SOME ACTIONS OF ADRENALIN UPON THE LIVER.

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We have pointed out elsewhere(1) that adrenalin, if injected slowly and continuously into the blood stream, gives rise to some obstruction to the flow of blood through the liver, and that, if the obstruction is prolonged, the general circulation becomes profoundly modified and the animal passes into a condition of "shock." We propose in this paper to describe more fully the immediate effects of adrenalin upon the blood flow through the liver and to discuss the means by which they are produced.

Methods. The experiments were made on cats and dogs anæsthetised with C.E. mixture; the dogs received a preliminary dose ($\frac{1}{2}$–1 grain) of morphia, and the cats usually received 1 gm. of urethane per kilo in addition to the volatile anæsthetic. The portal pressure was recorded from the splenic vein and the vena cava pressure from the iliac vein; the latter was exposed extraperitoneally and the cannula inserted close to the opening of the vein into the inferior vena cava. The pressures recorded were those obtaining respectively in the portal vein just below its entrance into the liver and in the vena cava just below the diaphragm. The recording manometers were filled with a 3·5 % solution of sodium citrate. Graphic records of the portal pressure were obtained by connecting a moderately sensitive piston recorder with the recording manometer. Changes in the volume of the liver were studied by inserting between the lobes of the liver a small balloon containing water and connected with a piston recorder. This method has previously been shown by Dale and one of us (F. A. B.) to give reliable qualitative records of changes in the volume of the liver, provided that precautions are taken to expose the liver freely and to hold back the walls of the chest and abdomen so as to avoid pressure on the liver from contiguous organs and from the diaphragm. In some experiments, in which adrenalin was injected continuously for fifteen minutes or longer, the alteration in the volume of the liver was sufficiently large to be directly observed. A small

dose of atropin was given early in each experiment in order to exclude reflex vagus inhibition.

Whether adrenalin is injected into the systemic circulation or into a branch of the portal vein, it produces almost immediately a rise of portal pressure, an increase in the volume of the liver and a greater flow of lymph from the thoracic duct.

The portal pressure. In the dog, the first effect of rapidly injecting a large dose (1 c.c. of ·01 %) of adrenalin into a systemic vein is a fall of pressure amounting to 10–20 mm. sodium citrate solution and lasting from 15–30 seconds; this is succeeded by a rapid and enormous rise of pressure, which reaches its maximum 2–3 minutes after the injection. The pressure then falls slowly, and does not return to its original level until several minutes after the arterial pressure has fallen to its previous level. Diminution of the amount of adrenalin injected lessens the secondary rise much more than the primary fall of portal pressure; and after a small dose (*e.g.* 1 c.c. of ·001) of adrenalin, the rise of pressure may amount to only a few (10–20) mm. of sodium citrate solution. When adrenalin is continuously injected at a very slow rate for several minutes, the portal pressure remains high throughout the period of the injection. An equally striking rise of portal pressure follows the injection of adrenalin into a tributary of the portal vein although, if the injection is not made too rapidly, the arterial pressure may remain unaltered or may even fall considerably; in these circumstances, the initial fall of portal pressure does not occur. After ligature of the hepatic artery, the rise of portal pressure produced by adrenalin is quite as great as that observed in the intact animal.

Whatever the site of the injection of adrenalin, the vena cava pressure shows very little alteration. Usually it rises a few (5–15) mm. of sodium citrate, but occasionally it falls slightly; and if the injection of adrenalin is prolonged for a few minutes the vena cava pressure may be perfectly normal at a time when the portal pressure is 300 mm. or more above its original level.

Similar results were obtained in cats, but the rise of portal pressure is much smaller than that observed in dogs and rarely exceeds 80–100 mm. sodium citrate.

The volume of the liver. If adrenalin is injected slowly and continuously into a systemic vein for 10–20 minutes the liver in dogs can usually be observed by the naked eye to be swollen and intensely engorged with blood; this effect is produced only by very large doses of adrenalin (0·5–0·8 gm. per kilo) but the balloon method shows that even a single

Exp. 1. Dog. Weight 12 kilos. Venous pressures recorded in mm. sod. citrate solution (sp. gr. 1020).

Time	Art. pressure (mm. Hg.)	Portal pressure	V. cava pressure	
3.30	120	95	25	
				3.30½. Began slow, continuous injection of
3.32	150	285	12	adrenalin, ·04 % into jugular vein
3.41	140	235	18	
3.47	150	295	20	

Exp. 2. Dog. Weight 5 kilos.

2.35½	90	140	
			2.35½–2.36. Inject 1 c.c. ·01 % adrenalin into femoral vein
2.36½	180	125	
2.37	140	245	
2.37½	62	330	
2.39	56	220	
2.42	68	145	
			2.42–2.43. Inject 1 c.c. of ·005 % adrenalin into mesenteric
2.42½	—	185	vein
2.43	90	260	
2.44	60	360	
2.46	50	265	
2.49	56	190	

Exp. 3. Dog. Weight 6 kilos. Loose ligature placed round hepatic artery.

5.23	100	140	
			5.23. Inject 1 c.c. of ·01 % adrenalin into jugular vein
5.24	254	340	
5.25	124	405	
5.27	68	215	
			Ligature of hepatic artery. 5.28–5.30
5.33	90	155	
			5.33. Inject 1 c.c. of ·01 % adrenalin into jugular vein
5.34	220	355	
5.35½	114	415	
5.37½	80	220	

rapid injection of adrenalin (1 c.c. of ·005 %) causes an increase in the volume of the liver (Fig. 2). The increase begins almost simultaneously with the rise of arterial pressure, and lasts for a short time after this has again fallen to its original level. It must be noted that the balloon method merely shows approximately the time relations of the changes in liver volume, and that it gives no indication of the actual extent of the change. The increased volume of the liver, which was first noticed by Dale and one of us (F. A. B.)(2), is clearly due to the accumulation of blood in the capillaries of the liver. In several experiments small portions of the liver were isolated by double clamps in order to retain

the blood *in situ*, and were then excised and examined histologically. Two pieces were taken, one as a control at the beginning of an experiment, and a second one after the injection of adrenalin. The sections showed that the injection of adrenalin, especially in large amount, led to extreme engorgement of the capillaries and of the interlobular and intralobular veins with blood.

The lymph flow. It has recently been pointed out by Yanagawa (8) that the injection of adrenalin into the circulation increases the flow of

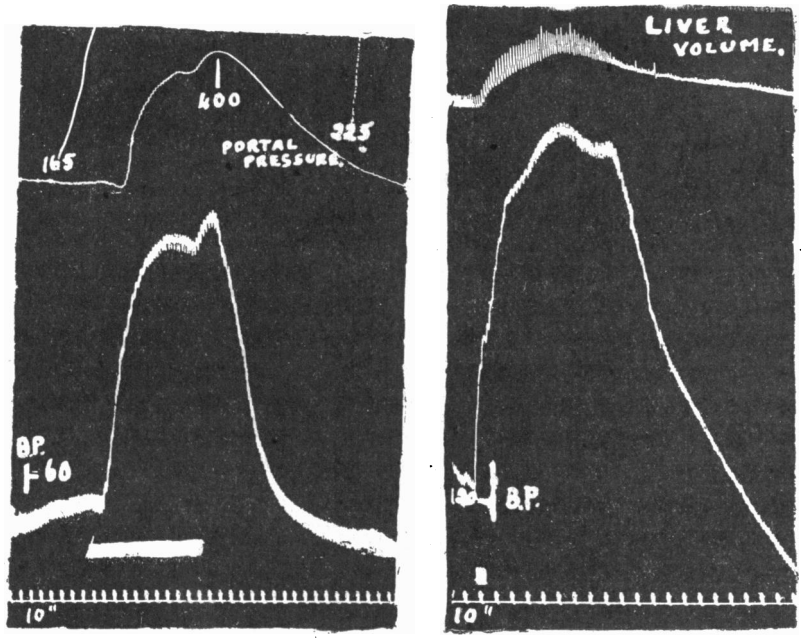

Fig. 1. Effect of injecting 2 c.c. of ·01 % adrenalin into a jugular vein.

Fig. 2. Injection, 2 c.c. of adrenalin (1 in 10,000) into a jugular vein. As a result of the injection the portal pressure rose 255 mm., sodium citrate solution.

lymph from the thoracic duct, and that the lymph becomes slightly more concentrated. Yanagawa made no observations on the cause of the increased flow, but he considered that it is probably due to increased capillary pressure and therefore to increased filtration. We find that the slow continuous injection of adrenalin into a systemic vein causes an increased flow of lymph from the thoracic duct. This begins very shortly after the injection is started, and the flow may become four or five times greater than that previous to the injection; further, the lymph becomes

slightly more concentrated. The same result is obtained if the adrenalin is injected into a branch of the portal vein, thereby eliminating any appreciable rise of arterial pressure.

Exp. 4. Dog. Weight 6·6 kilos.

Time	Art. pressure		Lymph flow	
5.5 –5.15	approx. 40 mm. Hg		5·9 c.c.	
5.15–5.25			5·6	
5.25–5.35	5.30	136	9·5	5.25–5.55. Slow continuous injection of ·04 %
5.35–5.45	5.44	144	12·5	adrenalin, 9 c.c. injected
5.45–5.55	5.55	146	12·0	

Exp. 5. Dog.

Time (10 mins periods)	Vena cava press.	Portal press.	Lymph	
1	55	120	2·2 c.c.	
2	55	200 (max.)	6·1	Injected 1 c.c. ·01 % adrenalin into jugular vein
3	45	370 (max.)	8·1	Injected 4 c.c. ·01 % adrenalin into jugular vein
4	45	395 (max.)	18	Injected 5 c.c. 0·01 % adrenalin into portal vein

The swelling of the liver and the extreme engorgement of its vessels clearly point to the production by adrenalin of some obstruction to the passage of blood from the liver into the vena cava. This view is adopted by Edmunds(6) who observed swelling of the liver after the injection of adrenalin, although this was only constant after ligature of the hepatic artery. Our observations show, however, that it occurs equally well in the intact animal, so that the obstruction to the blood flow through the liver arises independently of its arterial supply. It is evident that the occurrence of an obstruction of this kind must result in a rise of portal pressure; and there is undoubtedly a close connection between swelling of the liver and the rise of portal pressure as regards their time of onset and their duration. Regarded from this point of view the engorgement of the liver and the rise of portal pressure are merely the outward manifestations of obstruction to the escape of blood from the liver.

Other observers however have put forward a different explanation of the rise of portal pressure which follows the injection of adrenalin. Schmid(7) attributed the rise of portal pressure which he observed to increased resistance and tone in the blood vessels of the liver, though it is not clear whether he regards this as occurring in the capillaries or in the radicles of the portal vein. Burton-Opitz(4), who confirmed Schmid's observation, concludes that the effect is due to constriction of the branches of the portal vein as it breaks up in the liver; this conclusion harmonises with the observation of Bayliss and Starling(3) that stimulation of the splanchnic nerves raises the portal pressure, a

result which they regarded as showing that the radicles of the portal vein as it breaks up in the liver are supplied with vaso-constrictor nerves. A rise of portal pressure thus produced would lessen the blood flow to the liver and would therefore tend to diminish its volume. The fact that both a rise of portal pressure and swelling of the liver are simultaneously produced either by adrenalin or, as Edmunds has shown (6), by stimulation of the splanchnic nerves makes it clear that the rise of portal pressure is primarily due to the setting up of some obstruction to the escape of blood from the liver. It is possible, however, that some constriction of the portal vein may also occur, since rings of portal vein contract under the influence of adrenalin (Edmunds).

The increased capillary pressure brought about in the liver by this obstruction readily accounts for the observed increase in the lymph flow from the thoracic duct. The high portal pressure must also raise the capillary pressure in the intestinal capillaries, particularly when the arterioles relax as the effect of adrenalin on the vessels passes off; and some of the additional lymph must be intestinal in origin. But the slight increase in the concentration of the lymph shows that it is derived mainly from the liver.

Investigation of the nature of the obstruction to the flow of blood through the liver has proved very difficult. The occurrence of an intensely engorged liver and a high portal pressure concurrently with a normal vena cava pressure at once excludes the possibility that the obstruction is caused by back pressure from the systemic veins; moreover these effects are observed whether the arterial pressure is raised or whether it is unaffected by the injection of adrenalin. It is evident that the obstruction must arise in the liver itself, and the most obvious explanation is constriction of the hepatic or sublobular veins. Unfortunately the anatomical arrangement of the hepatic veins is such that we have been unable to test directly the effect of ligaturing them partially or completely. There are difficulties, however, in accepting this explanation. Although there is some evidence that adrenalin causes contraction of the muscular coat of the large veins, its action in this respect appears to be comparatively trivial; and it is not easy to believe that it could give rise to the marked obstruction to the blood flow which is actually observed in our experiments. It seemed possible that, if the effect of adrenalin were due to constriction of the hepatic veins, barium chloride and pituitary extract might bring about a similar result. But this is not the case. The injection of barium chloride leads to a trivial rise (20–40 mm.) of portal pressure; and pituitary extract causes a considerable fall of

pressure which is succeeded, as the arterial pressure falls, by a return of the portal pressure to, or just above, its original level.

Exp. 6. Dog.

Time	Art. pressure	Portal pressure	
2.49	56	190	
			Inject ½ capsule of pituitary extract into jugular vein
2.50	86	165	
2.50½	—	120	
2.51½	—	230	
2.52	82	205	

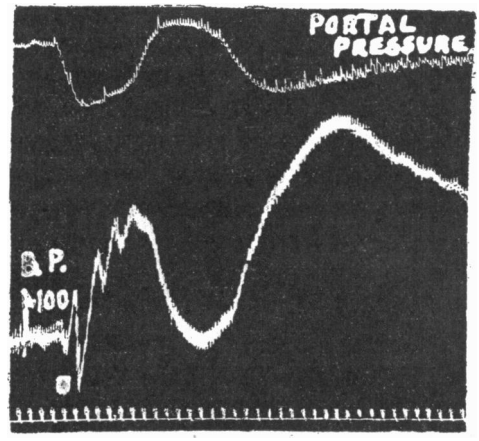

Fig. 3. Effect of injecting half capsule of pituitary extract into jugular vein.

An alternative site of the obstruction is the capillaries of the liver, the resistance to the blood flow being increased either by active constriction of the capillaries or by narrowing of the capillary channels as a result of sudden swelling of the columns of liver cells. Cotton, Lewis and Slade(5) have recently brought forward evidence that adrenalin can cause active constriction of capillaries, and the occurrence of such a process in the liver is conceivable. With regard to the second possibility, there does not appear to be anything inherently improbable in the view that adrenalin may exert some action on the liver cells which results in their rapidly taking up fluid from the blood and lymph. Indeed its influence on the glycogen content of the liver indicates that it does affect the metabolic activity of the liver. We attempted, therefore, to determine the effect on the portal pressure of sudden swelling of the liver cells. Acting on a suggestion of H. H. Dale, we injected a moderate amount of distilled water into a branch of the portal vein. It produced not only

swelling of the liver, as observed by the balloon method, but also a considerable rise of portal pressure, whereas the injection of an equal volume of normal saline solution was almost without effect on either the volume of the liver or the portal pressure.

Exp. 7. Dog.

Time	Art. pressure	Portal pressure	
4.24	82	90	
			4.28. Inject 25 c.c distilled water at 37° C. into a branch of the portal vein
4.30	94	180	
4.32	—	113	
4.34	114	98	
			4.35. Inject 25 c.c. normal saline at 37° C. into a branch of the portal vein
4.36	—	109	
4.38½	136	98	

The rise of pressure is not large as compared with that produced by large doses of adrenalin, but it is significant that it should occur under conditions which appear to preclude constriction of either the hepatic veins or the capillaries. We are disposed, therefore, to regard narrowing of the capillary channels by swelling of the liver cells as the most probable explanation of the obstruction produced by adrenalin to the blood flow through the liver, although it must be admitted that the available evidence does not justify any very definite conclusion. Whatever may be the cause of the obstruction, the fact that it is produced not only by adrenalin but also by strong stimulation of the splanchnic nerves may be regarded as evidence that its occurrence in the normal animal is possible, though perhaps only in conditions of extreme emotional stress. If it does take place under these conditions, the holding up of blood in the liver must reduce for the time being the effective volume of the circulation and the filling of the heart, thereby tending to lessen the strain thrown upon the heart in these circumstances.

Summary.

1. In confirmation of other observers we find that the injection of adrenalin either into a systemic vein, or into a tributary of the portal vein, produces a rise of pressure, increase in the volume of the liver, and an increased lymph flow from the thoracic duct. The vena cava pressure shows little or no alteration.

2. These effects are equally well produced whether the hepatic artery is intact or has been ligatured.

3. They are all due to the setting up, by adrenalin, of some obstruction to the flow of blood from the liver into the systemic circulation.

Constriction of radicles of the portal vein may possibly be a contributory factor to the rise of portal pressure.

4. The most probable cause of the obstruction is narrowing of the capillary channels by swelling of the columns of liver cells.

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