LII. RÔLE OF INSULIN IN PHOSPHORUS METABOLISM.

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THE work of Harden and Young, Lebedev and others has established the rôle of phosphoric acid in the process of fermentation of sugars. This viewpoint has been adapted by Embden and his school to the metabolism of sugar in animal tissues. As Embden expressed the opinion that the first stage of sugar utilisation is the formation of hexosephosphoric acid (lactacidogen), one could *a priori* accept that insulin administration would produce a marked disturbance of the phosphorus metabolism, especially in the equilibrium between the inorganic and organic phosphorus moiety. That this is really the case has been shown by several authors. Among these Wigglesworth, Woodrow, Smith and Winter [1923] have demonstrated that, on introduction of insulin into the animal organism, the inorganic phosphorus of the blood is suddenly lowered and is maintained at a low level for a considerable time, whereas the introduction of glucose causes the reverse process to occur. Similarly Sokhey and Allan [1924] have performed a series of experiments on the influence of insulin on the excretion of phosphorus in the urine. They have observed that in certain animals six hours after the insulin injection the inorganic phosphates diminished whilst in the subsequent stage a corresponding increase was noticed. The total phosphorus output calculated on a 24-hour basis was higher than normal to the extent of 25 to 35 %. Similar results were obtained by supplying sugar alone or insulin with sugar.

Based on these results we have thought for a long time [1925, 1, 2] that the lack of proportionality between small and high doses of insulin preparations, an observation which has been also described by Laqueur and de Jongh [1925], might be due to the quantity of phosphorus immediately available to the animal to effect the lactacidogen formation. The unequal activity of identical doses of insulin could, perhaps, also be explained on that basis. We must immediately state here that our experiments performed to test this hypothesis point to the minor part played by phosphorus in the insulin action and that the explanation of the mechanism of the reaction has to be thought of in a different direction. Our results show that whilst insulin may cause a shifting of the mode of occurrence of the phosphorus (inorganic into organic com-

bination or the reverse) it seems that it exerts a minor influence on the general phosphorus metabolism. To test the points in question we made first a whole series of experiments on the phosphorus distribution in the blood under the influence of insulin. The analytical results obtained (not recorded here) show such a lack of constancy (due probably to the various stages of lactacidogen formation and decomposition, owing perhaps to the particular stage of synthesis or decomposition which might be found in the animal at the time of bleeding) that we decided to attack the problem in a different way.

The experiments which were performed on rats can be divided as follows: (1) experiments on the excretion of phosphorus in the urine and faeces under the influence of insulin (and also vitamine B), on a diet containing phosphorus only in the form of caseinogen; (2) experiments on rats, showing the phosphorus metabolism under the influence of insulin and vitamine B on a phosphorus-free diet; (3) experiments on rats kept, previous to the administration of insulin, on a diet entirely devoid of phosphorus.

EXPERIMENTAL.

The first experiment was performed on four male rats, kept in special cages, which are described elsewhere [Funk, 1925], and which permit a quantitative separation of the excreta. The animals were fed on an artificial diet with a salt mixture free from phosphorus, prepared according to Pappenheimer, McCann and Zucker [1922]. The experiment lasted 16 days: two preliminary periods, one insulin period (2 doses, 4 units per kg.) and one vitamine B period. Here is the summarised result of the experiment.

Periods	Change in weight g.	P intake mg.	P in urine mg.	P in faeces mg.	Total P excretion mg.	P balance mg.
Preliminary	- 3.5	31.05	4.41	26.78	30.94	- 0.13
Insulin	- 2.2	28.02	3.55	23.57	27.12	+ 0.9
Vitamine B	+ 2.2	33.69	2.57	29.83	32.42	+ 1.29

The second experiment was performed on a phosphorus-free diet (egg-albumin instead of caseinogen). 24 hour collections of urine and faeces were made on four animals continued for 34 days. Here follow the results.

Diet	Food intake g.	Change in weight g.	P in urine mg.	P in faeces mg.	Total P excretion mg.
P-free diet alone	5.0	- 1.37	0.79	1.89	2.6
P-free diet and insulin	4.8	- 1.93	1.09	1.70	2.68
P-free diet and vitamine B	7.4	+ 3.25	0.40	2.61	2.99

The third experiment was made on three groups of rats of four animals each, all kept on a phosphorus-free diet. The animals themselves were analysed for phosphorus. The first group of rats were killed on the tenth day of the phosphorus-free diet, the second group were injected with 4 units of insulin every third day and the third group were used as controls and were killed on the day on which the animals treated with insulin died.

Group of animals	Initial weight g.	Final weight g.	Average P content per rat g.	P %
I. Killed on the 10th day of the P-free diet	122	116	0.921	0.82
II. Insulinised animals	122	94	1.019	1.07
III. Controls	124	86	0.979	1.14

Results of these three experiments show that insulin exerts only an insignificant influence on the total phosphorus metabolism.

SUMMARY.

1. The change in the phosphorus distribution of the blood under the influence of insulin does not give us the true picture of its influence on the total phosphorus metabolism.

2. The metabolism experiments on the phosphorus partition in the urine and faeces under the action of insulin on a diet containing phosphorus, as well as on a diet devoid of phosphorus, show that the total phosphorus metabolism remains practically unaffected.

3. The same conclusions can be reached if the animals are analysed *in toto* on a phosphorus-free diet under the influence of insulin. No difference in the phosphorus content of insulinised animals was found as compared with the controls.

4. Insulin seems to play an insignificant rôle in the total phosphorus metabolism.

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