—the weaker animal—to class *f*—the class of the stronger animal, if it is injected only a short time previously. Then there can be no doubt either about the fact that yakriton can raise a weaker rabbit to class *f*, or, in other words, make a weak animal strong. It may thus seem quite safe to conclude that an individual with strong detoxicating power of the liver is a strong individual.

Here is another example. A man is stronger when he is fed than when he is hungery; this is a matter of course; the longer he fasts, the weaker will he become. Now a rabbit of class *f* remains quite unaffected in spite of an intraperitoneal injection of ammonium chloride (in the amount of 10 c.c. of 3% solution per kilo of body weight), when it is daily fed.

1) A. Sato, 4th Report on Yakriton, Tohoku J. Exp. Med., 1927, **8**, 353; Sato and Sakurada, 3rd Report, Ibid, 1927, **8**, 347.

But it will develop severe convulsions in consequence of the same amount of the same poison, if it is fasting.[2] Nobody will doubt that such a rabbit has become weaker through starvation, nor that it is a weak individual that will develop severe convulsions with ammonium chloride.

Now yakriton, through previous yakritisation, can save such a rabbit in a state of hunger from ammoniac convulsions. In other words yakriton, the detoxicating hormone of the liver, can make a 'weak' individual 'strong.'

Further, a rabbit of class I[3] is quite unaffected in spite of repeated intra eritoneal injections of urea, while one of class II will succumb to the same amount of urea. So there can be no doubt about the conclusion that an animal of class I is stronger than one of class II. Now yakriton, previously injected, can again raise one of the inferior urea-detoxicating ability to class I, or it can make a 'weak' animal 'strong.' It may thus again seem quite safe to conclude that an individual with strong detoxicating liver power is a strong individual. But here a further consideration is important before forming any hasty conclusion.

Problem of Anaphylaxis.

Let us now turn to the problem of anaphylaxis. Of two patients who have received a re-injection of antidiphtheric serum, for instance,—if one has developed a severe anaphylactic shock and the other has remained healthy, the former is, in the opinion of laymen, certainly much weaker than the latter. There can be no doubt about that.

But if, as Wells[4] presumes, anaphylactic intoxication is but an exaggeration of the normal process of defence of the body against foreign proteins (including bacteria) through digestion, then it is not easy to determine which is the stronger of the two. The patient who has developed the severe shock may well be the stronger.

If the detoxicating liver power is taken into consideration, it is an individual with high classed detoxicating liver power that will develop grave anaphylaxis. As already explained, an individual with high-classed detoxicating liver power must be regarded as a strong individual. And such a patient as has remained quite unaffected in spite of the reinjection of serum must be a weak individual, because he has only a low-classed de-

2) A. Sato, 6th Report, Tohoku J. Exp. Med., 1928, **11**, 265.
3) H. Sakurada, 13th Report, Ibid., 1929, **13**, 468.
4) H. G. Wells, Chemical Pathology, 3rd Ed., 1918 Philadelphia and London, 198.

toxicating liver power. This is, however, utterly inconsistent with the opinion of laymen, who will never regard the one that has died of anaphylaxis as a strong individual.

Judging by the results[5] obtained in our laboratory I must acknowledge that, if an individual with a strong detoxicating activity for ammonia and urea is strong, then one that develops a fatal anaphylactic shock on the re-injection of serum should be regarded as a strong individual. One with low-classed liver power of detoxication must be a weak individual in spite of the fortunate result of such a one being safe from severe anaphylaxis.

Problem of Hunger.

It is a matter of course, as already stated, that an individual, when fed, is stronger than when he is fasting and that the longer he fasts the weaker he will become.

But now suppose he happens to be attacked by a severe peptone shock. Then he may die of it if he has normally been fed, while he will be very safe from it, if he has been somewhat longer in a state of hunger. This is not difficult to surmise from the experimental result shown by Yanagawa. And laymen will not hesitate to call one 'strong' who has shown no or only a slight reaction to the peptone shock, though the one has long been in a state of hunger.

On the other hand it has been shown by myself[2] that the detoxicating liver power will become weaker according as hunger is prolonged. Strange inconsistency!

A 'Strong Individual' in the Eyes of the Layman.

What is a 'strong individual,' then, in the medical philosophy of laymen? Such a one should *ceteris paribus* be furnished with a strong liver in the case of detoxication for ammonia and urea, while the same one should be furnished with a weak liver in the case of threatening anaphylactic shock and pepton shock. But is the satisfaction of such an exorbitant demand possible?

As already stated, the detoxicating liver power is subject to individual fluctuation, but each individual has an almost constant liver power, so that an individual with low-classed detoxicating liver power remains such at

5) K. Suzuki and A. Sato, 8th Report, Tohoku J. Exp. Med., 1928, **11**, 277; K. Suzuki, 9th Report, Ibid, 1928, **11**, 282; Sh. Yanagawa, 19th Report, Ibid, 1929, **14**, 188.

least for a certain length of time. Thus it is impossible to be possessed of a liver, the power of which varies as one desire. Under such a state of things, we must be satisfied, in order to be 'strong individuals,' with a liver of detoxicating power rather of medium strength. Thus we have come to the strange conclusion that one should be furnished with a liver of medium detoxicating strength (i. e. not of high classed detoxicating strength) to be a strong individual.

In such a case we may not be able to detoxicate all the injurious effects of ammonia or urea; but then we shall not be fatally affected by anaphylaxis or peptone shock either.

A Further Difficulty in the Solution of the Problem.

The 'Strong individual' in the view of laymen has not ended with the conclusion we have just arrived at. They will regard one fatally poisoned with phosphorus as a weak individual, while a strong one should, according to them, outlive intoxication with the same amount of phosphorus.

This condition is an exceedingly unreasonable demand by laymen, especially if they regard a strong liver as necessary for a strong individual. If we conclude from experimental results of F. Fischler's[6] Eck fistula dogs, one without the liver will be much less severely poisoned than one with the liver. According to the experiment of Asakura[7] in my laboratory, rabbits of high-classed detoxicating liver power will succumb to phosphorus poisoning earlier than those of low-classed liver power.

From these experiments of Fischler and of Asakura leading to the conclusion in the same sense, it is clear that one with a very strong liver will be most severely poisoned with phosphorus. To be safe from phosphorus intoxication one would have to be without the liver, far from critisizing the strength of the organ. 'Life* without the liver' is, however, an utter impossibility of course.

Adaptation of Liver for the Three Different Conditions.

Let us accept (which is not unreasonable) that a liver with strong detoxicating activity is a 'strong liver.' Then the detoxicating strength of

6) F. Fischler, Physiologie und Pathologie der Leber, 2nd edition. Berlin 1925, p. 54.

7) Ky. Asakura, to appear in the near future.

* Long life, of course.

the liver necessary for each of the following three conditions—for the detoxication of urea and ammonia, for the prevention of severe anaphylactic shock and lastly for the safe escape from phosphorus poisoning will be shown below :—

TABLE I.

For detoxication of urea and ammonia.....life with 'strong' liver.
For prevention from severe anaphylaxis .....life with 'weak' liver.
For safe escape from phosphorus poisoning.....life without liver (only if this were possible).

Now that the liver power is a fairly constant one in the normal life, at least for a certain length of time, it is of course impossible for one and the same liver to adapt itself for the first and the second conditions at the same time. As to the third condition, this itself is an utter impossibility —life without liver.

To repeat : what kind of liver shall a 'strong individual' be possessed of? Not a strong liver ; not a weak liver. The only right answer is a 'time-serving' liver which will rise to the occasion. And such a liver does not exist of course.

II. Effect of Yakritisation.

It is above stated that a 'time-serving' liver which will rise to the occasion cannot exist and that such a liver is a mere phantasy.

Now as the investigation of yakritisation[8] in my laboratory has attained the present stage, it has become clear that the difference between a 'strong' liver and a 'weak' liver is the difference of yakriton content or yakritisation. Not only that, even 'life without liver' explained in the above paragraph, may be actualized by a special method of yakritisation.

1. Liver Made 'Strong' by Yakriton.

If a liver which detoxicates ammonia and urea efficiently is a high-classed or a 'strong' one, then yakriton can make a low-classed or 'weak' liver 'strong' instantly.

A rabbit of class *b* (for ammonia) can be raised to class *f*, if yakriton is administered rectally or subcutaneously a few minutes previously. This

8) A. Sato, 15th Report, Tohoku J. Exp. Med., 1929, **13**, 502.

state does not last long, so that it will be restored to the former class *b*— after a certain time.

A rabbit of class II (for urea) can be raised to class I, if yakriton is administered in a large number of units a few minutes previous to the intraperitoneal injection of urea. This state does not last very long either, so that after a certain time it will be restored to the former class.

Thus a 'weak' liver can be made 'strong' by yakritisation.

2. Liver Made 'Weak' by Yakriton.

From the papers of Suzuki, of Suzuki and A. Sato,[5] and of Yanagawa,[9] it was clear that a 'weak' liver—liver of low detoxicating power —will react more weakly to anaphylactic or pepton shock than a 'strong' liver—liver of high classed detoxicating ability.

Such a 'weak' state of liver can be aroused again by yakritisation ; this weakening action is the more pronounced, the larger number of R. A. U. is used and the shorter is the lapse of time after yakriton injection. Thus a 'strong' liver can be made 'weak' by yakritisation.

3. 'Life without Liver' Actualized by Yakriton.

As already stated, it seems that one should be without the liver in order to be safe from phosphorus poisoning. Then it may be very probable that yakriton will be harmful in any amount, because yakriton injection may mean 'furnishing more liver' and the more liver will be the more harmful.

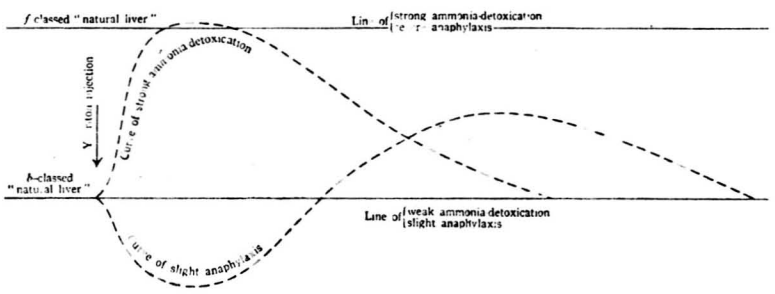
But yakriton has, according to Asakura and T. Sato,[10] and to Asakura,[11] a very peculiar effect in its $\frac{1}{2}$ or $\frac{1}{4}$ R. A. U., besides the meaning that $\frac{1}{2}$ (or $\frac{1}{4}$) R. A. U. is $\frac{10 \text{ R. A. U.}}{20}$ (or $\frac{10 \text{ R. A. U.}}{40}$ respectively). $\frac{1}{2}$ R. A. U. (or $\frac{1}{4}$ R. A. U.) of yakriton produces a state which may be said almost ideal for being safe from subacute (or acute) phosphorus poisoning. If the liverless state is the ideal state for such a case, $\frac{1}{2}$ or $\frac{1}{4}$ R. A. U. actualizes that ideal state. Most of animals with $\frac{1}{2}$ or $\frac{1}{4}$ R. A. U. will be saved from phosphorus poisoning, while control animals without yakriton injection or animals with many R. A. U. will succumb invariably to the intoxication.

9) Sh. Yanagawa, 19th Report, Tohoku J. Exp. Med., 1929, **14**, 187.
10) Ky. Asakura and T. Sato, 18th Report, Tohoku J. Exp. Med., 1929, **14**, 180.
11) Ky. Asakura, 23rd Report, Ibid., 1930, **15**, 476.

III. *The Advantage of 'Yakritized' Liver over Natural Liver.*

1. Difference between Natural Liver and Artificial Yakritisation

10 R. A. U. of yakriton raises a rabbit of class *b* to class *f*, as repeatedly shown. Then if a *b*-classed rabbit has received 10 R. A. U. of the hormone, is it simply a *f*-classed rabbit in all respects? No, it is not. A naturally *f*-classed animal has a strong ammonia detoxicating ability, but is at the same time strongly reactive to anaphylaxis, whereas one, just made *f*-classed by yakriton, is weakly reactive—more weakly reactive than a naturally *b*-classed liver—to anaphylaxis while it has acquired a strong ammonia detoxicating ability all the same, as will be shown in the following diagram.



Continual line.....natural liver.
Discontinuous line.....“yakritized” liver (—*b* classed liver, raised up to class *f* by yakriton).

As far as ammonium, for instance, is concerned, the *f*-classed liver seems to be of a better detoxicating ability than the *b*-classed. But as already explained in the foregoing paragraph, it is in a certain instance an animal with *f*-classed liver that will be poisoned more severely than one with a *b*-classed liver. In such a case the liver appears to be an offensive organ than a defensive. It is very interesting to me to have come across a correspondence 'Estimation of Hepatic Insufficiency' by Delicati,[12] because there was such a passage: 'was the liver the offender in these cases?' I also expect to write further in the future about the liver as an offensive organ.

(12) Leo Delicati, British Med. J., 1929 I., 621.

A naturally *f*-classed liver detoxicates ammonia excellently, but cannot detoxicate the injurious effects of anaphylaxis. A naturally *b*-classed liver cannot detoxicate ammonia excellently, yet it can 'detoxicate' anaphylaxis. A sufficiently yakritised liver cannot only detoxicate ammonia excellently, but detoxicate the injurious effects of anaphylaxis excellently. Such is an example of advantages of artificial yakritisation.

The ammonium detoxicating ability and the anaphylactic reacting property seem to be two different manifestations of the same activity pertaining to a natural liver. But the use of yakriton, one and the same substance, shows that these are two different effects of yakritisation, which are in phase in the case of a natural liver and which are not in phase in the case of a yakritized liver.

2. Further Difference between Natural Liver and Yakritisation.

A natural liver is—so to speak—a peace-time organisation for detoxication; it disposes skilfully of a number different poisons produced in the physiological life. It is not, however, an organisation in case of emergency. It cannot dispose of an excess of ammonia, in spite of the fact that yakriton, the detoxicating principle of the natural liver, can detoxicate that poison in a specific way. It does not know what to do with an excess of urea in spite of the fact that this can be detoxicated by the same yakriton.

The natural liver remains in a natural state and cannot adapt itself to circumstances. It remains—so to speak—in a 'static detoxicating state'. Artificial yakritisation puts it in a 'dynamic detoxicating state'. If a further allegory be required, the natural liver may be the oxygen in an inactive state, while yakriton injected is the oxygen in statu nascendi.

The natural liver is, as I have said above, in a 'static detoxicating state.' The fact that it cannot detoxicate an excess of ammonia or urea may be due to the possibility that it may not have a sufficient amount of yakriton in stock. This may appear to be the whole reason why an injection of yakriton should be necessary. But it is not. For the detoxication of phosphorus administered in a sublethal or lethal dose an injection of $\frac{1}{2}$ or $\frac{1}{4}$ R. A. U.—a very minute amount of yakriton—is necessary. And it is highly probable that the natural liver has many more units of yakriton in stock, yet it invariably succumbs to phosphorus poisoning. This is because the natural liver is in a 'static detoxicating state.' $\frac{1}{2}$ or $\frac{1}{4}$ R. A. U. of yakriton puts it into a 'dynamic detoxicating state, necessary for the detoxication of phosphorus.

When I isolated the detoxicating hormone of the liver for the first time, I thought that, if this was the detoxicating principle of the liver, yakriton could detoxicate any poison that the liver could detoxicate, provided that it was used in a very large amount (i. e. in a large number of units). And I found out that the larger the amount of yakriton, so much the better it could detoxicate ammonia. Next, the detoxication of urea was tried with the same result: for the detoxication of a large amount of urea, a large amount (i. e. a large number of units: the amount itself need not be large) of yakriton was necessary. In the mean time Yoshimatsu,[10] in our laboratory tested (1926) if yakriton could detoxicate phosphorus poisoning and failed to see a favorable result. And I attributed this negative result to the fact that the amount of yakriton used for the purpose was exceedingly too small, especially in consideration of the fact that phosphorus was a very drastic liver poison (admitting of no comparison with ammonia or urea). The work of Yoshimatsu was then to be discontinued owing to the reason that I was unable to prepare such a large amount of yakriton sufficient for the purpose at that time. This failure of the detoxication of phosphorus by yakriton was due to our utter ignorance at that time of the fact that yakriton injected in an organism would bring it into a 'dynamic detoxicating state.' As to further mechanism of detoxication of different poisons including phenol and alkaloids by yakriton I expect to report in the near future.

Conclusions.

1. A naturally high-classed liver detoxicates ammonia and urea much more excellently than a naturally low-classed liver. In the case of anaphylaxis, however, the former reacts much worse than the latter. 'Yakritisation' can make the former refractory to anaphylactic shock, while it can make the latter excellently detoxicating for ammonia and urea. This is because yakritisation can arouse two apparently contrary effects.

2. Both kinds of livers above mentioned will succumb to phosphorus poisoning, because even a naturally high-classed liver is—so to speak—in a 'static detoxicating state.' A minute amount of yakriton can save both kinds of them from the intoxication, because yakriton brings them into a 'dynamic detoxicating state.'

3. A truly 'strong' individual should be furnished neither with a high-classed liver nor with a low classed one. He should be furnished with a 'time-serving' liver. 'Time-serving' liver is a liver in a 'dynamic detoxicating state.'