FURTHER OBSERVATIONS ON THE CIRCULATORY ACTIONS OF DIGITALIS AND STROPHANTHUS WITH SPECIAL REFERENCE TO THE LIVER, AND COMPARISONS WITH HISTAMINE AND EPINEPHRINE

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In a previous paper (1) it was shown that digitalis in dogs caused a fall in venous pressure at the time when the minute volume flow of blood was diminished. This fall in venous pressure, and hence in return flow of blood to the heart, was correlated with a peripheral vasocontrictor action of the digitalis. It was indicated that constriction of the hepatic veins was the major factor in causing a redistribution of blood, with pooling in the splanchnic area. This venous action of digitalis agreed with results on the perfused liver and on excised veins reported in the literature. Kobert (2), in 1886, and Lampe and Mehes (3), in 1926, demonstrated that digitalis and allied glucosides caused a marked constriction of the vessels of the perfused liver, and Franklin (4), in 1925, reported constriction of excised veins by digitalis. In our experiments on dogs there was a progressive increase in volume of the liver *in situ* and a simultaneous constriction of the intestines after doses of digitalis corresponding to the full therapeutic. Although the significance of these changes in the splanchnic region were appreciated at the time, it was thought that additional data on the state of the portal circulation were desirable, particularly with reference to confirmation or denial of the constrictor action of digitalis on the hepatic veins. In the present paper, therefore, further experiments on this portal mechanism are presented, the results with digitalis being compared and correlated with those with histamine and epinephrine as controls.

DIGITALIS AND STROPHANTHUS

The same tincture of digitalis was used as in our previous experiments (1). The potency was equivalent to 88 mgm. of leaves, or

0.88 cc. of the tincture, per cat unit, and the pigeon minimal emetic dose was 25 mgm. per kilogram of body weight. The tincture of strophanthus had a minimum fatal dose for the cat of about 0.02 cc. per kilogram. These were administered intravenously throughout, being first diluted with an equal volume of normal saline solution

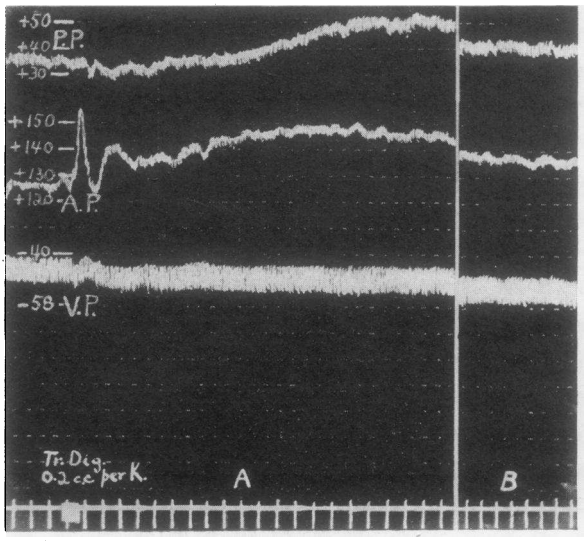

FIG. 1. EFFECTS OF DIGITALIS INTRAVENOUSLY ON THE PORTAL, ARTERIAL AND VENOUS PRESSURES OF AN ATROPINIZED DOG

Dog 4, 15 kgm. Tr. digitalis 0.2 cc. (20 mgm.) per kilogram. *A*, at time of injection; *B*, 14 minutes later.

In all figures *PP* = portal pressure, *AP* = arterial pressure (carotid), *VP* = venous pressure (intra-auricular). Portal and venous pressures in millimeters water, arterial pressure in millimeters Hg. Bottom line is base line for arterial pressure as well as time and injection markers; each stroke = 20 seconds. All tracings read from left to right.

(0.85 per cent NaCl). The usual dose of digitalis was 0.2 cc. per kilogram, corresponding to the full therapeutic dose in man, and of strophanthus 0.01 cc. per kilogram. All the dogs received morphine hypodermatically (20 mgm. per kilogram) and this was supplemented with ether as necessary. Heparin (20 mgm. per kilogram) was usually injected to prevent blood clotting in the cannulae.

Effects on venous and portal pressures. The direction and magnitude of the changes in venous and portal pressures after giving digitalis were observed in 5 dogs. For this purpose the arterial pressure in the carotid artery was recorded by means of a cannula and mercury manometer. The venous pressure was recorded from a large cannula in-

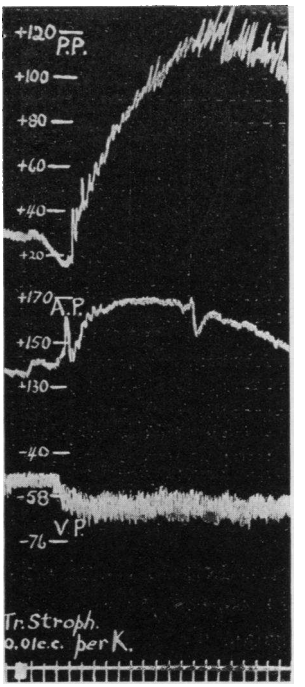

FIG. 2. EFFECTS OF STROPHANTHUS INTRAVENOUSLY ON THE PORTAL, ARTERIAL AND VENOUS PRESSURES OF AN ATROPINIZED DOG

Dog 4, 15 kgm. Tr. strophanthus 0.01 cc. (1 mgm.) per kilogram

serted through the jugular vein into the heart, and attached to a water manometer and piston recorder. The portal pressure was recorded from a cannula in the central stump of the splenic vein close to the portal vein, the spleen being ligated. In this way interference with portal flow was reduced to a small but fixed minimum. This cannula was joined to a second water manometer and piston recorder.

The changes in a typical experiment were as follows: after the

TABLE 1*

Effects of digitalis, strophanthus, histamine and epinephrine on arterial, venous and portal pressures and pulse rate in dogs

Drug and dose per kilogram intravenously	Time after injection	Arterial pressure		Venous pressure		Portal pressure		Pulse	
		Hg	Change	Water	Change	Water	Change	Rate per minute	Change
Dog 1 (11.4 kgm.)									
	minutes	*mm.*	*per cent*	*mm.*	*per cent*	*mm.*	*per cent*		*per cent*
	0	145		−40		+57		80	
Tr. digitalis 0.2 cc.									
	1	132	−9	−24	+40	+70	+23	72	−10
	6	180	+23	−35	+13	+78	+37		
	20	143	−1	−35	+13	+45	−21	128	+60
Tr. strophanthus 0.01 cc.									
	3	170	+19	−38	−9	+70	+56		
	7	185	+29	−15	+57	+75	+67	220	+72
	12	110	−23	−15	+57	+20	−56		
Dog 2 (12.3 kgm.)									
	0	116		−50		+84		180	
Tr. digitalis 0.2 cc.									
	5	125	+8	−57	−14	+120	+43	152	−16
	14	110	−5	−61	−22	+44	−48		
	25	95	−18	−55	−10	+64	−24	160	−11
Histamine 0.1 mgm.									
	1	37	−61	−80	−45	+84	+91		
	6	65	−32	−63	−16	+50	−22	208	+30
Epinephrine 0.016 mgm.									
	1	128	+98	−36	+44	+40	−20	72	−65
	2	70	+8	−60	+5	+105	+110		
	5	65	0	−63	0	+55	+10	212	+2
Dog 3 (20.7 kgm.). Atropinized (1 mgm. per kilogram.)									
	0	95		−45		+123			
Tr. digitalis 0.2 cc.									
	1	160	+68	−60	−33	+80	−35	272	
	2	175	+84	−62	−38	+110	−11		
	7	147	+55	−60	−33	+70	−43	272	0
	15	95	0	−60	−33	+45	−64		
Epinephrine 0.01 mgm.									
	½	118	+25	−62	−3	+23	−49		
	1	95	0	−50	+17	+60	+33	304	+12
	1½	85	−11	−58	+3	+83	+84		
	5	75	−21	−60	0	+35	−22		
Histamine 0.07 mgm.									
	1	30	−60	−80	−33	+40	+14		

TABLE 1—*Concluded*

Drug and dose per kilogram intravenously	Time after injection	Arterial pressure		Venous pressure		Portal pressure		Pulse	
		Hg	Change	Water	Change	Water	Change	Rate per minute	Change
Dog 4 (15 kgm.). Atropinized (0.5 mgm. per kilogram)									
	minutes	*mm.*	*per cent*	*mm.*	*per cent*	*mm.*	*per cent*		*per cent*
	0	127		−43		+35			
Tr. digitalis 0.2 cc.									
	2	143	+13	−49	−14	+36	+3	208	
	5	150	+18	−49	−14	+50	+43		
	10	138	+9	−54	−26	+40	+14	220	+6
	20	137	+8	−52	−21	+28	−20	220	+6
Tr. strophanthus 0.01 cc.									
	2	170	+24	−62	−19	+80	+186		
	5	170	+24	−62	−19	+122	+336	220	0
	7	147	+7	−61	−17	+95	+239		
	20	127	−7	−42	+19	+45	+61		
Epinephrine 0.013 mgm.									
	1	220	+73	−50	−19	+60	+33		
	3	120	−5	−33	+21	+128	+184		
	8	127	0	−62	−48	+48	+7		
Dog 5 (11 kgm.). Atropinized (1 mgm. per kilogram)									
	0	150		−15		+45		184	
Tr. digitalis 0.2 cc.									
	2	160	+7	−11	+27	+78	+73	184	0
	4	160	+7	−15	0	+90	+100		
	11	163	+9	−24	−60	+28	−36		
	15	155	+3	−21	−40	+26	−42		
Tr. strophanthus 0.01 cc.									
	2	153	+1	−28	−33	+34	+31		
	4	213	+37	−39	−86	+38	+47	180	−2
	15	175	+13	−30	−43	+40	+54		
Histamine 0.045 mgm.									
	1	130	−23	−39	−30	+120	+200		
	2	160	−9	−30	0	+170	+325		
	4	170	−2	−3	+90	+40	0		
	10	120	−31	−7	+77	+45	+13		
Epinephrine 0.005 mgm.									
	1	135	+13	−17	−143	+76	+69		
	3	125	+4	−10	−43	+72	+60		
	15	75	−38	−22	−214	+37	−18		
Histamine 0.23 mgm.									
	1	44	−41	−39	−77	+80	+117		

* The plus (+) sign means increase, and minus (−) sign, decrease, in all tables.

injection of digitalis or strophanthus, the arterial pressure rose gradually and the venous pressure fell simultaneously, as was to be expected, but the portal pressure increased. These changes are illustrated in the case of digitalis in figure 1, and in that of strophanthus, in figure 2. The portal pressure reached its maximum increase about the same time as the arterial pressure and then returned gradually towards its original level. The venous pressure continued to fall during the relatively brief period of observation. In some dogs, the portal pressure fell transiently during the first minute after the injection of digtalis, and then recovered. This was presumably the result of a diminished inflow of blood into the splanchnic region caused by the onset of splanchnic vasoconstriction, reported in our previous paper (1).

Table 1 presents the details of the five experiments. It is seen that all 5 dogs responded to digitalis with the usual increase of arterial pressure, the median rise being 18 per cent; three injections of strophanthus in as many dogs gave a median rise of 29 per cent. Since strophanthus was injected after digitalis, the results after strophanthus would correspond to those of maximal rather than average therapeutic doses. The venous pressure fell in four out of five dogs. Dog 1 responded abnormally with a transient rise of venous pressure and fall of arterial pressure immediately after the injection of the digitalis. At the end of two minutes the arterial pressure had returned to normal and the venous pressure began to fall. The median effect on venous pressure of the eight injections of digitalis and strophanthus in the 5 dogs was a fall of 38 per cent. At the same time the portal pressures rose above the initial values in all the dogs, except in dog 3, in which splanchnic vasoconstriction predominated. At the height of the response to the drugs, the smallest increase in portal pressure after digitalis was 37 per cent (dog 1), and the greatest, a rise of 336 per cent after strophanthus (dog 4). There was thus a considerable variation in the degree, but not in the kind, of response.

In dogs 1 and 2, atropine was not used, and therefore, digitalis slowed the pulse. Bradycardia usually causes a rise of venous pressure, but in dog 2 the venous pressure fell despite the opposing influence of the cardiac slowing. The remaining three dogs were atropinized before the injections of digitalis, so that changes in pulse

rate could not influence the venous pressure, which nevertheless was decreased in all dogs.

The consistent action of digitalis and strophanthus in increasing the portal pressure and diminishing the venous pressure points to an interference in portal drainage. This could only be caused by a block in the liver. Since the volume of the liver increases (1), these drugs must cause a constriction of the emissary or hepatic veins. Such an action is physiologically possible because these veins are richly endowed with smooth muscle. Furthermore, constriction from digitalis has already been demonstrated in perfused livers (3). The constriction *in situ* would result in pooling of blood in the portal region and thus lowering of the venous pressure, as demonstrated. A recent study by Wollheim (5) indicates that such a pooling also occurs in man, since he demonstrated a sudden diminution in the volume of the actively circulating blood after digitalis was administered.

The rise in portal pressure is most striking for a short time (5 to 12 minutes) after giving the drug, but does not parallel the progressive fall in venous pressure. This might be due to removal of the intrahepatic block (recovery of the hepatic vein from constriction), to opening up of the capillary bed in the portal area, or to other intervening factors. In order to determine whether hepatic vein constriction was the paramount factor in producing the fall in venous pressure, observations were made of the actions of digitalis in dogs in which the portal area was excluded from the circulation, and in those whose hepatic veins could not influence the portal flow. As far as we know, the only other observer who has reported portal pressure changes after digitalis is Schmid (6). Schmid also found an increase in portal pressure, but he attributed it to splanchnic vasodilatation. However, relaxation of the splanchnic vessels does not occur, as shown by ourselves and others, but on the contrary there is constriction. Splanchnic vasoconstriction would lower the portal pressure, by diminishing the inflow, and not increase it, as is the case.

Digitalis in dogs with Eck fistulae. One kind of evidence on the rôle of the liver was obtained after shunting the blood directly from the portal vein into the inferior cava, without passing through the liver. A T-cannula was inserted between the portal vein and the caval end of the right renal vein of a series of dogs after the kidney had been

TABLE 2

Effects of digitalis, histamine, epinephrine and atropine on arterial and venous pressures and pulse rate in dogs with ligated livers and portal blood shunted into the inferior vena cava

Drug and dose per kilogram intravenously	Time after injection	Arterial pressure		Venous pressure		Pulse	
		Hg	Change	Water	Change	Rate per minute	Change
		Dog 6 (17 kgm.)					
	minutes	*mm.*	*per cent*	*mm.*	*per cent*		*per cent*
	0	83		−24		92	
Tr. digitalis 0.2 cc.							
	1	127	+53	−20	+17	128	+39
	4	90	+8	−24	0	176	+91
	20	50	−39	−24	0	164	+78
Epinephrine 0.03 mgm.							
	1	160	+220	−11	+54		
	3	140	+180	−20	+17		
		Dog 7 (14.5 kgm.)					
	0	124		−26		220	
Tr. digitalis 0.2 cc.							
	4	143	+15	−19	+27	160	−27
	10	130	+5	−12	+54	200	−9
Atropine 0.3 mgm.							
	2	138	+6	−44	−267	260	+30
	4	105	−19	−39	−225	260	+30
Histamine 0.1 mgm.							
	1	50	−52	−39	0		
	4	90	−14	−39	0	260	0
		Dog 8 (16 kgm.)					
	0	88		−36		260	
Tr. digitalis 0.2 cc.							
	1	100	+14	−42	−17		
	3	125	+42	−38	−5	260	0
	10	127	+44	−31	+14		
	12	135	+53	−32	+11		
	15	110	+25	−32	+11	260	0
Histamine 0.1 mgm.							
	1	57	−48	−37	−16		
	2	73	−34	−41	−28	260	0
	5	80	−27	−36	−16		

removed. The hepatic artery and portal vein were then tied close to the liver. This caused all the portal blood to drain directly into the inferior vena cava through the renal vein, and therefore avoided all influence of the liver upon the circulation. The cannula was paraffined and the dogs heparinized to prevent clotting of the blood. With this technic the portal circulation was interrupted only at the moment of inserting the cannula and the splanchnic viscera quickly acquired

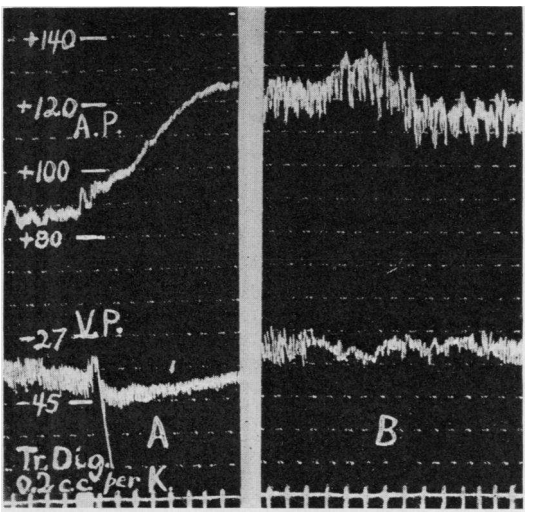

FIG. 3. EFFECTS OF DIGITALIS INTRAVENOUSLY ON THE ARTERIAL AND VENOUS PRESSURES OF A DOG WITH AN ECK FISTULA

Dog 8, 16 kgm. Tr. digitalis 0.2 cc. (20 mgm.) per kilogram. *A*, at time of injection; *B*, 9 minutes later.

their normal color. The viscera maintained their normal color throughout the experiments and the cannulae were shown to be patent at autopsy. Digitalis was injected after a short period of recovery from the operation, when the circulation was constant. Table 2 presents the results on 3 such dogs, in which changes in arterial and venous pressures and pulse rate were observed after digitalis.

The results obtained are seen to be in striking contrast to those in dogs with livers intact (table 1); the digitalis now failed to diminish the venous pressure, but on the contrary caused it to rise. The arterial

TABLE 3

Effects of digitalis, strophanthus, epinephrine and atropine on arterial and venous pressures and pulse rate in dogs with the entire splanchnic circulation ligated

Drug and dose per kilogram intravenously	Time after injection	Arterial pressure		Venous pressure		Pulse	
		Hg	Change	Water	Change	Rate per minute	Change
Dog 9 (10 kgm.)							
	minutes	*mm.*	*per cent*	*mm.*	*per cent*		*per cent*
	0	138		−15		120	
Tr. digitalis 0.2 cc.							
	1	143	+4	−5	+67	110	−9
	5	147	+7	+3	+120	84	−30
	11	147	+7	+9	+167	68	−43
Atropine 0.5 mgm.							
	3	148	+1	−12	−233	160	+138
	8	145	−1	−6	−167		
	15	142	−3	−8	−189	230	+238
Dog 10 (23 kgm.). Atropinized (0.5 mgm. per kilogram) Cardiac output measured*							
	0	134		−32		224	
Tr. digitalis 0.2 cc.							
	4	145	+8	−22	+31	240	+7
	18	132	−2	+12	+138		
	30	110	−18	−15	+53	224	0
Dog 11 (26 kgm.). Atropinized (0.5 mgm. per kilogram.)							
	0	123		−60		190	
Tr. digitalis 0.2 cc.							
	2	128	+4	−51	+15		
	12	140	+15	−23	+62		
	18	130	+6	−4	+93		
	25	127	+3	−22	+63	208	+9
Tr. strophanthus 0.01 mgm.							
	1	140	+10	−36	−64		
	3	142	+12	−24	−9	216	+4
	11	160	+26	+136	+718	200	−4
	30	110	−13	−15	+32	220	+6
Epinephrine 0.04 mgm.							
	1	270	+145	−11	+27		
	3	190	+73	+15	+200	220	0
	9	110	0	+7	+147		

* Control output before digitalis, 2990 cc. per minute; 18 minutes after digitalis, 6118 cc. per minute (105 per cent increase).

pressure was typically increased, and the pulse rate was variably affected, being increased, slowed and unchanged. Typical changes in the venous and arterial pressures are illustrated by an actual record in figure 3, where, after an initial sigh, the venous pressure rose steadily, and remained elevated during an observation period of 15 minutes. In this record the pulse rate was constant, so that the rise of venous pressure was not due to a slowing of the heart. It was evident from

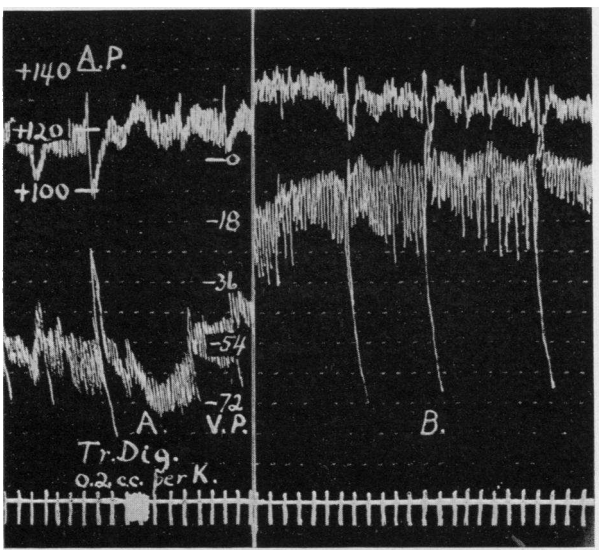

FIG. 4. EFFECTS OF DIGITALIS INTRAVENOUSLY ON THE ARTERIAL AND VENOUS PRESSURES OF AN ATROPINIZED DOG WITH SPLANCHNIC CIRCULATION LIGATED

Dog 11, 26 kgm. Tr. digitalis 0.2 cc. (20 mgm.) per kilogram. *A*, at time of injection: *B*, 15 minutes later.

the results of these experiments that digitalis did not cause pooling of blood in the splanchnic region and a fall of venous pressure, when the liver was excluded. Apparently as the result of arteriolar constriction there was a shunting of blood into the venous reservoir with a resulting increase in the venous pressure. At any rate, the difference in the responses to digitalis of dogs with and without livers was mediated by the only variant, namely the presence or absence of the liver in the circulation.

Effects of digitalis and strophanthus in the absence of the entire splanchnic circulation. Further confirmatory evidence was sought by eliminating not only the liver but the entire splanchnic region from the circulation. This was accomplished with a minimum of operative trauma by tying off the coeliac axis and superior mesenteric arteries where they branched off the aorta. The inferior mesenteric artery in the dog is either entirely absent or negligible in size. Under these

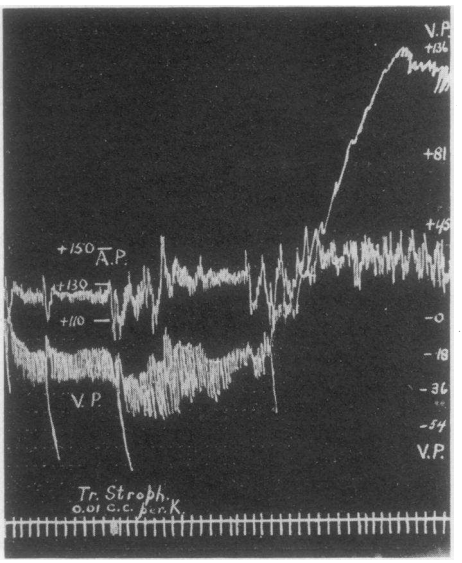

FIG. 5. EFFECTS OF STROPHANTHUS INTRAVENOUSLY ON THE ARTERIAL AND VENOUS PRESSURES OF AN ATROPINIZED DOG WITH SPLANCHNIC CIRCULATION LIGATED

Dog 11, 26 kgm. Tr. strophanthus 0.01 cc. (1 mgm.) per kilogram

conditions the splanchnic vessels quickly drain themselves of blood and are not reached by injected drugs. The detailed results on 3 such dogs, in which arterial and venous pressures and pulse rate changes were observed, are presented in table 3.

It is seen that digitalis and strophanthus caused small rises of arterial pressure (7 to 26 per cent) but very marked increases in venous pressure (93 to 718 per cent). These changes could not be accounted for by pulse rate changes since an appreciable change in rate occurred

only in 1 dog (dog 9). The rise of venous pressure in dog 9 was very marked and was only partially antagonized by more than doubling the heart rate caused by atropine. Figure 4 shows the response of dog 11 to digitalis; the rise of venous pressure is very marked and persistent. Figure 5 shows the tremendous increase in venous pressure caused by strophanthus in dog 11. It is rather striking from the results obtained in these 3 dogs, in which digitalis and strophanthus could not act on the splanchnic arteries and hepatic veins, that the increases in arterial blood pressure were comparatively small. Consequently, splanchnic vasoconstriction determines not only the fall of venous pressure, but also contributes to the rise of arterial pressure after digitalis in normal dogs. Since in the absence of hepatic vein constriction, the venous pressure rose, the results leave no doubt that digitalis, in dogs, causes a portal pooling of blood, which is the most important, if not indispensable, element in diminishing the venous pressure, and therefore, the venous return to the heart.

In our previous paper (1) it was pointed out that diminution in cardiac output after digitalis was probably due to lowered venous pressure and consequent inadequate cardiac filling. An opportunity was taken to demonstrate again the dependence of cardiac output on venous filling in dog 10 in which digitalis increased venous pressure. The cardiac output was measured by the Fick principle and found to be 2.99 liters per minute before digitalis and 6.12 liters per minute when the digitalis had raised the venous pressure. In this dog, therefore, in which the usual fall of venous pressure was reversed to an increase by cutting off the splanchnic circulation, the usual diminution in cardiac output was likewise reversed to an increase. This result testifies to the importance of the vasoconstrictor action of digitalis in the splanchnic, but especially the liver, regions, to its diminishing effect on cardiac output, and denies the alleged importance of the cardiac action (7) in the latter phenomenon.

At this point we may recapitulate our interpretation of the changes just described. The rise in venous pressure in digitalized dogs with splanchnic circulation ligated indicates a general vasoconstriction from the drug, enhanced by a relative increase in blood volume due to ligation of the intestine. This rise causes a shift of blood into the great veins. In normal dogs receiving digitalis, this shift is pre-

vented by pooling of blood in the portal area, the liver and spleen, when the hepatic veins are constricted by the drug. This pooling in the portal area is accompanied by a marked but not necessarily long sustained rise in portal pressure, at a time when the systemic venous pressure is falling. A large volume of blood is locked, so to speak, between constricted splanchnic arteries and the constricted hepatic veins. It is conceivable that the accumulation of blood in the portal area, without continued rise in portal pressure, might be due to capillary dilatation as a result of ischemia from prolonged arteriolar constriction. We have no evidence of such a compensatory mechanism for digitalis although it is known or assumed to exist in other conditions. However, there is the inescapable experimental result that digitalis causes a simultaneous fall in systemic, and rise in portal vein pressures, which is valid evidence of constriction of the hepatic vessels, that is, the hepatic veins, which are interposed between the vena cava and the portal vein. Since these reciprocal changes in venous pressures do not continue strictly parallel, and vary quantitatively over wide limits, it can not be concluded from the records of portal and systemic pressures alone that the fall in venous pressure in digitalized dogs is due solely to hepatic vein constriction. But, the failure to demonstrate any fall in venous pressure in dogs, the portal blood in which escaped directly into the vena cava through a shunt, establishes the dominant importance of the liver vessels (the hepatic veins) in controlling venous pressure in digitalized dogs. This mechanism likewise determines the venous return to and output of blood from the heart after digitalis.

The correctness of our results on portal and venous pressures, and therefore the action on hepatic veins, is further testified to by the similar effects of histamine and epinephrine, obtained in this laboratory and also reported in the literature. These drugs were not exhaustively studied, but, since the results are interesting in themselves and also important in connection with digitalis, they may be briefly described.

HISTAMINE

The importance of the liver in histamine shock has been the subject of considerable study. Most of the evidence bearing on this problem

has been indirect or derived from *in vitro* experiments. Franklin (4), in 1925, showed that histamine constricted excised veins, and Inchley (8), in 1926, pointed out that in perfused organs the veins were more sensitive to histamine than were the arteries. Mautner and Pick (9) had previously perfused excised livers of dogs, cats and monkeys and shown that the hepatic veins were constricted by histamine causing a stasis and dilatation of the liver capillaries. This was confirmed in the case of the perfused liver of dogs by Baer and Rössler (10). Dale and Laidlaw (11) argued against the existence of such a mechanism in the intact cat, in which they thought the portal system was not engorged with blood during histamine shock, but rather appeared collapsed. Direct and conclusive evidence that portal block was actually produced in histamine shock was obtained by von Haynal (12), who compared the effects of histamine upon cardiac filling and blood pressure in dogs with Eck fistulae and reversed Eck fistulae. Feldberg, Schilf and Zernik (13) analyzed the rôle of the liver in intact dogs, and found that histamine could cause a rise of portal pressure through hepatic vein constriction, but they also showed that the latter was not the predominant mechanism in histamine shock, and that other vascular regions were also concerned in the result. Nevertheless, there is a definite action of histamine on the hepatic veins with corresponding changes in liver volume and portal pressure, similar to those of digitalis and strophanthus described in this paper. The results of four injections in as many dogs may now be briefly described.

The changes in portal, venous and arterial pressures are shown in table 1. It is seen that the changes after histamine were rather uniform throughout. There was a median fall of arterial pressure of 50 per cent and of venous pressure of 39 per cent. At the same time the portal pressure rose 104 per cent (median). The simultaneous changes, i.e., fall in venous and rise in portal pressures, confirm those of Feldberg, Schilf and Zernik (13). Inasmuch as the blood pressure fell precipitously during the relaxation of the peripheral vessels, it can not be claimed that the rise of portal and fall of venous pressures were due solely to hepatic block, although this might contribute to the effect. More definite evidence on this point was sought in two Eck fistula dogs. In these (table 2), histamine caused no definite change in venous pressure in one (dog 7), and a 28 per cent fall in the other

(dog 8). In these 2 dogs there was no chance of hepatic vein constriction or of splanchnic-pooling, since the livers were eliminated from the circulation. Yet, in one of these dogs (dog 8) at least, the usual effect on venous pressure, i.e., a fall, was demonstrated. This is in agreement with the claim of Feldberg, Schilf and Zernik (13), namely, that the liver does not predominate in the mechanism of histamine shock in dogs. However, the rise of portal pressure in our experiments indicated that histamine constricted the hepatic veins, and it has been shown on different occasions in this laboratory that this drug increases liver volume. By pooling blood in the splanchnic bed, the action on the liver may therefore contribute to histamine shock. But, more important than the latter question for our work with digitalis is the fact that histamine acted identically like digitalis on the venous and portal pressures in the same dogs (table 1), and thus helped to establish the validity of the results with digitalis.

EPINEPHRINE

The effect of epinephrine on the liver and its circulation has been studied much more than that of histamine, or of digitalis. There appears to be a good agreement on the character of the responses. It was established by Crawford and Twombly (14), in 1913, and confirmed by Franklin (4), in 1925, that excised veins are constricted by epinephrine similarly to arteries. Livers of dogs and other species have been perfused by many investigators (Mautner and Pick, (9); Lampe, (15); Lampe and Mehes, (16); Baer and Rössler, (10); McLaughlin, (17)), through the heptic artery, portal vein or hepatic vein. The invariable response was a constriction of these vessels and diminution in outflow. The diminution in portal flow after epinephrine in the intact dog was measured under various conditions by Schmid (6), in 1909, and by Burton-Opitz (18), in 1912. The predominant effect on liver volume in the intact dog and cat was shown to be a constriction by Edmunds (19), and by Griffith and Emery (20). This contradicted the observations of Bainbridge and Trevan (21) who had found marked swelling of the liver and pooling of the blood in the portal region after epinephrine. Using dogs, von Haynal (12) was able to show the influence of the liver on the circulatory responses by alternately shunting all or none of the blood through

this organ. He found that, in the ordinary Eck-fistula dog, when no blood was going through the liver, the cardiac filling and blood pressure responses to epinephrine were normal, but when all the blood passed through the liver, in reversed Eck-fistula dogs, the pressor response was almost abolished, and the liver was blocked (vessels constricted) by the drug. Our data on six dogs are shown in tables 1, 2 and 3.

In the normal circulation, where the portal pressure was measured, the blood pressure rose 49 per cent (median) and the portal pressure, 97 per cent (median), after epinephrine. In view of the generalized vasoconstriction resulting from the epinephrine, which cut down the inflow into the portal region and caused a transient fall of portal pressure (table 1, dogs 2 and 3), the later rise of portal pressure was probably caused by a slowly developing hepatic vein constriction and pooling of the portal blood. The influence of the latter upon the venous pressure was not very pronounced, as was also observed by Bainbridge and Trevan (21). In three dogs the venous pressure fell (table 1), and in the fourth dog (dog 2), it rose during a marked slowing of the pulse. A dog with an Eck fistula (table 2) showed only a rise of venous pressure, as did also one with the entire splanchnic arterial tree tied off, (table 3). Our conclusions from these experiments are that epinephrine raised the portal pressure by constricting the hepatic venules, that it caused an associated fall of intra-auricular pressure, which was at least partly the result of pooling in the splanchnic area, since it was not observed when the splanchnic vessels were ligated, or when an Eck fistula was present. Since these actions of epinephrine resemble those produced in the same dogs with digitalis, they confirm our conclusions as to the mechanism by which digitalis diminishes the venous return.

SUMMARY AND CONCLUSIONS

1. When dogs are given, by intravenous injection, doses of digitalis corresponding to the full therapeutic dose for man, they exhibit a rise in arterial and fall in right auricular pressure, but a simultaneous rise in portal vein pressure. These changes are also caused by strophanthus. The fall in systemic and rise in portal vein pressure are due to constriction of hepatic veins. This agrees with the hepatic

engorgement in digitalized dogs, which we reported previously, and also with the effects of digtalis on excised veins and in liver perfusion experiments which other observers have reported.

2. After eliminating the liver from the circulation by shunting the portal blood directly into the inferior vena cava, or by ligating the arteries which supply the splanchnic area, digitalis or strophanthus did not cause a fall of venous pressure, but in several instances raised it, and did not cause as marked an elevation of arterial pressure as in the animals with the splanchnic circulation intact.

3. Therefore the fall in right auricular pressure, after giving digitalis to dogs with the hepatic circulation intact, was due to diminished venous return flow, and ultimately to an accumulation of blood in the splanchnic or portal region as a result of obstructed hepatic outflow (hepatic vein constriction).

This mechanism adequately explains the diminution in cardiac output after digitalis, since a diminished venous return must result in deficient cardiac filling. This conclusion agrees with that of our previous paper.

4. The experimental procedures used to determine the actions of digitalis and strophanthus were controlled by comparisons in the same organism with known actions of histamine and epinephrine which cause a similar pooling of portal blood through a similar mechanism, the actions being modified, however, by changes in other vessels.

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