THE NATURE OF THE HYPERGLYCEMIA ASSOCIATED WITH ANAPHYLACTIC SHOCK IN THE DOG.

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The experiments reported in this paper were carried out with the purpose of gaining further data on the factors which are involved in the release of glycogen from the liver. Anaphylactic shock was used as a means of radically altering the blood sugar level and producing a condition in which glycogenolysis is known to occur.

The hyperglycemia resulting from the injection into rabbits of killed bacteria of various types (Menten and Manning (1), Zeckwer and Goodell (2), Levine and Kolars (3)) was found to be prevented by removing one adrenal and cutting the splanchnic nerve of the opposite side (Evans and Zeckwer (4)), and in such animals the bacterial injection caused often a pronounced fall in blood sugar, sometimes to a convulsive level. It was thought that anaphylactic hyperglycemia, in which the curve is quite similar to that of bacterial hyperglycemia, might be altered by a similar surgical procedure, and could be more completely studied in dogs.

Several studies have been made of carbohydrate metabolism in anaphylaxis. O'Neill, Moy, and Manwaring (5) found a marked disappearance of liver glycogen during canine anaphylactic shock. The occurrence of hyperglycemia associated with anaphylactic shock has been reported in the guinea pig (Zunz and La Barre (6)), in the dog (McCullough and O'Neill (7), Achard and Feuillé (8)), and in rabbits (Zeckwer and Goodell (9)). The mechanism of this hyperglycemia has recently been studied, chiefly in the guinea pig by La Barre (10), and his results will be discussed later.

Contradictory data on whether the adrenals discharge adrenalin in anaphylactic shock have been given by Houssay and Molinelli (11), who report a slight discharge of adrenal secretion in dogs as determined by the denervated heart method; by Smith and Ravitz (12), who found no change in the epinephrin content of the

adrenals, by chemical determination, during anaphylactic shock in guinea pigs and rabbits; and by La Barre (10), who anastomosed the adrenal vein of one dog to the jugular vein of a second dog, and reports that when anaphylaxis was evoked in the first dog there was no adrenalin effect in the second dog.

The frequency of contradictory results and interpretations by different workers studying the mechanism of hyperglycemia under various experimental conditions is probably due to the fact that the blood sugar level is a peculiarly delicate balance between opposing forces, so that in attempting to study the rôle of a given factor it is almost impossible to avoid complicating the picture by other factors which may vitiate the results. There are, however, certain conditions which should be eliminated from all studies of carbohydrate metabolism which frequently are not. Anesthetics such as ether or chloroform upset so obviously the carbohydrate metabolism that it is difficult to draw any conclusions from experiments carried out under them. This error has entered unavoidably into much of the work before 1923, when amytal was found by Page (13) to be an anesthetic which has little effect on the blood sugar level. In many experiments, drastic operative procedures have been performed immediately preceding the experiment proper. The trauma and shock of such an operation leads to unavoidable discharge of liver glycogen and circulatory changes which complicate the picture and lead to incorrect conclusions.

The present experiments were designed to avoid all unnecessary complicating conditions. Amytal was used as the anesthetic which in the hands of many workers, and in our own previous experience, has permitted the continuance of a low steady blood sugar level, which does not interfere with the production of experimental hyperglycemia and hypoglycemia. In those animals in which adrenalectomy and splanchnic section were carried out, the operation was performed several weeks antecedent to the acute experiment, so that at the time when shock was induced the animals were in vigorous health.

The present experiments were limited to the phenomenon of anaphylaxis as seen in the dog. In the guinea pig, where bronchial spasm is the outstanding feature, an asphyxial hyperglycemia is to be expected. Likewise in the rabbit, the asphyxial element undoubtedly enters into the condition. In the cat, the unsensitized animal reacts so strongly to serum, that a toxicity quite apart from anaphylaxis obscures the picture. In the dog, however, the phenomenon is one fundamentally of profound fall in blood pressure, with intense engorement of liver and intestine. There is no important respiratory disturbance in the anesthetized anaphylactic dog according to Pearce

and Eisenbrey (14), and no pulmonary vascular phenomena according to Drinker and Bronfenbrenner (15). The dog then would seem to be a good animal in which to study the release of glycogen uncomplicated by asphyxia.

In canine anaphylaxis there is evidence that the liver cell is directly affected. Weil (16) found that when antigen is injected directly into a portion of the liver in a sensitized dog, that portion of the liver becomes intensely congested. Numerous observations by Manwaring and his collaborators (17) indicate the essential part the liver plays in canine anaphylaxis. The lessened coagulability of the blood and the liver's reduced capacity to form urea from ammonium lactate (Rumpf (18)) also point to the involvement of the liver cell in the process. It is conceivable then that without the intervention of the adrenals the liver cell might be stimulated directly to give up its glycogen under the circumstances of anaphylaxis by some such mechanism as change of pH in venous stasis, or by direct toxic effect.

Experimental Procedure.

Dogs were divided into two groups, (1) normal intact animals, and (2) those which had been operated upon, under ether anesthesia, through the lumbar route on each side, the left adrenal being excised and the right splanchnic nerve being transected beneath the diaphragm, and usually a piece of nerve trunk being removed. Sensitization was begun after recovery from the operation.

Both groups of dogs were sensitized according to the method used by Manwaring, Marino, McCleave, and Boone (19), being given about 0.5 cc. horse serum per kilo body weight subcutaneously followed on the next day by the same amount intravenously. Shock was produced from 24 to 43 days later.

Just before the acute experiment, the animals were fasted 14 hours. They were then anesthetized with amytal in alkaline solution given intraperitoneally in doses of 50 to 80 mg. per kilo body weight. Enough N/2 NaOH was added to the amytal to put it into solution. With the first twelve dogs, amytal in tablet form was used, and this required more alkali for solution than the amytal in powdered form used in all subsequent experiments, which required about 8.8 cc. of the alkali per 1 gm. of amytal. The dogs varied greatly in their susceptibility to amytal. In many, the calculated dose was given and did not lead to complete anesthesia, so that additional doses, with corresponding amount of alkali, had to be given.

The animals were placed on a warmed table; one carotid artery cannulated for blood pressure tracings; a tracheal tube inserted for artificial respiration, which was used routinely to offset any respiratory disturbance which might arise during shock; one femoral artery prepared for taking blood for blood sugar analyses, and one femoral vein incannulated for the injection of serum. A number of blood sugar determinations were made during the preparation of the animal and

over a period of about an hour after the minor operative procedures had been completed and before the serum was injected, in order to have evidence that the blood sugar level was quite steady at the time when anaphylaxis was induced. A blood pressure tracing was secured usually before the artificial respiration was turned on, as a standard to insure that there was no change in blood pressure resulting from the artificial respiration. Another control of hyperventilation or hypoventilation was given by the series of blood sugar analyses after the artificial respiration was instituted and before anaphylactic shock had been induced.

To produce anaphylactic shock, serum was introduced very slowly into the femoral vein until the blood pressure began to fall. From 0.17 to 0.81 cc. serum was used per kilo body weight. Immediately after injecting the serum, blood samples were taken every few minutes for the first half hour, thereafter at less frequent intervals.

The blood samples were oxalated, the proteins immediately precipitated, and the filtrates allowed to accumulate until the whole series was finished. The Hagedorn and Jensen (20) method for blood sugar was used because it requires only 0.1 cc. blood for each analysis, and permits of running a large number of filtrates at the same time. This method gives slightly lower values than the Folin and Wu method, but relative not absolute values sufficed for the purpose of this investigation.

At the end of each experiment in the operated animals, the removal of the left adrenal and the denervation of the right was verified by dissection. In seven animals the glycogen content of the liver was determined at death in order to demonstrate the presence of available glycogen. In four dogs the oxygen content of the arterial blood was determined before and during shock.

RESULTS.

A typical experiment is given in Table I.

The chief results are given in Table II and Fig. 1. A control for the effect of serum administration and the effect of the experimental procedure on the blood sugar in the absence of anaphylaxis was given by Dog 1 (operated) and Dog 21 (unoperated).

Two experiments (Dogs 4 and 5) were carried out to repeat the curves of hyperglycemia in anaphylaxis obtained by McCullough and O'Neill (7). These two experiments resulted in hyperglycemia but of a lower degree, as McCullough and O'Neill had used ether and had consequently a high level of blood sugar to begin with.

Having thus checked the effective but non-fatal dose of serum and the proper time intervals, and having demonstrated the occurrence of hyperglycemia under the given experimental conditions, anaphylactic shock was then induced in a series of animals, in which one

TABLE I.

Showing a Typical Experiment, with Marked Rise of Blood Sugar in Anaphylactic Shock of Unoperated Dog in Presence of Adequate Ventilation.

Time		Blood sugar	Oxygen content of arterial blood
		per cent	*Volume per cent*
5/14/28	Dog 26, male, weight 11 kg.		
5/15/28	4.4 cc. horse serum injected subcutaneously		
5/16/28	4 cc. horse serum injected intravenously		
6/27/28	Weight 11.5 kg.		
a.m.			
9.45	Blood from femoral vein for blood sugar. Amytal 0.700 gm. given intraperitoneally, 60 mg. per kg. body weight	0.082	
10.00	Partial anesthesia		
10.10	Well under anesthesia. Strapped on heated table. Right carotid incannulated		
10.17	Tracheal tube inserted but not connected with artificial respiration apparatus. Anesthesia deep		
10.40	Blood pressure recorded. Blood pressure 140 mm. Hg.		
10.52	Blood from femoral artery for blood sugar	0.107	
11.06	Blood from femoral artery	0.103	
11.15	Blood pressure being recorded. Artificial respiration turned on		
11.23	Blood from femoral artery. Rectal temperature 38°C.	0.098	
11.48	Blood from femoral artery. Blood pressure 140 mm. Hg.	0.100	
p.m.			
12.15	Blood from femoral artery, collected under oil	0.100	17.62
12.25	Began injecting serum slowly into femoral vein		
12.25½	Blood pressure beginning to fall. Injection stopped		
12.28	Blood pressure 30 mm., has fallen 110 mm. Hg below previous level. Absence of the usual accessory respiratory movements	0.087	
12.34	Blood from femoral artery	0.087	
12.40	Blood from femoral artery, collected under oil	0.177	18.90
12.47	Blood pressure beginning to rise, 50 mm. Hg		
12.52	Blood from femoral artery. Blood pressure rising. 80 mm. Hg	0.171	
1.00	Accessory respiratory movements. Blood from femoral artery	0.145	
1.06	Blood pressure has returned to about normal level		
1.08	Blood from femoral artery	0.120	
1.15	Blood from femoral artery	0.092	
1.30	Blood from femoral artery	0.073	
1.50	Blood from femoral artery	0.073	
2.20	Blood. Liver glycogen 1.6 per cent	0.084	
	Animal killed		

adrenal had been removed and the opposite splanchnic nerve cut (Dogs 3, 6, 11, 12, 13, 15). There was a slight rise in blood sugar, which occurred usually within 5 minutes, reached its maximum in 7 to 15 minutes, and returned to normal in about 30 minutes. In no

TABLE

		Controls		Anaphylaxis			
Animal	Dog	1	21	4	5	17	20
	Weight in kg.	7.3	11.4	7.4	9.1	11.6	10
	Sex	F.	M.	M.	M.	F.	
Time of experiment	No. days after operation	42					
	No. days after sensitization			24	30	43	24
Dose of amytal	Total gm.	0.550	0.700	0.600	0.550	0.830	0.750
	Gm. per kg. body weight	0.074	0.061	0.081	0.061	0.071	0.075
Blood pressure after injection of serum	Time after beginning of injection when B.P. reached lowest. Min.			3¼	3	1½	2¼
	Fall in mm. Hg. below previous level	0	0	70	106	96	116
	Min. after injection when B.P. began to to rise			9	4	18	6
	Min. after injection when B.P. returned approximately to normal			35	8	60	20
Blood sugar	Minimum and maximum values before injection. Gm. per 100 cc. blood	0.063	0.103	0.090	0.101	0.064	0.082
		0.075	0.115	0.123	0.112	0.071	0.123
	Average of preliminary values	0.067	0.111	0.101	0.103	0.067	0.107
	Maximum value after injection	0.061	0.101	0.188	0.163	0.090	0.173
	Total gm. increase over average preliminary value	−0.006	−0.010	0.087	0.060	0.023	0.066
				Mean of series is 0.057 ±			
	Time after injection of highest B.S. value. Min.			35	60	28	16
	Time after injection of return to preliminary level. Min.			80		60	90
Liver glycogen per cent at end of experiment			2.4				

* Return of blood pressure incomplete.

† Figures refer to events after ligation of hepatic vein instead of after injection of serum.

instance was there a fall such as occurred in rabbits with adrenals inactivated, after bacterial injections (4). The preliminary level of blood sugar was low in the surgically treated animals. The same low level had been found previously to occur in rabbits submitted to the same operation (4).

In most of the dogs there was noticeable soon after the beginning of shock, alteration in the respiration. This consisted of spontaneous deep respiratory movements with increase in rate, in spite of the fact that abundant oxygen was being supplied to them by artificial respira-

II.

in unoperated dogs					Anaphylaxis after left adrenalectomy and section of right splanchnic nerve						Temporary constriction of hepatic veins	
25	26	28	29	30	3	6	11	12	13	15	21	31
10.2	11.5	12.5	12	10	7.5	9.0	11.3	9.7	7.8	9.4	11.4	15.0
M.	M.	M.	F.	M.	M.	F.	M.	M.	M.	M.	M.	M.
					42	27	33	49	60	38		
36	43	39	28	34	24	25	28	27	28	32		
0.627	0.700	0.750	0.780	0.750	0.500	0.700	0.800	0.750	0.550	0.480	0.700	0.900
0.061	0.060	0.060	0.065	0.075	0.066	0.077	0.071	0.076	0.070	0.051	0.061	0.060
5½	3	3½	4	5	2½	2	1¾	5	2½	3	1½†	3†
80	110	80	116	116	112	94	90	80	90	86	70	60
6	22	4½	8	17	Death	18	7	8	9	5½	12†	8†
10	41	6	30	60	*	*	14	40	*	13	20†	40†
0.091	0.082	0.105	0.110	0.077	0.061	0.055	0.074	0.062	0.064	0.067	0.103	0.096
0.122	0.100	0.109	0.127	0.131	0.081	0.077	0.080	0.078	0.084	0.076	0.115†	0.109†
0.107	0.098	0.106	0.115	0.108	0.072	0.068	0.078	0.069	0.071	0.071	0.111	0.103
0.129	0.177	0.114	0.217	0.177	0.075	0.081	0.106	0.121	0.094	0.109	0.212†	0.197†
0.022	0.079	0.008	0.102	0.069	0.003	0.013	0.028	0.052	0.023	0.038	0.101	0.094
0.006					Mean of series is 0.026 ± 0.004							
14	15	12	12	27		15	10	15	15	7	19†	10†
60	50	20	53			50	30	45	30	13	60†	60†
+	1.6	3.3			1.0					+		

tion. Spontaneous respiratory movements, however, could not be depended upon, for with Dogs 3 and 7, in which artificial respiration was not carried out, death occurred at the beginning of shock. Every attempt was made to ensure adequate ventilation, but when the experiments on the operated animals were completed, it was thought

that the greater increase in the blood sugar in the unoperated dogs might have been due to hypoventilation, especially in Dog 4, which had shown a temporary rise in blood sugar before the injection of serum had been made. Accordingly, anaphylaxis was induced in other unoperated sensitized dogs (Dogs 17, 20, 25, 26, 28, 29, 30). The rate and depth of the artificial respiration was set so as to secure roughly the maximum ventilation without causing hyperventilation with its associated fall in blood pressure. The adequacy of the ventilation was checked in Dogs 25, 26, 28, 30 by determining the

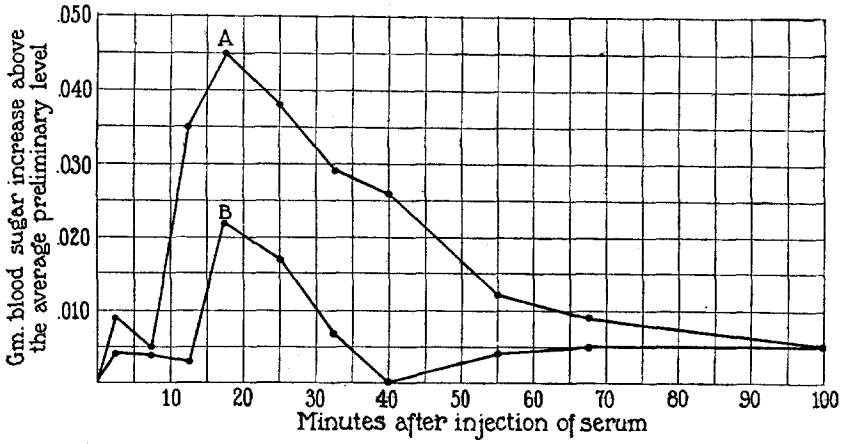

FIG. 1. Increase in blood sugar over preliminary level during anaphylaxis.
A = average of nine intact sensitized dogs.
B = average of six sensitized dogs in which one adrenal had been removed and the opposite splanchnic nerve cut.

oxygen content of the arterial blood withdrawn under oil before shock and at the height of shock (see Table III).

It was found that in two of these animals (Dogs 25 and 28), there was a slight decrease in the oxygen content during shock, as compared with that before shock, but these two dogs showed the least rise in blood sugar of the entire series of unoperated dogs, while in Dogs 26 and 30 which had shown a marked rise in blood sugar, there was a slight increase in oxygen content. These slight fluctuations in oxygen content were within the normal limits and probably represent minor alterations in the experimental conditions. These results seem to rule out asphyxia as a basis for the rise in blood sugar, as what altera-

tion occurred was in the opposite direction. However, since there is the possibility of slight change in the ratio of red cells to serum during shock, and such a change was found to occur in one dog in which the oxygen capacity of the blood when saturated with air was determined, it was thought that the determination of the percentage unsaturation of the blood would be a more accurate index of adequate ventilation than simply the oxygen content. Accordingly, in Dog 30, the oxygen content and the oxygen capacity when saturated with air were determined, and from these figures calculations of the percentage unsaturation were made before and during shock. The results (Table III) indicate a low percentage of unsaturation with no increase during shock. The hyperglycemia, then, associated with anaphylaxis is definitely not dependent upon hypoventilation.

TABLE III.

Showing Adequacy of Ventilation of Test Animals.

	Dog 25	Dog 26	Dog 28	Dog 30
Oxygen content, volume per cent				
Before anaphylaxis	19.89	17.62	19.09	16.95
After anaphylaxis	19.08	18.90	18.80	17.18
Oxygen capacity, volume per cent				
Before anaphylaxis				17.80
After anaphylaxis				17.80
Percentage unsaturation				
Before anaphylaxis				6.5
After anaphylaxis				5.2

In tabulating the results comparison was made between the operated and unoperated dogs, calculating the results both as percentage increase and as gm. blood sugar increase over the average preliminary level. It was realized that to express the change in the sugar content of the blood resulting from anaphylactic shock, in terms of percentage increase of blood sugar above the preliminary level does not give a fair picture of the change, as the lower preliminary blood sugar level commonly found in the operated animals would result in a relatively higher percentage increase than in the intact animals who showed a similar rise in gm. of blood sugar. Expressing the change in terms of the difference in gm. between the average preliminary level and the

highest level gave the fairest measure of comparison, and is the method of expressing the difference used in Table II.

From the results it is seen that all unoperated dogs showed some rise in blood sugar and six out of nine showed greater than 60 mg. increase, with a maximum of 102 mg. The operated dogs also showed a rise but of lesser degree, the maximum being 52 mg. One unoperated dog (Dog 17) differed from the others in this group, in that the preliminary level of blood sugar, for some unknown reason, was very low, like that of the operated animals. On analysis of these results, the mean percentage increase in blood sugar during anaphylaxis over the average preliminary level was 54.8 $\pm$ 5.9 per cent in the unoperated, and 36.6 $\pm$ 6.2 per cent in the operated, with a difference of 18.2 $\pm$ 8.5 per cent. Or expressing the comparison in terms of gm. blood sugar increase, which seems the preferable method of comparison, the mean increase in blood sugar during anaphylaxis over the preliminary level was 0.057 $\pm$ 0.006 gm. for the unoperated, and 0.026 $\pm$ 0.004 gm. for the operated dogs, with a difference of 0.031 $\pm$ 0.007 gm. However, the number of observations is too few to warrant precise mathematical analysis, and the problem did not justify carrying out additional experiments. In these experiments there are naturally wide deviations, but the operated animals tended to be more uniform in their reaction. The complexity of the uncontrollable physiological factors, such as degree of sensitization of the animal, amount of available liver glycogen, and individual variability in the activity of the autonomic nervous system, makes it possible to form only a rough estimate of the effect of any one factor such as operation.

DISCUSSION.

Effect of Operation.—The results then show a slight difference between the operated and unoperated animals. Cutting the splanchnic nerves obviously deprives of their innervation other structures than the adrenals, chiefly the liver, as far as carbohydrate metabolism is concerned. That the denervation of the liver, even when completely done, by stripping off the sympathetic fibres which course along the duodenohepatic artery, has little effect on the mobilization of glycogen such as by emotional stimuli, has been shown by Britton (21). Cutting the splanchnics appears to affect carbohydrate metabolism chiefly by cutting off impulse over them to the adrenal glands.

In our experiments the operation of removing one adrenal and cutting the opposite splanchnic nerve decreased the hyperglycemic reaction, but did not abolish it. The operated animals were in good health, had not lost weight, and the liver glycogen was abundant. The effect, therefore, was not due to any obvious fault in the metabolism of the animal. Probably sympathetic stimulation directly associated with anaphylactic shock is responsible for discharge of adrenalin and consequent glycogenolysis. The question then arises at to why, if the adrenals are concerned in anaphylactic hyperglycemia, there is still a positive, though relatively slight increase in blood sugar in the operated dogs. Were the adrenals only partly inactivated, or is there another factor in the production of the hyperglycemia? As far as could be determined by postmortem dissection, the operations had been complete. The same technique when employed by one of us had resulted in abolishing the effect of the adrenals in rabbits (4), but it may be that cutting the splanchnic nerve does not so completely denervate the adrenal in the dog as in the rabbit and cat. After these experiments were finished, publication was made of more elaborate operations for inactivating the adrenals (Izquierdo and Cannon (22), Zwemer and Newton (23)). Even if the operation as performed in the present experiments does not completely remove the activity of the adrenals the fact that there was a decrease in the blood sugar curves gave evidence that the operation had been at least partly effective, and that at least the adrenals were factors in the hyperglycemia. Furthermore the low preliminary blood sugar level gave evidence of the adrenals not being active. This being so, there must be a second factor concerned in the rise.

Effect of Mechanically Produced Venous Stasis of the Liver.

The question was considered whether purely mechanical venous stasis of the liver could release glycogen, and thus be responsible for the rise in blood sugar in the operated animals. In the dog, muscular bundles are particularly well developed in the hepatic veins, and Simonds (24) suggests that just as in the guinea pig where smooth muscle is particularly prominent in the bronchioles the manifestations of anaphylaxis are chiefly bronchial spasm, just so in the dog the engorgement of the liver can be accounted for as the effect of spasm of

the hepatic veins, and he found that in canine anaphylaxis there is very slight flow of blood from the hepatic veins. Whether contraction of the hepatic vein really contributes to the engorgement of the liver or whether the stasis of blood in the liver is entirely due to capillary dilatation in the splanchnic area, at least the condition of the liver is a conspicuous feature of canine anaphylaxis.

With Simonds' view in mind, the effect on the blood sugar level of temporarily constricting the hepatic veins was tried.

Preliminary experiments were carried out to develop a technique by which the venous outflow through the hepatic veins could be temporarily ligated without constricting the vena cava. Our technique differed from that of Simonds. In our experiments, a tape or narrow rubber tube was passed from right to left through the foramen of Winslow behind the hepatic artery and portal vein and bile ducts. This was then carried upward and backward between the liver and the diaphragm, then anteriorly across to the right between liver and diaphragm, then downward in the fissure dividing the right lobe of the liver from the main portion. The two ends of the ligature could then be drawn tightly together, and intense venous engorgement of the main portion of the liver occurred, without constricting the vena cava or obstructing the arterial supply to the liver. The right lobe of the liver was thus excluded from the constriction. This was found necessary, for if a ligature was thrown around the whole liver, the vena cava was definitely constricted. This ligation could be carried out rapidly with little trauma to the liver.

In Dog 21 this procedure was carried out. After a series of preliminary blood sugar determinations were made, the ligature was put in place but left loose. Two blood sugar determinations following this showed that the manipulation had had no appreciable effect on releasing liver glycogen. The tape was then tightly constricted. The main portion of the liver became blue and tense and the blood pressure fell to a low level. Blood samples were taken at short intervals. The ligature was held for 12 minutes, in order to simulate on the blood pressure record the effect usually obtained in anaphylaxis. On release of the ligature, the blood pressure promptly rose to normal, and the blood sugar rose to a high level, with subsequent fall. A similar experiment was carried out on Dog 31, constricting the liver 8 minutes, with resulting hyperglycemia (Table II). At the end of the experiment, histological sections were made of the liver, and no microscopic evidence of injury to the liver cells was found to have resulted from the constriction. In fact, a section from the portion of the liver

that had been constricted was indistinguishable from one taken from the unconstricted right lobe. The degree of hyperglycemia resulting from mechanical constriction was much higher than in anaphylaxis, as the mechanical occlusion of the hepatic vein is an exaggerated reproduction of the venous stasis occurring spontaneously in anaphylaxis. Further confirmation of the effect of venous stasis was thought unnecessary, as when these experiments had been completed, an investigation was published by Simonds and Brandes (25), in which they obtained a similar hyperglycemia on obstructing the hepatic vein.

The only previous study of the mechanism of hyperglycemia in anaphylaxis has been by La Barre (1927) (10), who found that hyperglycemia occurred in adrenalectomized guinea pigs, and although he states that the arterial blood became blue, he believes that asphyxia showed a much later effect on the blood sugar, and was not responsible for the immediate rise. He concluded that it was due to peripheral vagal stimulation because it occurred after vagal section and was not prevented by ergotamine. Since in the guinea pig asphyxia is the predominating feature of anaphylaxis, and the rapidity of the rise in blood sugar in asphyxia is well known, it does not seem convincing to rule out this factor. He did not use artificial respiration, and his operative procedures were done at the time of the acute experiment, which introduces many complicating factors. His view that vagal stimulation results in glycogenolysis is contrary to the opinion of most investigators who believe that the sympathetic, not the vagal fibres, are responsible for the release of glycogen.

From our experiments we conclude that in anaphylaxis as manifested in the dog, there are probably two factors responsible for the hyperglycemia, (1) sympathetic stimulation by way of the splanchnic nerves, involving the activity of the adrenals, and (2) increased glycogenolysis resulting directly from venous stasis of the liver.

SUMMARY AND CONCLUSIONS.

1. Nine unoperated dogs showed a rise of blood sugar during anaphylactic shock. In six of these dogs the rise was 60 mg. or over.

2. Six dogs in which one adrenal had long previously been extirpated and the opposite splanchnic nerve cut, showed a low preliminary level

of blood sugar, and a relative rise of blood sugar during anaphylaxis, but of less degree than in the unoperated animals. In no case was it greater than 52 mg.

3. Anoxemia did not appear to be a complicating factor, as evidenced by determination of the oxygen content of the arterial blood before and during shock.

4. The rise in blood sugar, which occurs in spite of the loss of adrenal activity, is probably due to the venous stasis of the liver seen in anaphylaxis in the dog, because this rise in blood sugar can be simulated in a normal non-sensitized dog by mechanically constricting the hepatic veins for a brief interval.

5. There are, therefore, probably two factors responsible for the hyperglycemia associated with anaphylaxis in the dog, sympathetic stimulation by way of the splanchnic nerves involving the activity of the adrenals, and glycogenolysis resulting directly from venous stasis of the liver.

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