Effect of D-glucose or D-ribose on the Turnover of Glucose in Pancreatectomized Dogs Maintained on a Matched Intraportal Infusion of Insulin

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SUMMARY

It was found previously that in normal dogs D-glucose or D-(-)-ribose decrease the rate of endogenous (hepatic) glucose production. To investigate whether this effect is due to the release of extra insulin only, or to other factors as well, the following experiments were performed: Endogenous insulin secretion was replaced by intraportal porcine or canine insulin infusion of 200 μU./kg./min. in conscious dogs. Such an insulin infusion commenced at time of removal of the remnant pancreatic autograft was able to maintain unchanged the plasma glucose level and the tracer determined glucose production and utilization. Three main conclusions emerged from this study: (1) Since an infusion of D-(-)-ribose did not affect concentration and turnover rates of glucose, it was concluded that ribose affects glucose metabolism only through an increase of the rate of insulin secretion. (2) The endogenous glucose production did not decrease in response to a glucose infusion at two thirds to twice the basal normal glucose production, even when the concentration of glucose in plasma exceeded 200 mg./100 ml. It is concluded that the release of extra insulin is indispensable for the regulation of glucose production in the normal dog. (3) The utilization of glucose rose in proportion to its concentration in the plasma in the absence of any change in the rate of insulin supply. DIABETES *18*:820-27, December, 1969.

The intravenous injection or infusion of D-ribose has been shown to decrease the concentration of glucose in the blood plasma of normal animals[1,2] and humans,[3] but not in pancreatectomized dogs[1] or diabetic patients.[4] This finding has been interpreted as an effect of ribose on the rate of release of insulin from the beta cells of the islets of Langerhans. This interpretation has been corroborated by the results of the experiments of Steinberg et al.[5] who found an increase in the plasma insulin level during the infusion of ribose in dogs, and also by the demonstration of an effect of ribose on isolated beta cells in vitro by Montague et al.[6] Whereas there is little doubt that ribose indeed releases insulin from the pancreas in the intact animal, a discrepancy between the apparent amount of the insulin released and the extent and duration of the ensuing hypoglycemia has been noticed.[3,5] Although the effects of ribose on the time course of the changes in rates of endogenous glucose production and over-all glucose utilization have been successfully simulated by an intraportal infusion of canine insulin in dogs,[1] considerable doubt remained about the existence of a second effect of ribose interfering with the compensatory increase of (hepatic) glucose production during hypoglycemia.

The aim of the experiments to be described was to investigate the effect of the infusion of ribose on the plasma concentration and the turnover of glucose in dogs in which the pancreas has been replaced by an infusion of insulin into the portal vein at a matched physiological rate.[7] If ribose has the same effects in this preparation as in normal dogs, this proves the existence of a mechanism dependent on the presence of physiological amounts of insulin but not upon the release of extra insulin. If, on the other hand, ribose has no effects, (as it has no effect in diabetic animals), its entire effect could be accounted for by the release of extra insulin. If such be the case, the reported[3,5] discrepancy between the rate of insulin secretion and hypoglycemic activity has to be due to differences between the effects of endogenous insulin secreted into the portal

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vein and of heterologous insulins injected by other routes.

Since the injection or infusion of glucose has been reported to decrease endogenous (hepatic) glucose production in both normal[8,9] and pancreatectomized[9] dogs, the effect of an intravenous infusion of glucose has also been investigated on all dogs on which the effect of ribose has been tested. In two additional experiments it has been attempted to obtain more detailed information about the effect of glucose; in this way we expected to obtain an answer to the question of whether glucose infused intravenously at relatively moderate rates is able to decrease the rate of hepatic glucose production without the release of extra insulin.

METHODS

Animal and surgical procedures

All experiments were carried out on nonanesthetized dogs trained to stand or lie quietly in a Pavlov stand during the experiment. Partial pancreatectomy and the exteriorization of the uncinate process of the pancreas into a subcutaneous pouch was carried out under general anesthesia six days prior to the experiment as described by Rappaport et al.[10] At the same time a vinyl catheter filled with heparin was inserted into a tributary of the splenic vein pointing towards the portal vein. The postoperative care and diet of the operated dogs has been described previously.[7] On the day of the experiment three more plastic catheters were inserted under local (procain) anesthesia, two of these into each one of the cephalic veins for the infusion of the tracer and the sugars respectively, the third introduced into the vena cava (with the tip below the entry of the hepatic veins) via the saphenous vein. This catheter was used for the collection of blood samples.

After the insertion of the catheters the uncinate process was removed under local anesthesia and an infusion of insulin* at the approximate rate of 200 μU./kg./min. into the portal circulation was started immediately.[7]

Porcine insulin was used in the first six, and canine in the additional two experiments. The animal was then transferred into the Pavlov stand and the experiment started after a sixty-minute period of equilibration.

Experimental design

All but the two experiments to be described subsequently strictly followed the same design. They consisted of four sequential periods of ninety, seventy, eighty and sixty minutes, in this order. During the first and third period 0.9 per cent NaCl was infused, during the second and fourth the infusion was changed to ribose (3 mg./kg./min.) or glucose (1.8 mg./kg./min.). In the first three experiments ribose was infused in the second, and glucose in the fourth periods. In the fourth, fifth and sixth experiment this sequence was reversed. Minor adjustments in the rate of the infusion of insulin were carried out early in the first period if the blood sugar level, estimated by a Dextrostix (Ames) test, warranted it. All infusions were given at a constant rate with help of Harvard or Sage infusors.

In two experiments 0.9 per cent saline was infused during the first and fourth periods and glucose in the second and third. (In these experiments both middle periods lasted eighty minutes. The rate of glucose infusion was 1.9 and 2.6 mg./kg./min. respectively in the second periods and was doubled in the third periods in both experiments.

Tracer methods and calculations

Rates of endogenous (hepatic) glucose production ("rate of appearance" R_a) and utilization ("rate of disappearance" R_d) were calculated by the method of primed infusion of tracer according to Wall et al.[11] as simplified by de Bodo et al.[12] Metabolic clearance of glucose was calculated as the ratio of R_d and the concentration of plasma glucose.[1] The time of the priming injection of tracer was taken as $t = 0$. R_a, R_d and metabolic clearance values were not calculated prior to $t =$ fifty minutes. All calculations were carried out on a CGE time sharing computer system. When the effect of glucose was tested on the rates of production and utilization, a mixture of C-14-labeled and ordinary C-12 glucose of a specific activity (SA) close to the one of plasma glucose was infused in order to avoid artefacts arising from the slow mixing of the glucose load with the labeled glucose pool in the body.[8] The calculated R_a was corrected for differences between the SA's of plasma and infused glucose.

In the additional two experiments the use of glucose-1-C-14 as tracer permitted the correction of the calculated rates of appearance and disappearance and also the metabolic clearance for the small inaccuracies arising from the incorporation of C-14 into the newly released glucose from the metabolized molecules of the infused tracer.

Processing of blood samples

The collection and processing of blood samples have been described.[1,9] The heparin solution was withdrawn

*The solution infused was 40 mU./ml. insulin and 5 mg./ml. of gelatin (Upjohn Co., Kalamazoo) in an acid-saline solution of pH 3.9-4.0. Thus the binding of insulin to glassware and tubing was prevented.

from the portal cannula prior to the experiment. A solution of heparin (5 I.U./ml.) was used only during the first forty-five minutes of the experiment to keep the sampling catheter patent. During later stages this catheter was filled with saline.

The isolation of glucose with help of an ion exchange resin (IRA-410, Rohm and Haas) and determination of glucose (Huggett and Nixon[13]), as well as the counting procedures, have been described.[1] In the additional two experiments the incorporation of C-14 into the sixth carbon atom was determined and the proper correction for recirculation of C-14 into newly formed glucose was carried out as described by Reichard et al.[14] Free fatty acid (FFA) in plasma was measured according to Dole and Meinertz[15] and the concentration of ribose according to Roe and Rice.[16]

MATERIALS

Glucose labeled uniformly with C-14 was used as tracer in the first six experiments, and glucose-1-C-14 in the additional two. The tracers were obtained from the Radiochemical Center, Amersham,England. D-(-)-ribose and D-glucose (Analar grade) were obtained from Eastman Organic Chemicals and from the British Drug Houses, respectively.

RESULTS

The plasma concentration and the rates of production and utilization of glucose

The results of the first six experiments are summarized in tables 1 and 2 showing the effects of an infusion of D-ribose (3 mg./kg./min.) and D-glucose (1.8 mg./kg./min.) on the plasma concentration and on the rates of production (R_a), over-all utilization (R_d) and the metabolic clearance (M) of glucose. It appears that in dogs maintained in (or near) a dynamic steady state by a constant supply of intraportally infused insulin, the plasma concentration and the rate of production of glucose was increased marginally by the intravenous infusion of D-ribose. In the experiments shown in table 2 the infusion of glucose during the second period increased glucose concentration at an average rate of 0.21 mg./100 ml./min. This was changed to an average decrease of 0.41 mg./100 ml./min. in the third period during which saline was infused. In the experiments shown in table 1 the average increase in concentration was 0.47 mg./100 ml./min. during the final period of glucose infusion.

When the data were tested by variance analysis, no evidence was found that infusion of ribose exerted any effect on the rate of glucose production (R_a). In this analysis the rates before and during the infusion of glucose were compared: "before" referring to the rates calculated between the 180th to 240th minutes of the experiment in table 1, and the fiftieth to ninetieth in table 2. The results of the analysis are summarized in table 3. Neither did the differences in the rates of utilization prove to be of statistical significance when subjected to a similar analysis.

The results of one of the two additional experiments carried out with glucose-1-C-14 as tracer and yielding rates of production and utilization of glucose unaffected by the reincorporation of C-14 into endogenously produced glucose are shown in figure 1. The concentration of glucose in the plasma has been increased at a rate of 0.63 and 1.06 mg./100 ml./min. during the infusion of 1.9 and 2.6 mg./kg./min. glucose respectively. No effect on the rate of appearance of glucose has been observed. The increase in the rate of disappearance in the two middle periods is not entirely commensurable with the increase of the plasma glucose level as indicated by the somewhat increased metabolic clearance. The fall in the latter during the final period of saline infusion is noteworthy.

Plasma concentration of free fatty acids

As shown in table 4, the level of FFA in plasma tended to rise during the experiments of the first series. This is most evident if one compares the average levels of FFA of the first and third periods, during both of which saline was infused. Ribose did not interfere with this pattern, whereas during three of the six infusions of glucose plasma FFA was decreased (Dogs 30, 33, 34). A similar decrease was noticeable in the two additional experiments (see figure 1), in both of which the plasma FFA concentration increased during the final infusion of saline. This effect, however, was not consistent in view of the three negative experiments of the first series. A more consistent decrease of about 30 per cent in the concentration of FFA in plasma has been found by Vranic et al.[17] after the injection of 0.5 gm./kg. glucose in dogs maintained on matched infusion of insulin exactly similar to our experiments.

Plasma concentration of ribose

During the infusion of ribose the concentration of the pentose reached a value between 9.4 and 14.0 mg./100 ml. Maximal levels have been closely approximated by forty minutes after the beginning of the infusion. After the cessation of the infusion, ribose was cleared from the plasma within twenty minutes.

DISCUSSION

In previous experiments, Vranic and Wrenshall[7]

TABLE 1

Effect of the intravenous infusion of D-ribose or D-glucose on plasma glucose concentration and glucose utilization and the production and the metabolic clearance of glucose

Infusion:	Saline				Ribose 3 mg./kg./min.					
Time (min.)	35-50	50-65	65-80	80-90	90-100	100-110	110-125	125-140	140-150	150-160
Expt. #										
				Plasma glucose concentration mg./100 ml.						
28	225	235	227	229	213	217	212	239	256	254
30	111	106	106	100	99	96	95	99	99	103
32	119	111	115	112	107	106	116	112	110	119
Mean		151	149	147	140	140	141	150	155	159
				R_d (glucose utilization) mg./kg./min.						
28	4.22	4.34	4.07	3.88	5.12	2.90	4.27	3.50	4.90	5.40
30	2.96	2.95	3.04	2.59	2.13	3.27	3.05	2.14	3.32	2.40
32	3.23	3.60	2.58	3.15	3.68	3.60	2.22	3.46	3.72	2.11
Mean		3.60	3.23	3.21	3.64	3.26	3.18	3.03	3.98	3.30
				R_a (glucose production) mg./kg./min.						
28	5.31	5.00	3.53	4.05	3.51	3.33	3.95	5.32	6.63	5.19
30	2.38	2.36	3.07	1.58	1.95	2.87	2.93	2.51	3.42	2.98
32	2.94	2.91	2.96	2.63	3.11	3.36	3.12	3.15	3.41	3.43
Mean		3.42	3.19	2.75	2.86	3.19	3.33	3.66	4.49	3.87
				Metabolic clearance of glucose ml./kg./min.						
28		2.01	1.76	1.70	2.31	1.34	1.98	1.55	1.97	2.11
30	2.61	2.72	2.87	2.52	2.15	3.35	3.18	2.20	3.35	2.37
32	2.68	3.13	2.28	2.77	3.37	3.38	2.01	3.04	3.36	1.84
Mean		2.62	2.30	2.33	2.61	2.69	2.39	2.26	2.89	2.11

Infusion:	Saline						D-glucose 1.8 mg./kg./min.			
Time (min.)	160-170	170-180	180-195	195-210	210-225	225-240	240-250	250-265	265-280	280-300
Expt. #										
					Plasma glucose concentration mg./100 ml.					
28	260	260	283	284	286	258	279	279	281	292
30	96	102	92	89	84	86	90	90	103	105
32	118	121	116	110	116	117	119	124	133	142
Mean	158	161	164	161	162	154	163	164	172	180
					R_d (glucose utilization) mg./kg./min.					
28	3.80	5.56	8.93	2.04	7.14	5.88	8.01	7.81	5.86	5.59
30	4.77	2.80	4.45	2.47	3.56	2.27	3.00	3.90	1.89	3.44
32	3.03	2.01	3.20	3.18	2.23	2.17	4.05	3.81	2.87	3.36
Mean	3.87	3.46	5.52	2.56	3.23	3.44	5.02	5.17	3.54	4.13
					R_a (glucose production) mg./kg./min.					
28	4.39	5.52	6.82	5.80	7.26	4.00	8.35	5.95	4.17	4.32
30	3.81	3.83	3.38	2.13	2.94	2.57	1.74	2.09	1.53	1.73
32	2.87	2.38	2.71	2.68	2.74	2.30	2.59	2.43	1.88	2.15
Mean	3.69	3.91	4.30	3.54	4.31	2.96	4.22	3.49	2.53	2.73
					Metabolic clearance of glucose ml./kg./min.					
28	1.47	2.13	3.64	0.79	2.49	2.15	2.97	2.78	2.08	1.98
30	4.79	2.82	4.58	2.73	4.11	2.67	3.41	4.35	1.95	3.31
32	2.25	1.68	2.71	2.82	1.97	1.91	3.44	3.13	2.24	2.45
Mean	2.84	2.21	3.64	2.11	2.86	2.24	3.27	3.42	2.09	2.58

TABLE 2

Effect of intravenous infusion of D-glucose or D-ribose on plasma glucose concentration and glucose utilization and production and the metabolic clearance of glucose

Infusion:	Saline				D-glucose 1.8 mg./kg./min.					
Time (min.)	35-50	50-65	65-80	80-90	90-100	100-110	110-125	125-140	140-150	150-160
Expt. #										
				Plasma glucose concentration mg./100 ml.						
33	103	92	77	81	80	86	87	86	80	86
34	93	96	85	85	88	97	101	100	108	111
35	89	82	88	77	77	79	79	86	89	95
Mean	95	90	83	81	82	87	89	91	92	97
				R_d (glucose utilization) mg./kg./min.						
33	3.47	3.08	4.40	1.92	3.06	2.28	3.92	3.22	5.06	1.53
34	4.06	2.54	3.73	2.66	3.06	3.43	3.67	4.06	3.32	2.68
35		2.70	3.82	2.53	5.61	4.18	4.21	5.07	3.32	4.81
Mean		2.77	3.98	2.37	3.91	3.30	3.93	4.11	3.90	3.01
				R_a (glucose production) mg./kg./min.						
33	3.59	1.53	2.36	2.67	1.10	1.72	2.15	1.26	2.07	0.91
34	2.47	2.90	2.24	2.75	1.67	3.49	2.52	2.10	3.02	2.06
35		3.28	2.77	2.52	3.76	2.06	2.68	3.07	2.09	2.58
Mean		2.57	2.46	2.65	2.18	2.42	2.45	2.14	2.39	1.85
				Metabolic clearance of glucose ml./kg./min.						
33	3.37	3.15	5.20	2.43	3.81	2.74	4.54	3.74	6.10	1.84
34	4.11	2.69	4.13	3.13	3.54	3.73	3.71	4.03	3.19	2.46
35		3.17	4.63	3.29	7.31	5.31	5.35	5.89	3.75	5.04
Mean		3.00	4.65	2.95	4.89	3.93	4.53	4.55	4.35	3.11

Infusion:	Saline						D-ribose 3 mg./kg./min.			
Time (min.)	160-170	170-180	180-195	195-210	210-225	225-240	240-250	250-265	265-280	280-300
Expt. #										
					Plasma glucose concentration mg./100 ml.					
33	76	74	64	57	51	50	51	56	57	58
34	97	98	87	76	75	68	66	72	70	70
35	96	92	87	80	85	70	72	68	72	72
Mean	90	88	79	71	70	63	63	65	66	67
					R_d (glucose utilization) mg./kg./min.					
33	3.93	2.23	3.38	2.77	2.50	2.08	1.91	1.86	2.56	2.37
34	4.65	3.20	3.32	3.39	2.88	2.90	2.53	2.15	3.19	3.16
35	3.90	2.84	3.56	2.23	3.95	2.52	3.75	2.92	3.43	3.76
Mean	4.16	2.76	3.42	2.80	3.11	2.50	2.73	2.31	3.06	3.10
					R_a (glucose production) mg./kg./min.					
33	1.95	1.75	1.99	1.94	1.65	1.96	2.14	2.42	2.74	2.45
34	1.80	3.31	1.77	1.94	2.62	2.02	2.04	2.94	2.91	3.20
35	3.33	2.24	2.85	2.72	2.50	2.74	3.13	2.92	3.43	3.76
Mean	2.36	2.43	2.21	2.20	2.26	2.24	2.44	2.76	3.03	3.14
					Metabolic clearance of glucose ml./kg./min.					
33	4.85	2.98	4.92	4.57	4.59	4.10	3.76	3.48	4.56	4.13
34	4.46	3.28	3.59	4.16	3.82	4.06	3.77	3.13	4.52	4.54
35	4.17	3.17	4.25	2.70	5.08	3.54	5.34	3.71	4.66	4.25
Mean	4.49	3.14	4.25	3.81	4.50	3.90	4.29	3.44	4.58	4.31

TABLE 3

The effect of the infusion of glucose on the rate of endogenous glucose production (R_a). Summary of the analysis of variance of the data shown in tables 1 and 2.

	table 1				table 2			
Source of variation	df	SS	MS	F*	df	SS	MS	F*
Total	23	86.247	—	—	26	12.865	—	—
Between rows (dogs)	2	64.869	32.434	2.12	2	4.988	2.494	6.22
Between columns (times)	7	10.997	—	—	8	1.463	0.183	—
Before vs. during infusion	1	1.707	1.707	1.10	1	0.608	0.608	5.04
Discrepancy	6	9.290	1.5484	—	7	0.855	0.121	—
Error	14	10.381	0.7415	—	16	6.414	0.401	—

*None of the F values shown indicate a statistically significant difference.

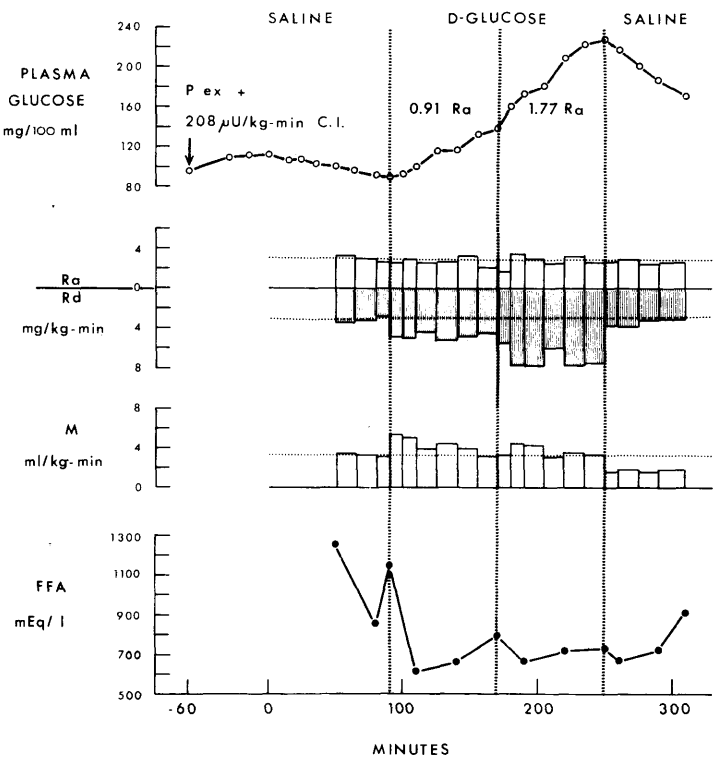

FIG. 1. Effect of an infusion of D-glucose on the concentration of glucose and FAA in the plasma and the calculated rates of appearance and disappearance and metabolic clearance of glucose. Glucose was infused between t = 90 and 170 at a rate of 2.6 mg./kg./min. and between t = 170 and 250 min. at a rate of 5.2 mg./kg./min. These rates correspond to 0.91 and 1.77 times R_a respectively. Abscissa: time in minutes. Uppermost ordinate: concentration of glucose in plasma as mg./100 ml. Second ordinate: rates of appearance R_a (above zero) and rates of disappearance R_d (below zero) of glucose as mg./kg./min. Third ordinate: metabolic clearance (M) of glucose as ml./kg./min. Lowest ordinate: concentration of FFA in plasma as mEq./L.

The intravenous infusions are indicated at the top of the figure. P_{ex} indicates the removal of the pancreatic graft and the beginning of the intraportal infusion of canine insulin (C.I.).

demonstrated that a portal infusion of insulin at a rate of 200 μU./kg./min. matched the endogenous secretion of insulin in the fasted dog. Such an infusion commenced at the time of the removal of the remnant pancreatic autograft was able to maintain the plasma glucose level and the rates of glucose production and utilization at normal levels. This rate of insulin infusion was considered to be "basal." In spite of the normoglycemia and normal turnover of glucose, dogs maintained on a basal infusion of insulin exhibited a lower than normal tolerance (smaller exponential decay constant) to intravenously injected glucose.[17]

From the data of the experiments presented in this paper three conclusions emerge:

(a) *D-ribose* does not decrease either the plasma concentration or the rate of production of glucose in dogs in which glucose homeostasis is maintained at a normal level by a basal infusion of insulin into the portal vein. Thus the hypoglycemic effect of ribose in the normal animal can be accounted for entirely by the release of extra insulin.

(b) *D-glucose,* when infused at a rate of about two thirds to twice the basal normal R_a to dogs in which the pancreas has been replaced by the intraportal infusion of insulin, was also ineffective in altering R_a significantly. This finding corroborates the conclusion of

TABLE 4

Changes in plasma FFA concentration during the infusion of D-glucose (1.8 mg./kg./min.) or D-ribose (3 mg./kg./min.) in normal dogs

Expt.	Infusion: time	Saline 65	90	Ribose 110	160	Saline 180	240	Glucose 250	280	300
28		1,122	1,107	1,076	1,123	—	1,499	1,578	1,280	1,248
30		1,030	999	1,094	1,189	1,030	1,078	919	650	713
32		682	666	1,141	1,094	1,094	999	1,062	1,411	1,411
Mean		945	924	1,104	1,135	1,062	1,192	1,186	1,113	1,124
± S.E.M.		134	133	19	28	—	155	200	235	211

	Infusion: time	Saline 65	90	Glucose 110	150	160	Saline 180	240	250	Ribose 280	300
33		920	780	499	749	764	849	1,264	1,139	952	—
34		655	764	718	640	686	780	976	936	983	976
35		864	769	729	895	1,075	1,035	1,283	1,283	1,140	1,190
Mean		813	771	649	761	841	886	1,174	1,119	1,073	1,083
± S.E.M.		81	5	75	74	118	77	99	101	58	—

Time refers to the injection of the priming dose of the tracer (t = 0) and is in minutes.

Steele et al.[8] who ascribed the effect of an intravenous glucose infusion of about this magnitude on R_a in normal dogs to a release of extra insulin. On the other hand, Hetenyi and Wrenshall[9] have demonstrated that an intravenous infusion of glucose decreased R_a in both normal and pancreatectomized dogs deprived of insulin for forty-eight hours. More recent experiments, however, carried out with more refined technics by Cowan and Hetenyi,[18] demonstrated a marked decrease of a very consistent pattern in R_a after or during the injection or infusion of glucose in normal dogs, but only a small and rather inconsistent one in insulin-deprived diabetic animals.

Thus it appears that in normal dogs the release of extra insulin is essential for an adaptation in endogenous glucose production during an infusion of glucose at a moderate rate. This finding is in agreement with those of Wrenshall et al.[19] who demonstrated that a sudden interruption of the endogenous insulin secretion results in a large increase in hepatic glucose production in spite of a rapidly rising level of plasma glucose, indicating thereby a sudden change in the normal relation between the plasma level and hepatic production of glucose. It is possible that when high glucose levels are being reached and maintained in the diabetic dog, the liver may regain its ability to respond with a decreased rate of production to an elevation of plasma glucose concentration. This could represent a second, not necessarily physiological, mechanism in the adaptation of endogenous production to exogenously injected glucose. It is also possible that the decrease of net glucose release observed on the perfused rat liver[20] in response to a raised glucose level in the perfusing fluid also represents a mechanism different from the physiological, insulin-dependent one that has been demonstrated to operate the fine balance in normal dogs. In this preparation the decrease of the net glucose output might be the result of an increased glucose uptake by the perfused liver, a mechanism entirely different from any change in the actual release of glucose. Tracer methods in general measure this latter one.

(c) The rate of glucose disappearance (R_d) increased with an increased glucose concentration in the absence of any change in insulin secretion (figure 1). The metabolic clearance of glucose was calculated to illustrate this relationship between the concentration and uptake of glucose. A relatively unaltered clearance indicates a linear relationship between the two parameters, i.e., when the concentration of glucose in plasma is doubled, its over-all uptake (R_d) is doubled as well. More detailed studies are being planned to investigate this correlation in the absence of variations in the rate of the secretion of insulin. As shown on figure 1, however, the metabolic clearance is higher at increasing plasma glucose concentration than it is at a decreasing one. This might be due to a nonlinear relationship between the concentration and uptake of glucose or, alternatively, to an artefact inherent in the tracer method used, causing an underestimation of the true size of the glucose pool. Evidently, if the pool size of glucose is underestimated some glucose being distributed into the pool contributes to the calculated "disappearance" during a rising concentration of glucose. Conversely when the concentration of glucose in the plasma is

falling, an underestimated pool size will lead to an underestimation of R_d.

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