CCXXIII. HYPOGLYCAEMIC AND OTHER ACTIONS OF PHOSPHOTUNGSTIC ACID, PHOSPHOMOLYBDIC ACID AND ALLIED SUBSTANCES.

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ON account of their chemical properties phosphotungstates and phosphomolybdates have been long used in the laboratory for colorimetric estimations but their actions on the living system have not been properly studied. Administered internally these substances, however, were found to have definite effects on metabolism. In a previous communication [Mukherjee, 1935] it was shown that phospho-24-tungstic acid had hypoglycaemic action. As mentioned in that paper experiments were also done with some allied substances. It was found from these experiments that phosphomolybdic acid, molybdic acid, silicotungstic acid, sodium tungstate, ammonium phospho-18-tungstate and also sodium vanadate had hypoglycaemic actions when administered by mouth. Some of these substances were found to have diuretic actions as well. It was also found from experiments that these substances acted like oxidizing enzymes. From a consideration of these properties the author was led to try the effect of these substances in a few cases of cancer [Mukherjee, 1936]. This work is being continued. In the present paper the hypoglycaemic and other actions of these substances will be dealt with.

EXPERIMENTAL.

Excepting phosphotungstic and silicotungstic acids (Schering-Kahlbaum) the other substances used were Merck's. Ammonium phospho-18-tungstate (Wu's B form) was prepared in the laboratory [Wu, 1920].

Hypoglycaemic action. For studying the hypoglycaemic action white rabbits were used. In a few cases experiments were also done on diabetic human subjects. Blood sugar was estimated by the Folin-Wu colorimetric method. The hypoglycaemic effect was measured by the fall of blood sugar 3 hours and also 5 hours after administration of the material in rabbits fasting for about 20 hours. The samples were administered in 5 ml. of distilled water by stomach tube to the

Table I.

Rabbits	Wt. kg.	Sex	Insulin 0.6 unit subcutaneously. Blood sugar in mg. per 100 ml.			Phosphotungstic acid (0.3 g.). Blood sugar in mg. per 100 ml.			Phosphomolybdic acid (0.3 g.). Blood sugar in mg. per 100 ml.		
			Initial	3 hr.	5 hr.	Initial	3 hr.	5 hr.	Initial	3 hr.	5 hr.
I	1.26	F	105	67	80	102	71	67	89	77	74
II	1.16	F	91	63	65	87	71	71	87	80	63
III	1.22	M	100	74	—	83	67	—	95	83	80
IV	1.20	M	80	59	—	91	77	74	83	74	71
V	1.31	F	111	67	91	118	87	83	111	85	83
VI	1.14	F	91	77	80	95	91	87	100	83	83

rabbits, usually at intervals of 2-3 days. The hypoglycaemic effects of 0.3 g. of phosphotungstic acid and 0.3 g. of phosphomolybdic acid compared with 0.6 unit of insulin (Eli Lilly and Co.), 0.5 unit per kg. body weight, given subcutaneously are shown in Table I.

The effects by mouth of 0.3 g. of molybdic acid and 0.3 g. of sodium tungstate compared with 0.7 unit of insulin, 0.5 unit per kg. body weight, given subcutaneously are shown in Table II.

Table II.

Rabbits	Wt. kg.	Sex	Insulin 0.7 unit subcutaneously. Blood sugar in mg. per 100 ml.			Molybdic acid (0.3 g.). Blood sugar in mg. per 100 ml.			Sodium tungstate (0.3 g.). Blood sugar in mg. per 100 ml.		
			Initial	3 hr.	5 hr.	Initial	3 hr.	5 hr.	Initial	3 hr.	5 hr.
VII	1.43	F	105	74	91	105	91	91	100	95	87
VIII	1.22	F	91	67	74	95	83	80	105	74	74
IX	1.56	M	95	80	—	105	80	77	95	91	80
X	1.60	M	100	67	91	91	77	74	—	—	—

The hypoglycaemic effects by mouth of 0.2 g. of sodium vanadate (meta) and of 0.3 g. of silicotungstic acid and 0.3 g. of ammonium phospho-18-tungstate were also similarly determined (Table III).

Table III.

Rabbits*	Sodium vanadate (meta) (0.2 g.). Blood sugar in mg. per 100 ml.			Silicotungstic acid (0.3 g.). Blood sugar in mg. per 100 ml.			Ammonium phospho-18- tungstate (0.3 g.). Blood sugar in mg. per 100 ml.		
	Initial	3 hr.	5 hr.	Initial	3 hr.	5 hr.	Initial	3 hr.	5 hr.
I	95	80	77	—	—	—	—	—	—
II	91	74	69	—	—	—	—	—	—
VII	100	74	74	—	—	—	—	—	—
VIII	91	67	—	—	—	—	—	—	—
V	—	—	—	—	—	—	102	74	77
VI	—	—	—	83	71	67	95	67	67
IX	—	—	—	87	77	71	87	83	74
X	—	—	—	111	74	77	—	—	—

* The same rabbits as in Tables I and II.

As a control test the rabbits were given 5 ml. of distilled water each by stomach tube. There was in this case only insignificant variation in blood sugar level (after 3 and 5 hours). In some rabbits there was rather a slight rise of blood sugar.

Diuretic action. While studying the hypoglycaemic effects of the substances it was observed that the rabbits micturated rather more frequently. The hypoglycaemic and diuretic effects by mouth of 0.9 g. of phosphotungstic acid in 30 ml. of distilled water were also determined in 4 diabetic patients. The material was administered by mouth to the fasting patient in the morning. The initial fasting blood sugar before administration of the material and blood sugar 3 hours after administration of material were estimated. The patients were also given the same dose of phosphotungstic acid (0.9 g. in 30 ml. of distilled water) in the evening and the diuretic effect was determined by measuring the 24 hours' urine volume before and after administration of material. The hypoglycaemic effect of 0.9 g. phosphotungstic acid by mouth in diabetics compared with that of 5.0 units of insulin given subcutaneously and the diuretic effect of 0.9 g. phosphotungstic acid given by mouth morning and evening are shown in Table IV.

Table IV.

Diabetic patients*	Age	Sex	Wt. kg.	5.0 units of insulin subcutaneously.		0.9 g. of phosphotungstic acid by mouth (morning and evening)			
				Blood sugar in mg. per 100 ml.		Blood sugar in mg. per 100 ml.		Urine volume in litres	
				Initial (7 A.M.)	3 hr.	Initial (7 A.M.)	3 hr.	Before	After
A	42	M	37.4	286	182	286	200	1.94	2.46
D	40	M	51.0	220	67	182	87	1.51	2.22
R	50	M	52.0	268	133	250	160	1.90	2.62
M	45	M	42.4	167	65	191	95	1.68	2.10

* Breakfast given after 10 A.M.

Oxidizing action. It was found from experiments that these substances acted like oxidizing enzymes. Crystals of phosphomolybdic acid (about 0.1 g.) when dropped into a test-tube containing about 5 ml. of a solution of benzidine in acetic acid gave a blue colour to the solution even without addition of hydrogen peroxide. On addition of hydrogen peroxide the blue colour became deeper with evolution of oxygen. Crystals of phosphomolybdic acid (about 0.1 g.) when dropped into a test-tube containing about 5 ml. of "Merckozone" (Merck's hydrogen peroxide) caused evolution of oxygen.

With the benzidine reagent phosphomolybdic acid alone gave a definite positive reaction. With reduced alkaline phenolphthalein reagent [Johannessen, 1921; Stammers, 1926], however, phosphotungstic acid, silicotungstic acid, sodium tungstate, ammonium phospho-18-tungstate, phosphomolybdic acid, molybdic acid, ammonium molybdate, sodium vanadate in about 0.05 g. amounts all gave positive reactions (red colour).

DISCUSSION.

From the experiments it is evident that phosphotungstic acid, phosphomolybdic acid and many allied substances have definite effects on metabolism when administered internally in sufficient amounts. Vanadates also appear to have similar effects. When compared with insulin the hypoglycaemia given by these substances apparently runs a more prolonged course. These substances also act like oxidizing enzymes and the association of oxidizing action with hypoglycaemic action in the same substance suggests that the hypoglycaemia is perhaps due to oxidation of sugar in the tissues. Some of the substances were found to have diuretic actions also. These substances (vanadates excepted) were not found to have any toxic effect in the doses administered.

SUMMARY.

1. Phosphotungstic acid, phosphomolybdic acid and many allied substances (also vanadates) cause hypoglycaemia when administered by mouth in proper amounts (about 0.3 g. in rabbits).

2. These substances also act like oxidizing enzymes.

3. Some of these substances (e.g. phosphotungstic acid) have diuretic actions as well.

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