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Excretion of Insulin by Normal and Pathologic Rabbit Kidney.

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Recently, Jourdonais and one of us¹ demonstrated the presence of insulin in the blood stream for 60 to 90 minutes after the intravenous injection of massive doses of insulin in rabbits. After that period, insulin was not detected in the blood by the procedures used. To determine the fate of at least part of the injected insulin, the present experiments on the renal excretion of this hormone were planned. Moreover, since insulin is readily adsorbed to proteins, we endeavored to determine whether insulin is lost in greater amounts through the pathologic kidney exhibiting proteinuria than through the normal kidney. These preliminary studies will indicate our results to date.

Three rabbits received 200 units of insulin* intravenously and one the same amount subcutaneously. Urine specimens (by catheter) were collected before and at regular intervals after the injection of insulin for the next 5 or 6 hours. The bladder was washed with 2 or 3 cc of water after the collection of each urine specimen. Gentle abdominal massage over the bladder area was then employed to insure complete emptying of the bladder. All urines, including the controls, were preserved by the addition of 2 or 3 drops of 1/1000 solution of merthiolate (Lilly). Thirty urine specimens, including 6 controls, were obtained from these 4 rabbits, each of which was injected intravenously into a fasting test rabbit, in most instances within 48 hours of its collection.

Proteinuria was induced in 3 rabbits by the subcutaneous injection of 2 mg per kg of uranium nitrate. The same experimental procedure as outlined above was carried out on the pathologic rabbits. Eighteen urines, including 3 controls, were obtained from these animals; these were injected intravenously into fasting test rabbits.

Table I represents one of the 4 experiments carried out on the excretion of insulin by the normal rabbit kidney, and Table II one

¹ Jourdonais, L. F., and Bruger, M., unpublished results.

* 10 mg of insulin powder assaying about 20 units per mg dissolved in 5 cc of physiological saline. We are indebted to the Eli Lilly Company for a generous supply of this insulin.

TABLE I.
Adult White Rabbit, Male, Fasting 24 Hours, Urethral Catheterization. 250 cc Water by Stomach Tube Evening Before Experiment.

Time	Specimen	Vol. of urine cc	Blood Sugar of expt rabbit mg%	Blood sugar of test rabbits after urine injection				Max. decrease of blood sugar after urine injection mg	Remarks
				Control mg%	1/4 hr mg%	1 hr mg%	2 hr mg%		
9:30-10:00	Control urine 1	7.6		101	93	102	97	8	
10:00-10:30	" " 2	6.6		118	123	125	111	7	
11:00	Control blood		150						
11:00-11:30	Expt urine 1	7.0		115	57	37	47	78	200 units of insulin intravenously at 11:05
11:20	Blood (15 min after insulin)		167						Convulsions in test rabbit
11:35	" (30 min)		152						
11:30-12:00	Expt urine 2	5.7		94	74	79	60	34	Trace of blood in urine
12:05	Blood (1 hr)		81						
12:35	" (1 1/2 hr)		82						
1:05	" (2 hr)		67						
1:00-1:30	Expt urine 3	6.4		104	75	71	75	33	+++ to ++++ blood in urine in this and in subsequent specimens
2:05	Blood (3 hr)		63						
2:00-2:30	Expt urine 4	9.2		96	80	96	103	16	
3:05	Blood (4 hr)		47						
3:00-3:30	Expt urine 5	4.8		96	112	100	116	0	
4:05	Blood (5 hr)		52						
4:00-4:30	Expt urine 6	5.6		115	109	111	127	6	
5:05	Blood (6 hr)		44						Rabbit died at 6:15 p.m.

TABLE II.
 Adult White Rabbit, Male, 2.5 kg Weight, 5 mg Uranium Nitrate Subcutaneously 48 hr Before Experiment. 200 cc Water by Stomach Tube 30 min Before Experiment.

Time	Specimen	Vol. of urine cc	Sugar of expt rabbit mg%	Blood sugar of test rabbits after urine injection				Max. decrease of blood sugar after urine injection mg	Remarks
				Control mg%	1/2 hr mg%	1 hr mg%	2 hr mg%		
11:15	Control urine	3.0		100	103	114	120	0	Contains 0.436 g of protein per 100 cc of urine
11:15	" blood		140						
11:20-11:50	Expt urine 1	5.5		107	50	29	55	78	200 units of insulin intravenously at 11:20
11:50	Blood (30 min after insulin)		165						
11:50-12:20	Expt urine 2	4.7		103	64	44	64	59	Convulsions in test rabbit
12:20	Blood (1 hr)		119						
12:20-1:20	Expt urine 3	5.0		99	58	54	57	45	Blood macroscopic in all urines except control
1:20	Blood (2 hr)		77						
1:20-2:20	Expt urine 4	4.0		94	110	104	120	0	
2:20	Blood (3 hr)		61						
2:20-3:30	Expt urine 5	7.0		104	114	116	125	0	Rabbit found dead in cage the following morning
3:20	Blood (4 hr)		64						

of the 3 experiments on the excretion of insulin by the rabbit kidney rendered pathologic with uranium nitrate. These protocols show (1) insulin is not a constituent of the urine of normal rabbits or of the urine excreted by the rabbit kidney rendered pathologic with uranium nitrate, at least in the quantities employed. (2) Following the intravenous administration of insulin, insulin or an insulin-like substance† is excreted readily by the rabbit kidney. The greatest concentration of insulin in the urine occurs directly after its administration, the rate of excretion tapering off until 3 to 3½ hours later when insulin no longer could be detected in the urine. (3) After the intravenous administration of insulin, this hormone is not excreted in greater amounts by the pathologic kidney than by the normal rabbit kidney.‡

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Influence of Thyroid Hormone on Estrin Action.

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The interference of hyperthyroidism with the response of castrate female rats to estrogenic hormones was first reported by Reiss and Perény.¹ These authors came to the conclusion that there is

† Although no definite proof can be offered to substantiate the claim that this insulin-like substance is insulin, the following will be of interest. 148 cc of urine was obtained from 1 rabbit within a period of 4 hours after the intravenous injection of 200 units of insulin. A modified Dudley's procedure (picric acid precipitation) was then employed for the precipitation of insulin from this urine. The final precipitate thus obtained, though very small in quantity, was dissolved in distilled water and the solution injected subcutaneously into a fasting rabbit. In 2 hours, the blood sugar decreased from 132 mg to 66 mg %. Evidently, this hypoglycemic principle present in rabbit urine after the administration of insulin, either is insulin or a substance having identical properties.

‡ Since blood was present frequently in the urines collected after the injection of insulin (due to trauma or to a nephrotoxic action of the insulin protein), it is possible that the insulin detected in the urine was not eliminated by the kidney but represents contamination with blood containing insulin. For this reason, the amount of blood present in the urine was quantitated chemically during those times when this blood was known to contain insulin; values of 1 part of blood in 2000 parts of urine to 1 in 5000 were obtained. Obviously, the quantity of blood present in the urine could not have accounted for its content of insulin.

¹ Reiss, M., and Perény, S., *Endokrinologie*, 1928, **2**, 181.