AN EXPERIMENTAL STUDY INTO THE CAUSE OF THE INCREASED PORTAL PRESSURE IN PORTAL CIRRHOSIS.[1]

By FREDERICK C. HERRICK, Cleveland.

I.

In reviewing the subject of portal cirrhosis, it is evident that our understanding of the cause, course and pathological physiology of the disease is far from clear. The pathological anatomy is fortunately well understood and one need but to refer to the recent compilation by Dr. Rolleston to find a clear description and statistics of every phase of the process. But when we enter the domain of the pathological physiology of the disease not one of its chief departures from the normal physiology is satisfactorily explained.

The increase in the portal blood pressure is one of the most marked abnormal conditions developed. As evidence that this condition exists we have the frequent hæmorrhages, the collateral circulation and the ascites, by many considered as a result of increased portal pressure. The fact of this increase in pressure cannot be doubted, but the cause of this condition, heretofore considered to be the obstruction to the portal vessels by the fibrosis and its contraction, is, in the light of the following observations, open to question.

The object of this research was to explain the increased portal pressure in this disease and thus to throw further light on the collateral circulations frequently developed naturally as well as following the operation of Talma and similar operations. In order to gain this end the circulation of the normal liver was first studied.

A short historical resume may not be out of place.

[1] The following experimental work was done in the Pathological Laboratory of the London Hospital, London, England. I am greatly indebted to Dr. W. C. Miller, pathologist to the hospital, for this privilege and also for the material which was necessary for the work.

Betz[2] in 1863 worked in Ludwig's laboratory on the question: Does the amount of blood entering the liver through the two vessels depend on their relative pressures? If this is so he recognized that the arterial flow if of large enough volume would exclude the portal. He injected many livers of dogs with hardening fluid and measured the corresponding arteries and veins, finding their proportion in size to be as 1:5 though there were wide variations. Large arterial trunks were frequently near relatively small portal vessels. The relative volume flow between the hepatic artery and the portal vein he found to be as 1: from 2 to 4 when the two vessels were flowing at different times. When flowing during the same time, they were as 1:50. His arterial pressure was twice the portal which is of course much below the normal ratio (1: from 13 to 15). Still this shows the influence of the portal pressure in decreasing the arterial flow.

Gad[3] in 1873 wrote a dissertation based upon experimental work in which he concluded that the arterial circulation in the liver performed a double function in that it brought oxygen and mechanically controlled the portal flow. A further point suggested by Gad was the aspirating action of the arterial on the portal current as the former passed by the openings of the latter, joining with them at an acute angle. He further found by experiments with rabbit's livers that a current through the arteries retarded the portal flow.

To this observation may be added the fact that the hepatic artery is capable of bringing the pre-urea bodies to the liver for their formation into urea and even in health this occurs to a certain extent.[4] At least four cases are on record in which the portal vein was entirely obliterated and the individuals lived for years; two were congenital malformations.[5] Dogs with Eck fistulas and with their portals tied excrete a normal amount of urea and have been kept for months in good health. It is therefore certain that the arterial circulation has for its functions (1) the nourishment of the connective tissue of the liver, (2) an influence on the amount of blood passing through the portal vessels, this influence being a factor in the circulatory balance within the liver, (3) the power to carry sufficient blood to the liver lobule to ensure a normal excretion of urea and an activity of the liver function sufficient to maintain health.

II.

Within the normal liver there are six factors to be considered.

1. A large volume-circulation with a low pressure.

2. A small volume-circulation with a high pressure.

3. A common channel of exit for fluid entering by these two circulations.

[2] Betz, *Zeit. für rat. Med.*, 1863, xviii, 44.

[3] Gad, Dissertation, Berlin, 1873.

[4] Hahn, Massen, Nencki, Pawlow, *Arch. f. exper. Path. und Pharm.*, 1893, xxxii, 161. Herrick, *Jour. of Exper. Med.*, 1905, vii, 751.

[5] Abernethy, *Philosophical Trans.*, 793, p. 61; Kierman, *Philosophical Trans.*, 1833, p. 758; Lawrence, *Medico-Chirurg. Trans.*, 1814, v, 174; Osler, Practice of Med., 1905.

4. A freely expansible tissue framework.

5. Two methods by which the entering circulations may influence each other, *i. e.,* by direct communication or by lateral pressure.

6. A vaso-motor mechanism to both sets of vessels.

Considering the large volume-circulation, Quincke (5) quotes von Basch who estimated the portal pressure when the splanchnic nerve was cut in a dog, at from 7 to 16 mm. of mercury, and Heidenhain who found it from 5.2 to 7.2 mm. without nerve section. The volume-flow of the portal vein was estimated by Cybulski (5) in a "small dog" at from 2.4 to 2.7 c.c. per second (a proportionate estimate in a man of 70 kilos would give the portal flow as about 35 c.c. per second). I have not been able to find a record of estimates of the volume-flow of the hepatic artery or its blood pressure. So far as size is concerned it may be considered as at least equal to the brachial artery, which has a pressure of 130 mm.

The freely expansible tissue framework is a most important factor towards the maintaining of the proper balance between the two circulations. This point and the next one will be discussed later when the experimental data have been given. Schäfer[6] concludes that both the intrahepatic arterial and portal vessels possess vaso-motor constricting powers. His evidence is not entirely convincing. A study of this influence, however, has not been included in this research, the aim being to draw some conclusions regarding the capacities of the intrahepatic veins and arteries, considering them as so many anastomosing, more or less expansive tubules lying adjacent to each other in a framework of varying expansibility.

That the widely differing pressures of the portal vein and hepatic artery at the porta hepatis come to a common level at the junction of their inter-lobular or intra-lobular venules is certain. This equalization comes about through the medium of the following factors:

1. A direct communication exists between the veins returning from the arterial supply and the portal venules. Regarding this I quote from Landois.[7] "The branches of the hepatic artery

[6] Schäfer, Text-book of Physiology, 1900, 140, 643.

[7] Landois, Text-book of Physiology. p. 308.

throughout their entire course accompany the larger branches of the portal vein (to which as well as to the adjacent larger bile ducts they supply nutrient capillaries). These branches enter into numerous anastomotic communications among themselves. The small capillaries pass mainly from the periphery of the acinus into the capillaries, however, that lie in the thicker connective tissue upon the larger venous and biliary branches and pass over chiefly into two venous trunks that, accompanying the corresponding arterial branches for some distance, empty into branches of the portal vein. Individual arterial branches pass up to the surface of the liver, where they form a wide nutritive network, particularly under the peritoneal covering. The small venous radicles collecting from this point also reach the ramifications of the portal vein."

The arterial supply thus passes through a capillary system arranged in Glisson's capsule about the portal interlobular veins and its pressure becomes reduced to an ordinary venous one. This arterial division has also been described as resulting in the formation of three or four arterioles which wind spirally about their accompanying portal vein. This spiral arrangement can be demonstrated in microscopical sections.

2. The vaso-motor influence in balancing these flows must be considered. Thus it has been shown by Bayliss and Starling that a stimulation of the splanchnic nerves causes an increased flow of blood from the liver, although the portal vein was tied. It has also been shown by Mall[8] that the portal vein receives fibers from the splanchnics. In my work in making the Eck fistula, I have frequently noticed slow vermicular contractions of the portal vein following mechanical stimulation of its walls. Two Italian authors ascribe both constrictor and dilator fibers to the splanchnic nerves and dilator fibers to the vagus (Cavazzani and Manca[9]).

Thus, in the normal liver through the medium of these two factors the arterial and portal pressures reach a common level at the points where their currents join to form the intralobular veins. If the arterial supply to a given area is relatively increased a disturbance of the balance will occur. Also, a fibrosis will make the vessel

[8] Mall, *Arch. f. Physiol.*, 1892, 409 (from Schäfer).

[9] Cavazzani and Manca, *Arch. ital. de biol.*, 1895, xxiv, 35, 295.

walls more rigid, less variable in caliber and if this intra-hepatic balance is partly due to a vaso-motor influence, this must be altered by an advancing fibrosis. I therefore sought to determine the influence on each other as to pressure and volume-flow of changes in the portal and arterial pressures and to measure the volume-flow of the two currents entering the liver at pressures considered as normal. I next made the same observations upon cirrhotic livers and found a marked difference, as will be shown.

III.

The methods employed were as follows:

For normal livers only those were used which were free from possible disease. The history and pathological diagnosis will be given. No livers altered by passive congestion were used; only typical cirrhotic livers were used for that part of the research which concerns this condition. Microscopical sections were made of each liver and the condition verified. The livers were taken never longer than twenty-four hours post mortem and were never kept longer than twenty-four hours after being removed from the body. When they were kept over night it was always in normal saline in cold storage. Comparisons of the two circulations in the *same* liver only were made. The two circulations in different livers were not compared. The circulating fluids used were normal saline solution at 38–39° C. At the end of the experiments I used defibrinated sheep's blood fresh from the animals for verification. The livers were always immersed in their natural position in normal saline at body temperature. Mercury manometers were used to measure pressures. In every case the liver was washed of blood at the normal pressures of 130 mm. for the arterial and 10 mm. for the portal vessels. They were next washed backward by a pressure of 10 to 20 mm. through the hepatic veins. It required from ten to fifteen minutes to wash a liver preparatory to the experiments. Bits of washed fibrin were occasionally floated out and especially backward from the hepatic to the portal vein. The first estimations were always made on both circulations together at normal pressures. These were then varied within the limits of from zero to 140 mm. arterial, and zero to 20 mm. portal pressure. The pressures were always put on together, and variations made as nearly as possible in the normal ratio. The portal circulation was next studied alone at variable pressures. The arterial was then considered alone with its higher pressures. By this order an unnatural dilatation of the vessels was prevented.

After the experiments the livers were sliced into sections one centimeter thick and the macroscopic vessels examined for possible occluding fibrin. In but one case was fibrin found in a portal vessel of importance, a vein of about three millimeters diameter. Sections for histological study were then made.

IV.

The effects on the portal pressure of changes in the arterial pressure and vice versa were first studied.

Arterial Pressure.	Portal Pressure, Normal Liver.	Portal Pressure Cirrhotic Liver.
0	10	10
30	10	15
70	10	18
100	11	20
130	12	30
150	14	35

Portal Pressure.	Arterial Pressure, Normal Liver.	Arterial Pressure, Cirrhotic Liver.
5	130	130
30	130	135
40	135	140
10	127 (?)	133

In normal livers an increase in the arterial pressure, when the portal was flowing at normal pressure of 10 mm., caused a very slight rise in the portal pressure, *i. e.*, about 1 mm. rise of portal for every 40 mm. rise of arterial pressure. In making this observation the portal was first set at 10 mm. and, when flowing evenly, the arterial flow was gradually turned on. Thus, raising the arterial pressure from zero to 130 mm. caused a rise of but 3 or 4 mm. in the portal pressure. When this same observation was made on a liver with marked portal cirrhosis a great difference was noted. In this case a rise of 130 mm. in the arterial pressure caused a rise of from 20 to 30 mm. in the portal pressure.

With the normal liver the rise of *portal* pressure was 1 mm. for every 40 mm. of arterial pressure increase; with the cirrhotic liver it was 1 mm. for every 6 mm. of arterial pressure increase.

When in a normal liver the *arterial* pressure was first set at 130 mm. and the portal gradually opened a similar result was noted. The arterial rise was 1 mm. for every 7 mm. increase in portal pressure.

A similar observation in a cirrhotic liver was obviously impossible, for so soon as the arterial pressure was set at 130 mm. the portal pressure rose immediately to from 20 to 25 mm., although the portal flow had not been opened, and this occurred, though more slowly, regardless of whether the portal vessels were *full*

or not. If they had been drained *before* this observation the fluid flowed into them, as will be shown in the next observation, filled them and registered the pressure.

After this arterial pressure was thus set and the portal pressure was stationary at say 25 mm., a further rise in portal pressure, caused by turning on its flow, was followed by a rise in arterial pressure of 1 mm. for every 3 mm. increase in portal pressure. Thus in the normal liver the *arterial* pressure rose 1 mm. for every 7 mm. increase in portal pressure; in the cirrhotic liver it rose 1 mm. for every 3 mm. increase in portal pressure.

It will be seen that arterial rise in pressure did not affect the portal pressure in normal livers until it had passed 100 mm. I did not measure the effects of pressures above 150 mm. In cirrhotic livers the effect on the portal pressure was evident at 30 mm. arterial pressure. These effects of one pressure on the other occurred immediately on changing a pressure and show as clearly as possible the mutual influence between the portal and arterial pressures within the liver, and is, I believe, an important explanation of the rise in portal pressure in portal cirrhosis.

As an explanation of this marked effect on each other in portal cirrhosis I may offer the following suggestions:

1. The arterial supply to the fibrous tissue of a cirrhotic liver is increased. Thus an increased amount of fluid passes through the arterial capillaries, enters the portal venules and raises the portal pressure there.

2. This would be especially the case if the hepatic veins were not quite able to give passage to the increased volume of fluid. (During life a slight weakening of the heart muscle might favor this backward pressure.)

3. There was a freer flow of fluid through the arterial capillaries into the portal veins, as will be shown later. This could occur by a dilation of these capillaries which would favor a greater influence of the arterial on the portal pressure.

V.

The arterial and portal pressures in the normal liver are perfectly balanced at the point where the arterial return veins enter

the portal venules. In the liver of portal cirrhosis this balance is disturbed by (1) the larger arterial supply, (2) the loss of portal influence by lateral pressure on the arterial capillaries and the freer communication of the arterial with the portal vessels by means of dilated capillaries. This free anastomosis between the arterial and portal vessels within the liver has been shown above (Landois). As further evidence of these communications I wish to cite the following observation:

The arterial flow alone was connected, leaving the portal and hepatic veins with a glass cannula tied in each for collecting the fluid returning through them. There was always a free return flow through both veins from an arterial inflow. Further, in the normal liver, the portal return flow was less in volume than that from the hepatic vein. In the markedly portal cirrhotic liver the portal return flow was always greater than that from the hepatic vein. This is what we would expect from the previous observations on pressure.

When the inflow was through the *portal* vein and the hepatic vein and artery were left open the return flow was *entirely* through the hepatic vein in both normal and cirrhotic livers. No fluid returned through the hepatic artery. This observation may be explained in one of the following ways:

1. Gad described the arterial return venules as uniting with the portal at an acute angle leaving a wedge-shaped valve between them. With a like pressure in the portal veins and these entering venules there would be a free flow through both; but if the pressure of either was increased there would be a narrowing of the other's lumen and reduction in its flow. If there is no arterial flow it is evident the large portal volume will entirely occlude the entering veins from the arterial capillaries, and fluid cannot flow back through them, as seen above. When, on the other hand, there is no portal flow and there is a flow through the arteries, their channels being of much less volume than the portal veins, are manifestly unable to occlude the portal vessels and hence the fluid returns through them.

2. The fact that no fluid returned through the hepatic artery from a portal inflow may also be explained by the intralobular capil-

laries and hepatic vein offering less resistance than the arterial capillaries. Against this, however, is the fact that in the cirrhotic livers where the arterial capillaries are dilated no fluid returned through them and the hepatic artery.

3. Any obstruction in the hepatic veins might cause this regurgitation of fluid through the portals. I cannot find any evidence of such obstruction. There was no intra-lobular fibrosis in these livers and, from the experimental side, there were no occluding blood clots. We must, therefore, conclude that this is not an explanation of the above facts. The wedge-shaped valves of Gad, together with the difficulty of fluids regurgitating through a capillary network, must explain the fact that an inflow through the portal returns entirely through the hepatic veins.

VI.

The volume of flow from the portal and arterial vessels is the subject of the next observations to which I wish to draw attention. Certain proportions were evident, as shown in the following table. The time during which each flow was measured was one minute.

	Volume flow of portal vein.				Vol. flow of portal vein in cirrhosis calculated proportionately to weight of normal livers.
		10 mm.	20 mm.	30 mm.	
Normal	45 oz.	230 c.c.	313 c.c.		
	52 oz.	422 c.c.	662 c.c.		
Cirrhotic	68 oz.	758 c.c.	1144 c.c		10 mm. 20 mm.
	128 oz.	880 c.c.	1230 c.c.	2100 c.c.	668 c.c. 996 c.c.
					Actual vol. flow.
					819 c.c. 1187 c.c.

From this table it will be seen that the average volume flow of the portal vein in the cirrhotic livers was, in the proportion to their weights, greater than that of the normal livers. In a normal liver weighing 45 oz. the flow from the portal vein alone was 230 c.c. in one minute at 10 mm. pressure; in another weighing 52 oz. the flow was 422 c.c. at the same pressure.

In a cirrhotic liver weighing 68 oz. (portal cirrhosis) with roughened surface and adherent thickened capsule the portal volume flow in one minute at 10 mm. pressure was 758 c.c. In another weighing 128 oz. a typical large "hob nailed" liver with marked peri-portal fibrosis, opaque thickened capsule, many adhesions, the

portal vessel allowed a flow of 880 c.c. in one minute at 10 mm. pressure. Thus the portal vascular capacity in portal cirrhosis, so far from being *decreased,* appears to be proportionately *increased.* These comparisons were verified on other livers as well and it was found that from a cirrhotic liver flowed at the same pressure at least as much fluid proportionately to its weight as from the normal one. This shows that there can be no obstruction to the portal vessels within the liver from fibrous tissue. The portal vessels allowed fluid to pass freely and it was evident as soon as such a liver was transfused that the flow was quite as free as that through a normal liver.

So soon as the arterial flow was added a different state of affairs existed. Now the portal flow was decidedly limited.

With a normal liver weighing 61 oz.

Art. Pres.	Port. Pres.	Time.	Vol.
130 mm.	10 mm.	1 min.	1024 c.c. Art.
			632 c.c. Port.
		Repeated.	1032 c.c. Art.
			650 c.c. Port.
130 mm.	20 mm.	1 min.	1100 c.c. Art.
			1300 c.c. Port.
		Repeated.	1060 c.c. Art.
			1280 c.c. Port.

With a cirrhotic liver weighing 128 oz.

Art. Pres.	Port. Pres.	Time.	Vol.
130 mm.	25 mm.	1 min.	1250 c.c. Art.
			1050 c.c. Port.
130 mm.	30 mm.	1 min.	1750 c.c. Art.
			1250 c.c. Port.
130 mm.	40 mm.	1 min.	1550 c.c. Art.
			2750 c.c. Port.
130 mm.	50 mm.	1 min.	1525 c.c. Art.
			2950 c.c. Port.

Thus at 130 mm. arterial and 10 mm. portal pressure the arterial volume-flow was the larger. It is generally conceded that the portal volume-flow is normally greater. This relation occurred between 10 and 20 mm. portal pressure. In the cirrhotic liver this relation occurred only at a portal pressure between 30 and 40 mm. Up to this point the arterial flow was decidedly preponderant.

In the above observations on a cirrhotic liver the portal pressures are seen to be very high. As shown in Part IV, when such a liver was placed under observation it was found that the influence of one circulation on the other was much more marked than in a normal organ. With an arterial pressure of 130 mm. in the hepatic artery it was found impossible to have a normal portal pressure of 10 mm. The portal pressure immediately went to 20 mm., although the portal flow *had not been opened.* In making the above observations, therefore, the arterial pressure was first set at 130 mm., and after it was flowing evenly and the pressure in the manometer connected with the portal vein had risen to its maximum, the portal flow was opened and regulated so as to add from 5 to 30 mm. more pressure.

In a normal liver, to overcome the arterial resistance to the portal flow the portal pressure had to be raised above 10 mm. At 10 mm. portal pressure and 130 mm. arterial pressure the arterial flow was greater. When the portal pressure was 20 mm. its flow became greater.

In a cirrhotic liver the portal pressure necessary to resist 130 mm. arterial pressure was much higher, being 40 mm. The circulatory balance is maintained in a cirrhotic liver at a portal pressure much above that considered as normal. By circulatory balance I have meant the pressures at which the arterial and portal vessels, when flowing together, allowed the flow of the largest amounts of fluid.

Conclusions.

1. In the liver of portal cirrhosis there is a far freer communication between the arterial and portal currents than in the normal liver.

2. Factors contributing to the increased portal pressure in portal cirrhosis are (1) the direct communication of the arterial pressure to the portal vessels through dilated capillaries, (2) the larger volume-flow of the hepatic artery in proportion to the portal flow in cirrhosis as compared to that in the normal liver.

3. A portal cirrhotic liver gives passage to an amount of portal fluid proportionate to its weight. There is no obstruction to the portal vessels from fibrosis in the large portal cirrhotic liver.

4. From an arterial inflow there is a free return flow through the portal as well as through the hepatic veins in both normal and cirrhotic livers.

5. From a portal inflow the return is through the hepatic vein only. The Gad's theory of valves and the arterial capillary network account for this fact.

6. The portal pressure has a decided influence on the arterial volume-flow and vice versa. This influence is more marked in the cirrhotic than in the normal liver.

7. The communication of the arterial pressure to the portal pressure is an important factor in an explanation of the increased portal pressure in portal cirrhosis.

AUTOPSY 959. (Year 1905.) Female, 18 yrs., burned on thorax, head, arms; death eighteen hours later. Liver normal, wt. 52 oz. Histological examination showed normal liver tissue.

AUTOPSY 953. Female, 21 yrs. Perforating gastric ulcer; death twenty hours later from general peritonitis. Liver, normal, wt. 45 oz. Microscopical examination showed a normal liver tissue.

AUTOPSY 970. Male, 48 yrs., brought in dead. Post mortem diagnosis: fibrosis of mycardium and partial occlusion of the coronary arteries by atheroma. Liver, 61 oz. Capsule thin, normal. Microscopical examination showed normal liver tissue.

AUTOPSY 998. Female, 60 yrs., general arterio-sclerosis, bronchitis, emphysema; arterio-sclerotic kidneys. Liver wt. 68 oz., surface rough and irregular, diaphragm adherent, capsule thickened, substance of liver brown, fibrous, tough. Microscope showed peri-portal fibrosis.

AUTOPSY 1055. Male, 44 yrs. Cause of death, injury. Liver, large, tough, pale. Microscopical examination shows rather a marked peri-portal fibrosis, in places isolating the lobules from each other.

AUTOPSY 1086. Male, 63 yrs. Epithelioma of penis. Liver wt. 128 oz., hob nailed, tawny yellow, tough, capsule opaque and thickened. Many adhesions about porta hepatis, and between the capsule and the diaphragm. Microscopical examination showed a typical, peri-portal fibrosis of marked degree.