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Blood Inorganic Phosphates in Carbohydrate Metabolism.

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Depression of the blood inorganic phosphates after the administration of dextrose has been demonstrated by Perlzweig, Latham, and Keefer.¹ This observation has been confirmed by Sokhey and Allen,² Harrop and Benedict,^{3, 4} and Bolliger and Hartman⁵ with both humans and animals receiving dextrose orally and parenterally. Although this fall in blood inorganic phosphates after the administration of dextrose appears to be the rule, it does not occur invariably. Blatherwick, Bell, and Hill⁶ in a series of experiments in which dextrose was given orally to human subjects, found no consistent change in the phosphate level and state that there is "sometimes an increase, or a decrease or no change at all."

Insulin, on the other hand, has been found by Wigglesworth, Woodrow, Smith and Winter⁷ to produce a marked drop in the plasma inorganic phosphate level of the rabbit. Cori and Cori,⁸ Perlzweig, Latham and Keefer,¹ and Vollmer⁹ have reported similar results, and further, have demonstrated that injections of epinephrin produce the same effect. Cori¹⁰ and Cori and Cori¹¹ in seeking an explanation for these changes found a marked increase in the hexose-phosphate content of the skeletal musculature of the normal animal after the injection of either insulin or epinephrin. No change in blood or muscle phosphates could be demonstrated in the adrenalectomized animal, and they concluded that the depression of the blood inorganic phosphate level following the injection of insulin

¹ Perlzweig, William A., Latham, E., and Keefer, C. S., *PROC. SOC. EXP. BIOL. AND MED.*, 1923, **21**, 33.

² Sokhey, S. S., and Allen, F. N., *Biochem. J.*, 1924, **18**, 1170.

³ Harrop, G. A., and Benedict, E. M., *PROC. SOC. EXP. BIOL. AND MED.*, 1923, **20**, 430.

⁴ Harrop, G. A., and Benedict, E. M., *J. Biol. Chem.*, 1924, **59**, 683.

⁵ Bolliger, A., and Hartman, F. W., *J. Biol. Chem.*, 1925, **64**, 91.

⁶ Blatherwick, N. R., Bell, M., and Hill, E., *J. Biol. Chem.*, 1924, **61**, 241.

⁷ Wigglesworth, V. B., Woodrow, C. E., Smith, W., and Winter, L. B., *J. Physiol.*, 1923, **57**, 447.

⁸ Cori, C. F., and Cori, G. T., *Arch. exp. Path. Pharmak.*, 1933, **172**, 249.

⁹ Vollmer, H., *Biochem. Z.*, 1923, **140**, 410.

¹⁰ Cori, C. F., *Physiol. Rev.*, 1931, **11**, 143.

¹¹ Cori, C. F., and Cori, G. T., *J. Biol. Chem.*, 1931-32, **94**, 581.

was the result of an increase in the secretion of epinephrin called forth by hypoglycemia. Ellsworth and Weinstein¹² found varying degrees of change in the blood inorganic phosphates in adrenalectomized dogs after the injection of insulin.

Thus, the mechanism of the drop in plasma inorganic phosphates after injection of insulin or epinephrin appears to be quite different from that following the administration of dextrose. Cori¹⁰ and Cori and Cori¹¹ have shown that after normal rats are fed dextrose there is no change in the hexose-phosphate content of muscle such as occurs following the injection of insulin or epinephrin. Furthermore, Pollock¹³ found that the parenteral administration of glucose produces the same fall in blood inorganic phosphates in normal and adrenalectomized animals.

In the literature on this subject little attention has been paid to the factors of diet and fasting. In this work dogs were used which had been fed a high-carbohydrate, low-fat diet (CHO 170, F 70, P 80) for at least 3 weeks before any experiment was carried out. Food was withheld from 8 such dogs for 20 hours, and their intake of water limited to 650 cc. each. They were then given one gm. of dextrose (Baker, C. P.) per kilo intravenously in 50% solution, and blood samples taken every 10 minutes for 2 hours. Blood sugar levels were determined by Folin's micromethod¹⁴ (using venous blood), and inorganic phosphates by the technic described by Fiske and Subbarow.¹⁵ This procedure was repeated at 3 intervals, after fasts of 10, 8, 4, and 2 hours. The results are about the same in the 8 dogs; for purposes of convenience only one is shown in the accompanying table. It will be seen that the depression of the blood inorganic phosphates varied directly with the duration of the fast beyond 8 hours.

The same experiment was repeated, substituting 1 unit of insulin (Mulford) per kilo for dextrose. Here the drop of the blood sugar seemed to depend to some extent on the length of the fasting period, while the drop in inorganic phosphates (average = 48% drop) was fairly constant, and was related to the point of maximal or "critical" hypoglycemia.

The adrenal glands were carefully removed in 2 stages from several of the dogs and 4 were maintained in sufficiently good condition for 3 weeks to allow the same studies to be made. The results are not in agreement with the Coris'⁸ hypothesis that the adrenals are

¹² Ellsworth, R., and Weinstein, A., *Bull. Johns Hopkins Hosp.*, 1933, **53**, 21.

¹³ Pollock, H., *Am. J. Physiol.*, 1933, **105**, 79.

¹⁴ Folin, O., *N. E. J. Med.*, 1932, **206**, 727.

¹⁵ Fiske, C. H., and Subbarow, Y., *J. Biol. Chem.*, 1925, **66**, 375.

TABLE I.
Effect of Fasting on Blood Glucose and Blood Inorganic Phosphates Following Administration of 1 gm. per kilo of Dextrose in the Normal Dog.

Dog	Duration of fast, hr.	Fasting		20 Min.		40 Min.		60 Min.		80 Min.		100 Min.		Maximum % Drop in Phosphates
		G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %	
1	2	102	5.4	242	5.6	194	5.0	182	5.1	164	5.2	141	5.3	7
	4	100	5.6	250	4.9	181	4.8	160	4.7	148	4.8	132	5.0	16
	8	102	5.6	200	5.0	184	4.6	152	4.5	141	4.8	128	4.8	20
	10	86	5.8	196	4.8	178	4.6	138	4.0	120	4.1	118	4.0	31
	15	82	5.6	210	4.8	180	4.1	140	3.6	132	3.6	110	3.6	35
	20	80	5.8	230	4.6	161	4.0	137	3.8	123	3.2	100	3.4	45

TABLE II.
Blood Glucose and Plasma Inorganic Phosphates in Adrenalectomized Pancreatectomized Dogs Following 25 Units of Insulin Intravenously.

Dog	Fasting	10 Min.		20 Min.		40 Min.		60 Min.		70 Min.			
		G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %	G mg. %	P mg. %		
1	300	6.	3.0	310	3.0	250	5.0	270	0	250	3.	240	1.
2	140	8.	4.1	170	4.1	120	4.3	90	4.6	110	5.	110	4.

intimately associated with changes in the blood phosphate level during the metabolism of carbohydrates since a consistent, although irregular depression followed the injection of dextrose (as in Table I). On the other hand, their view that insulin acts on the blood inorganic phosphates through the adrenals is supported to some extent in that there was very little or no drop at all in these phosphates after adrenalectomy.

In view of the fact that insulin increases glycogen-storage in the diabetic animal, it was thought of interest to study its effect on the blood phosphorus in adrenalectomized animals with pancreatic diabetes. The pancreas and adrenals were removed from 2 dogs in 2 stages. About 5 hours after the second stage of the procedure (removal of the left adrenal) each animal had apparently completely recovered from the light ether anesthesia and was only slightly less than normally active. Twenty-five units of insulin were then given intravenously (Table II).

In these animals a marked fall in blood phosphates, and a moderate depression of the blood sugar level occurred. Both dogs died in about 8 hours after the second operation. Further work on this phase of the problem is in progress. Control animals showed a steady decline of the blood glucose as had been previously demonstrated, in the cat, by Long.¹⁶

The results, in general, suggest that the blood inorganic phosphates may be depressed by both glycogenesis and glycogenolysis. Thus, the fall in these phosphates may well be linked with the conversion of dextrose to glycogen in the liver, or glycogen to lactic acid in muscle. The ultimate fate of these phosphates in such processes has not as yet been revealed.

1. Starvation increases the degree of fall in blood inorganic phosphates occurring in normal dogs after intravenous administration of dextrose.
2. Removal of the adrenals does not influence the fall of blood inorganic phosphates following dextrose administration.
3. The injection of insulin has no effect on the level of blood inorganic phosphates after removal of the adrenals.
4. Removal of the pancreas and the adrenals accelerates the fall in inorganic phosphates, and decelerates the fall in blood sugar following the intravenous injection of insulin.

¹⁶ Long, C. N. H., *Ann. Int. Med.*, 1935, **9**, 166.