Hyperglycaemic Action of Lobelin and the Suprarenal Glands.

By

Masari Tiba.

(千葉勝)

*(From the Physiological Laboratory of Prof. Y. Satake,
Tohoku Imperial University, Sendai.)*

According to previous writers, the hyperglycaemic action of lobelin is lost if the suprarenal capsules are excised or the splanchnic nerves interfered with.

The experimentalists¹⁾²⁾ who gave the drug soon after double decapsulation concluded so, but such an experimental condition can not be taken as satisfactory, as is, for example, emphasized by Randles³⁾ in the lobelin experiments.

Bertram¹⁾ injected lobelin into rabbits in a subcutaneous dose of 5 mgrms. per kilo 3 hours after double decapsulation under ether. The rapidity with which the blood sugar concentration was falling under the normal level was not altered by lobelin. Tsuchiya²⁾ experimented quite similarly with Bertram, except that no narcosis was resorted to, and gave the drug earlier, i.e. 15–30 minutes after the decapsulation. The magnitude of hyperglycaemia in the rabbits poisoned with lobelin did not differ from that in the rabbits injected with the Ringer.

Randles³⁾ tried to intervene various length intervals of time between the double removal of the suprarenal bodies and the lobelin administration, and came to conclude that it is not safe to use rats under 3 weeks following suprarenalectomy.

While an intraperitoneal application of lobelin in doses of 22 to 44 mgrms. per kilo caused in normal rats an increase of blood sugar concentration by 66–68%, a markedly less degree of the increase was noted in the rats doubly suprarenalectomized, such as 10% 3–7 days after decapsulation, 19% 27–40 days

1) Bertram, Arch. f. exp. Path. u. Pharm., 1928, **28**, 179.

2) Hara and Tsuchiya, Nippon Yakubutugaku Zassi, 1935, **20**, Proc. 95; Jap. J. of med. Sci., Pharm., 1936, **9**, 124 (Proc.); Tsuchiya, Zikken Yakubutugaku Zassi, 1937, **13**, 234 ff; Nissin Igaku, 1937, **26**, 629.

3) Randles, Am. J. of Physiol., 1931, **97**, 553 (Proc.); J. of Pharm. & Exp. Ther., 1931, **42**, 272 (Proc.).

and 3% 36–56 days. Consequently he concluded that epinephrine is a factor, but not the only one, in lobelin hyperglycaemia.

In another set of experiments, i. e. with double splanchnicotomy, Tsuchiya allowed 18 days or more to elapse after the nerve section till lobelin injection. There was also no increase or a very slight one in the blood sugar content on lobelin poisoning: from 0.113% to 0.122%, from 0.120% to 0.124% and from 0.106% to 0.120%.

On the other hand, that lobelin can induce an oversecretion of epinephrine from the suprarenal gland has been established, although there is a marked difference in respect to its scale of the augmentation between the report of Houssay and Molinelli⁴⁾ and that of Inaba.⁵⁾ The former reported further that a complete denervation of the suprarenal gland does not suppress the epinephrine liberation due to lobelin. This suggests some possible existence of causal relationship between the epinephrine oversecretion and the blood sugar increase in the case of lobelin.

Anitschkow⁶⁾ and Kusnetzow⁷⁾ saw that lobelin increases the epinephrine concentration of the fluid from the suprarenal gland of a cow or an ox, perfused with Ringer. Hara⁸⁾ detected a diminished load of epinephrine, determined by the Suto-Inouye, in the rabbit suprarenal capsule on poisoning with lobelin.

The experiments which will be given in the following pages have been done under conditions not disturbing the carbohydrate metabolism by any factors other than the lobelin poisoning, and certain features from some previous have been yielded.

Methods: Healthy rabbits, fed on tofukara, carrot and straw, were experimented on. The splanchnic nerves were bilaterally cut beforehand. They were bilaterally interfered with either through the lumbar route in two sittings or per laparotomiam. The suprarenal glands were removed by the lumbar route in two sittings. No narcosis was resorted to in these operations. At least two weeks were allowed to elapse between the last operation and the lobelin injection.

The blood sugar content was estimated by the method of Fujita

4) Houssay and Molinelli, *Rev. Soc. Arg. de Biol.*, 1925, 1 year, No. 5 (reprint); *C. r. Soc. Biol.*, 1925, **93**, 1124; *Am. J. of Physiol.*, 1926, **76**, 551; Molinelli, *La secrecion de adrenalina*, Buenos Aires 1926, 211 ff.

5) Inaba, *Tohoku J. of Exp. Med.*, 1935, **27**, 348.

6) Anitschkow, *Arch. f. exp. Path. u. Pharm.*, 1928, **118**, 242.

7) Kusnetzow, *Ibid.*, 1928, **135**, 333.

8) Hara, *Nissin Igaku*, 1929–30, **19**, 1903; *Nippon Yakubutugaku Zassi*, 1930, **10**, Proc. 7; *Jap. J. of Med. Sci., Pharm.*, 1931, **5**, 11. Hara and Tsuchiya, *Nissin Igaku*, 1937, **26**, 629.

and Iwatake.⁹⁾

Alpha lobelin (Ingelheim) was injected as 1% solution intravenously (in 3-5-10 seconds and in a few instances in 20-30 seconds) in doses of 3.5 mgrms. or 7 mgrms. per kilo of body weight, and subcutaneously (in 2-7 seconds) in doses of 5, 10 or 20 mgrms. per kilo.

The blood sugar experiment was carried out without fastening and without narcotizing the animal. The heart rate, respiration frequency, and the rectal and room temperatures were measured from time to time.

RESULTS.

As the control, some normal rabbits were also injected with lobelin.

Intravenous cases will be presented in the first place, and followed by the subcutaneous cases. All

9) Fujita and Iwatake, Biochem. Z., 1931, 242, 43.

TABLE I.
Effect of intravenous injection of lobelin upon the blood sugar content of normal rabbits.

Number of rabbits	Sex	Date of experiment	Body weight (kilos)	Blood sugar					Body temperature (°C.)	Frequency of respiration (per min.)	Frequency of heart beat (per min.)	Room temperature (°C.)
				Initial (grm. %)	Maximum during experiment (grm. %)	Time to maximum (hrs.)	Duration of hyperglycaemia (hrs.)	Absolute increase (grm. %)				
<i>Application of lobelin : 3.5 mgrms. per kilo of body weight.</i>												
C 16	♂	1. VII. '35	2.10	0.114	0.172	1 1/2	2 1/2	0.058	50	162~252	130~240	23
" 17	♀	15. VII. '35	2.37	0.105	0.147	1 1/2	1	0.042	40	120~225	115~240	27~28
" 18	♂	18. VII. '35	1.90	0.105	0.152	1 1/2	1 1/2	0.047	44	60~120	186~210	20~21
" 21	♂	22. VII. '35	2.40	0.103	0.138	1 1/2	1 1/2	0.035	34	158~336	132~370	27~28
" 69	♂	15. VII. '35	2.21	0.105	0.161	3	3	0.056	53	42~276	180~228	27~28
<i>Application of lobelin : 7 mgrms. per kilo of body weight.</i>												
C 61	♀	21. XI. '35	2.65	0.103	0.186	1	3	0.083	81	48~144	132~216	14~17
" 63	♂	25. V. '36	1.92	0.113	0.242	1 1/2	3 1/2	0.129	115	42~114	240~252	13~15
" 70	♀	9. XI. '35	2.45	0.104	0.203	1 1/2	3	0.099	95	48~132	138~216	12
" 78	♀	25. V. '36	2.19	0.103	0.200	1	3	0.097	94	42~96	156~228	14~16
" 7	♀	21. XI. '35	2.10	0.108	0.190	1 1/2	4	0.082	76	72~192	216~348	15~17

the data are epitomized in 6 tables.

(A) Intravenous Injection.

(1) *Normal rabbits* (Tab. I).

3.5 mgrm. lobelin per kilo of body weight was the dose for 5 rabbits, which showed hyperglycaemia of a moderate degree. 0.138–0.161 grm. % was the maximum reached at 1/4–1/2 hour after the injection. (The blood samples were taken as a rule with intervals such as 5, 15, 30, 60 minutes after the injection, and so on.) The hyperglycaemic spell continued for 1–3 hours.

A few minutes after the injection, miosis and convulsions occurred, the breathing became deep and slow for a while, then speeded up 15 minutes or so after the injection. 2 or 2.5 hours later the animal looked almost normal. The heart rate about 15 minutes after the injection, was measured having increased, and 1–1.5 hours later it resumed the initial value. The body temperature descended, with the bottom 37.3°–38.4° 15–12 minutes, usually 30 minutes after the injection.

Double dose, i. e. 7 mgrms. lobelin was dosaged in another 5 rabbits, resulting in severe clinical symptoms and profound and prolonged hyperglycaemia. 0.186–0.242 grm. % was the greatest blood sugar content, measured 1–1.5 hours after the injection, and the hyperglycaemic period covered over 3–4 hours.

At the end of observation extending for 3 hours after the injection, the blood sugar content showed in all the cases about the same value with the initial or else a lower. In a case with 3.5 mgrm. lobelin (C) 18 it was 0.087%, and in a case with 7 mgrms. (C70) 0.09%.

The decrease of respiratory frequency and of the anal temperature was also considerable. 42–72 breathings per minute contrast 42–162 breathings in the cases of 3.5 mgrms. per kilo, and 36.1°–36.7° in these experiments, 37.3°–38.3° in those experiments with the smaller dosage.

(2) *Doubly splanchnicotomized rabbits* (Tab. II).

16–246 days after double splanchnicotomy, lobelin experiment was carried out.

8 rabbits were dosaged with 3.5 mgrms. per kilo. In 6 cases the clinical symptoms were slight, and no noticeable hyperglycaemia was discovered; there was only a slight increase such as from 0.111 grm. % to 0.126%, from 0.102% to 0.117%, from 0.104% to 0.114%, from 0.105% to 0.117%, from 0.089% to 0.106% and from 0.092% to 0.126%. 10 minutes to 1 hour were needed to see the highest level, and the hyperglycaemic period covered 15 minutes to 3 hours.

TABLE II.
Effect of intravenous injection of lobelin upon the blood sugar content of doubly splanchicotomized rabbits.

Number of rabbits	Sex	Splanchnicotomy		Date of experiment	Body weight (kilos)	Blood sugar						Frequency of respi-ration (per min.)	Frequency of heart beat (per min.)	Room temperature (°C.)	
		Date	Body weight (kilos)			Initial (gram. %)	Maximum during experiment (gram. %)	Time to maximum (hrs.)	Duration of hyperglycaemia (hrs.)	Absolute increase (gram. %)	Relative increase %				
Application of lobeline : 3.5 mgrms. per kilo of body weight.															
C 40	♀	16. VII. '35	2.00	1. VIII. '35	1.92	0.111	0.126	1	2	0.015	13	39.0~40.2	180~372	192~264	30~32
" 60	♂	6. XII. '35	1.68	16. VI. '36	1.88	0.112	0.155	1	2½	0.043	38	38.0~39.2	54~198	192~240	21~22
" W 9	♂	15. II. '36	2.04	14. VI. '36	2.34	0.102	0.117	1	4	0.015	15	37.7~38.7	36~120	180~276	20~22
" 12	♂	"	1.79	3. VI. '36	2.22	0.104	0.114	"	4	0.010	10	38.0~39.0	36~108	180~216	18~21
" 19	♂	7. III. '36	1.53	12. VI. '36	2.16	0.103	0.165	" 2	3	0.082	60	37.7~38.7	72~150	180~288	20~22
" 20	♂	"	1.62	16. VI. '36	2.05	0.105	0.117	1½	2	0.012	11	38.6~39.3	48~120	180~228	21~22
" 21	♀	"	1.52	12. VI. '36	2.08	0.089	0.106	1	3	0.017	19	38.2~39.1	36~174	150~216	22
" 27	♀	15. II. '36	1.64	14. VI. '36	2.06	0.092	0.126	1½	2½	0.034	37	37.8~38.8	48~132	180~264	20~22
Application of lobeline : 7 mgrms. per kilo of body weight.															
C 40	♀	16. VII. '35	2.00	13. XI. '35	2.10	0.110	0.174	1	3½	0.084	58	36.1~38.5	42~156	216~252	11~13
" 60	♂	6. XII. '35	1.68	10. I. '36	1.83	0.089	0.139	1	3½	0.050	56	36.3~38.3	54~156	186~268	10~15
" W 9	♂	15. II. '36	2.04	2. VI. '36	2.30	0.102	0.150	" 2	2	0.048	47	36.2~38.6	36~156	168~240	16~19
" 12	♂	"	1.79	8. V. '36	2.19	0.110	0.115	1½	1½	0.005	5	37.2~38.8	42~90	180~276	13~17
" 19	♂	7. III. '36	1.53	22. V. '36	1.99	0.104	0.162	3	4	0.058	55	36.7~38.3	48~126	144~228	16~19
" 20	♂	"	1.62	3. VI. '36	2.09	0.098	0.136	1	3	0.038	39	37.6~39.3	60~108	156~240	17~20
" 21	♀	"	1.52	22. VI. '36	1.97	0.085	0.165	1	3	0.080	95	37.3~38.7	42~120	180~240	16~19
" 27	♀	15. II. '36	1.64	2. VI. '36	2.02	0.088	0.154	1	2½	0.066	75	36.6~38.8	42~144	168~276	17~20

In two other cases (C60 & W19) poisoning was severe, and correspondingly the blood sugar concentration increased largely, just as in normal rabbits, above given: from 0.112 grm. % to 0.155% and from 0.103% to 0.165%, the maximum being noted respectively 15 minutes and 2 hours after the injection. The hyperglycaemic period covered about 3 hours.

In Rabbit C 60, convulsions occurred soon on injecting lobelin, urination, miosis followed, conjunctiva cyanotic, respiration deep, and then slow (60 breathings per minute 3 minutes after the injection). 5 minutes after the injection dyspnoeic, the animal lay down, 27 minutes after the injection it stood up, mydriasis, deep & slow respiration. Almost similar symptoms were noted in Rabbit W19; in this case convulsive seizures took place repeatedly.

The body temperature fell on a similar scale with the normal rabbits poisoned with the same dose of drug; in the two cases with a larger increase in the blood sugar content the body temperature fell similarly. The respiration became commonly slow.

7 mgrms. lobelin per kilo was capable of bringing about an evident hyperglycaemia in nearly all the cases, 8 in number, W12 being a single exception where the blood sugar remained almost unchanged (from 0.110% to 0.115%). In 7 cases the maximum was 0.136 grm. %–0.174%, definitely smaller than in normal rabbits poisoned with the same amount of lobelin (0.186%–0.242%). 45–60 minutes elapsed till the maximum was reached, the hyperglycaemic period covered 2–4 hours.

In the doubly splanchnicotomized rabbits the blood sugar content was often estimated having gone down in the later stage of poisoning. In Rabbit W9 0.092% 2 hours after the injection of 3.5 mgrms. per kilo, in Rabbit W12 0.093% 1.5 hours and in Rabbit W21 0.096% 2.5 hours, and in Rabbit W27 0.075% 3 hours; in the series of 7 mgrms. per kilo, 0.088% 3 hours in Rabbit C 60, 0.079% 4 hours in Rabbit W-9, 0.093% 3.5 hours in Rabbit W20, 0.076% 4 hours in Rabbit W21, and 0.097% 4 hours in Rabbit W29. There were thus some strong tendencies of hypoglycaemia developing in the doubly splanchnicotomized rabbits, especially when heavily poisoned.

Clinical symptoms were severe in general, but if examined case by case, they were rather moderate in some animals (C40, C60, W12, W27). The body temperature fall corresponded to the amount of drug, and was about the same with that of the normal rabbits poisoned with the same dosage. Respiration became invariably slow.

Double splanchnicotomy inhibits to some extent a full development of the lobelin hyperglycaemia; this does not check well with the

report of Tsuchiya, who was able to see a rather complete disappearance of lobelin hyperglycaemia in the rabbits surviving the same operation over 18 days. In the present experiments, lobelin was administered 76-188 days after the denervation.

(3) *Doubly suprenalec-tomized rabbits* (Tab. III).

In 6 rabbits, 97-265 days after double suprenalectomy lobelin was administered in the dose of 3.5 mgrms. per kilo. The blood sugar concentration increased in all the cases, but only in-

TABLE III.
Effect of intravenous injection of lobelin upon the blood sugar content of doubly suprenalec-tomized rabbits.

Number of rabbits	Sex	Suprenalec-tomy (L.)		Date of experiment	Body weight (kilos)	Blood sugar						Body tempera- ture (°C.)	Frequency of respi- ration (per min.)	Frequency of heart beat (per min.)	Room temperature (°C.)	
		Date	Body weight (kilos)			Initial (gm. %)	Maximum during experiment (gm. %)	Time of maximum (hrs.)	Duration of hyperglycaemia (hrs.)	Absolute increase (gm. %)	Relative increase %					
<i>Application of lobeline : 3.5 mgrms. per kilo of body weight.</i>																
C 7	♀	27. X. '34	2.15	19. VII. '35	2.50	0.098	0.104	1½	1	0.006	6	37.0~38.5	60~138	162~216	18~19	
" 9	♂	24. XI. '34	1.99	20. VII. '35	2.17	0.095	0.116	"	½	0.021	22	36.6~38.6	138~180	180~240	18~21	
" 12	♂	15. IV. '35	2.00	21. VII. '35	1.90	0.102	0.115	½	½	0.013	13	38.0~39.1	36~128	144~210	21~22	
X 14	♀	15. I. '35	2.00	24. VII. '35	2.13	0.109	0.119	1½	1	0.010	9	38.4~38.7	72~168	168~228	25~26	
" 15	♂	19. II. '35	1.92	"	2.15	0.113	0.122	½	½	0.009	8	37.3~38.5	48~138	174~276	24~26	
" 16	♂	12. II. '35	2.30	25. VII. '35	2.25	0.092	0.096	1½	½	0.004	5	37.1~38.7	84~192	180~258	22~23	
<i>Application of lobeline : 7 mgrms. per kilo of body weight.</i>																
C 1	♀	13. X. '34	1.85	18. XI. '35	2.39	0.098	0.128	1½	1	0.030	30	36.7~38.3	78~150	180~240	12~17	
" 7	♀	27. X. '34	2.15	20. XI. '35	2.57	0.096	0.124	"	½	0.028	29	37.0~38.3	66~120	158~216	15~19	
" 12	♂	15. IV. '35	2.00	27. V. '36	2.00	0.104	0.117	½	1	0.013	12	35.9~38.5	48~66	192~240	13~15	
" 13	♂	21. V. '35	1.95	20. XI. '35	2.10	0.099	0.117	1½	½	0.018	18	37.4~39.0	48~132	204~288	17~19	
" 14	♂	18. VI. '35	1.60	26. V. '36	2.13	0.101	0.094	"	0	(-0.007)	(-7)	35.8~38.7	36~108	156~240	12~13	
" 15	♂	"	1.75	"	2.33	0.097	0.097	"	0	0	0	35.2~38.4	54~150	192~228	12~13	
X 14	♀	15. I. '35	2.00	27. V. '36	2.06	0.106	0.097	"	0	(-0.009)	(-9)	35.4~38.1	36~108	204~240	14~16	

significantly, 0.096 grm. %–0.122% being the highest against 0.092%–0.113% of the initial. The hyperglycaemic period covered only a short interval, 1 hour being the longest.

7 mgrms. lobelin per kilo were also incapable of causing an evident increase in the blood sugar level in the doubly suprarenalectomized rabbits as in the smaller dosage. The intravenous injection was carried out 183–499 days after the decapsulation. In 4 cases out of 7 a small hyperglycaemia, such as from 0.098 grm. % to 0.128%, from 0.096% to 0.124%, from 0.104% to 0.117% and from 0.099% to 0.117%, developed, the time when the highest value was measured and the time course of the hyperglycaemia were similar with the cases of the small dosage. In the remaining 3 cases there was no increase, but only a small decrease.

In the decapsulated animals hypoglycaemia was detectable in most of the cases, only this tendency was doubtful in No. X 15; the smallest concentration was in some cases under 0.07% and over 0.05% (3.5 mgrms.: C 9, X 16; 7 mgrms.: C 14, X 14).

Among 3.5 mgrms. series, in Rabbits C 12 & X 15 clinical symptoms were slight, in Rabbit X 14 no convulsive attacks took place, but the animal excited for a while; among the cases heavily dosaged, severe symptoms were noted in C 12 and C 15.

The body temperature fall was of almost the same degree as the normal rabbits, only in 3 rabbits (C 14, C 15 & X 14) which showed no increase in the blood sugar concentration at all, the body temperature fell more so; at that moment the blood sugar content was already diminishing.

Of the respiratory frequency there was no material difference compared with the other series of experiments.

The removal of the suprarenal capsules thus abolishes very largely the hyperglycaemic response of the rabbit against lobelin. This checks well with the conclusion of the previous observers¹⁾²⁾, who gave the drug soon or a few hours after the decapsulation per laparotomiam. And apparently this corresponds to the findings of Housay and Molinelli that the denervation of the suprarenal capsule does not prevent oversecretion of epinephrine due to lobelin.

(B) Hypodermical Injection.

In some groups of rabbits lobelin was injected subcutaneously in doses of 5 mgrms., 10 mgrms. and 20 mgrms.

(1) *Normal rabbits* (Tab. IV).

5 mgrms. lobelin per kilo did not produce convulsions in 3 rabbits,

TABLE IV.
Effect of subcutaneous injection of lobelin upon the blood sugar content of normal rabbits.

Number of rabbits	Sex	Date of experiment 1936	Body weight (kilos)	Blood sugar					Body temperature (°C.)	Frequency of respiration (per min.)	Frequency of heart beat (per min.)	Room temperature (°C.)
				Initial (grm. %)	Maximum during experiment (grm. %)	Time to maximum (hrs.)	Duration of hyperglycaemia (hrs.)	Absolute increase (grm. %)				
<i>Application of lobelin : 5 mgrms. per kilo of body weight.</i>												
C 75	♀	11. VII.	2.10	0.109	0.152	1½	1½	0.043	37.6~39.0	60~120	156~216	20~23
" 76	♂	"	2.20	0.105	0.132	"	"	0.027	37.1~39.0	35~54	156~216	"
" 78	♀	20. VI.	2.37	0.094	0.147	¾	2	0.053	37.8~39.0	60~120	156~204	23~26
<i>Application of lobelin : 10 mgrms. per kilo of body weight.</i>												
C 76	♂	29. VI.	2.40	0.093	0.182	2	4	0.089	36.5~38.8	48~144	156~216	20~21
" 78	♀	7. VII.	2.35	0.100	0.172	2	"	0.072	36.8~39.0	48~90	168~192	17~18
" 79	♀	29. VI.	2.18	0.105	0.170	2	3	0.065	36.8~39.2	36~192	144~210	20~21
<i>Application of lobelin : 20 mgrms. per kilo of body weight.</i>												
C 74	♂	20. VI.	2.23	0.100	0.225	2	4	0.125	36.4~38.8	60~180	168~328	22~22
" 76	♂	28. VI.	2.30	0.094	0.172	1	"	0.078	35.3~39.0	42~109	192~216	16~18
" 78	♀	20. VI.	2.28	0.115	0.202	1½	3	0.087	36.8~39.0	72~132	156~240	22~22
" 79	♀	28. V.	2.23	0.106	0.198	"	"	0.092	35.8~38.7	36~156	168~300	15~18

but miosis, and deep and slow respiration appeared, and the animals lay down on their side and finally mydriasis took place 1 or 1.5 hours after the injection.

10 mgrms. lobelin per kilo was enough to cause convulsive seizures; usually 1 hour was needed before the animal with mydriasis could get up. Clinical symptoms were slight in Rabbit C 78.

With 20 mgrms. lobelin per kilo, the animals, 4 in number, looked more heavily intoxicated, but in Rabbit C 76 the poisoning was not heavy, judging from clinical symptoms, and correspondingly the hyperglycaemia was of a somewhat lesser degree. In Rabbit C 79 the poisoning symptoms

TABLE V.
Effect of subcutaneous injection of lobelin upon the blood sugar content of doubly splanechnicotomized rabbits.

Number of rabbits	Sex	Splanchnicotomy		Date of experiment 1936	Body weight (kilos)	Blood sugar								Frequency of respi- ration (per min.)	Frequency of heart beat (per min.)	Room temperature (°C.)
		Date	Body weight (kilos)			Initial (grm. %)	Maximum during experiment (grm. %)	Time of maximum (hrs.)	Duration of hyperglycaemia (hrs.)	Absolute increase (grm. %)	Relative increase %					
Application of lobelin : 5 mgrms. per kilo body weight.																
C 60	♂	25. X. '35	1.68	16. VII.	2.01	0.096	0.122	1 1/2	3	0.027	27	37.9~39.1	192~240	23~26		
W 19	♂	7. III. '36	1.53	19. VII.	2.36	0.097	0.150	1 1/2	"	0.053	54	38.1~39.3	168~228	27~28		
" 20	♂	"	1.62	15. VII.	2.20	0.104	0.129	"	"	0.025	24	38.3~39.6	180~228	22~24		
" 21	♀	"	1.52	19. VII.	2.37	0.104	0.123	"	2	0.019	18	39.0~39.2	180~228	27~28		
" 27	♀	15. II. '36	1.64	15. VII.	2.20	0.104	0.131	1 1/2	1	0.027	26	37.8~39.2	180~240	22~24		
Application of lobelin : 10 mgrms. per kilo of body weight.																
C 40	♀	16. VII. '35	2.00	18. VII.	2.43	0.104	0.125	1 1/2	1 1/2	0.021	20	37.9~39.2	180~192	26~28		
" 60	♂	25. XI. '35	1.68	28. VI.	2.00	0.096	0.155	1	3	0.059	61	37.7~39.6	204~240	23		
" 64	♀	6. XII. '35	2.35	7. VII.	2.76	0.104	0.150	"	2 1/2	0.046	44	36.4~38.9	156~228	17~18		
W 9	♂	15. II. '36	2.04	18. VII.	2.46	0.097	0.114	1 1/2	1 1/2	0.017	17	37.7~39.0	156~252	26~28		
" 19	♂	7. III. '36	1.53	9. VII.	2.26	0.103	0.164	2 1/2	3	0.061	59	37.5~38.4	180~276	20~21		
" 20	♂	"	1.62	28. VI.	2.20	0.109	0.145	1 1/2	1	0.036	33	38.0~39.3	168~216	23		
" 21	♂	"	1.52	9. VII.	2.25	0.094	0.143	1 1/2	4	0.051	52	37.2~39.1	192~228	20~21		
" 27	♂	15. II. '36	1.64	27. VI.	2.11	0.103	0.147	1 1/2	2 1/2	0.044	43	37.0~39.2	168~240	23~26		
Application of lobelin : 20 mgrms. per kilo of body weight.																
C 40	♀	16. VII. '35	2.00	22. VI.	2.30	0.096	0.130	2	3	0.034	36	37.5~39.3	216~312	26~28		
" 64	♀	6. XII. '35	2.35	30. VI.	2.60	0.110	0.152	1 1/2	3 1/2	0.042	38	35.4~39.0	204~228	14~16		
W 9	♂	15. II. '36	2.04	27. VI.	2.43	0.100	0.115	1 1/2	1 1/2	0.015	15	36.4~39.0	144~204	23~26		
" 12	♂	"	2.04	22. VI.	2.24	0.103	0.118	1 1/2	3	0.015	14	37.6~39.1	168~216	25~28		
" 19	♂	7. III. '36	1.53	26. VI.	2.28	0.110	0.140	1 1/2	4	0.030	27	37.2~38.8	156~300	21~22		
" 20	♂	"	1.62	24. VII.	2.20	0.101	0.143	1 1/2	4	0.042	42	38.0~39.6	132~240	20~24		
" 21	♀	"	1.52	26. VI.	2.19	0.101	0.154	1 1/2	3	0.053	52	37.1~39.1	168~264	21~22		
" 27	♀	15. II. '36	1.64	24. VI.	2.19	0.099	0.130	1 1/2	3	0.031	31	37.5~39.3	144~240	20~25		

were not so heavy and the blood sugar concentration was also correspondingly not so large.

In all the cases the blood sugar concentration increased, and just in correspondence to the amount of lobelin, 0.15% for 5 mgrms., 0.18% for 10 mgrms. and 0.2% for 20 mgrms. and the interval of time elapsed to the maximum concentration also corresponded to those values. The hyperglycaemic spell was 1.5–2 hours in the cases of the smallest dosage, and 3–4 hours in the cases with heavier dosages.

The body temperature fell by 2 degrees in the cases with 5 mgrms. per kilo, and by 3° or more in those with 10 mgrms. and 20 mgrms. Of the slow respiration there was no material difference between the various dosages.

Of the blood sugar events subcutaneous 5 mgrms. per kilo corresponds to intravenous 3.5 mgrms., but the clinical symptoms lasted much longer in the former, and they seemed somewhat heavier. Subcutaneous 20 mgrms. per kilo caused hyperglycaemia of almost the same degree as intravenous 7 mgrms. per kilo; clinically the poisoning lasted much longer in the former, as is to be anticipated.

(2) *Doubly splanchnicotomized rabbit* (Tab. V).

In these rabbits, long surviving double splanchnicotomy (111–368 days), subcutaneous application of lobelin caused some rise in the blood sugar concentration. 5 mgrms. lobelin per kilo induced 0.122–0.150 gm. % blood sugar in 5 rabbits, mean 0.13%, a little smaller degree of hyperglycaemia in comparison to the normal animals. 10 mgrms. per kilo 0.14% (0.114–0.164%) in 8 rabbits and 20 mgrms. per kilo 0.13% in 8 others.

In this set of experiments, that is the doubly splanchnicotomized rabbits with subcutaneous application of lobelin, the blood sugar variation during the lobelin intoxication was not simple, contrary to the other sets.

As Example III shows, (Here are three examples displayed from normal animals, doubly splanchnicotomized and doubly suprarenalectomized, in order to show general experimental routine and symptoms.) the blood sugar content started to increase soon on the injection, and it did not decrease with the elapse of time, but it was apt again to increase, so that there are two acmes in the hyperglycaemic curves. In the case quoted here, Rabbit W19, there were some convulsive attacks before and during the second increase of blood sugar. In the other examples the second summit was not preceded or accompanied by convulsive seizures or anything of that nature (10 mgrms: C40, W21, 20 mgrms.: C

EXAMPLE I.

Normal rabbit No. C 79. ♀ 2.28 kilos. 28. V. '36.

Time before or after injection (min.)	Rate of heart beat (per min.)	Frequency of respiration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Blood sugar content		Remarks
					per 100 c.c. blood (grm.)	Rate	
before 20	180	48	38.7	15	0.101	95	8.1. '36 (1.68 kilos) cut auri- cular nerves on both sides.
„ 10	168	42	38.7	15	0.106	100	
9:50 a.m. 4.5 c.c. 1% lobelin (20 mgrms. per kilo) subcutaneously injected in 7 seconds.							
after 15	300	156	37.5	16	0.144	136	3 minutes after the injection violent convulsions, miosis, respiration deep & slow, then lay down on its side. 5 minutes after injection Respiration be- came frequent, shallow(120 per min.). 10 minutes after injec- tion convulsions, respiration frequent and shallow as before. 15 minutes after injection my- driasis, and got up, but not yet completely recovered.
„ 30	240	132	36.7	16	0.162	153	
„ 45	192	132	36.0	16	0.176	166	
„ 60	168	54	35.8	16	0.194	183	
„ 90	180	48	36.3	17	0.198	187	
„ 120	180	54	37.1	17	0.174	164	
„ 150	180	48	37.8	17	0.136	128	
„ 180	180	36	38.1	17	0.118	112	
„ 210	180	48	38.1	18	0.110	104	
„ 240	180	48	38.5	18	0.101	95	

40, W9, W12, W20, W21, W27). The time when the summits appeared was 15 min. & 150 min. in W19, 45 min. & 180 min. in W21, 15 min. & 120 min. in W12, 15 min. & 180 min. in W19, 45 min. & 150 min. in W20, 15 min. & 90 min. in W21, and 30 min. & 150 min. in W29.)

The blood sugar curve without two summits was rare in the doubly splanchnicotomized rabbits poisoned by subcutaneous injection of greater doses of lobelin such as 20 mgrms. per kilo. In the experiments with 10 mgrms. per kilo, the curve with two summits was rather infrequently met with (W19, W21 among 8 cases).

Such a fluctuation, showing two summits, was seldom observable in some cases of the other series of experiments, that is in the doubly suprarenalectomized cases: 7 mgrms. i. v. C7, C12, C13, C15; 5 mgrms. subc. C1, 10 mgrms. C1, 20 mgrms. C7. Although the scale of the fluctuations was small in these suprarenalectomized animals, it must be taken as definitely having established that there are some processes in the carbohydrate metabolism in the organism poisoned with lobelin to bring about two summits in the blood sugar curve, provided the splanchnic nerves or the suprarenal capsules are ruled out. This occurred more frequently when the drug was given in a large amount, such as 7 mgrms. per kilo intravenously or 20 mgrms. per kilo subcutaneously.

EXAMPLE II.

Doubly splanchnicotomized rabbit No. W 19. ♂ 2.26 kilos. 9. VII. '36.

Time before or after injection (min.)		Rate of heart beat (per min.)	Frequency of respiration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Blood sugar content		Remarks
						per 100 c.c. blood (grm.)	Rate	
before	20	204	96	38.4	20	0.096	93	29. II. '36 (1.59 kilos) r. splanchnicotomy, 7. III '36 (1.53 kilos) l. splanchnicotomy and cut auricular nerves on both sides.
,,	10	192	114	38.4	20	0.103	100	
9:50 a.m. 2.3 c.c. 1% lobelin (10 mgrms. per kilo) subcutaneously injected in 3 seconds.								
after	15	228	96	37.9	20	0.143	139	2 minutes after injection miosis, respiration deep & slow, 2 minutes later slight convulsions for 3 seconds, 5 minutes further later slight convulsions, then sprang out of the basin, convulsions, lay down, dyspnoeic, 15 minutes after injection the animal get up, but was attacked several times by convulsions and rolled over. 90 minutes and 130 minutes after injection convulsive seizures. 3 hours after injection the animal looked nearly normal.
,,	30	240	120	37.7	21	0.107	104	
,,	45	228	90	37.5	21	0.096	93	
,,	60	276	96	37.6	21	0.101	98	
,,	90	240	120	37.5	21	0.112	108	
,,	120	228	96	37.5	21	0.156	152	
,,	150	228	84	37.7	21	0.164	159	
,,	180	180	72	38.1	21	0.105	102	
,,	210	180	60	38.1	21	0.096	93	
,,	240	228	96	38.2	21	0.096	93	

Some co-relation can be considered of both facts that the large dose, i.e. 20 mgrms. per kilo, was capable of eliciting only a rather small degree of hyperglycaemia, that is smaller than 10 mgrms. and almost the same as 5 mgrms., and there were usually fluctuations presenting two summits in those cases.

The time when the highest content was reached was short in the cases with 5 mgrms. lobelin per kilo; it was variable in the cases with 10 and 20 mgrms., and there was rather commonly a tendency that this time interval was longer, when the maximum value was larger. Clinical symptoms in the cases of 5 mgrms. per kilo were of similar intensities with the normal rabbits; only in Rabbit W 21 convulsions occurred, and all the rabbits got up 1-1.5 hours after the injection, when mydriasis was persisting.

Among 8 doubly splanchnicotomized rabbits which received, under the skin, lobelin in a dose of 10 mgrms. per kilo, one (W 19) suffered seriously from poisoning, convulsions occurred repeatedly, and 3 hours were needed for recovery, hyperglycaemia was the largest in this case (0.164%); in other cases the animals got up about 1 hour after the injection, some rabbits earlier, some later. In a few cases mydriasis did not occur. No convulsions took place in Rabbit C 60, in which hyperglycaemia was of a great degree (0.155%).

EXAMPLE III.

Doubly suprarenalectomized rabbit No. C 12. ♂ 2.0 kilos. 27. V. '36.

Time before or after injection (min.)		Rate of heart beat (per min.)	Frequency of respiration (per min.)	Body temperature (°C.)	Room temperature (°C.)	Blood sugar content		Remarks
						per 100 c.c. blood (gm.)	Rate	
before	20	180	60	38.4	13	0.104	100	3. X. '34 (1.75 kilos) r. supra- renalectomy (132 mgrms.), 15. IV. '35 (2.0 kilos) l. supra- renalectomy (950 mgrms.) and cut auricular nerves on both sides.
"	10	192	66	38.5	13	0.104	100	
9:40 a.m. 1.4 c.c. 1% lobelin (7 mgrms. per kilo) intravenously injected in 4 seconds.								
after	5	228	60	—	—	0.112	107	45 seconds after the injection lay down on its side, convulsions, miosis, conjunctivae cyanotic. Respiration deep & slow. 3 minutes after injection respiration 36 per min.. 4 minutes after injection convulsions began to occur again, and up to 12 minutes several times. Somewhat dyspnoic. 30 minutes after injection mydriasis, and got up, respiration almost normal.
"	10	228	90	—	—	0.106	102	
"	15	228	96	36.5	13	0.110	106	
"	30	216	96	35.6	14	0.117	112	
"	45	216	66	35.5	14	0.115	110	
"	60	228	54	35.6	14	0.115	110	
"	90	216	66	35.9	14	0.101	97	
"	120	222	60	36.5	14	0.090	86	
"	150	228	48	36.7	14	0.082	79	
"	180	240	48	37.0	14	0.082	79	
"	210	240	48	37.6	14	0.083	80	
"	240	216	48	37.8	14	0.087	83	

In general the big dose of lobelin (i. e. 20 mgrms. per kilo) produced heavy, prolonged symptoms, only in Rabbits C 64 (0.152%), W 12 (0.118%), W 21 (0.154%), especially in Rabbit W 9 (0.115%) symptoms were somewhat slight and continued not long.

The body temperature fell invariably in all cases, the larger the dose, the larger the fall, but this time the fall was in general of relatively small degree and there were only small differences in the magnitude of the temperature fall between the doses, the average lowest body temperature being 38.2° for 5 mgrms. lobelin per kilo, 37.4° for 10 mgrms., and 37.1° for 20 mgrms., while they were respectively 37.5°, 36.7° and 36.0° in the normal rabbits and further 37.2°, 36.3° and 34.6° in the doubly suprarenalectomized ones, the data of which will be quoted below. This peculiarity in these doubly splanchnicotomized rabbits is not effected by the loss of the impulses by the way of these nerves, as the cases of the intravenous application gave no corroborating evidences, the figures being 38.1° on 3.5 mgrms. per kilo and 36.4° on 7 mgrms. in the normal rabbits, 38.1° and 36.7° in the doubly splanchnicotomized ones and 37.4° and 36.2° in the doubly suprarenal-ectomized.

These relatively small falls of the body temperature can be explained by the comparatively high room temperature, compared with the other groups of experiments; and this can be testified by the comparing the figures in cases quoted in Table V, for example. Among 8 cases with 10 mgrms. lobelin per kilo, the

room temperature in the case of Rabbit C 64 was lower (17° – 18°) than in the other cases, and the body temperature of that rabbit fell to 36.4° , the lowest in that group of experiments, and the experiment of C 64 with 20 mgrms. lobelin per kilo was carried out at the room temperature of 14° – 16° , and its body temperature fell to 35.4° , the lowest level among 8 rabbits poisoned with 20 mgrms. per kilo.

Respiratory frequency diminished in the doubly splanchnicotomized rabbits too.

(3) *Doubly suprarenalectomized rabbits* (Tab. VI).

319–639 days after the double suprarenalectomy, lobelin was given hypodermically. In these cases the blood sugar content increased only insignificantly in some cases or did not increase at all in other cases. When the increase occurred, it reached its maximum 15 minutes after the injection, that is at the blood sample first collected after the injection, and the hyperglycaemic period was correspondingly short also. It is only in the realm of remote possibility that some relationship exists between the doses and the magnitude of hyperglycaemia.

In these suprarenalectomized animals, hypoglycaemia was sometimes noted (5 mgrms.: W25, 10 mgrms.; C1, C15, W25, 20 mgrms. C1, C7, C15, H9, & W25); the more the dose, the more frequent and the more profound it was. The minimum noted was 0.044% in W25 with 20 mgrms. per kilo, but this was of the sample collected 4 hours after the injection, i.e. the last sample, so that it remains unrecorded whether or not it was the lowest in that rabbit during the poisoning. All the experiments in the present investigations were extended for 3 or 4 hours after the injection; when the dose was smaller and the hypoglycaemia was accordingly of smaller magnitude, consequently there was always measured already some recovery in the blood sugar value in the elapse of 3 or 4 hours.

Among 4 cases of 5 mgrms. lobelin per kilo some severe symptoms were observed in a case (W25), where convulsive attacks and dyspnoeic respiration were noted, and 3 hours were not sufficient to see a complete recovery. In 3 other cases no convulsions took place, and one hour was sufficient to see a complete recovery. In Rabbit W29 with severe symptoms no increase was ever detected, while in the remaining cases there was trace of hyperglycaemia though very insignificant.

10 mgrms. lobelin per kilo brought about rather slight intoxication symptoms in two rabbits without the suprarenals (C 1, H 9), and somewhat stronger ones in the remaining 3 instances.

20 mgrms. lobelin per kilo were capable of causing severe, prolonged symptoms, only in Rabbit W25 miosis was slight and of a short interval and no con-

vulsions took place, but there was a large fall in the body temperature and a considerable decrease of the blood sugar level, such as from 0.09% to 0.04%.

The anal temperature fall was of about the same degree as in the normal rabbits. It was especially large in the cases with 20 mgrms. per kilo, 34.6° and 36.0° being the average values for the doubly suprarenalectomized ones and the normal.

Lobelin, applied either intravenously or hypodermically, was thus capable of causing an increase in the blood sugar concentration in normal rabbits, which corresponds on the whole to the doses applied. Clinical symptoms, especially the body temperature fall also roughly corresponded to the doses, though some irregularities were observable in the former.

The double splanchnicotomy effected some reduction in the hyperglycemia causable by lobelin, but when larger doses were applied the reduction was of smaller scale. However, there were some tendencies of developing the hypoglycaemic phase. And there were commonly detectable two summits of hyperglycaemia, say one 15–30 minutes after the injection, the second 2–3 hours after the injection, when a greater subcutaneous dose, such as 20 mgrms. per kilo, was applied, and usually the hyperglycaemia caused by subcutaneous 20 mgrms. per kilo was of smaller height than by 10 mgrms. in the doubly splanchnicotomized rabbits. The hyperglycaemic curve with two summits rarely occurred in other cases even with denervated or decapsulated animals.

The double removal of the suprarenal capsules almost inhibits an appearance of the hyperglycaemia causable by lobelin, though not entirely. In the rabbits without suprarenals, hypoglycaemia took place frequently, and the more the dose, the more frequent and profound it was.

From the above data, the suprarenal capsules are definitely indispensable for bringing about the lobelin hyperglycaemia, which fact corresponds to the findings of Houssay and Molinelli, viz: that lobelin acts to liberate the epinephrine by acting on the suprarenal glands.

On the other hand the double splanchnicotomy diminishes without doubt the lobelin hyperglycaemia to some extent. Does then the lobelin act to increase the blood sugar concentration through the central mechanism for the carbohydrate metabolism?

This can be answered in the affirmative if the figures in the doubly suprarenalectomized rabbits in the present investigations and in those of Hatano,¹⁰⁾ who carried out the puncture of Bernard, be compared

10) Hatano, Tohoku J. of Exp. Med., 1936, 29, 455.

TABLE VI.
Effect of subcutaneous injection of lobelin upon the blood sugar content of doubly suprarenalctomized rabbits.

Number of rabbits	Suprarenalectomy (L.)		Date of experiment 1936	Body weight (kilos)	Blood sugar.								Frequency of respi-ration (per min.)	Frequency of heart beat (per min.)	Room temperature (°C.)
	Sex	Date			Body weight (kilos)	Initial (erm. %)	Maximum during experiment (erm. %)	Time of maximum (hrs.)	Duration of hyperglycaemia (hrs.)	Absolute increase (erm. %)	Relative increase %				
<i>Application of lobelin: 5 mgrms. per kilo of body weight.</i>															
C	1	♀	13. X. '34	1.85	13. VII.	2.41	0.100	0.105	1	1	0.005	5	37.3~38.8	156~204	21~22
"	7	♀	27. X. '34	2.15	"	2.49	0.103	0.108	1	1	0.005	5	37.1~38.6	144~192	"
H	9	♂	16. VII. '35	1.65	14. VII.	2.40	0.098	0.109	1	1	0.011	11	37.5~38.8	168~228	20~24
W	25	♂	19. VI. '35	1.55	"	2.26	0.106	0.100	1	0	-0.006	-6	37.1~38.7	192~252	"
<i>Application of lobelin: 10 mgrms. per kilo of body weight.</i>															
C	1	♀	13. X. '34	1.85	2. VII.	2.42	0.104	0.104	1	0	0	0	36.3~38.6	132~204	20~21
"	7	♀	27. X. '34	2.15	"	2.48	0.105	0.115	1	1	0.010	7	36.7~38.3	168~216	20~21
"	15	♂	18. VI. '35	1.75	5. VII.	2.25	0.103	0.107	1	1	0.004	4	36.3~38.6	156~228	20~21
H	9	♂	16. VII. '35	1.65	"	2.38	0.097	0.107	1	1	0.010	10	36.3~38.3	156~216	20~21
W	25	♂	19. VI. '35	1.55	3. VII.	2.38	0.100	0.097	1	0	-0.003	-3	36.0~38.5	192~300	19~21
<i>Application of lobelin: 20 mgrms. per kilo of body weight.</i>															
C	1	♀	13. X. '34	1.85	29. V.	2.43	0.096	0.118	1	1	0.022	23	34.4~37.9	216~300	14~16
"	7	♀	27. X. '34	2.15	"	2.53	0.094	0.099	1	1	0.005	6	34.0~38.2	180~240	"
"	15	♂	18. VI. '35	1.75	17. VI.	2.23	0.112	0.112	1	1	0.012	12	36.5~38.4	192~264	21~25
H	9	♂	16. VII. '35	1.65	31. V.	2.30	0.102	0.116	1	1	0.014	14	33.6~38.6	192~240	15~16
W	25	♂	19. VI. '35	1.56	3. V.	2.22	0.092	0.097	1	1	0.005	6	34.4~37.9	156~228	"

with each other.

As above discussed, the lobelin highly probably acts to increase the blood sugar concentration by acting on the suprarenal glands, but there is still reason to take it as resulting by an oversecretion of epinephrine thereby; it is a question of the quantitative nature.

Some reduction in the lobelin hyperglycaemia in the doubly splanchnicotomized rabbits cannot be explained by the fact that that operation diminishes the glycogen storage, though small,¹¹⁾ since it is without doubt that adrenaline can cause quite the same degree of hyperglycaemia in the rabbit so operated on as in the normal ones.¹²⁾

SUMMARY.

Alpha lobelin was administered in rabbits, normal, doubly splanchnicotomized or doubly suprarenalectomized, intravenously (3.5 mgrms. or 7 mgrms. per kilo of body weight) or subcutaneously (5 mgrms., 10 mgrms., or 20 mgrms. per kilo). The latter two kinds of animals were indefinitely surviving and quite healthy.

Double splanchnicotomy diminishes the hyperglycaemia causable by lobelin to some extent, but if a large amount be given, lobelin is capable of causing some distinct increase in the blood sugar concentration. If subcutaneously heavily dosaged, there are rather commonly two summits in the hyperglycaemic curve and they are of smaller height.

Double suprarenalectomy is capable of causing the lobelin hyperglycaemia of an insignificant degree only, and if largely dosaged there develops frequently the hypoglycaemic stage.

From these facts it is deducible that the suprarenals are almost indispensable in causing the hyperglycaemia by lobelin, which act also to increase the blood sugar through the central mechanism for the carbohydrate metabolism, though not strongly so.

11) Morita, *Ibid.*, 1921, 2, 423 & 436, Mikami, *Jap. J. of Med. Sci., Pharm.*, 1926, 1, 125-129; etc.

12) Tiba, *Tohoku J. of Exp. Med.*, 1938, 32, 419.