4. Repeated oral administration of carbon tetrachloride prior to the subcutaneous injection of mercury bichloride in 3 dogs prevented the hyperlipemia in 2 of the animals.

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Hyperglycemia Induced by Certain Insulin Preparations.*

NORMAN S. OLSEN† AND J. RAYMOND KLEIN.

From the Department of Psychiatry, University of Illinois College of Medicine, Illinois Neuropsychiatric Institute, Chicago.

In an attempt to demonstrate electroencephalographic changes characteristic of hypoglycemia, a preparation of insulin was injected intravenously into a paralyzed, artificially respirated cat at 30-minute intervals, the initial dose being one unit per kg body weight and each subsequent dose twice that of the preceding one. Four hours after the initial dose, no change in the electroencephalogram was evident. In similar experiments a transitory increase in blood glucose concentration usually followed each injection of insulin and hypoglycemia did not develop.

Since the cats used in the experiments considered above were paralyzed with dihydro-β-erythroidine hydrobromide and the blood glucose levels were high, the effect of intravenous injection of insulin preparations on the concentration of blood glucose was tested in anesthetized (amytal) and intact cats. Representative data are given in Tables I and II. In addition to the experiments summarized in the tables, others were carried out in which different times of collection of blood were used, no injection was made, other preparations of amorphous insulin were used, arterial blood was assayed, doses of insulin intermediate to and greater than those indicated were employed, and in which insulin was given subcutaneously and intramuscularly. The effect of intravenous injection of insulin during hypoglycemia, induced by insulin, and hyperglycemia, induced by administration of glucose, was also tested.

The results of the experiments may be summarized as follows. Intravenous injection of water or salt solution in volumes comparable to the volumes of insulin used provoked no marked change, or certainly no consistent change, in blood glucose level. With intravenous injection of all preparations of insulin tested (except NOVO) the blood glucose concentration increased, the maximum occurring 5-10 minutes after injection. The glucose concentration returned to the control level 20-30 minutes after injection at which time hypoglycemia began to develop. The increase in glucose concentration was evident with 0.1 unit of insulin per kg body weight and marked with one unit. The hyperglycemic effect seemed to be somewhat more pronounced in the anesthetized than in the intact or paralyzed cat.

The effect was apparently independent of the blood glucose level, *e.g.* intravenous injection of 2 units of a preparation of crystalline zinc insulin per kg when, after intramuscular administration of insulin, the blood glucose level was gradually falling and had reached 18 mg per 100 ml, was followed by an increase in glucose level to 82 mg per 100 ml and disappearance of electroencephalographic changes characteristic of hypoglycemia; likewise, intravenous injection of insulin, at high blood glucose levels, induced by administration of glucose, was followed by increases in glucose level. With subcutaneous and intramuscular administration of the several preparations of insulin no increase in blood glucose level occurred.

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† Present address: Department of Biological Chemistry, Washington University, St. Louis, Mo.

TABLE I.

Effect of Intravenous Injection of Insulin on Blood Glucose Concentration of Intact Cats. The cats were fasted about 24 hr. Just after collection of a control blood sample from a femoral vein, the material indicated was injected. Additional blood samples were obtained 5, 10, 20, and 40 minutes after the injection. Glucose was estimated by the method of Nelson.[2]

Substance injected	Dose, ml or units per kg bodywt	Blood glucose, mg per 100 ml				
		Control	5 min.	10 min.	20 min.	40 min.
Water	0.1	84	86	78	80	85
	0.3	79	82	84	78	79
	1.0	91	97	94	94	92
0.156 *M* NaCl	0.1	83	82	87	82	87
	0.2	85	84	86	79	80
	1.0	90	92	87	91	90
Crystalline zinc insulin, Lilly	0.1	67	70	70	41	24
	2.0	54	72	86	51	30
" " " Sharp & Dohme	0.1	70	81	76	64	55
	2.0	65	80	57	42	31
" " " Squibb	0.1	72	82	78	59	42
	2.0	61	83	81	56	38
Amorphous insulin, Squibb	0.1	71	89	86	54	43
	2.0	67	93	83	42	32
Crystalline zinc insulin,* Lilly, pH 7	0.1	65	70	71	63	52
pH 7	2.0	81	94	89	76	47
pH 11	2.0	103	135	119	106	75
pH 3	2.0	71	112	101	83	62
NOVO insulin	0.1	75	70	64	57	40
	1.0	78	70	61	52	24
	2.0	80	78	64	48	28

* Solid material dissolved in 0.01 *M* HCl followed by sufficient 0.01 *M* NaOH to give pH indicated.

Transitory hyperglycemia was a common occurrence following administration of earlier preparations of amorphous insulin, but with the advent of crystalline insulin it appeared that the hyperglycemic effect was due to impurities in the amorphous material.[3,4] Dr. R. Levine, with whom the findings considered above were discussed, pointed out that Duve[5] recently stated that intravenous injection of one insulin preparation (Lilly) had a hyperglycemic effect and that another (NOVO) did not. Thus, test of the latter preparation was made in anesthetized and intact cats. As indicated by the data in the tables and other experiments, injection of NOVO insulin in doses up to 10 units per kg body weight was followed only by a decrease in glucose level.

Test for hyperglycemic response in species other than the cat was not made in the present work. However, it has been stated that in the dog constant intravenous injection of certain insulin preparations has a hyperglycemic effect,[6] and that in man the fall of blood glucose level begins more rapidly following intravenous injection of NOVO insulin than with other preparations.[7] Further, the glycogenolytic effect of some insulin

[1] Olsen, N. S., and Klein, J. R., *Fed. Proc.*, 1947, **6**, 282.

[2] Nelson, N., *J. Biol. Chem.*, 1944, **153**, 375.

[3] Geiling, E. M. K., and DeLawder, A. M., *J. Pharm. Exp. Therap.*, 1930, **39**, 369.

[4] Burger, M., and Kramer, H., *Arch. exp. Path. Pharmakol.*, 1930, **156**, 1.

[5] Duve, C. de, *Glucose, Insuline et Diabète*, pp. XXVII, 307, Masson et Cie, Paris, 1945.

[6] Levine, R., and Caren, R., *Am. J. Physiol.*, in press.

[7] McCulloch, W. S., unpublished data obtained in this laboratory.

TABLE II.

Effect of Intravenous Injection of Insulin on Blood Glucose Concentration of Anesthetized Cats.

The cats were anesthetized by subcutaneous injection of 0.07 g sodium amytal per kg body weight. The other experimental details were the same as indicated in Table I.

Substance inj.	Dose. ml or units per kg body wt	Blood glucose, mg per 100 ml				
		Control	5 min.	10 min.	20 min.	40 min.
Water	0.1	53	51	56	57	66
	0.3	95	85	86	96	93
	1.0	89	95	95	80	83
0.156 *M* NaCl	0.1	58	62	55	58	45
	0.2	61	63	50	77	56
	1.0	60	58	62	59	60
Crystalline zinc insulin, Lilly	0.1	74	90	81	62	50
	2.0	82	138	137	86	48
" " " Sharp & Dohme	0.1	61	78	62	50	37
	2.0	73	121	130	102	87
" " " Squibb	0.1	63	91	86	51	39
	2.0	72	115	122	115	72
Amorphous insulin, Squibb	0.1	59	73	56	40	24
	0.2	63	101	71	59	42
Crystalline zinc insulin, Lilly, pH 7	0.1	71	84	79	66	52
pH 7	2.0	93	120	109	97	63
pH 11	2.0	78	104	84	88	52
pH 3	2.0	66	98	110	95	66
NOVO insulin	0.1	66	64	66	54	23
	1.0	70	65	48	35	19
	2.0	68	66	69	56	43

preparations on rat and rabbit liver *in vitro* is not obtained with NOVO insulin.[8]

The cause of the increase in blood glucose following intravenous injection of certain preparations of insulin is not known at present and for many purposes, *e.g.* the therapeutic, it is of no importance. However, in experiments concerned with the effect of these preparations of insulin on metabolism *in vitro* or in carbohydrate balance studies following intravenous injection of insulin, the hyperglycemic effect should obviously be considered.

[8] Sutherland, E. W., and Cori, C. F., *Fed. Proc.*, 1947, **6**, 297. The observation cited was given in the amplified, verbal report.

Summary. Intravenous injection into cats of certain preparations of amorphous and crystalline insulin was found to provoke a transitory increase in blood glucose level. With one preparation, NOVO, no increase in glucose level occurred.

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