BLOOD SUGAR STUDIES.

II. Blood Sugar Changes in Fatal Bacterial Anaphylaxis in the Rabbit.

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Chemical studies of anaphylaxis have been directed more toward the agents causing anaphylaxis than to the chemical reactions of the body resulting from this condition. Certain chemical changes associated with this condition have been investigated, involving, for example, the blood chlorides (Zunz and La Barre (1)), antitrypsin content of the blood (Ando (2)), substances excreted in the urine (Pfeiffer (3)), serum proteins and ferments of the blood (Jobling (4)), protein destruction (Major (5)), amino acids (Auer and Van Slyke (6)), and blood urea nitrogen (Hisanobu (7)). Interest has been directed chiefly toward protein rather than carbohydrate metabolism.

With a view of determining any changes in the blood sugar level, bacterial anaphylaxis was produced in rabbits, by giving several sensitizing injections of killed organisms and then allowing a period of 6 to 8 weeks to elapse, when the injection was given which induced anaphylaxis. Organisms were used which in themselves produced changes in the blood sugar level of unsensitized animals and also those which had no such effect (8).

A. The effect on the blood sugar level of the production of anaphylaxis by organisms which have no effect on the blood sugar level of the unsensitized animal is given in the following experiments.

Experiment 1. Anaphylaxis (B. fæcalis alkaligenes).—See Fig. 1.

Time.		Blood sugar.	Temperature.
		per cent	°*F.*
Mar. 29, 1925			
p.m.			
2.45	Before injection.	0.075	102.2
3.10	*B. fæcalis alkaligenes* injected.		
3.40		0.076	100.3
4.10		0.106	99.8
4.27		0.195	99.4
4.35		0.227	
4.55	Death.	0.400	

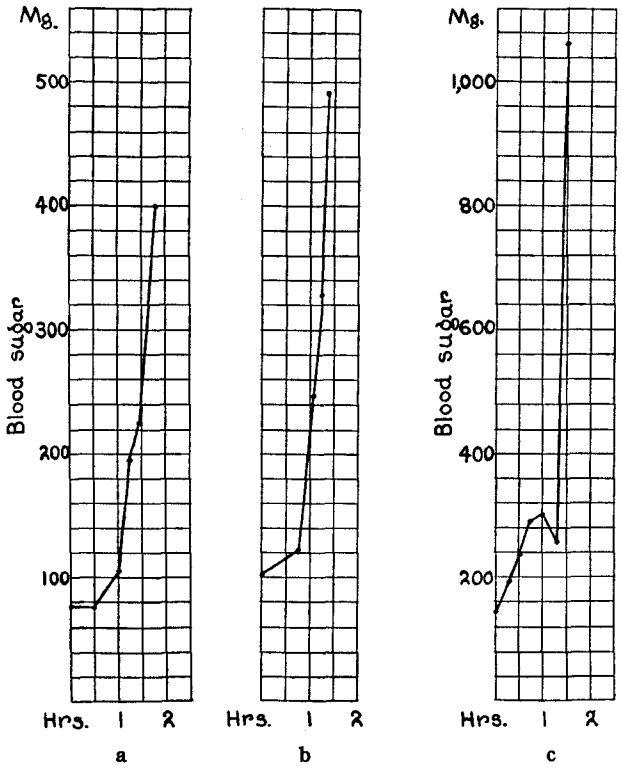

FIG. 1, *a* to *c*. (*a*) Experiment 1. Anaphylaxis (*B. fæcalis alkaligenes*). (*b*) Experiment 2. Anaphylaxis (*Streptococcus viridans*) (*c*) Experiment 3. Anaphylaxis (*Streptococcus viridans*).

Experiment 2. Anaphylaxis (Streptococcus viridans.)—See Fig. 1.

Time.		Blood sugar.
		per cent
Mar. 24, 1925		
a.m.		
10.55	Before injection.	0.103
11.00	*Streptococcus viridans* injected.	
11.45		0.122
p.m.		
12.10	Restless.	0.247
12.13	Convulsions, gasping respiration.	0.326
12.15	Death.	0.490

Experiment 3. Anaphylaxis (Streptococcus viridans).—See Fig. 1.

Time.		Blood sugar.	W.B.C.
		per cent	
Jan. 16, 1925			
a.m.			
10.30		0.146	4,000
10.45	*Streptococcus viridans* injected.		
11.00		0.191	1,600
11.15		0.239	1,400
11.30		0.286	1,800
11.45		0.306	1,000
m.			
12.00		0.253	800
p.m.			
12.18	Death.	1.060	2,000

B. The effect on the blood sugar level of the production of anaphylaxis by organisms which have a slight effect on the blood sugar level in the unsensitized animal is given in the following experiments.

Experiment 4. Anaphylaxis (B. enteritidis of Gaertner).—See Fig. 2.

Time.		Blood sugar.	W.B.C.
		per cent	
Feb. 13, 1925			
a.m.			
9.20	Before injection.	0.132	7,500
9.30	*B. enteritidis* of Gaertner injected.		
9.45		0.130	2,700
10.00		0.122	2,200
10.15		0.131	1,700
10.35		0.156	1,200
10.42		0.190	6,000
10.44	Death.	0.345	5,600

Experiment 5. Anaphylaxis (B. paratyphosus A).—See Fig. 2.

Time.		Blood sugar.
		per cent
Mar. 29, 1925		
p.m.		
1.25	Before injection.	0.099
1.32	*B. paratyphosus* A injected.	
2.05		0.084
2.20		0.111
2.23		0.186
2.24		0.188
2.25	Death.	0.230

C. The effect on the blood sugar of the production of anaphylaxis induced by organisms which produce a marked hyperglycemia in the unsensitized animal, is given in the following experiments.

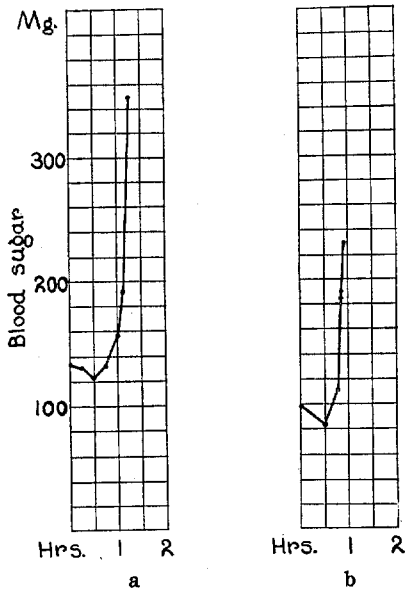

FIG. 2, *a* and *b*. (*a*) Experiment 4. Anaphylaxis (*B. enteritidis*). (*b*) Experiment 5. Anaphylaxis (*B. paratyphosus* A).

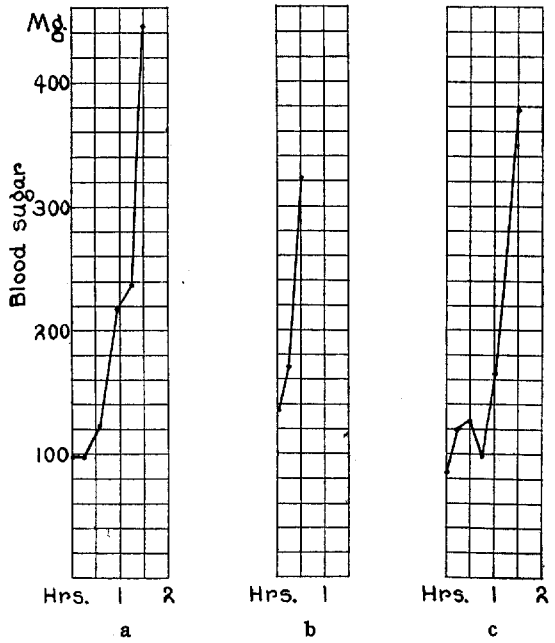

FIG. 3, *a* to *c*. Anaphylaxis (*B. coli*). (*a*) Experiment 6. (*b*) Experiment 7. (*c*) Experiment 8.

Experiment 6. *Anaphylaxis* (*B. coli*).—See Fig. 3.

Time.		Blood sugar.	W.B.C.	Temperature.
		per cent		°F.
Mar. 23, 1925, *a.m.*				
9.05	Before injection.	0.098	5,500	102.4
9.15	*B. coli* injected.			
9.30		0.098	2,600	102.2
9.50		0.123	1,800	102.6
10.10		0.218	2,800	102.2
10.25		0.238	2,300	102.2
10.45		0.444	5,800	
10.48	Death.			

Experiment 7. *Anaphylaxis* (*B. coli*).—See Fig. 3.

Time.		Blood sugar.	W.B.C.
		per cent	
Dec. 5, 1924 *p.m.*			
3.45	Before injection.	0.134	12,800
4.15	*B. coli injected.*		
4.30		0.168	1,300
4.45	Death.	0.321	3,200

Experiment 8. *Anaphylaxis* (*B. coli*).—See Fig. 3.

Time.		Blood sugar.	W.B.C.	Temperature.
		per cent		°F.
Mar. 10, 1925 *a.m.*				
11.00	Before injection.	0.084	8,000	102.8
11.05	*B. coli* injected.			
11.20		0.120	1,600	102.6
11.35		0.127	800	103.6
11.50		0.099	600	104.2
p.m.				
12.05		0.167	800	104.3
12.30	Death.	0.377	2,500	

It will be seen from these results that in general there is a gradual rise in blood sugar during the latent period before symptoms of anaphylaxis are manifested. Then, when the animal becomes restless, prostrated, with fall of blood pressure, and develops convulsions and becomes dyspneic, there is a more rapid rise in the blood sugar which reaches an unusually high level at time of death. Often the final sharp ascent is preceded by a short downward curve of relatively lower blood sugar.

There is no material difference in the blood sugar curve in anaphylaxis produced by organisms which in themselves have an effect on the blood sugar and by those which have no such effect on the unsensitized animal. The height of the blood sugar seems to depend on the degree of hypersensitivity of the animal rather than on the agent producing it.

GENERAL DISCUSSION.

In considering the mechanism by which rapid alterations in the sugar content of the blood are produced by the introduction of killed bacteria intravenously in sensitized and unsensitized rabbits, two possibilities are to be considered: (1) whether there is a failure in the breaking down of glucose and its utilization, with consequent accumulation in the blood of glucose which is being thrown into the blood stream in normal amounts; or (2) whether there is a sudden mobilization of glycogen, and the increase in the blood sugar level represents increased glycogenolysis, and hence an increase in the amount of sugar thrown into the blood stream.

Failure in the breaking down and utilization of glucose can be conceived of as being produced in two ways:

(*a*) As result of a general depressed state of all metabolic activities including depression of those cells functioning to break down and utilize glucose. If this were the case there would be an agonal rise in blood sugar in every case in which the moribund state is prolonged. This, however, does not occur, and hence this possibility can be excluded.

(*b*) Through injury to special cells controlling the utilization of sugar. Menten and Manning (9) stress the importance of histological changes in the islands of Langerhans, together with changes in the

liver, spleen, and kidneys, in explaining the increase in blood sugar in their experiments after the injection of organisms of the paratyphoid B-enteritidis group. It does not seem likely to us that injury to the islets with resultant suspension in the activity of these cells can fully account for such marked hyperglycemia as developed in our experiments after a single injection of organisms. Usually transient functional changes are not registered as anatomical changes that can be detected by ordinary histological methods. It requires a more permanent injury to produce anatomical changes. To be responsible for such high blood sugar levels, the cells would have to be profoundly injured, and it is inconceivable that the cells could be restored to normal function in a few hours time if the injury was profound.

In the absence of indications that the rise in blood sugar is due to interference with utilization of sugar, the alternative mechanism, a sudden increased production of sugar, remains to be considered.

Hyperglycemia secondary to increased glycogenolysis can be produced by various well known methods.

The hyperglycemia caused by adrenalin is apparently produced by this mechanism. Macleod (10) showed that stimulation of the sympathetic nerves to the liver caused rapid mobilization of glycogen and hyperglycemia. The intact adrenals were found to be necessary for this effect of sympathetic stimulation. Griffith (11) has shown that hyperglycemia of nervous origin may be produced reflexly by stimulation of the sciatic and vagus nerves. Henderson and Underhill (12) have emphasized the effect of acapnia in mobilizing glycogen of the liver with resultant hyperglycemia. That asphyxia is potent in producing hyperglycemia has been evidenced by many investigators. Cannon (13) has stressed the emotions of rage and fear in producing stimulation of the sympathetic nervous system and hyperglycemia.

In our experiments, the picture had every appearance of sympathetic effect. The rapidity of development of the hyperglycemia, the associated vasomotor phenomena in the animals, and the swift restoration of equilibrium indicated a temporary effect, as one produced by nervous stimulation. Actual increase in the sugar discharged into the blood stream could alone account for the high levels attained.

Proof of this hypothesis was furnished by the fact that microchemical determinations showed disappearance of glycogen in the

livers of animals dying in anaphylaxis, in contrast to the abundant glycogen present in the normal animal. Furthermore, O'Neill, Manwaring, and Moy (14) have recently shown that in serum anaphylaxis produced in dogs, the liver is almost completely depleted of glycogen.

If sympathetic stimulation of glycogenolysis is the mode of production of the hyperglycemia in the present experiments, the question remains how this sympathetic stimulation is effected. Is it by the chemical stimulation of some constituents of the bacterial body—or, in the defence reaction of the body in response to the introduction of foreign bacteria, are substances elaborated by the tissues which exert a stimulating effect upon the sympathetic nervous system? The fact that the injection of any organism causes hyperglycemia in the animal sensitized to it suggests that the animal furnishes the stimulating substance rather than the bacterium. If so, why do certain organisms elicit this substance in unsensitized animals, while other organisms do not? The solutions to these questions remain to be found.

In anaphylaxis the effect of asphyxia, which is well known to cause hyperglycemia, may play a rôle in the production of glycogenolysis. The extreme heights in blood sugar are reached when there is violent respiratory difficulty, although the sugar rises markedly before any symptoms of asphyxia are manifested. This effect of asphyxia probably augments the effect of sympathetic stimulation. In the hyperglycemia produced by organisms in the unsensitized animal, asphyxia plays no rôle, as there is no respiratory difficulty in these animals.

The fact that the curve of blood sugar in anaphylaxis was the same whether organisms were used which caused hyperglycemia in the unsensitized animal or whether organisms were used which had no effect in the unsensitized animal, suggests that the mechanism of the production of these blood sugar changes is the same in anaphylaxis as in the reaction to bacteria in the unsensitized animal. If a certain type of mechanism controlled the one and another type the other, two effects would be superimposed in the case in which anaphylaxis was produced by organisms such as *Bacillus coli*, and there would be an augmentation in the height of the curve as compared with that of

anaphylaxis produced by such organisms as streptococci. No such augmentation occurred in our experiments. In fact, the opposite occurred, that is, the highest rise, of a phenomenally high value, occurred in anaphylaxis produced by *Streptococcus viridans*, which had no effect whatever on the blood sugar of the unsensitized animal.

In anaphylaxis, apparently, the degree of hypersensitivity of the animal determines the height of the blood sugar, not the agent used in producing it.

In searching the literature for previous work along these lines, a recent preliminary report was noted of experiments by McCullough (15), in which, during serum anaphylaxis in the dog, a slight increase in blood sugar was found, up to 0.27 per cent. It is of interest that the values were not as high as in our experiments, because in the dog, in which changes in the liver apparently play a conspicuous rôle in anaphylaxis (Manwaring (16)), one might expect a relatively great disturbance in the glycogen output. Petersen, Jaffe, Levinson, and Hughes (17), in experiments undertaken for the purpose of demonstrating endothelial permeability in anaphylaxis in the dog, determined various constituents of the thoracic duct lymph. Though they were interested chiefly in other chemical substances, sugar determinations were made in some experiments, and their tables show a distinct increase in the lymph sugar in anaphylaxis.

SUMMARY.

1. During bacterial anaphylaxis there is a gradual rise in the blood sugar level, which attains an extremely high value at the time of death.

2. The curve of blood sugar is quite similar whether anaphylaxis is induced by organisms which affect the blood sugar in the unsensitized animal or by organisms which have no such effect.

3. No instances occurred in which there was not a marked hyperglycemia in anaphylaxis.

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