EPINEPHRINE HYPERGLYCEMIA

With Particular Reference to the Arteriovenous Blood Sugar Difference in Hepatic Disease

By A. CANTAROW and G. RICCHIUTI

(From the Laboratory of Biochemistry and the Department of Medicine,
Jefferson Hospital, Philadelphia)

Interest in the significance of the post-absorptive arteriovenous blood sugar difference was stimulated by the early observations of Hagedorn (1), Holst (2), Foster (3) and Henriques and Ege (4). The great advances made during the past decade in our knowledge of carbohydrate metabolism have thrown considerable light upon the mechanisms involved in the production of normal and abnormal blood sugar responses to the ingestion of glucose. Friedenson, Rosenbaum, Thalheimer and Peters (5) believe that the initial rise of arterial and venous blood sugar is an expression of the absorption of glucose from the intestine. The subsequent fall in the bood sugar concentration is the result of two factors: (1) removal of sugar by the liver to form glycogen and (2) removal of sugar by the tissues, especially muscle, for the formation of glycogen and for combustion. The arteriovenous blood sugar difference, i.e., the difference between the quantity of sugar supplied to and that leaving the tissues, is naturally assumed to represent the quantity stored or otherwise utilized in the tissues. These authors state that one should expect certain abnormalities in the curve of alimentary glycemia in individuals with hepatic disease: namely, an excessively high or prolonged blood sugar response, because glucose is not removed in the normal manner from the blood by the liver, but with retention of the normal arteriovenous difference, the ability of the tissues to utilize glucose being unimpaired. The observations of Friedenson and his associates (5) were well in accord with these theoretical expectations. However, it was found that the range of normal variation was so wide and the deviation from the normal in some cases of hepatic disease so slight, that this method of investigation was considered to be of doubtful value in the study of such patients.

The effect of epinephrine on carbohydrate metabolism has been rather clearly demonstrated in recent years although certain important phases of its action are still obscure. The extensive literature which has arisen in this connection cannot be reviewed here in detail; an excellent discussion of the subject is available in the recent review by Cori (6). A few sig-

nificant points may, however, be mentioned. In 1906, Velich (7) found that epinephrine glycosuria, first demonstrated by Blum in 1901 (32), did not develop in the hepatectomized frog. The important part played by the liver in the production of epinephrine hyperglycemia was also demonstrated by Mann (8) and Soskin (9), who showed that the injection of epinephrine has no effect on the blood sugar of hepatectomized dogs. Observations such as these naturally suggest that the rise in blood sugar caused by this substance is due to increased glycogenolysis in the liver.

It soon became apparent, however, that this factor alone does not suffice to explain the effects of epinephrine on carbohydrate metabolism (viz. the observation of Cori and Cori (10a) that the liver glycogen content of rats to which glucose was administered remained unchanged or was increased after the injection of epinephrine). Bodo, Benaglia and Friedman (11) found that a post-epinephrine increase in hepatic glycogen occurred only in animals (dogs) fasted for 6 to 14 days, a definite decrease being noted in fed animals. The preponderance of evidence, however, is in accord with the findings of Cori and Cori (10a). The work of Cori and Cori (10b, c), Zimmermann (12), Geiger (13), Corkill and Marks (14), Goldblatt (15) and others indicates rather definitely that acceleration of glycogenolysis in the muscles, with decrease in their glycogen content, is one of the significant physiological effects of epinephrine. Cori (6) argues that the fundamental action of this hormone in liver and muscle is the same, namely, increased glycogenolysis, the chief end product in the liver being glucose and in the muscles lactic acid. The decrease in muscle glycogen after the administration of epinephrine is due to the fact that glycogenolysis proceeds more rapidly than new formation of muscle glycogen; the secondary increase in liver glycogen is due to the fact that, after a brief interval, hepatic glycogen formation proceeds more rapidly than hepatic glycogenolysis. The action of epinephrine may be therefore summarized as follows: increased glycogenolysis in the liver and muscles, decreased carbohydrate utilization in the muscles, with consequent increased formation of lactic acid which subsequently increases the glycogen content of the liver. Loeb, Reeves and Glasier (16) state that epinephrine hyperglycemia results from an initial, transient glycogenolysis in the liver, the hyperglycemia being then maintained by decreased glucose utilization in the muscles.

Markowitz (17) and Olmsted and Coulthard (18) concluded that the blood sugar response to the injection of epinephrine depends to a considerable degree upon the glycogen content of the liver. Brill (19), Brill and Fitz-Hugh (20), Kugelmann (21) and Loeb, Reeves and Glasier (16) found that this response was not as great in individuals with hepatic disease as in normal persons, who show an average increase of 35 to 45 mgm. per 100 cc., usually within one-half to one hour. However, there was no apparent definite correlation between the severity of liver damage and the

blood sugar response, and the findings in border-line cases with slight hepatic lesions were in many cases essentially normal.

PRESENT INVESTIGATION

We have studied the concentration of sugar in capillary and venous blood following the injection of epinephrine in 16 individuals without and 31 patients with some lesion of the liver or bile passages. Blood sugar determinations were made upon capillary and venous blood obtained simultaneously in the fasting state and 30, 60 and 120 minutes after the intramuscular injection of 1 cc. of a 1–1000 solution of epinephrine, the site of injection being thoroughly massaged. The 1931 micro method of Benedict (22) was employed in all determinations, being checked by parallel determinations by the 1931 macro method of Benedict (22) upon the venous blood samples. In accordance with the findings of the great majority of workers, the sugar content of capillary blood, obtained by deep puncture of the finger, is regarded as practically identical with that of arterial blood and is designated " arterial-blood " sugar for purposes of convenience. Jonas (23) has recently reported a considerable variation between arterial and capillary blood sugar values but this is contrary to the experience of the majority of workers, particularly if care is exercised to insure a deep puncture.

The experimental material was as follows: (1) 16 patients with no evidence of disease of the liver or bile passages; (2) 6 patients with non-calculous cholecystitis; (3) 5 patients with cholelithiasis; (4) 2 patients with obstructive jaundice due to carcinoma of the pancreas; (5) 4 patients with advanced carcinoma of the liver, one primary and three secondary; (6) 6 patients with " catarrhal " jaundice; (7) 2 patients with post-arsphenamine jaundice; (8) 6 patients with portal cirrhosis. The detailed findings are presented in the accompanying charts.

RESULTS

No hepatic or biliary tract disease (16 cases)

The data obtained in this group are presented in Table I. The fasting arterial blood sugar concentration varied between 63 and 95 mgm. (average 81) and the venous blood sugar between 62 and 93 mgm. (average 79) per 100 cc. In our experience, the normal range by the method employed is from 60 to 105 mgm. per 100 cc. Following the administration of epinephrine, the maximum rise above the resting level ranged from 34 to 74 mgm. (average 47) in the arterial blood and 28 to 63 mgm. (average 36) in the venous blood. The maximum increase in the arteriovenous blood sugar difference, above that present in the fasting state, ranged from 3 to

29 mgm. (average 14) per 100 cc. The peak of both arterial and venous blood sugar curves occurred in the 60 minute sample in 6 cases, and in the 30 minute sample in 10 cases. The maximum arteriovenous blood sugar difference was present at 60 minutes in 10 cases, at 30 minutes in 4 cases and at 120 minutes in 2 cases.

TABLE I

Extra-hepatic disease

Case	Condition	Serum bilirubin*	Bromsulphalein retention	Blood sugar						
					Minutes after epinephrine				Maximum rise	Maximum increase A-V†
					0	30	60	120		
		mgm. per 100 cc.	per cent		mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.
C. E.	Hysteria	0.36	0	A*	86	121	133	102	47	16
				V*	86	110	117	88	31	
L. O.	Normal			A	90	160	151	116	70	9
				V	90	152	142	107	62	
A. B.	Emphysema	0.48	0	A	82	117	133	83	51	21
				V	82	100	112	86	30	
A. P.	Convalescent pneumonia			A	63	137	133	76	74	24
				V	62	125	108	66	63	
L. M.	Osteoarthritis			A	80	142	133	102	62	16
				V	80	133	117	100	53	
W. F.	Autonomic imbalance			A	83	117	105	90	34	3
				V	76	111	100	80	35	
S. L.	Sacro-iliac sprain	0.36	0	A	72	101	136	101	64	16
				V	69	82	119	85	50	
E. B.	Ureteral calculus	0.26	0	A	84	106	148	104	64	19
				V	81	95	126	88	45	
A. R.	Psychoneurosis			A	74	131	114	68	57	14
				V	74	117	100	62	43	

TABLE I (*continued*)

Case	Condition	Serum biliru-bin*	Brom-sulph-alein reten-tion		Blood sugar					
					Minutes after epinephrine				Maxi-mum rise	Maxi-mum in-crease A-V†
					0	30	60	120		
		mgm. per 100 cc.	*per cent*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
R. C.	Prostatitis	0.51	0	A	⁻75	127	112	80	52	18
				V	74	119	93	74	45	
G. W.	Osteoarthritis			A	80	117	111	100	37	11
				V	80	108	100	95	28	
P. S.	Emphysema	0.44	0	A	95	125	142	125	47	12
				V	90	111	133	108	43	
H. H.	Neurosis	0.43	0	A	73	140	108	86	67	21
				V	71	117	86	66	46	
M. B.	Colitis	0.3	0	A	95	151	133	107	56	18
				V	93	131	125	95	38	
V. M.	Anthracosis			A	78	111	142	90	64	29
				V	77	100	112	76	35	
W. B.	Mitral stenosis	0.25	0	A	83	131	111	91	50	8
				V	82	125	102	83	43	
Average				A	81	127	128	95	47	14
				V	79	115	112	85	36	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

Non-calculous cholecystitis (6 cases)

The data obtained in this group are presented in Table II. The fasting arterial blood sugar concentration varied between 73 and 111 mgm. (average 92) and the venous blood sugar between 71 and 110 mgm. (average 92) per 100 cc. Following the administration of epinephrine, the maximum rise above the resting level ranged from 17 to 70 mgm. (average 33) in the arterial blood and from 12 to 56 mgm. (average 28) in the venous

blood. The maximum increase in the arteriovenous blood sugar differ-
ence, above that present in the fasting state, ranged from 3 to 27 mgm.
(average 10) per 100 cc. The peak of both arterial and venous blood sugar
curves occurred in the 60 minute sample in 3 cases, in the 30 minute sample

TABLE II

Cholecystitis

Case	Serum bilirubin	Brom-sulph-alein retention	Blood sugar						
				Minutes after epinephrine				Maximum rise	Maximum increase A-V†
				0	30	60	120		
	mgm. per 100 cc.	*per cent*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
W. S.	0.34	0	A*	93	121	149	104	56	14
			V*	95	133	137	100	42	
D. S.	0.6	0	A	90	129	105	76	39	4
			V	90	125	102	72	35	
J. R.	1.32	0	A	111	181	142	115	70	14
			V	110	166	132	111	56	
M. C.	0.55	0	A	73	80	90	80	17	8
			V	71	83	80	74	12	
F. L.	0.52	0	A	92	131	139	99	47	27
			V	93	105	116	90	23	
J. K.	2.68	55	A	95	111	121	104	26	3
			V	93	111	119	99	26	
Average			A	92	125	124	96	33	10
			V	92	120	114	91	28	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

in 2 cases and in 1 case the maximum arterial blood sugar value was attained
at 60 minutes and the maximum venous blood sugar value at 30 minutes.
The maximum arteriovenous difference was present at 60 minutes in 2
cases, at 30 minutes in 3 cases and at 120 minutes in 1 case.

Cholelithiasis (5 cases)

The data obtained in this group are presented in Table III. The fasting arterial blood sugar concentration varied between 82 and 106 mgm. (average 90) and the venous blood sugar between 82 and 105 mgm. (aver-

TABLE III

Cholelithiasis

Case	Serum bilirubin	Brom-sulph-alein retention		Blood sugar					
				Minutes after epinephrine				Maximum rise	Maximum increase A-V†
				0	30	60	120		
	mgm. per 100 cc.	per cent		mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.
L. P.	1.45	60	A*	82	90	104	86	22	8
			V*	82	89	100	78	18	
H. C.	2.2	35	A	88	114	130	97	42	12
			V	86	109	123	83	37	
J. N.	5.6	100	A	106	143	163	129	57	11
			V	105	131	153	118	48	
A. C.	1.28	15	A	85	112	133	111	48	13
			V	85	99	121	100	36	
T. F.	41.6	100	A	87	160	147	94	60	6
			V	86	153	144	93	58	
Average			A	90	124	135	103	45	8
			V	89	116	128	94	39	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

age 89) per 100 cc. Following the administration of epinephrine, the maximum rise above the resting level ranged from 22 to 60 mgm. (average 45) in the arterial blood and from 18 to 58 mgm. (average 39) in the venous blood. The maximum increase in the arteriovenous blood sugar difference, above that present in the fasting state, ranged from 6 to 13 mgm. (average 8) per 100 cc. The peak of both arterial and venous blood sugar curves occurred in the 60 minute sample in 4 cases and in the 30 minute

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sample in 1 case.   The maximum arteriovenous difference was present at 30 minutes in 3 cases and at 120 minutes in 2 cases.

Carcinoma of pancreas (2 cases)

The data obtained in this group are presented in Table IV.   The fasting arterial blood sugar concentrations were 108 and 112 mgm. (average 110) and the venous blood sugars 111 and 114 mgm. (average 112) per

TABLE IV

Carcinoma of pancreas

Case	Serum bilirubin	Brom-sulph-alein retention	Blood sugar						
				Minutes after epinephrine				Maximum rise	Maximum increase A-V†
				0	30	60	120		
	mgm. per 100 cc.	*per cent*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
A. R.	27.2	100	A*	108	123	137	115	29	8
			V*	111	118	133	114	22	
J. S.	16.7	100	A	112	147	166	148	54	16
			V	114	133	155	141	41	
Average			A	110	135	151	131	41	12
			V	112	125	144	127	32	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

100 cc.   Following the administration of epinephrine, the maximum rise above the resting level was 29 and 54 mgm. (average 41) in the arterial blood and 22 and 41 mgm. (average 32) in the venous blood.   The maximum increase in the arteriovenous difference, above that present in the fasting state, was 8 and 16 mgm. (average 12) per 100 cc., respectively. The peak of both arterial and venous blood sugar curves occurred in the 60 minute sample in both cases.   The maximum arteriovenous difference was present at 30 minutes in both cases.

Carcinoma of liver (4 cases)

The data obtained in this group are presented in Table V.   The fasting arterial blood sugar concentration varied between 63 and 111 mgm. (average 81) and the venous blood sugar between 62 and 111 mgm. (average

TABLE V

Carcinoma of liver

Case	Serum bilirubin	Brom-sulph-alein retention		Blood sugar						
					Minutes after epinephrine				Maxi-mum rise	Maxi-mum in-crease A-V†
				0	30	60	120			
	mgm. per 100 cc.	*per cent*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	
D. B.	1.72	55	A*	63	64	60	59	1	0
			V*	62	64	59	58	2	
J. C.	8.0	40	A	71	82	88	87	17	7
			V	68	72	83	79	15	
C. L.	4.0	80	A	80	90	95	86	15	0
			V	71	83	86	81	15	
F. M.	1.92	30	A	111	117	129	114	18	4
			V	111	113	125	111	14	
Average			A	81	88	93	86	12	2
			V	78	83	88	82	10	

* A = arterial blood; V = venous blood.

† Maximum increase in arteriovenous difference.

78) per 100 cc. Following the administration of epinephrine, the maximum rise above the resting level ranged from 1 to 18 mgm. (average 12) in the arterial blood and from 2 to 15 mgm. (average 10) in the venous blood. The maximum increase in the arteriovenous difference, above that present in the fasting state, ranged from 0 to 7 mgm. (average 2) per 100 cc. The peak of both arterial and venous blood sugar curves occurred in the 60 minute sample in 3 cases and in the 30 minute sample in 1 case. The maximum arteriovenous difference was present at 30 minutes in the 2 cases in which an increase in this factor was noted.

"Catarrhal jaundice" (6 cases)

The data obtained in this group are presented in Table VI. The fasting arterial blood sugar concentration varied between 86 and 99 mgm. (average 93) and the venous blood sugar between 84 and 99 mgm. (average 91) per 100 cc. Following the administration of epinephrine, the

TABLE VI

Catarrhal jaundice

Case	Serum bilirubin	Brom-sulph-alein retention	Blood sugar						Maximum rise	Maximum increase A-V†
				Minutes after epinephrine						
				0	30	60	120			
	mgm. per 100 cc.	*per cent*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
R. H.	13.32	100	A*	93	136	112	100	43	5
			V*	93	133	111	95	40	
C. T.	11.0	100	A	95	108	106	100	13	13
			V	94	102	105	86	11	
M. K.	14.1	100	A	86	100	136	104	50	5
			V	84	101	132	97	48	
E. H.	18.6	100	A	92	95	102	103	11	4
			V	88	91	96	95	8	
F. H.	15.33	100	A	99	105	121	95	22	9
			V	99	105	114	86	15	
M. D.	3.52	10	A	91	111	119	97	28	3
			V	89	106	114	92	25	
Average			A	93	109	116	100	23	6
			V	91	106	112	92	21	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

maximum rise above the resting level ranged from 11 to 50 mgm. (average 23) in the arterial blood and from 8 to 48 mgm. (average 21) in venous blood. The maximum increase in the arteriovenous difference, above that present in the fasting state, ranged from 3 to 13 mgm. (average 6) per 100 cc. The peak of both arterial and venous blood sugar curves occurred in the 60 minute sample in 3 cases, in the 30 minute sample in 1 case; in 2 instances the maximum arterial values occurred at 30 and 120 minutes respectively and the maximum venous values at 60 minutes. The maximum arteriovenous difference was present at 30 minutes in 1 case and at 120 minutes in 5 cases.

Post-arsphenamine jaundice (2 cases)

The data obtained in this group are presented in Table VII. The fasting arterial blood sugar concentrations were 71 and 72 mgm. and the venous blood sugars 62 and 70 mgm. per 100 cc. Following the adminis-

TABLE VII

Post-arsphenamine jaundice

Case	Serum bilirubin	Brom-sulph-alein retention		Blood sugar					
				Minutes after epinephrine				Maxi-mum rise	Maxi-mum in-crease A-V†
				0	30	60	120		
	mgm. per 100 cc.	*per cent*		*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*	*mgm. per 100 cc.*
R. B.	12.8	100	A*	71	74	80	66	9	0
			V*	62	71	73	64	11	
J. B.	10.4	100	A	72	78	86	75	14	4
			V	70	76	80	69	10	
Average			A	71	76	83	70	12	2
			V	66	73	76	66	10	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

tration of epinephrine, the maximum rise above the resting level was 9 and 14 mgm. in the arterial blood and 11 and 10 mgm. in the venous blood. The maximum increase in the arteriovenous difference, above that present in the fasting state, was 0 and 4 mgm. per 100 cc. respectively. The peak of both arterial and venous blood sugar curves occurred in the 60 minute sugar sample in both cases.

Portal cirrhosis (6 cases)

The data obtained in this group are presented in Table VIII. The fasting arterial blood sugar concentration varied between 78 and 92 mgm. (average 85) and the venous blood sugar between 74 and 86 mgm. (average 81) per 100 cc. Following the administration of epinephrine, the maximum rise above the resting level ranged from 10 to 24 mgm. (average 16) in the arterial blood and from 9 to 25 mgm. (average 15) in the venous blood. The maximum increase in the arteriovenous difference, above that present in the fasting state, ranged from 0 to 15 mgm. per 100 cc. The

TABLE VIII

Portal cirrhosis

Case	Serum bilirubin	Brom-sulph-alein retention		Blood sugar					
				Minutes after epinephrine				Maxi-mum rise	Maxi-mum in-crease A-V†
				0	30	60	120		
	mgm. per 100 cc.	per cent		mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.	mgm. per 100 cc.
J. F.	2.6	15	A*	90	93	100	96	10	0
			V*	83	93	97	97	14	
A. B.	1.2	40	A	82	87	90	95	13	4
			V	82	85	89	91	9	
F. W.	0.56	0	A	78	102	93	86	24	15
			V	78	100	82	71	22	
S. K.	1.6	20	A	78	88	98	88	20	4
			V	74	80	94	84	20	
H. M.	0.44	0	A	90	97	114	106	24	2
			V	86	95	111	100	24	
G. R.	2.43	55	A	90	102	111	86	21	7
			V	85	90	104	84	19	
Average			A	85	95	101	93	16	1
			V	81	90	96	88	15	

* A = arterial blood; V = venous blood.
† Maximum increase in arteriovenous difference.

peak of both arterial and venous blood sugar curves occurred in the 60 minute sample in 4 cases, in the 30 minute sample in 1 case and in the 120 minute sample in 1 case. The maximum arteriovenous difference was present at 30 minutes in 2 cases and at 120 minutes in 3 cases.

DISCUSSION

Our findings with regard to the changes in the arteriovenous blood sugar difference in individuals without hepatic disease differ from those of Wiechmann (24), Cori and Cori (25) and Samson and Jacobs (26).

These authors observed no increase in the arteriovenous difference in normal men and animals following the injection of epinephrine and concluded that the increased tissue utilization of glucose, which occurs during alimentary hyperglycemia, does not take place during epinephrine hyperglycemia. We cannot explain this discrepancy. However, Jonas (23), in a few instances, noted an increase above the fasting difference one hour after the injection of 1 cc. of epinephrine. Furthermore, the observations of Samson and Jacobs (26) were made at intervals of several hours after the administration of epinephrine was begun and at subsequent varying intervals during its continuous injection into the blood stream. Their data are therefore not comparable to those reported here, which represent a rapid and transient response to the injection of this agent. In connection with the observed variations in the hepatic glycogen content following epinephrine administration, Cori (6) has pointed out that data of this sort can be compared only if obtained under identical conditions, and that the basic action of a hormone in one direction is often obscured by simultaneous or subsequent changes which it produces in other directions.

Our findings with regard to the degree of epinephrine hyperglycemia in individuals without hepatic disease are in accord with those of other observers previously referred to. The glycemic response in the patients with cholecystitis, cholelithiasis and carcinoma of the pancreas was extremely variable and was apparently unrelated to the degree of hyperbilirubinemia or bromsulphalein retention. If the extent of the initial hyperglycemia is assumed to be an index of the readily available glycogen reserve of the liver, this lack of correlation may be regarded as indicative of dissociation of impairment of excretory and metabolic functions of the liver in disease of the biliary tract. This has been emphasized by Cantarow (27), Althausen (28) and Cantarow and Gehret (29). A few of the cases of cholecystitis (Table II) and cholelithiasis (Table III) and one case of carcinoma of the pancreas (Table IV) showed a venous blood sugar response which might be regarded as subnormal (increase less than 30 mgm. per 100 cc.). A subnormal response was observed in similar cases by Loeb, Reeves and Glasier (16).

Although there was a marked degree of variation in the maximum increase in the arteriovenous blood sugar difference, the average values in the groups of patients with cholecystitis and cholelithiasis were slightly below that observed in the non-hepatic group. However, no significance can be attached to this fact because of the small number of cases and the extreme variation in the findings. One point of interest, however, is the fact that the increase in the arteriovenous difference bore no apparent relation to the rise in either the arterial or the venous blood sugar level. This was also true of the control group. It may be of interest to note that Case W. F. of the latter group, in which the arteriovenous difference increased only 3 mgm. per 100 cc., had marked autonomic imbalance, which may con-

ceivably have influenced the response to epinephrine. Excluding this case, the smallest increase in the A–V difference in the control group was 8 mgm. per 100 cc.

Of the group of 18 patients with various forms of intrahepatic disease, including metastatic and primary carcinoma of the liver (Table V), " catarrhal jaundice " (Table VI), post-arsphenamine jaundice (Table VII), and portal cirrhosis (Table VIII), in only 2 did the venous blood sugar increase 30 mgm. or more per 100 cc.; both of these were patients with " catarrhal jaundice " (Cases R. H. and M. K., Table VI). In the remainder, the blood sugar curves were essentially the same as those obtained by Brill and Fitz-Hugh (20), Brill (19), Kugelmann (21), and Loeb, Reeves and Glasier (16) in individuals with advanced intrahepatic disease. In these cases, too, the discrepancies between the degree of epinephrine hyperglycemia, bilirubinemia and retention of bromsulphalein are striking. Of particular interest in these groups of patients are the changes in the arteriovenous blood sugar difference. The maximum increase in this fraction was below 8 mgm. per 100 cc. in all but 3 cases; two of these were patients with " catarrhal jaundice " (Cases C. T. and F. H., Table VI) and one was a patient with portal cirrhosis (Case F. W., Table VIII). Essentially normal findings were obtained in 3 of the 6 patients with " catarrhal jaundice " upon repetition of the studies following recovery. The average values for this group during the height of the attack and during convalescence are presented in Figures 1 and 2.
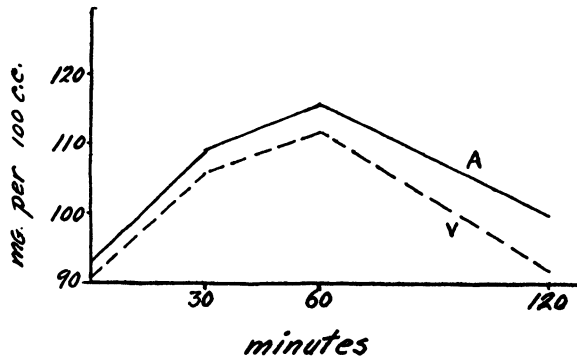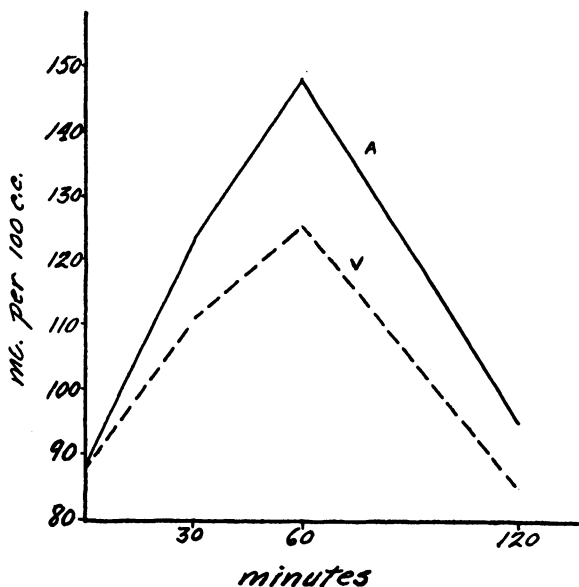

FIG. 1. AVERAGE POST-EPINEPHRINE ARTERIAL (*A*) AND VENOUS (*V*) BLOOD SUGAR VALUES IN 6 PATIENTS WITH " CATARRHAL JAUNDICE "

The significance of these observations is conjectural. They confirm the findings of previous investigators with regard to the subnormal glycemic response to epinephrine in patients with intrahepatic disease. We believe that the subnormal response in occasional patients with cholecystitis and cholelithiasis may be of significance in suggesting possible depletion of hepatic glycogen, even though no evidence of hepatic disease may be

demonstrable clinically.   It is of interest to note that although Loeb and his associates (16) obtained in patients with hepatic disease results like those observed in other patients with a variety of disorders, these conditions were in many instances of such a nature as might be expected to be associated with a low hepatic glycogen content.   These authors advance the hypothesis that this subnormal response to epinephrine may be dependent, not upon depleted hepatic glycogen stores but upon inhibition of certain epinephrine effects by factors still unknown.   Although this view is sup-

FIG. 2. AVERAGE POST-EPINEPHRINE ARTERIAL (*A*) AND VENOUS (*V*) BLOOD SUGAR VALUES IN 3 PATIENTS CONVALESCING FROM " CATARRHAL JAUNDICE "

ported by their studies of blood lactic acid in these conditions, the former and more widely accepted opinion is the more plausible.

The frequently subnormal A–V difference in patients with intrahepatic disease is incapable of satisfactory explanation at the present time.   A very logical explanation would be that the extent of removal of glucose from arterial blood in the tissues is diminished in such cases because the degree of elevation of the arterial blood sugar concentration is subnormal.   Holst (2) stated that the magnitude of the A–V difference varies directly with the existing degree of hyperglycemia following the ingestion of glucose. However, this view is not supported by the observations of Friedenson and his associates (5) nor by the data presented here.   This factor may, however, play some part in the production of this deviation from the normal response.   The decreased A–V difference is suggestive of inhibition of glucose utilization by the muscles, which is generally recognized as one of the

important effects of epinephrine upon carbohydrate metabolism. Why this particular action should be exaggerated in the presence of hepatic disease, however, is difficult to understand. The point raised by Soskin, Priest and Schutz (30) may be of importance in this connection. These observers state that, according to the dosage employed, epinephrine either increases or decreases the blood flow through the muscles; this variability, they say, together with the hemoconcentrating effect of the hormone, renders inaccurate any observations of the arteriovenous blood sugar difference. Although the dosage of epinephrine employed in this study was identical in all cases, the well-recognized individual variation in the vascular response to this hormone, particularly in disease states, may have been responsible in part for the supposed changes in the A–V blood sugar difference in patients with intrahepatic disease. On the other hand, it may be that these changes are dependent upon decreased peripheral utilization of glucose resulting from diminished insulin activity. This may be due to a quantitative decrease in what Himsworth (31) has termed insulin-kinase, the hypothetical " activator " of insulin, which he believes to be diminished in the presence of intrahepatic disease.

SUMMARY

1. Studies were made of the deep capillary (arterial) and venous blood sugar concentration before and 30, 60 and 120 minutes after the injection of 1 cc. of epinephrine in 16 individuals without and 31 patients with some lesion of the liver or bile passages.

2. In the control group, the arterial blood sugar showed an average increase of 47 mgm. and the venous blood sugar 36 mgm. per 100 cc. The arteriovenous blood sugar difference showed an average maximum increase of 14 mgm. per 100 cc. above the resting level.

3. The glycemic response in patients with cholecystitis, cholelithiasis and pancreatic carcinoma was extremely variable and was apparently unrelated to the degree of hyperbilirubinemia or bromsulphalein retention. A subnormal response was obtained in 5 cases in these groups.

4. Of the group of 18 patients with various forms of intrahepatic disease, including metastatic and primary carcinoma of the liver, " catarrhal jaundice," portal cirrhosis and post-arsphenamine jaundice, only 2 exhibited a normal glycemic response to epinephrine. There was a striking discrepancy between the degree of epinephrine hyperglycemia and that of bilirubinemia and bromsulphalein retention.

5. The post-epinephrine increase in the arteriovenous blood sugar difference was extremely variable in the patients with disease of the bile passages but tended to be slightly below the average of the control group. This factor was rather consistently and markedly subnormal in the patients with intrahepatic disease.

6. It is believed that the subnormal glycemic response to epinephrine in patients with disease of the liver and bile passages is probably indicative of a state of hepatic glycogen depletion or unavailability. This may at times occur in the absence of clinically demonstrable evidence of hepatic disease.

7. The observed variations in the post-epinephrine arteriovenous blood sugar difference cannot be explained at the present time and may be of little significance. They may possibly be dependent upon diminished peripheral utilization of glucose in the presence of hepatic disease, due perhaps to decreased insulin activity.

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