JCI The Journal of Clinical Investigation

The Acute Effect of Hydrocortisone on Hepatic Glucose Output and Peripheral Glucose Utilization

Frank R. Lecocq, … , David Mebane, Leonard L. Madison

J Clin Invest. 1964;43(2):237-246. https://doi.org/10.1172/JCI104908.

Research Article

Journal of Clinical Investigation
Vol. 43, No. 2, 1964

The Acute Effect of Hydrocortisone on Hepatic Glucose Output and Peripheral Glucose Utilization *

FRANK R. LECOCQ,† DAVID MEBANE,‡ AND LEONARD L. MADISON

(From the Department of Internal Medicine, The University of Texas, Southwestern Medical School, Dallas, Texas)

There is abundant experimental evidence indicating that adrenal glucocorticoids have a profound effect on carbohydrate metabolism (1–9). Agreement is general that they accelerate hepatic gluconeogenesis and increase liver glycogen stores (5–9), but their action on peripheral glucose utilization is still unsettled (5, 6, 8). Although the effects of the chronic administration of glucocorticoids are well defined and changes in carbohydrate metabolism have been recorded as early as 2 to 4 hours (10–18) after adrenocorticoid administration, the precise time of onset of glucocorticoid-induced alterations in carbohydrate metabolism has not been established. An immediate action on glucose metabolism has not been demonstrated *in vivo;* indeed, recent studies have suggested that the effect of adrenocorticoids on carbohydrate metabolism is delayed for at least 2 hours, beginning at a time when steroid concentrations are decreasing (10, 13, 14). The changes in glucose metabolism occurring in the earliest period after glucocorticoid administration are especially important to define since obscuring secondary effects are less likely to be present.

The purpose of the present study was *1*) to delineate the earliest detectable change in carbohydrate metabolism after acute glucocorticoid administration, *2*) to characterize the early effects of glucocorticoids on hepatic glucose output, and *3*) to determine whether glucocorticoids alter peripheral glucose utilization. Changes in hepatic glucose output and peripheral glucose utilization were followed during the initial 90 to 120 minutes after the intravenous injection of cortisol in dogs with chronic end-to-side portacaval shunts. This preparation was chosen because it separates the liver from the extrahepatic splanchnic circulation and therefore permits measurement of hepatic rather than splanchnic glucose balance. From the changes in hepatic glucose output and arterial glucose concentration, changes in peripheral glucose utilization can be calculated (19).

Methods

Thirteen studies were done on dogs with complete end-to-side portacaval shunts. At least 1 month was allowed for complete recovery from the operative procedure before experiments were performed. Stable weights were maintained in these animals by a diet, supplemented with vitamins, containing 50% of the total calories as carbohydrate, 20 to 30% as protein, and the remainder as fat. Studies were performed after a 15-hour, overnight fast with Nembutal anesthesia (25 mg per kg). Hepatic venous samples were collected through a cardiac catheter inserted deep into the hepatic vein under fluoroscopic control. Femoral arterial blood specimens were obtained through an indwelling Cournand needle.

In all 13 experiments hepatic glucose output was determined at 10-minute intervals for two to four control periods and then at 10- or 15-minute intervals during the 60- to 150-minute period of hydrocortisone infusion. Hydrocortisone was administered intravenously both as hemisuccinate and phosphate in normal saline. An average priming dose of 33 mg of hydrocortisone (range, 0 to 50) was given and then infused at the rate of approximately 1.3 mg per minute for the remainder of the

* Submitted for publication July 12, 1963; accepted October 17, 1963.

This work was supported in part by a U. S. Public Health Service grant (A-4236) from the National Institute of Arthritis and Metabolic Diseases, Bethesda, Md., and by grants from the Upjohn Co., Kalamazoo, Mich., and Chas. Pfizer & Co., New York, N. Y.

A preliminary report of this work has been published in abstract form (The paradoxical effect of hydrocortisone on hepatic glucose output. Clin. Res. 1961, **9**, 29).

† Work done during tenure of U. S. Air Force postdoctoral fellowship. Present address: Department of Medicine, Endocrine-Renal Section, Wilford Hall, U. S. Air Force Hospital, Lackland Air Force Base, San Antonio, Texas.

‡ Work done during tenure of U. S. Public Health Service postdoctoral fellowship (APD-17,224) of the National Institute of Arthritis and Metabolic Diseases. Present address: Department of Surgery, The University of Texas, Southwestern Medical School, Dallas, Texas.

TABLE I

*Effect of hydrocortisone on hepatic glucose output**

Dog no.	Weight		Control values −30	−20	−10	0	Mean control	Time in minutes during hydrocortisone infusion 10	20	30	40	50	60	70	80	90	100	110	120
	kg																		
1011	26.8	EHBF	164	169	174	141	162	163	164	163	158	147	137						
		HV	116.4	113.2	110.3	106.6	111.6	107.1	100.8	94.4	91.9	86.0	84.0						
		A	87.4	83.9	80.5	81.5	83.3	84.5	85.7	83.9	81.5	80.2	78.0						
		HV-A	29.0	29.3	29.8	25.1	28.3	22.6	15.1	10.5	10.4	5.8	6.0						
		HGO	47.6	49.5	51.9	35.4	46.1	36.8	24.8	17.1	16.4	8.5	8.2						
		Hydrocortisone						←50 mg, then 1.06 mg/min→											
117	20.5	EHBF	185	156	210	245	199	188	189	193	178	173	177						
		HV	101.7	124.9	108.9	88.8	106.1	94.0	89.1	89.4	96.9	103.8	110.2						
		A	75.9	78.8	80.1	71.7	76.6	71.2	69.7	72.2	73.8	79.7	82.2						
		HV-A	25.8	46.1	28.8	17.1	29.5	22.8	19.4	17.2	23.1	24.1	28.0						
		HGO	47.7	71.9	60.5	41.9	55.5	42.9	36.7	33.2	41.1	41.7	49.6						
		Hydrocortisone						←50 mg, then 0.98 mg/min→											
111	20.5	EHBF	317	370	332	375	349	444	479	452	416	439	521						
		HV	85.9	86.1	93.2	95.6	90.2	86.5	83.5	81.4	82.3	83.7	85.6						
		A	76.9	76.9	75.9	77.2	76.7	77.2	76.4	74.3	77.4	80.2	82.7						
		HV-A	9.0	9.2	17.3	18.4	13.5	9.3	7.1	7.1	4.9	3.5	2.9						
		HGO	28.5	34.0	57.4	69.0	47.2	41.3	34.0	32.1	20.4	15.4	15.1						
		Hydrocortisone						←50 mg, then 1.01 mg/min→											
1125	24.5	EHBF	263	239	246	249	249	285	233	211	249	200	237	224	216	210			
		HV	97.0	97.6	99.2	99.4	98.3	99.5	94.6	93.0	99.2	97.3	96.5	97.0	91.1	90.5			
		A	82.1	79.6	79.4	80.7	80.5	79.9	81.0	81.3	85.1	84.8	84.5	84.5	80.7	90.9			
		HV-A	14.9	18.0	19.8	18.7	17.8	19.6	13.6	11.7	14.1	12.5	12.0	12.5	10.4	9.6			
		HGO	39.2	43.0	48.7	45.4	44.1	55.9	31.7	24.7	35.1	25.0	28.4	28.0	22.5	20.2			
		Hydrocortisone						←20 mg, then 1.0 mg/min→											
726	14.5	EHBF	152	164	167	202	171	218	242	229	207	237	165	183	165	155			
		HV	115.8	118.5	117.9	115.5	116.9	112.5	114.3	116.6	122.4	120.6	120.6	121.6	116.1	120.2			
		A	86.8	87.8	90.8	96.0	90.3	94.5	95.4	99.9	101.3	102.2	106.7	103.5	101.7	104.4			
		HV-A	29.0	30.9	27.1	19.5	26.6	18.0	18.9	16.7	21.1	18.4	13.9	18.0	14.4	15.8			
		HGO	44.1	50.7	45.3	39.4	44.8	39.2	45.7	38.2	43.7	43.6	22.9	32.9	23.8	24.5			
		Hydrocortisone						←2.7 mg/min→											
323	27.3	EHBF		506	423	372	434	409	424	387	394	404	418	417	458	540			
		HV		112.9	112.6	113.6	113.0	109.6	107.4	101.2	102.9	102.1	99.0	98.0	94.4	92.9			
		A		100.1	96.8	98.2	98.4	96.3	95.8	94.0	94.0	93.2	91.6	89.6	88.5	87.4			
		HV-A		12.8	15.8	15.4	14.7	13.3	11.6	7.2	8.9	8.9	7.4	8.4	5.9	5.5			
		HGO		64.8	66.8	52.7	61.4	54.4	49.2	27.9	35.1	36.0	30.9	35.0	27.0	29.7			

* Abbreviations: EHBF = estimated hepatic blood flow in milliliters per minute. HV = hepatic venous glucose concentration in milligrams per 100 ml of blood. A = arterial glucose concentration in milligrams per 100 ml of blood. HV-A = hepatic venous-arterial glucose concentration difference in milligrams per 100 ml blood. HGO = hepatic glucose output in milligrams per minute.

TABLE I—(*Continued*)

Dog no.	Weight		Control values −30	−20	−10	0	Mean control	Time in minutes during hydrocortisone infusion 10	20	30	40	50	60	70	80	90	100	110	120
	kg	Hydrocortisone						←33 mg, then 1.4 mg/min→											
920	23.2	EHBF		366	358	397	373	314	324	308	291	255	240	224	229	230	231	168	
		HV		94.1	98.6	97.3	96.6	101.8	97.6	95.6	93.6	98.9	101.3	103.7	101.8	102.9	104.0	110.7	
		A		83.9	85.0	86.3	85.1	86.9	86.1	84.6	83.1	86.6	86.0	85.3	86.9	87.9	87.8	87.1	
		HV-A		10.2	13.6	11.0	11.5	14.9	11.5	11.0	10.5	12.3	15.3	18.4	14.9	15.0	16.2	23.6	
		HGO		37.3	48.7	43.7	43.2	46.8	37.3	33.9	30.6	31.4	36.7	41.2	34.1	34.5	37.4	39.6	
		Hydrocortisone						←50 mg, then 1.07 mg/min→|←0.53 mg/min→											
927	18.2	EHBF		101	119	107	109	108	111	117	122	124	117	111	109	111	113	116	
		HV		127.0	125.4	133.7	128.7	128.3	118.1	108.8	99.4	89.5	89.1	88.7	93.0	88.0	82.9	74.8	
		A		75.9	73.8	75.9	75.2	81.3	77.8	75.7	73.5	69.8	60.6	51.3	63.4	56.7	50.0	60.7	
		HV-A		51.1	51.6	57.8	53.5	47.0	40.3	33.1	25.9	19.7	28.5	37.4	29.6	31.3	32.9	14.1	
		HGO		51.6	61.4	61.8	58.3	50.8	44.7	38.7	31.6	24.4	33.3	41.5	32.3	34.7	27.3	16.4	
		Hydrocortisone						←50 mg, then 1.64 mg/min→											
930	25.5	EHBF		154	156	151	154	135	134	132	129	128	126	123	122	120	117	116	115
		HV		114.7	106.9	106.4	109.3	112.3	109.7	107.0	101.6	102.9	104.2	102.4	106.0	109.6	97.3	91.4	85.5
		A		81.3	75.9	74.8	77.3	79.1	79.4	79.7	78.6	75.5	72.4	74.8	73.9	73.0	68.7	66.2	63.6
		HV-A		33.4	31.0	31.6	32.0	33.2	30.3	27.3	23.0	27.4	31.8	27.6	32.1	36.6	28.6	25.2	21.9
		HGO		51.4	48.4	47.7	49.2	44.8	40.6	36.0	29.7	35.1	40.1	33.9	39.2	43.9	33.5	29.2	25.2
		Hydrocortisone						←20 mg, then 1.0 mg/min→											
913	20.0	EHBF		238	261	255	251	265	193	121	159	197	239	381	353	225	194	162	148
		HV		104.3	104.3	96.3	101.6	92.8	94.7	96.6	97.9	99.2	97.9	95.5	102.6	105.1	103.6	105.4	101.0
		A		89.8	88.0	86.1	88.0	83.7	83.2	82.6	83.8	85.0	87.7	90.4	91.8	93.1	90.8	88.5	86.8
		HV-A		14.5	16.3	10.2	13.6	9.1	11.5	14.0	14.1	14.2	10.2	5.1	10.8	12.0	12.8	16.9	14.2
		HGO		34.5	42.5	26.0	34.3	24.9	22.1	16.9	22.4	28.0	24.4	14.3	27.3	27.0	24.4	27.4	21.0
		Hydrocortisone						←20 mg, then 0.8 mg/min→|←0.27 mg/min→											
Mean	22.1	EHBF	216	146	245	249	245	253	249	231	230	230	238	238	236	227			
		HV	103.4	109.3	107.7	105	107	104	101	98	99	98	99	101	101	101			
		A	82	84	83	83	83	83.5	83	83	83	83	83	83	84	83			
		HV-A	21.5	25.5	25.0	22.5	24	21.0	18	15.5	15.5	14.5	15.5	18	17	18			
		HGO	41.5	49.0	53	46.5	48.5	44	36.5	30.0	30.5	29	29	32.5	29.5	30.5			
		Hydrocortisone						←34 mg, then 1.27 mg/min→|←1.22 mg/min→											

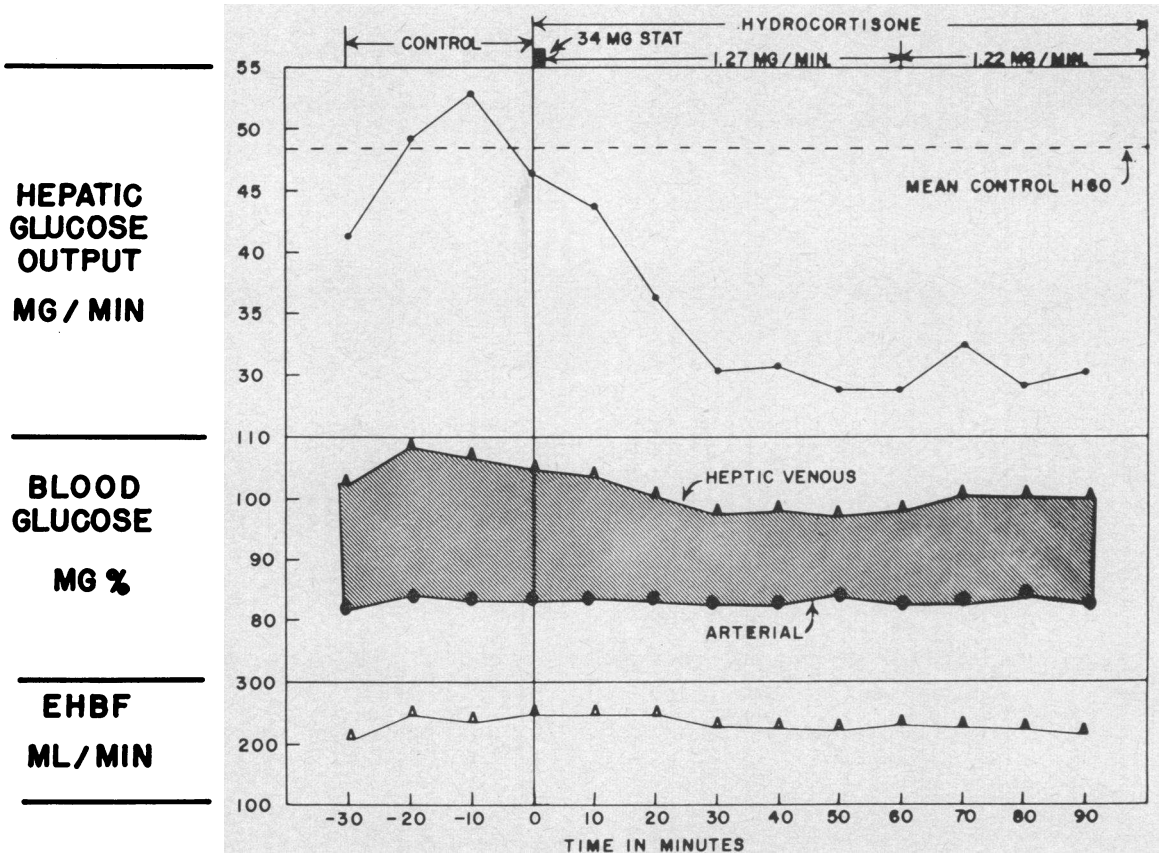

FIG. 1. MEAN CHANGES IN HEPATIC GLUCOSE OUTPUT DURING THE ACUTE ADMINISTRATION OF CORTISOL. Within 20 minutes there was a significant fall in hepatic glucose output that was depressed maximally by 30 minutes and maintained at this level for the remaining hour of hydrocortisone infusion. EHBF = estimated hepatic blood flow.

TABLE II

*Changes in hepatic glucose output from control during hydrocortisone infusion**

Dog no.	Mean control	Decrease from control: Minutes after start of hydrocortisone infusion 10	20	30	40	50	60	70	80	90	100
		mg/min									
1011	46.1	9.3	21.3	29.0	29.7	37.6	37.9				
117	55.5	12.6	18.8	22.3	14.4	13.8	5.9				
111	47.2	5.9	13.2	15.1	26.8	31.8	32.1				
1125	44.1	+11.8	12.4	19.4	9.0	19.1	15.7	16.1	21.6	23.9	
726	44.8	5.6	+ 0.9	6.6	0.9	1.2	21.9	11.9	21.0	20.3	
323	61.4	7.0	12.2	33.5	26.3	25.4	30.5	26.4	34.4	31.7	
920	43.2	+ 3.6	5.9	9.3	2.6	11.8	6.5	2.0	9.1	8.7	5.8
927	58.3	1.5	13.6	19.6	26.7	33.9	25.0	16.8	26.0	23.6	21.1
930	49.2	4.4	8.6	13.2	19.5	14.1	9.1	15.3	10.0	5.3	15.7
913	34.3	10.2	12.1	17.4	11.9	6.3	9.9	20.0	7.0	+ 3.1	1.7
Mean	48.4	4.7	11.7	18.5	16.8	19.5	19.5	15.5	18.4	15.8	11.1
p		> 0.1	< 0.03	< 0.001	< 0.001	< 0.005	< 0.005	< 0.005	< 0.010	< 0.050	

* + represents an increase in hepatic glucose output.

TABLE III

*Comparison of the effect of hydrocortisone infusion on hepatic release of new (unlabeled) glucose and hepatic glucose output**

Dog no.	Weight		Control values −30	−20	−10	0	Mean control	Time in minutes during hydrocortisone infusion 15	30	45	60	75	90
	kg												
317	20.5	EHBF	198	241	235	187	215	176	212	216	248	238	258
		HV	109.5	96.8	94.2	91.6	98.0	91.3	82.4	81.3	78.3	79.7	88.8
		A	80.2	79.4	76.6	74.4	77.7	73.9	70.5	71.6	70.8	73.3	79.2
		HV-A	29.3	17.4	17.6	17.2	20.3	17.4	11.9	9.7	7.5	6.4	9.6
		HGO	58.0	41.9	41.4	32.2	43.4	30.6	25.2	21.0	18.6	15.2	24.8
		HRNG	61.0	34.3	41.8	36.8	43.5	31.6	24.0	23.6	18.6	16.2	28.0
		Hydrocortisone						← 33 mg, then 1.3 mg/min →					
46	20.0	EHBF	268	276	302	263	277	288	258	271	303	286	282
		HV	93.4	95.6	97.2	103.5	97.4	111.4	96.7	91.2	87.9	85.7	85.2
		A	74.7	74.5	76.7	80.8	76.7	84.1	82.4	81.3	78.9	79.9	75.8
		HV-A	18.7	21.1	20.5	22.7	20.7	27.3	14.3	9.9	9.0	5.8	9.4
		HGO	50.1	58.2	61.9	59.7	57.5	78.6	36.9	26.8	27.3	16.6	26.5
		HRNG	51.3	58.6	70.6	64.7	61.3	78.3	39.1	31.1	31.1	20.8	26.9
		Hydrocortisone						← 33 mg, then 0.8 mg/min →					
314	25.0	EHBF		217		241	229	203	210	209	238	234	226
		HV		105.5		100.2	102.8	93.5	81.5	81.2	78.0	74.8	73.5
		A		78.6		75.8	77.2	70.5	66.5	65.4	64.3	63.2	61.5
		HV-A		26.9		24.4	25.7	23.0	15.0	15.8	13.7	11.6	12.0
		HGO		58.4		58.8	58.6	46.7	31.5	33.0	32.6	27.1	27.1
		HRNG		61.8		55.9	58.9	51.5	31.3	36.7	30.4	25.1	27.0
		Hydrocortisone						← 33 mg, then 1.3 mg/min →					
Mean	21.8	EHBF	236	245	268	230	240	222	227	232	263	253	255
		HV	101.5	99.3	95.7	98.4	99.4	98.7	86.9	84.6	81.4	80.1	82.5
		A	77.5	77.8	76.6	77.0	77.2	76.2	73.1	72.8	71.3	72.1	76.2
		HV-A	24.0	21.5	19.1	21.4	22.2	22.6	13.7	11.8	10.1	7.9	10.3
		HGO	54.0	50.4	51.6	50.2	53.2	52.0	31.2	26.9	26.2	19.6	26.1
		HRNG	56.2	51.6	56.2	52.5	54.6	53.8	31.5	30.5	26.7	20.7	27.3
		Hydrocortisone						← 33 mg, then 1.1 mg/min →					

* Abbreviations: EHBF = estimated hepatic blood flow in milliliters per minute. HV = hepatic venous glucose concentration in milligrams per 100 ml of blood. A = arterial glucose concentration in milligrams per 100 ml of blood. HV-A = hepatic venous-arterial glucose concentration difference in milligrams per 100 ml of blood. HGO = hepatic glucose output in milligrams per minute. HRNG = hepatic release of new glucose in milligrams per minute.

study. Estimated hepatic blood flow (EHBF) was estimated by the clearance and extraction method of Bradley, Ingelfinger, Bradley, and Curry (20) using I^{131}-labeled Rose Bengal as the extractable material (21). Blood glucose concentration was determined in triplicate on each sample by the Somogyi copper iodometric technique (22). Hepatic glucose output (HGO) in milligrams per minute at each interval was calculated as the product of the estimated hepatic blood flow and the hepatic venous-arterial glucose concentration difference (HV-A). The clinical methods and statistical analysis used in this report have been described in detail in a previous publication from this laboratory (19).

In three additional experiments hepatic output of glucose was measured simultaneously by determining the balance of glucose across the liver as in the initial 10 experiments and by determining changes in the specific activity of blood glucose across the liver (23) from the following formula: $G_R = G_T\ (1 - HV_{SA}/A_{SA})$, where HV_{SA} = specific activity of hepatic venous glucose, A_{SA} = specific activity of arterial glucose, G_R = amount of unlabeled glucose released from the liver in milligrams per minute, and G_T = total amount of glucose in milligrams per minute leaving the liver, calculated as the product of hepatic venous glucose concentration and hepatic blood flow. In these experiments, uniformly labeled C^{14} glucose was administered by the primer-infusion technique (24). Specific activity of hepatic venous and arterial blood glucose was determined in a liquid scintillation spectrometer after isolating the blood glucose as potassium gluconate according to the technique of Blair and Segal (25) modified for liquid scintillation counting.

TABLE IV

Effect of hydrocortisone infusion on peripheral glucose utilization

Dog no.	Weight	Estimated glucose space	Glucose pool			Hepatic glucose output			Change in glucose pool attributable to change in HGO†	Calculated change in peripheral glucose utilization
			Initial size	Size at 60 min	Change*	Mean control	Mean during 60 min	Change		
	kg	*L*		*mg*			*mg/mfn*			*mg/hr*
1011	26.8	8.04	6,697	6,271	−426	46.1	22.6	↓23.5	−1,410	− 984
117	20.5	6.15	4,711	5,055	+344	55.5	43.0	↓12.5	− 750	−1,094
111	20.5	6.15	4,717	5,086	+369	47.2	29.4	↓17.8	−1,068	−1,437
1125	24.5	7.35	5,917	6,211	+294	44.1	35.0	↓ 9.1	− 546	− 840
726	14.5	4.35	3,928	4,641	+713	44.8	39.7	↓ 5.1	− 306	−1,019
920	23.2	6.96	5,923	5,986	+ 63	43.2	37.1	↓ 6.1	− 366	− 429
927	18.2	5.46	4,106	3,309	−797	58.3	40.3	↓18.0	−1,080	− 283
930	25.5	7.65	5,913	5,538	−375	49.2	39.4	↓ 9.8	− 594	− 220
913	20.0	6.00	5,280	5,262	− 18	34.3	24.7	↓ 9.6	− 576	− 558
317	20.5	6.15	4,779	4,354	−425	43.4	27.8	↓15.6	− 936	− 511
46	20.0	6.00	4,602	4,734	+132	57.5	45.4	↓12.1	− 726	− 858
323	27.3	8.19	8,059	7,502	−557	61.4	42.1	↓19.3	−1,158	− 601
314	25.0	7.50	5,790	4,823	−977	58.6	40.5	↓18.1	−1,086	− 109
Mean	22.0	6.61	5,417	5,290	−128	49.5	35.9	↓13.6	− 816	− 688

* + denotes increase; − denotes decrease.
† Hepatic glucose output.

Results

Effect on hepatic glucose output. In each experiment hydrocortisone infusion resulted in a rapid decline in hepatic glucose output (Table I). Mean hepatic glucose output decreased significantly (Table II) from the control value of 48.5 mg per minute to 36.5 mg per minute within 20 minutes after starting the hydrocortisone infusion and averaged 30 mg per minute during the next 70 minutes. This 38% depression in the hepatic output of glucose persisted for the remainder of the hydrocortisone infusion (Figure 1). The change in hepatic glucose output was in large part attributable to a 30% decrease in mean hepatic venous-arterial glucose concentration difference, which fell from 24 mg per 100 ml during the control period to 16.6 mg per 100 ml during the 20- to 90-minute period after starting the hydrocortisone. In one study (dog 726, Table I) a priming dose of hydrocortisone was not administered, and hepatic glucose output did not fall until 60 minutes after the start of a constant hydrocortisone infusion.

The decrease in hepatic glucose output determined by measuring the balance of glucose across the liver was paralleled by a decline in the release of endogenously produced glucose by the liver (Table III). Hepatic release of new (isotopically unlabeled) glucose fell 24.1 mg per minute from a mean control of 54.6 to 30.5 mg per minute by 30 minutes. Hepatic output of glucose declined a similar amount, 26.3 mg per minute, from the mean control of 53.2 to 26.9 mg per minute during the same period of time.

The close correspondence between changes in the hepatic glucose output determined by measuring the balance of glucose across the liver and by following the changes in specific activity of blood glucose across the liver attests to the validity of the isotopic technic, but only under circumstance where the liver is not extracting and retaining large quantities of glucose from the perfusing blood (26).

Effect on peripheral glucose utilization. Approximations of the rate of peripheral glucose utilization were made from the data listed in Tables I and III (19). A glucose space of 30% of the body weight of the dog (4, 19, 27) was assumed, and the glucose pool was calculated before and after 1 hour of hydrocortisone infusion. The calculations show that an inhibition in the rate of peripheral glucose utilization occurred in each of the 13 studies during the initial 60 minutes after starting hydrocortisone (Table IV). This decrease in peripheral glucose utilization, which averaged 688 mg during the first hour after starting the hydrocortisone infusion, cannot be ascribed to a decreased delivery of glucose to the peripheral tissues consequent to the reduction in hepatic glucose output, since it persisted in the

five studies in which blood glucose concentration rose (Tables I and III) during the initial 60 minutes.

Although mean arterial glucose concentration was unchanged (Figure 1), it fell in seven and rose in five studies during the first hour. The ensuing level of the arterial glucose concentration after hydrocortisone is the result of the magnitude of the depression in hepatic glucose output in relation to the inhibition of peripheral glucose utilization. An unchanging arterial glucose concentration belies the profound alterations in carbohydrate metabolism that are occurring.

Discussion

These data show that two significant alterations in carbohydrate metabolism occur within 20 minutes after starting a hydrocortisone infusion in the fasted dog. Not only was hepatic glucose output significantly diminished, but this was accompanied by an inhibition of peripheral glucose utilization (Tables I and IV). The simultaneous inhibition of peripheral glucose utilization and fall in hepatic glucose output resulted in an unchanged mean arterial glucose concentration. The hazards of interpreting data based solely on observations of changes in arterial glucose concentration are obvious, since such observations would not have detected the profound alterations in glucose metabolism that occurred acutely during hydrocortisone administration.

Because of the experimental evidence indicating that prolonged glucocorticoid administration increases gluconeogenesis (1, 3, 5, 6, 9) and hepatic glucose production (4), the acute fall in hepatic glucose output found in these studies seems paradoxical and requires explanation. A fall in hepatic glucose output may be the result of a decrease in gluconeogenesis, a decrease in glycogenolysis, an increase in glycogenesis, or any combination thereof. Since previous studies have shown that both an acceleration of gluconeogenesis (8, 9, 28) and an increase in hepatic glycogen stores (28–32) occur within several hours after glucocorticoid administration, it seems unlikely that decreased gluconeogenesis could account for the fall in hepatic glucose output found in these studies. The combination of a decrease in hepatic glucose output noted in these studies and the early rise in liver glycogen reported by others (28–32) is best explained by either a decrease in hepatic phosphorylase or an increase in glycogen synthetase activity, or both, thereby diverting to glycogen glucose previously destined to leave the liver and maintain hepatic glucose output. No significant decrease in total hepatic phosphorylase activity after cortisol administration has been reported. In fact, most studies show an increased activity (33, 34) occurring as early as 12 hours after steroid administration (32). Although Steiner, Rauda, and Williams found an increase in mean glycogen synthetase activity from 2.4 to 3.7 μmoles per g of liver per hour within 5 hours after prednisolone injection in rats, they did not consider this rise significant (35). In recent studies, however, Hilz, Tarnowski, and Arend (36) reported an early increase in hepatic synthetase activity, the consequence of a rapid increase in glucose-6-phosphate concentration that rises considerably within 30 minutes after glucocorticoid administration. Not only is the activity of the enzyme increased early by the cortisol-induced increase in activator glucose-6-phosphate concentration, but within 6 hours an actual increase in enzyme protein is also very likely present (36). Possibly the early cortisol-induced stimulation of gluconeogenesis is too small to be easily measured or to increase hepatic glucose output but large enough to increase the glucose-6-phosphate pool, activate glycogen synthetase, and thereby decrease hepatic glucose output.

Apparently the decrease in the output of glucose by the liver that attends the acute administration of cortisol is the consequence of the shunting of glucose produced within the liver to glycogen. In these studies hepatic glucose output averaged 30 mg per minute (Table I) from 30 to 90 minutes after starting the cortisol infusion. Since mean control hepatic glucose output was 48.5 mg per minute, the liver was conserving and very likely shunting to glycogen 18.5 mg of glucose per minute or approximately 1 g per hour. The changes in hepatic glucose metabolism and hepatic glucose output postulated to occur immediately after glucocorticoids are contrasted in Figure 2 with those thought to occur with more prolonged administration.

The data from the present studies afford un-

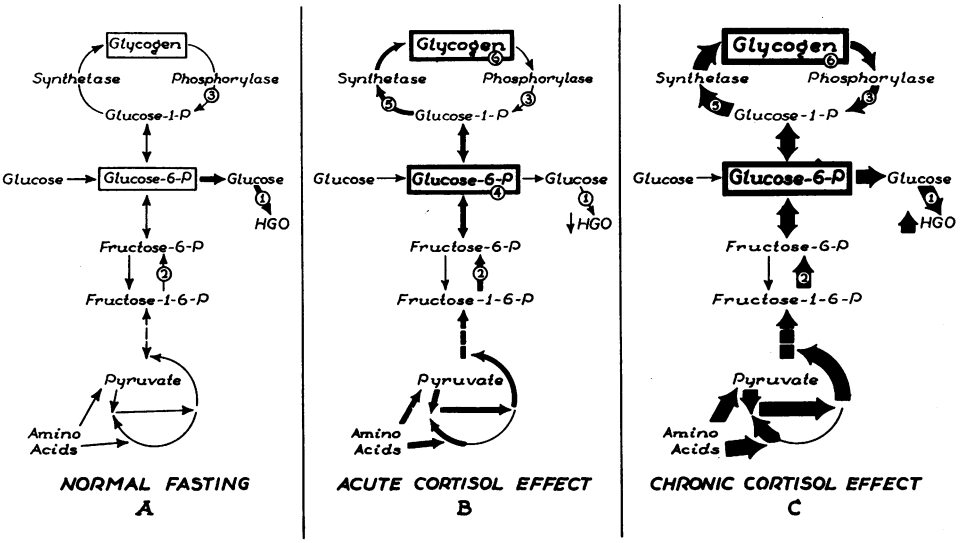

FIG. 2. COMPARISON OF THE EFFECTS OF THE ACUTE AND CHRONIC ADMINISTRATION OF GLUCOCORTICOIDS ON HEPATIC GLUCOSE METABOLISM AND OUTPUT. Panel A describes the conditions during the postabsorptive state when hepatic glucose output ① is maintained via gluconeogenesis ② and glycogenolysis ③. The acute administration of cortisol (panel B), probably by producing a small increase in gluconeogenesis ②, increases glucose-6-phosphate concentration ④, which stimulates glycogen synthetase activity ⑤ and diverts endogenously produced glucose to glycogen ⑥, thereby resulting in a reduction in hepatic glucose output ①. Prolonged adrenocorticoid administration (panel C) results in an increased hepatic glucose output ① and glycogen stores ⑥ despite increased phosphorylase activity ③, probably as a consequence of a greater stimulation of synthetase activity ⑤ coupled with a marked augmentation of gluconeogenesis ②.

equivocal evidence for an immediate inhibitory effect of glucocorticoids on peripheral glucose utilization, an action still being debated (5, 6, 8, 28). Many investigators have reported indirect evidence for an inhibition of peripheral glucose utilization by a variety of technics (1, 8, 15, 30, 37–40). Despite all these data, DE BODO and ALTSZULER in a recent critical review (6) concluded that there was no definitive evidence for an inhibition of peripheral glucose utilization by adrenocorticol steroids and suggested that they may indirectly enhance glucose utilization. THORN, RENOLD, and CAHILL (5) also seriously questioned the occurrence of a glucocorticoid-induced depression of peripheral glucose utilization and pointed out that the discrepancy between the increase in glucose stores and urinary nitrogen excretion may be explainable on mechanisms other than decreased metabolism of glucose by the extrahepatic tissues.

The results of our studies leave little room for doubt that hydrocortisone causes an inhibition of peripheral glucose utilization that is acute in onset and significant in amount. Moreover, this inhibition was underestimated in our experiments. Peripheral glucose utilization as calculated in these studies includes glucose metabolized by all the extrahepatic tissues including the central nervous system. Since the brain utilizes about 50% of the splanchnic glucose output in the postabsorptive state (41) and since the rate of glucose utilization by the brain does not change during glucocorticoid administration (42), the decline in utilization of the extracerebral peripheral tissues must have been even greater than our calculations indicate. The data from the present studies, however, give no insight into the biochemical mechanism responsible for this immediate inhibition of peripheral glucose utilization. This inhibition of peripheral glucose utilization cannot be attributed to an increase in plasma nonesterified fatty acids (NEFA) as postulated by RANDLE, GARLAND, HALES, and NEWSHOLME (43), since arterial plasma NEFA concentrations did not change during the acute infusions of hydro-

cortisone in the present studies. Recent *in vitro* investigations suggest that glucocorticoids depress the phosphorylation of glucose to glucose-6-phosphate and thereby decrease glucose utilization by muscle (39), heart (40), and adipose tissue (44).

Summary

Thirteen experiments were performed on dogs with complete end-to-side portacaval shunts to determine whether hydrocortisone acutely altered hepatic glucose balance and peripheral glucose utilization. Dogs with chronic end-to-side portacaval shunts were selected, since in this preparation the liver is completely separated from the extrahepatic splanchnic bed, allowing the measurement of glucose balance across the liver alone rather than across the entire splanchnic circulation.

Hydrocortisone infusion had an immediate effect on carbohydrate metabolism, producing both a prompt reduction in hepatic glucose output and a decrease in peripheral glucose utilization. The glucose output by the liver declined progressively and decreased about 38% from control values within 30 minutes after starting hydrocortisone administration. A quantitatively similar decline in peripheral glucose utilization occurred during the same time period. These changes persisted over the entire 90-minute period of hydrocortisone infusion.

References

1. Long, C. N. H., B. Katzin, and E. G. Fry. The adrenal cortex and carbohydrate metabolism. Endocrinology 1940, **26**, 309.
2. Abelove, W. A., and K. E. Paschkis. Comparison of the diabetogenic action of cortisone and growth hormone in different species. Endocrinology 1954, **55**, 637.
3. Welt, I. D., D. Stetten, Jr., D. J. Ingle, and E. H. Morley. Effect of cortisone upon rates of glucose production and oxidation in the rat. J. biol. Chem. 1952, **197**, 57.
4. Altszuler, N., R. Steele, J. S. Wall, and R. C. De Bodo. Effects of adrenocortical steroids on carbohydrate metabolism in hypophysectomized dogs; studies with C^{14}-labeled glucose. Amer. J. Physiol. 1957, **191**, 29.
5. Thorn, G. W., A. E. Renold, and G. F. Cahill, Jr. The adrenal and diabetes. Some interactions and interrelations. Diabetes 1959, **8**, 337.
6. De Bodo, R. C., and N. Altszuler. Insulin hypersensitivity and physiological insulin antagonists. Physiol. Rev. 1958, **38**, 389.
7. Ingle, D. J. Experimental steroid diabetes. Diabetes 1958, **5**, 187.
8. Long, C. N. H., O. K. Smith, and E. G. Fry. Actions of cortisol and related compounds on carbohydrate and protein metabolism *in* Metabolic Effects Of Adrenal Hormones. Boston, Little, Brown, 1960, p. 4.
9. Ashmore, J. The role of adrenal steroids in the regulation of hepatic metabolism *in* Metabolic Effects of Adrenal Hormones, Boston, Little, Brown, 1960, p. 25.
10. West, K. M. Response of the blood glucose to glucocorticoids in man. Determination of the hyperglycemic potencies of glucocorticoids. Diabetes 1959, **8**, *22*.
11. Perkoff, G. T., R. Hahn, H. Kent, C. A. Nugent, and F. H. Tyler. A delayed effect of adrenalcortical steroids on blood glucose levels and disappearance rates. Clin. Res. 1960, **8**, 143.
12. Frawley, T. F. The role of the adrenal cortex in glucose and pyruvic acid metabolism in man including the use of intravenous hydrocortisone in acute hypoglycemia. Ann. N. Y. Acad. Sci. 1955, **61**, 464.
13. Glenn, E. M., R. O. Stafford, S. C. Lyster, and B. J. Bowman. Relation between biological activity of hydrocortisone analogues and their rate of inactivation by rat liver enzyme systems. Endocrinology 1957, **61**, 128.
14. Hyde, P. M. Liver glycogen deposition after intravenous and intragastric administration of cortisol-4-C^{14} to rats. Endocrinology 1957, **61**, 774.
15. Kupperman, H. S., M. Persky, J. Linsk, M. Isaacs, and M. Rosenbluth. The paradoxical effect of intravenous hydrocortisone upon carbohydrate metabolism. Ann. N. Y. Acad. Sci. 1955, **61**, 494.
16. Papper, S., L. Saxon, T. E. Prout, and H. C. Alpert. The effects of cortisone on the fructose and glucose tolerance tests of normal men. J. Lab. clin. Med. 1956, **48**, 13.
17. Duncan, L. Cortisone-induced impairment of glucose tolerance in the detection of diabetic diathesis. Quart. J. exp. Physiol. 1956, **41**, 85.
18. Froesch, E. R., A. I. Winegrad, A. E. Renold, and G. W. Thorn. Mechanism of the glucosuria produced by the administration of steroids with glucocorticoid activity. J. clin. Invest. 1958, **37**, 524.
19. Madison, L. L., B. Combes, R. Adams, and W. Strickland. The physiological significance of the secretion of endogenous insulin into the portal circulation. III. Evidence for a direct immediate effect of insulin on the balance of glucose across the liver. J. clin. Invest. 1960, **39**, 507.
20. Bradley, S. E., F. J. Ingelfinger, G. P. Bradley, and J. J. Curry. The estimation of hepatic blood flow in man. J. clin. Invest. 1945, **24**, 890.

21. Combes, B. Estimation of hepatic blood flow in man and in dogs by I^{131}-labeled rose bengal. Simultaneous comparison with the sulfobromophthalein sodium. J. Lab. clin. Med. 1960, **56**, 537.
22. Somogyi, M. Determination of blood sugar. J. biol. Chem. 1945, **160**, 69.
23. Schambye, P., and F. Tarding. Changes induced by insulin and tolbutamide in the glucose output of the liver. Ann. N. Y. Acad. Sci. 1959, **74**, 557.
24. De Bodo, R. C., N. Altszuler, A. Dunn, R. Steele, D. T. Armstrong, and J. S. Bishop. Effects of exogenous and endogenous insulin on glucose utilization and production. Ann. N. Y. Acad. Sci. 1959, **82**, 431.
25. Blair, A., and S. Segal. The isolation of blood glucose as potassium gluconate. J. Lab. clin. Med. 1960, **55**, 959.
26. Madison, L. L., D. Mebane, F. Lecocq, and B. Combes. Physiological significance of the secretion of endogenous insulin into the portal circulation. V. The quantitative importance of the liver in the disposition of glucose loads. Diabetes 1963, **12**, 8.
27. Searle, G. L., E. H. Strisower, and I. L. Chaikoff. Glucose pool and glucose space in the normal and diabetic dog. Amer. J. Physiol. 1954, **176**, 190.
28. Renold, A. E., and J. Ashmore. Metabolic effects of adrenal corticosteroids *in* Diabetes, R. H. Williams, Ed. New York, Paul B. Hoeber, 1960, p. 194.
29. Ashmore, J., F. Stricker, W. C. Love, and G. Kilsheimer. Cortisol stimulation of glycogen synthesis in fasted rats. Endocrinology 1961, **68**, 599.
30. Glenn, E. M., B. J. Bowman, R. B. Bayer, and C. R. Meyer. Hydrocortisone and some of its effects on intermediary metabolism. I. *In vivo* studies. Endocrinology 1961, **68**, 386.
31. Dorsey, J. L., and A. Munck. Studies on the mode of action of glucocorticoids in rats: a comparison of the effects of cortisol and glucose on the formation of liver glycogen. Endocrinology 62, **71**, 605.
32. Eisenstein, A. B. Effect of cortisol on liver phosphorylase activity. Proc. Soc. exp. Biol. (N. Y.) 1962, **109**, 839.
33. Willmer, J. S. Changes in hepatic enzyme levels after adrenalectomy. I. Phosphorylase, phosphoglucomutase and phosphoglucoseisomerase. Canad. J. Biochem. 1960, **38**, 1095.
34. Hunter, N. W., and C. E. Johnson. The effects of hydrocortisone on glycogen storage and phosphorylase activity of frog liver. Cell and comp. Physiol. 1960, **55**, 275.
35. Steiner, D. F., V. Rauda, and R. H. Williams. Effects of insulin, glucagon, and glucocorticoids upon hepatic glycogen synthesis from uridine diphosphate glucose. J. biol. Chem. 1961, **236**, 299.
36. Hilz, H., W. Tarnowski, and P. Arend. Glucose polymerisation and cortisol. Biochem. biophys. Res. Commun. 1963, **10**, 492.
37. Russell, J. A. Adrenal and hypophysis in carbohydrate metabolism of the eviscerated rat. Amer. J. Physiol. 1943, **140**, 98.
38. Boutwell, R. K., and R. Chiang. The acute effect of cortisone treatment on the utilization of glucose by the mouse. Arch. Biochem. 1954, **50**, 461.
39. Riddick, F. A., Jr., R. M. Reisler, and D. M. Kipnis. The sugar transport system in striated muscle: effect of growth hormone, hydrocortisone and alloxan diabetes. Diabetes 1962, **11**, 171.
40. Morgan, H. E., M. J. Henderson, D. M. Regen, and C. R. Park. Regulation of glucose uptake in heart muscle from normal and alloxan-diabetic rats: the effects of insulin, growth hormone, cortisone, and anoxia. Ann. N. Y. Acad. Sci. 1959, **82**, 387.
41. Myers, J. D. Net splanchnic glucose production in normal man and in various disease states. J. clin. Invest. 1950, **29**, 1421.
42. Sensenbach, W., L. L. Madison, and L. Ochs. The effect of ACTH and cortisone on cerebral flood flow and metabolism. J. clin. Invest. 1953, **32**, 372.
43. Randle, P. J., P. B. Garland, C. N. Hales, and E. A. Newsholme. The glucose fatty-acid cycle. Its role in insulin sensitivity and metabolic disturbances of diabetes mellitus. Lancet 1963, **1**, 785.
44. Leboeuf, B., A. E. Renold, and G. F. Cahill, Jr. Studies on rat adipose tissue *in vitro*. IX. Further effects of cortisol on glucose metabolism. J. biol. Chem. 1962, **237**, 988.