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

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Previous studies from this laboratory,[1-3] recently confirmed,[4,5] have shown that insulin administered in a manner which minimized the counter-regulatory responses to a falling blood glucose concentration resulted in a prompt decline in hepatic glucose output, which accounted in large part for the concomitant decrease in the glucose pool.[2] The physiologic role of the liver in carbohydrate metabolism was defined further in studies which examined the effects of glucose loading on net hepatic glucose balance.[6,7] The administration of glucose resulted not only in a cessation of hepatic glucose output but also in a net uptake of glucose by the liver. This hepatic uptake of glucose occurred at a mean arterial glucose concentration only 36 mg. per 100 ml. above the fasting level[7] and was apparently insulin dependent.[6]

The purpose of the present study was to determine the quantitative importance of the liver in the disposition of exogenous carbohydrate by examining the capacity of the liver to take up glucose during glucose loading. Four groups of dogs were studied; each subsequent group received a progressively greater glucose load, varying in different dogs from as little as 53 mg. per minute to as much as 1,037 mg. per minute. In order to measure hepatic rather than splanchnic glucose balance, dogs with chronic end-to-side portacaval shunts were used, since this operation separates the liver from the extrahepatic splanchnic circulation.

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METHODS AND PROCEDURE

Eleven studies were performed on mongrel dogs with chronic end-to-side portacaval shunts. At least two weeks were allowed to elapse between construction of the shunt and experiment, to permit complete recovery from the operative procedure. Prior to study, the dogs were maintained on a ration containing 50 per cent of the total calories as carbohydrate, 22 per cent as protein and 28 per cent as fat.

Fifteen hours after their last meal, the dogs were anesthetized with Nembutal (25 mg. per kg. I.V.). Arterial blood samples were obtained through a Cournand needle placed in a femoral artery. Hepatic venous blood samples were collected through a cardiac catheter guided under fluoroscopic control deep into an hepatic vein. During each experiment proper positioning of the catheter was checked at frequent intervals.

Hepatic venous and arterial glucose concentrations and hepatic blood flow were determined at ten-minute intervals during the control period, and at fifteen-minute intervals during the 120-minute period of glucose infusion. Hepatic blood flow was estimated by the clearance-and-extraction method of Bradley, Ingelfinger, Bradley and Curry[8] utilizing I^{131}-labeled rose bengal as the extractable substance.[9] Triplicate determinations of blood glucose were made on each sample by the Somogyi copper iodometric method.[10] Net hepatic glucose balance in milligrams per minute was calculated as the product of estimated hepatic blood flow and hepatic venous-arterial glucose concentration difference. Net hepatic glucose conservation in milligrams per minute was estimated in the following manner: During glucose loading when the liver was still putting out glucose, net hepatic glucose balance during infusion was subtracted from the mean control hepatic glucose balance; when the liver was extracting glucose, the net positive hepatic glucose balance was added

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) the mean control value (see results for actual calcu-
:tions). The methods used in this laboratory already
ave been described in detail.[2]

After obtaining control measurements, changes in net
epatic glucose balance were followed for 120 minutes
uring a constant infusion of glucose administered
ito a hind limb vein. Four different rates of glucose
lministration were studied. The dogs in Group I re-
:ived glucose at a mean net* rate of 3.2 mg. per kg.
er min., and those in Groups II, III and IV at mean
et rates of 19.9, 31.2 and 50.0 mg. per kg. per min.
:spectively.

RESULTS

1. *Changes in net hepatic glucose balance.* As the
:t glucose loads were raised from a mean of 3.2 mg.
:r kg. per min. (70.5 mg./min.) (Group I) to 50
g. per kg. per min. (858 mg./min.) (Group IV),
ıe changes in net hepatic glucose balance increased
:ogressively (tables 1, 2, and figure 1). Hepatic *up-*
ke of glucose was present throughout the 120-minute
fusion period in all dogs in Groups II, III and IV and
'eraged 65.1, 112.6 and 171.5 mg. per min. respective-
(table 2). Since mean hepatic glucose output prior
infusion was 56.3, 59.0 and 53.3 mg. per min., mean
:t conservation of glucose by the liver equaled 121.4,
71.6 and 224.8 mg. per min. in Groups II, III and IV
figure 1). During the 120-minute period of glucose
lministration, total hepatic glucose conservation aver-
ged 4.4, 14.6, 20.6 and 27 gm. respectively in Groups
through IV (table 3, and figure 2).

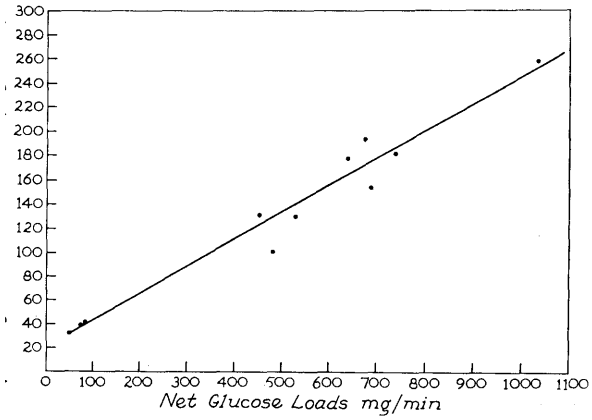
Since hepatic glucose uptake rose progressively as the
ucose loads were increased, the maximal capacity
the liver to extract glucose from the perfusing blood
could not be established or surpassed even with the massive glucose loads used in these studies (table 2, and figure 1). This capacity of the liver to take up glucose was in excess of 200 mg. per min. in Group IV for prolonged periods of time (table 2) and as high as 467 mg. per min. in Dog OL5 (table 1).

This progressive increase in net hepatic glucose conservation was the result in large part of changes in hepatic venous-arterial glucose concentration differences. Prior to glucose loading, mean hepatic venous-arterial glucose concentration differences equaled 23.1, 24.5, and 24.1 mg. per 100 ml. in Groups II, III and IV (table 2). During glucose administration, arterial glucose concentrations were higher than hepatic venous and averaged +18.3, +32.6 and +45.6 mg. per 100 ml., representing a total change of 41.4, 57.1 and 69.6 mg. per 100 ml. in Groups II, III and IV (table 2). Although mean hepatic blood flow increased during glucose loading and contributed to the progressive increase in hepatic glucose conservation, the changes in hepatic blood flow were small compared to the changes in hepatic venous-arterial glucose concentration differences (table 2); mean hepatic blood flow increased 42, 32 and 51 per cent in Groups II through IV, whereas hepatic venous-arterial glucose concentrations changed 179, 233 and 289 per cent respectively.

2. *Role of the liver and the peripheral tissues in the disposition of glucose loads.* From the observed changes in net hepatic glucose balance which attended glucose infusion, the approximate roles of the liver and the peripheral tissues in the disposition of glucose loads of varying magnitude can be calculated (table 3). The total amount of infused glucose which was utilized was estimated by subtracting the increment above control in the glucose pool at 120 minutes from the net amount of administered glucose. For these calculations, a glucose space of 20 per cent of body weight was used to prevent underestimating the role of the peripheral tissues. Corrections for urinary loss of glucose were made by using net glucose infusions (total glucose infused minus urinary loss) in these calculations. Peripheral glucose utilization was assumed to equal that amount of net infused glucose which could not be accounted for by both the changes in hepatic glucose balance and the increase in the glucose pool (table 3).

The liver accounted for 53.7 per cent of the utilized glucose when the glucose loads were small, and 32.7 per cent (27 gm.) of the utilized glucose during administration of the largest loads (table 3). Despite

*Net rate equals actual glucose infusion rate minus urinary ucose loss.



G. 1. Effect of increasing glucose loads on net hepatic glucose conservation.

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TABLE 1

Effect of glucose loads* of increasing magnitude upon hepatic glucose balance†

Dog No.		Control values Minutes —30	—20	—10	0	Mean control	Time during glucose infusion Minutes 15	30	45	60	75	90	105	120
Group I Glucose load 2.98 - 3.34 mg. per kg. per min.														
1B6	EHBF		466.0		366.0	416.0	313.0	205.0	222.0	174.0	168.0	133.0	121.0	127.0
17.7 kg.	HV		97.3		94.3	95.8	98.7	99.8	107.4	114.9	114.1	106.8	106.8	110.3
	A		81.6		78.1	79.8	83.0	84.9	93.8	94.9	92.7	89.5	89.2	85.1
	HV-A		15.7		16.2	16.0	15.7	14.9	13.6	20.0	21.4	17.3	17.6	15.2
	NHGB		73.2		59.3	66.2	49.1	30.5	30.2	34.8	36.0	22.9	21.3	19.3
	Glucose						←		2.98 mg./kg./min.		(52.9 mg./min.)			→
1A24	EHBF	541.0	510.0	636.0	555.0	567.0	453.0	432.0	370.0	362.0	436.0	495.0	496.0	441.0
25.8 kg.	HV	82.1	79.6	81.3	81.0	81.0	80.2	79.4	78.0	73.1	76.6	76.2	77.3	82.5
	A	73.4	73.4	73.1	70.6	72.6	82.1	84.0	77.7	76.4	75.8	75.7	73.8	75.4
	HV-A	8.7	6.2	8.2	10.4	8.4	+1.9	+4.6	+0.3	+3.3	0.8	0.5	3.5	7.1
	NHGB	47.1	31.6	52.1	57.7	47.1	+8.6	+19.9	+1.1	+11.9	3.5	2.5	17.4	31.3
	Glucose						←		3.2 mg./kg./min.		(82.5 mg./min.)			→
1A17	EHBF	442.0	463.0	382.0	509.0	449.0	474.0	441.0	429.0	369.0	343.0	324.0	366.0	302.0
22.7 kg.	HV	81.4	79.5	88.5	85.1	83.6	99.9	95.5	89.6	87.6	86.8	86.0	76.8	71.3
	A	67.5	65.9	64.8	67.5	66.4	82.7	84.1	82.7	82.2	78.7	78.7	71.9	65.9
	HV-A	13.9	13.6	23.7	17.6	17.2	17.2	11.4	6.9	5.4	8.1	7.3	4.9	5.4
	NHGB	61.4	63.0	90.5	90.0	76.2	81.5	50.3	29.6	19.9	27.8	23.7	17.9	16.3
	Glucose						←		3.34 mg./kg./min.		(76 mg./min.)			→
Group II Glucose load 18 - 21.1 mg. per kg. per min.														
1K11	EHBF	399.0		301.0	294.0	331.0	290.0	421.0	379.0	363.0	418.0	702.0	1,023.0	963.0
27.3 kg.	HV	87.6		90.0	92.3	90.0	146.2	167.5	177.3	188.2	181.4	180.7	177.8	173.4
	A	70.8		70.0	70.4	70.4	154.0	176.0	189.0	197.3	188.4	189.7	185.3	179.1
	HV-A	16.8		20.0	21.9	19.6	+7.8	+8.5	+11.7	+9.1	+9.0	+9.0	+7.5	+5.7
	NHGB	67.0		60.2	64.4	63.9	+22.6	+35.8	+44.3	+34.5	+37.6	+63.2	+76.7	+54.9
	Glucose						←		18 mg./kg./min.		(490 mg./min.)			→
1C6	EHBF	323.0	379.0	346.0	332.0	345.0	359.0	370.0	351.0	355.0	382.0	382.0	349.0	376.0
21.8 kg.	HV	93.3	94.9	94.4	89.6	93.1	178.9	202.2	210.3	217.8	208.1	231.7	231.7	235.5
	A	74.6	74.8	79.1	77.5	76.5	192.3	225.3	235.7	241.1	235.7	264.2	264.7	267.7
	HV-A	18.7	20.1	15.3	12.1	16.6	+13.4	+23.1	+25.4	+23.3	+27.6	+32.5	+33.0	+33.2
	NHGB	60.4	69.5	52.9	40.2	55.8	+48.1	+85.5	+89.2	+82.7	+105.4	+124.2	+115.2	+121.1
	Glucose						←		20.5 mg./kg./min.		(477 mg./min.)			→
0K15	EHBF	156.0	141.0	150.0	150.0	149.0	178.0	190.0	227.0	277.0	313.0	330.0	305.0	280.0
25.4 kg.	HV	105.6	112.2	102.3	109.4	107.4	156.4	173.3	183.5	194.9	191.9	200.1	190.7	180.8
	A	79.0	75.2	71.3	71.3	74.2	176.6	207.1	227.9	240.4	235.9	232.4	221.0	214.3
	HV-A	26.6	37.0	31.0	38.1	33.2	+18.2	+33.8	+44.4	+45.5	+44.0	+32.3	+30.3	+33.5
	NHGB	41.5	52.2	46.5	57.1	49.3	+32.4	+64.2	+100.8	+126.0	+137.7	+106.6	+92.4	+93.8
	Glucose						←		21.1 mg./kg./min.		(535 mg./min.)			→

*Net load, i.e., actual infusion minus urinary loss.

†Abbreviations as follows: EHBF, estimated hepatic blood flow in ml./min.; HV, hepatic venous glucose concentration in mg. per 100 ml.; A, arterial glucose concentration in mg. per 100 ml.; HV-A, hepatic venous minus arterial glucose concentration in mg. per 100 ml.; NHGB, net hepatic glucose balance in mg./min. Figures without preceding sign indicate net hepatic glucose output. Those preceded by + indicate net hepatic uptake of glucose.

variations in the large loads from 19.9 to 50 mg. per kg. per min., in no study did the liver account for the disappearance of less than 24.4 per cent of the utilized load (table 3).

DISCUSSION

From these data it is apparent that the liver plays a quantitatively important role in the disposition of administered glucose at any level of glucose loading (table 3). Despite the administration of massive loads of glucose to most of the dogs in these studies, the maximal capacity of the liver to take up or store glucose could not be established (figure 1) and was observed to be as much as 467 mg. per min. (table 1). In general, the greater the glucose load, the greater the amount of glucose disposal accounted for by a change in hepatic glucose balance from a net output prior to infusion to a net uptake during infusion (table 2, figure 1). With the largest glucose loads averaging 858 mg. per min., hepatic glucose conservation amounted to as much as 27 gm. in two hours (figure 2, table 3).

Although the per cent of the utilized load disposed of by the liver decreased with increasing loads, in no instance did it fall below 24.4 per cent and consequently

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TABLE 1 (Continued)

Effect of glucose loads* of increasing magnitude upon hepatic glucose balance†

Dog No.		Control values Minutes —30	—20	—10	0	Mean control	Time during glucose infusion Minutes 15	30	45	60	75	90	105	120
						Group III Glucose load 30.2 - 31.8 mg. per kg. per min.								
0L19	EHBF	294.0	360.0	320.0	317.0	323.0	346.0	335.0	353.0	384.0	383.0	303.0	288.0	398.0
24.5 kg.	HV	87.4		78.9	87.2	84.5	174.5	190.7	190.5	193.2	189.5	190.7	192.0	193.2
	A	69.0	69.5	66.7	68.5	68.4	206.2	236.8	238.8	244.0	238.3	235.8	238.8	240.8
	HV-A	18.4		12.2	18.7	16.4	+31.7	+46.1	+48.3	+50.8	+48.8	+45.1	+46.8	+37.6
	NHGB	54.1		39.0	59.2	50.8	+109.7	+154.0	+170.5	+195.0	+187.0	+137.0	+135.0	+150.0
	Glucose						← 30.25 mg./kg./min. (741 mg./min.) →							
0K22	EHBF	187.0	180.0	160.0	202.0	182.0	205.0	228.0	313.0	358.0	353.0	396.0	410.0	434.0
21.4 kg.	HV	106.2	103.6	117.0	111.3	109.5	159.7	178.7	183.8	183.8	176.1	167.5	170.5	167.0
	A	78.5	74.9	77.5	75.4	76.5	200.2	228.6	229.9	224.3	217.8	209.2	204.9	202.8
	HV-A	27.7	28.7	39.5	35.9	33.0	+40.5	+49.9	+46.1	+40.5	+41.7	+41.7	+34.4	+35.8
	NHGB	51.8	51.6	63.2	72.5	59.8	+83.0	+113.8	+144.3	+145.0	+147.2	+165.1	+141.0	+155.4
	Glucose						← 31.5 mg./kg./min. (674 mg./min.) →							
0K29	EHBF		267.0	279.0	271.0	272.0	284.0	332.0	332.0	326.0	302.0	307.0	345.0	423.0
21.8 kg.	HV		89.6	87.2	95.0	90.6	168.8	204.5	213.6	219.9	220.7	227.8	217.0	217.0
	A		69.1	66.0	64.2	66.4	191.8	232.7	249.8	256.3	257.2	263.8	253.0	252.0
	HV-A		20.5	21.2	30.8	24.2	+23.0	+28.2	+36.2	+36.4	+37.0	+36.0	+36.0	+35.0
	NHGB		54.8	59.1	83.5	65.8	+65.3	+93.6	+120.2	+118.7	+111.7	+110.5	+124.0	+148.0
	Glucose						← 31.8 mg./kg./min. (695 mg./min.) →							
						Group IV Glucose load 48.1 - 51.9 mg. per kg. per min.								
0L7	EHBF	237.0	217.0	163.0	165.0	196.0	195	248	224	248	301	355	370	347
14.1 kg.	HV	82.7	85.3	98.7	100.1	91.7	268	325	353	358	379	400	410	419
	A	62.9	63.2	64.7	70.0	65.2	295	367	406	420	442	456	477	496
	HV-A	19.8	22.1	34.0	30.1	26.5	+27	+42	+53	+62	+63	+56	+67	+77
	NHGB	46.9	48.0	55.4	50.0	50.0	+53	+104	+119	+154	+190	+197	+248	+267
	Glucose						← 48.1 mg./kg./min. (678 mg./min.) →							
0L5	EHBF	264.0	255.0	278.0	250.0	262.0	371	442	415	382	380	391	491	570
20 kg.	HV	98.2	97.4	85.3	95.5	94.1	303	415	492	578	617	708	744	766
	A	73.0	71.4	73.0	71.9	72.3	340	450	540	608	683	768	806	848
	HV-A	25.2	26.0	12.3	23.6	21.8	+37	+35	+48	+30	+66	+60	+62	+82
	NHGB	66.5	66.3	34.2	59.0	56.5	+137	+155	+199	+115	+250	+235	+304	+467
	Glucose						← 51.9 mg./kg./min. (1,037 mg./min.) →							

*Net load, i.e., actual infusion minus urinary loss.

†Abbreviations as follows: EHBF, estimated hepatic blood flow in ml./min.; HV, hepatic venous glucose concentration in mg. per 100 ml.; A, arterial glucose concentration in mg. per 100 ml.; HV-A, hepatic venous minus arterial glucose concentration in mg. per 100 ml.; NHGB, net hepatic glucose balance in mg./min. Figures without preceding sign indicate net hepatic glucose output. Those preceded by + indicate net hepatic uptake of glucose.

the total amount of glucose taken up by the liver increased progressively (table 3). During administration of the large glucose loads, despite variations in both the infused loads (447 to 1,037 mg. per min.) and in the total amount of glucose utilized (45-95 gm.) over the 120-minute period of infusion, an average of 29 per cent of the total glucose utilized was accounted for by a change in net hepatic glucose balance (table 3).

While these significant changes in hepatic glucose balance were associated with moderate to marked elevations of arterial glucose concentration, such hyperglycemia is not necessary for either an hepatic uptake of glucose or hepatic glucose conservation (tables 1 and 3).[7] Hyperglycemia of this magnitude was intentionally induced in an attempt to determine the maximal capacity of the liver to extract glucose and, in this manner, to define the maximal role of the liver in carbohydrate metabolism. When mean arterial blood glucose concentration was raised only 11.6 mg. per 100 ml. (Group I, table 2) by a glucose infusion averaging 70.5 mg. per min., 53.7 per cent of the infused load disappeared from the glucose pool as a consequence of changes in hepatic glucose metabolism (table 3). Moreover, other studies[6,7] from this laboratory, designed to determine the arterial glucose concentration at which hepatic glucose output stopped and hepatic uptake started, revealed that this change occurred at a mean arterial glucose concentration of 116 mg. per 100 ml. Recently Landau, Leonards and Barry, using the triply catheterized dog maintained on a high carbohydrate diet, confirmed these findings.[11] Examination of their data showed that hepatic glucose uptake occurred at a mean arterial plasma glucose concentration of 119 mg. per 100 ml.

Evidence indicating that this capacity of the liver to

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TABLE 2

Mean changes in hepatic glucose balance during glucose loading* of increasing magnitude†

		Control values Minutes					Time during glucose infusion Minutes							
		—30	—20	—10	0	Mean control	15	30	45	60	75	90	105	120
Group I	EHBF	497.0	480.0	509.0	477.0	477.0	413.0	359.0	340.0	305.0	316.0	317.0	328.0	290.0
	HV	81.8	85.5	83.9	86.8	86.8	92.9	91.6	91.7	91.9	92.5	89.7	87.0	88.0
	A	70.5	73.6	69.0	73.1	72.9	82.6	84.3	84.7	84.5	82.4	81.3	78.3	75.5
	HV-A	11.3	11.9	14.9	13.7	13.9	10.3	7.3	7.0	7.4	10.1	8.4	8.7	12.5
	NHGB	54.3	55.9	71.3	69.0	63.2	40.7	20.3	19.6	14.3	22.4	16.4	18.9	22.3
	Glucose						← 3.2 mg./kg./min. (70.5 mg./min.) →							
Group II	EHBF	293.0	260.0	266.0	263.0	271.0	276.0	327.0	319.0	332.0	371.0	471.0	559.0	540.0
	HV	95.5	103.6	95.6	97.1	96.8	160.5	181.0	190.4	199.6	193.8	204.2	200.1	196.2
	A	74.8	75.0	73.5	73.1	73.7	174.3	202.8	217.5	226.3	220.0	228.8	223.7	220.4
	HV-A	20.7	28.6	22.1	24.0	23.1	+13.8	+21.8	+27.1	+26.7	+26.2	+24.6	+23.6	+24.2
	NHGB	56.3	60.9	53.2	53.9	56.3	+34.4	+61.8	+78.1	+81.1	+93.6	+98.0	+94.8	+89.9
	Glucose						← 19.9 mg./kg./min. (494 mg./min.) →							
Group III	EHBF	241.0	269.0	253.0	263.0	259.0	278.0	298.0	333.0	356.0	346.0	335.0	348.0	418.0
	HV	96.8	96.6	94.4	97.8	94.9	167.7	191.3	196.0	199.0	195.4	198.7	193.2	192.4
	A	73.8	71.2	70.1	69.4	70.4	199.4	232.6	239.5	241.5	237.8	236.3	232.2	231.9
	HV-A	23.0	25.4	24.3	28.4	24.5	+31.7	+41.3	+43.5	+42.5	+42.4	+37.6	+39.0	+39.5
	NHGB	53.0	53.2	53.8	71.7	58.8	+86.0	+120.5	+145.0	+153.0	+149.0	+138.0	+133.0	+151.0
	Glucose						← 31.2 mg./kg./min. (704 mg./min.) →							
Group IV	EHBF	251.0	236.0	221.0	208.0	229.0	283.0	345.0	320.0	315.0	340.0	373.0	430.0	458.0
	HV	90.5	91.3	92.0	97.8	92.9	286.0	370.0	423.0	468.0	498.0	554.0	577.0	593.0
	A	68.0	67.3	68.9	71.0	68.8	318.0	409.0	473.0	514.0	563.0	612.0	642.0	672.0
	HV-A	22.5	24.0	23.1	26.8	24.1	+32.0	+39.0	+50.0	+46.0	+65.0	+58.0	+65.0	+79.0
	NHGB	56.7	57.2	44.8	54.5	53.3	+95.0	+130.0	+159.0	+135.0	+220.0	+216.0	+276.0	+367.0
	Glucose						← 50 mg./kg./min. (858 mg./min.) →							

*Net glucose loads, i.e. actual infusion minus urinary loss.
†See table 1 for abbreviations.

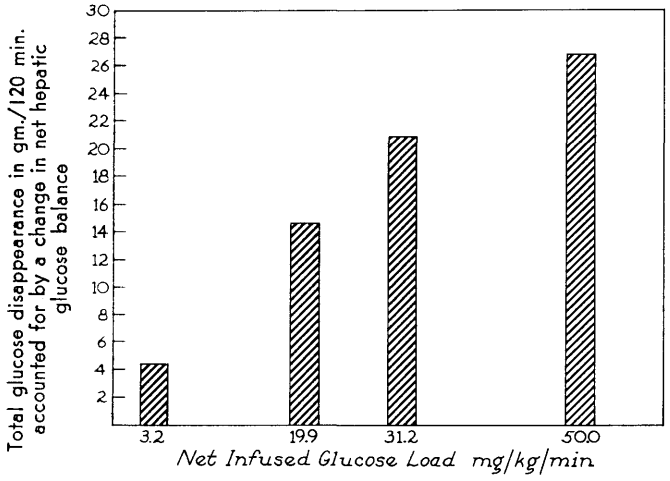

FIG. 2. Effect of increasing glucose loads on total glucose disappearance accounted for by a change in net hepatic glucose balance.

take up glucose during glucose loading is insulin dependent has been reported previously[6] and recently summarized.[7] In additional studies,[12] raising the arterial glucose concentration to levels as high as 901 mg. per 100 ml. in diabetic dogs by glucose infusions failed to result in a net uptake of glucose by the liver. Indeed the liver continued to deliver large amounts of glucose to the glucose pool despite this profound hyperglycemia. However, administration of insulin immediately prior to glucose loading produced an hepatic uptake of glucose at arterial concentrations *lower* than the preinfusion levels.[6,12] The failure of the liver of a diabetic dog to extract glucose despite elevation of arterial blood glucose to 525 mg. per 100 ml., and prompt return of the ability of the liver to take up glucose after brief pretreatment with insulin are illustrated in figures 3 and 4.

The effects of glucose loads on net hepatic glucose balance reported in these studies fail to agree either quantitatively[13,14] or qualitatively[15-17] with the results from isotopic dilution studies designed to characterize the response of the liver to glucose loading. However, these discrepancies can be understood in light of the *fundamental differences in the parameters that each* technic measures. In the present studies net balance of glucose across the liver was determined by measuring total hepatic influx and efflux of glucose. This net balance is the resultant of two opposing processes, i.e., hepatic new glucose production which contributes glucose to the perfusing blood, and hepatic glucose utilization which removes glucose and thereby diminishes efflux. On the other hand, all the isotopic dilution tech-

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TABLE 3

Disposition of infused glucose loads

Dog Group	Dog No.	Net infusion mg./120 min.	Mean hepatic glucose balance mg./min. Control	During infusion	Net hepatic glucose conservation* mg./min.	mg./120 min.	Glucose pool mg. Control	Final	Increase	Peripheral utilization Increase/ 120 min.	Per cent of utilized load accounted for by: Liver	Peripheral tissues
I	1B6	6,350	66.2	34.5	31.7	3,800	2,820	3,010	190	2,360	61.7	38.3
I	1A24	9,900	47.1	6.9	40.2	4,820	3,760	3,890	130	4,950	49.4	50.6
I	1A17	9,120	76.2	38.1	38.1	4,570	3,010	2,990	—20	4,570	50.0	50.0
Mean		8,460	63.2	26.5	36.7	4,400	3,197	3,297	100	3,960	53.7	46.3
II	1K11	58,810	63.9	+37.5	101.4	12,168	3,840	9,780	5,940	37,742	24.4	75.6
II	1C6	53,630	55.8	+79.5	135.3	16,236	3,340	11,670	8,330	29,074	35.8	64.2
II	0K15	65,400	49.3	+78.2	127.5	15,300	3,770	10,890	7,120	42,984	26.3	73.7
Mean		59,280	56.3	+65.1	121.4	14,570	3,650	10,780	7,130	36,600	28.8	71.2
III	0L19	88,940	50.8	+132.0	182.8	21,960	3,350	11,800	8,450	58,530	27.3	72.7
III	0K22	80,850	59.7	+115.0	174.7	20,960	3,270	8,680	5,410	54,776	27.7	72.3
III	0K29	83,700	66.4	+90.8	157.2	18,800	2,900	11,000	8,100	56,800	24.9	75.1
Mean		84,500	59.0	+112.6	171.6	20,570	3,173	10,493	7,320	56,700	26.6	73.4
IV	0L7	81,400	50.0	+142.4	192.4	23,100	2,800	14,000	11,200	47,100	32.9	67.1
IV	0L5	124,500	56.5	+200.7	257.2	30,860	4,000	33,900	29,900	63,740	32.6	67.4
Mean		102,950	53.3	+171.5	224.8	26,980	3,400	23,950	20,550	55,420	32.7	67.3

*Value for mean hepatic glucose balance during infusion subtracted from mean control hepatic glucose output, where liver was still putting out glucose, and added to mean control when a net uptake of glucose by the liver was observed.

nics[13-17] measure only new glucose production assumed to be hepatic in origin in its entirety. Such technics do not quantitate net hepatic glucose balance, nor can they distinguish hepatic glucose utilization from peripheral glucose utilization.[1] Therefore, the maximal change in hepatic glucose metabolism which such technics are capable of detecting during glucose loading can be no greater than the initial magnitude of hepatic new glucose production. The latter, in the postabsorptive state, has been shown to be similar to the hepatic glucose output (figure 5, part A).[18] Even if glucose loading resulted in a prompt decline in hepatic new glucose production, the data from the present study indicate that all isotopic dilution technics would seriously underestimate the changes in hepatic glucose metabolism which attend glucose loading (figure 5, parts B and C); the greater the glucose load the greater the discrepancy between the actual changes in net hepatic glucose balance and the changes measured by isotopic dilution technics (figure 5, part D). For these reasons, such isotopic dilution methods are not technically suited for defining the role of the liver in the disposition of glucose loads. Despite the fact that the terms "hepatic new glucose production" and "net hepatic glucose balance" are not synonymous, they continue to be confused and used interchangeably.[4,11,17]

While the data from the present studies provide evidence for the importance of the liver in blood glucose homeostasis during glucose loading, they probably represent an underestimation of the magnitude of its physiological role in the intact organism following a carbohydrate meal. In these studies on dogs with portacaval shunts, the endogenous insulin secreted under the impact of a rising blood glucose concentration reached

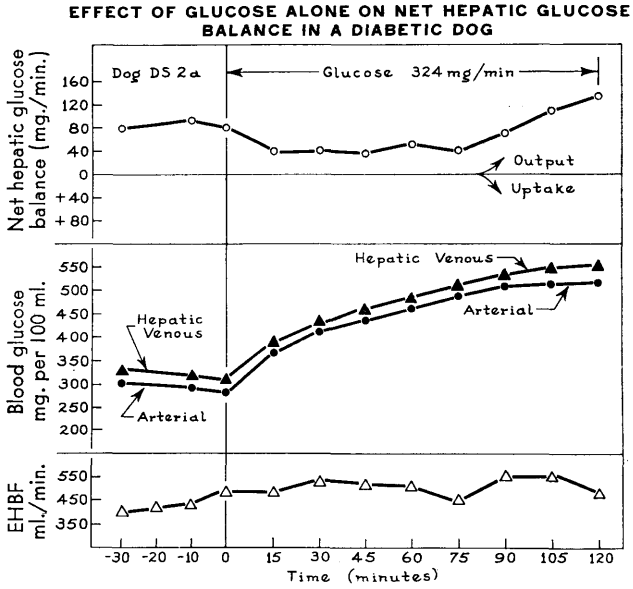

FIG. 3. Effect of glucose alone on net hepatic glucose balance in a diabetic dog. Although arterial blood glucose was raised to 525 mg. per 100 ml., hepatic glucose uptake was not observed.

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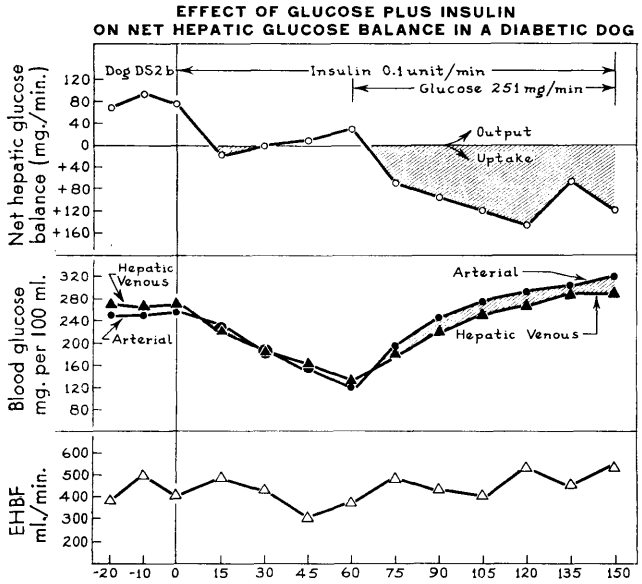

FIG. 4. Effect of brief pretreatment with insulin on net hepatic glucose balance during glucose loading in a diabetic dog. The administration of a glucose load in the same diabetic dog following pretreatment with insulin for only one hour resulted in uptake of glucose by the liver at an arterial glucose concentration of 196 mg. per 100 ml., a value 58 mg. per 100 ml. below the fasting control.

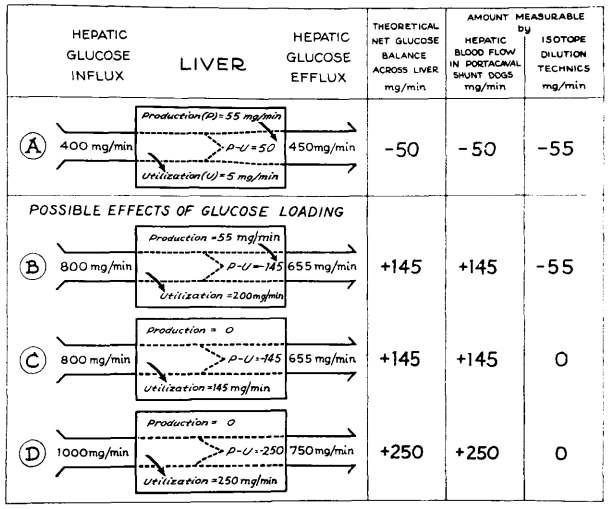

FIG. 5. Comparison of the theoretical changes in net hepatic glucose balance during glucose loading with those measured by the hepatic blood flow technic in dogs with portacaval shunts and by the isotopic glucose-C-14 dilution technics in the intact dog. The label A describes the conditions in the fasting state prior to glucose loading. Labels B, C, and D identify the possible changes in net hepatic glucose balance which may occur during glucose loading. Hepatic glucose efflux is equal to hepatic glucose influx plus hepatic glucose production minus hepatic glucose utilization. The theoretical change in net hepatic glucose balance is compared with the change which each method is technically capable of measuring. See text for details.

the peripheral circulation without first traversing the liver. In addition the glucose loads were infused into a peripheral vein. Under such circumstances, the peripheral tissues and the liver were exposed to identical concentrations of glucose and of insulin, a situation quite dissimilar from that which obtains during a carbohydrate meal in an intact animal. In the latter instance, all the secreted insulin and absorbed glucose first enter the portal circulation. As a consequence, the liver is exposed to concentrations and amounts of insulin and glucose not possible for any other tissue. Moreover, a large amount of this insulin is bound to the liver during its initial transhepatic passage.[19,20] It is not unreasonable, therefore, to infer that under such physiological circumstances the liver would be expected to play an even greater role in the disposition of ingested carbohydrate than has been herein demonstrated.

SUMMARY AND CONCLUSION

The quantitative importance of the liver in the disposition of glucose loads was studied in eleven dogs by examining the capacity of the liver to take up glucose during the infusion of graded loads of glucose varying from 53 to 1,037 mg. per min. Dogs with portacaval shunts were used to permit measurement of net hepatic rather than splanchnic glucose balance.

The data indicate that, at all levels of glucose administration, the liver plays a quantitatively significant role in disposing of the infused loads. The greater the glucose load, the greater the amount of glucose disposed of by a change in net hepatic glucose balance. With large loads not only did hepatic glucose output cease, but the liver extracted in excess of 200 mg. of glucose per min. from the perfusing blood, resulting in a net hepatic glucose conservation of as much as 13.5 gm. per hr. With small glucose loads averaging 70.5 mg. per min., the liver accounted for the disappearance of 53.7 and the peripheral tissues for 46.3 per cent of the infused load. When large loads varying from 447 to 1,037 mg. per min. were administered, no less than 24.4 per cent and an average of 29 per cent of the utilized load disappeared from the glucose pool as a consequence of a change in hepatic glucose balance.

SUMMARIO IN INTERLINGUA

Le Signification Physiologic del Secretion de Insulina Endogene ad in le Circulation Portal.

V. Le Importantia Quantitative del Hepate in le Disposition de Cargas de Glucosa

Le importantia quantitative del hepate in le disposition de cargas de glucosa esseva studiate in dece-un canes per medio de un examine del capacitate del hepate de acceptar glucosa durante le infusion de graduate

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cargas de glucosa amontante a inter 53 e 1.037 mg per minuta. Canes con shunting porto-caval esseva usate pro render possibile le mesuration del balancia de glucosa nettemente hepatic plus tosto que splanchnic.

Le datos indica que a omne nivellos del administration de glucosa, le rolo del hepate es quantitativemente significative in le disposition del infundite cargas. Quanto plus grande le carga de glucosa, tanto plus grande es etiam le quantitate de glucosa reflectite in le alteration del nette balancia de glucosa hepatic. In caso de grande cargas, le rendimento hepatic de glucosa cessava, sed non solmente isto: le hepate, in plus, extraheva glucosa in quantitates superior a 200 mg per minuta ex le perfusionante sanguine, con le resultato de un nette conservation de glucosa hepatic de usque a 13,5 g per minuta. In caso de micre cargas de glucosa amontante al media a 70,5 mg per minuta, le hepate esseva responsabile pro le disparition de 53,7 pro cento del infusionate carga e le tissus peripheric pro 46,3 pro cento. Quando grande cargas—i.e. cargas de inter 447 e 1.037 mg per minuta—esseva administrate, non minus que 24,4 pro cento (al media 29 pro cento) del utilisate carga dispareva ab le stock de glucosa in consequentia de un alteration in le balancia hepatic de glucosa.

ACKNOWLEDGMENT

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DR. LEVINE: Thank you very much, Dr. Madison, for the additional data from your laboratory in connection with this problem. Dr. Richard de Bodo, as Dr. Ellenberg has indicated, has worked for many years in the area of insulin action, as well as its interrelation to the antagonistic hormones. In the last few years he has contributed some elegant studies on the action of insulin and has discovered the so-called "braking effect" to which Dr. Weinhouse has alluded. We are all eager to hear of Dr. de Bodo's work and conclusions.

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