RELATION OF THE PORTAL BLOOD TO LIVER MAINTENANCE.

A Demonstration of Liver Atrophy Conditional on Compensation.

By PEYTON ROUS, M.D., and LOUISE D. LARIMORE, M.D.

(*From the Laboratories of The Rockefeller Institute for Medical Research.*)

Plates 67 to 71.

(Received for publication, February 2, 1920.)

In the course of observations on the rôle of the liver in blood formation and destruction, we have had occasion to ligate portal branches to the organ. The ensuing changes have been of such striking character as to merit study for their own sake; and the present paper is concerned with them. There already exists, of course, a considerable literature on so obvious a theme. For the moment it may suffice to state in this connection that according to the generally accepted view occlusion of a portal branch to the liver has no effect on the organ save when a grave derangement of the systemic circulation is also present. The complete local parenchymal atrophy that in our experiments regularly followed such occlusion was unforeseen, as was the further observation that the atrophy is conditional, being dependent upon a compensatory hypertrophy of the remainder of the organ.

Method.

The liver of the rabbit is singularly adapted for experiments involving the blood vessels and bile ducts, since it consists of two separate masses, each with its own vessels and ducts. The rabbit may indeed for operative purposes be said to possess two livers. They are of very unequal size, the larger, or main liver, as we shall call it, formed of the left anterior and posterior lobes and the right anterior lobe with the gall bladder, being three times as big as the smaller, or lobe mass, which consists of the right posterior and caudate lobes. The lobe mass contains just enough parenchyma, as Ponfick[1] showed, to suffice for the

[1] Ponfick, E., *Virchows Arch. path. Anat.*, 1889, cxviii, 209; 1890, cxix, 193.

needs of the organism when the main liver is ablated. Through it, under such circumstances, all of the portal stream finds room to pass.

In our experiments the portal trunk to the main liver of the rabbit has been ligated just above the caudate lobe. By such means the whole portal stream is diverted to the lobe mass. The caudate lobe, though a part of the latter by reason of its parenchymal connection with the right posterior lobe, has an added source of venous blood through a small branch arising from the portal trunk at the level of the ligature and frequently compromised by it. To avoid the irregularity thus introduced, the caudate lobe was tied off and cut away as a routine measure. A piece of the tissue was sectioned to determine the condition of the liver.

In ligating the portal trunk great care was taken not to interfere with the main bile duct and hepatic artery. The operation was carried out under ether on rabbits of from 1,400 to 2,300 gm. Closure was done in three layers. Occasionally a fatal necrotic process spread from the ligated caudate stump, but the great majority of the animals recovered without complication and remained in perfect health. They were killed with chloroform at periods of from 12 days to 6 months after the original operation. The liver masses were weighed separately after the blood, as yet unclotted, had flowed away from the severed vessels. This, it was felt, would result in a truer estimate of relative amounts of parenchyma than if the blood were retained by closing the vessels, as was Ponfick's method. According to Ponfick,[1] the normal liver of the rabbit averages 3.56 per cent of the gross body weight, though he prefers to use 4 per cent in calculations. On his estimation the main mass forms 74.7 per cent of the total, the right posterior lobe 19.3 per cent, and the caudate lobe 6 per cent. In fifteen normal rabbits we have obtained an average figure of 3.45 per cent for the liver's proportion of the body weight, with variations ranging from 2.18 per cent to 5.25 per cent. The main mass averaged 72.3 per cent of the total, the ablated caudate 4 per cent, and the right posterior lobe with the caudate stump 23.7 per cent.

Early Changes after Local Portal Occlusion.

The immediate results of diverting the stream are striking.

Within a minute or so the main liver becomes much smaller, of a deeper purple, and flaccid, whereas the isolated lobe, which now receives all the venous blood, is swollen, tense, and of a rather bright red. In animals dying after 1 or 2 days hemorrhages into spleen, stomach, and small intestines are sometimes found, such as Ponfick observed after removal of the main liver; but, as he also noted, these are infrequent in vigorous animals. The acute passive congestion responsible for them is quickly relieved as the stream bed in the lobe mass is widened through the hypertrophy of the latter.

The mass receiving the portal blood begins to hypertrophy within 3 days by cell proliferation within the lobules, as after ablation of the main liver,[2] and by the end of 12 days the tissue has usually more than doubled, and after 15 days may have trebled. Subsequently its bulk increases more slowly, but eventually reaches that of the entire original liver, and usually surpasses it. Concurrent with the hypertrophy is a progressive atrophy of the mass deprived of portal blood (Figs. 1 and 2).

Owing to reduced capillary distension the lobuli fall together to some extent immediately after the ligation, and within the next few days their cells, which now appear crowded, are noted to have grown smaller, especially near the central vein where the blood supply is poorest. If the animal is weak and dies early, a marked local widening of the capillaries may here be noted, with fine, brown pigmentation of the parenchyma. The condition then is identical with that known in human pathology as the "atrophic red infarct of Zahn." In vigorous rabbits the capillary widening is slight, often absent, and the intralobular atrophy alone attracts attention. The liver mass sometimes dwindles within 12 days to about one-half its original bulk (Table I), though usually the change is slower. Its lobes are flabby, wrinkled, purple, and at this particular period their surface is usually mottled with ill defined, slightly raised, pale spots which may be half a centimeter in diameter (Fig. 3). Several lobuli or parts of them are included in such areas. They are well seen only on the capsular surface, are not degenerative in character, become much more prominent when the blood has partially escaped from the tissues, and are probably areas of relative anemia. The general condition of the liver at this time has much in common with that in dogs during the period of adjustment after an Eck fistula.[3,4] But outspoken degenerative changes are rare in the rabbit liver as compared with the dog, though sometimes a moderate, central fatty degeneration may be noted. The tissue when cut is soft, dark purple, and spleen-like; the lobuli are very small and indistinct. Bile ducts, blood vessels, and interlobular connective tissue are all rendered unusually prominent by the dwindling in parenchyma, and, simulating trabeculæ, add to the spleen-like appearance of the tissue.

Microscopically, one finds many small lobuli to a field, and there is a great increase in the number of cells per unit of surface (Fig. 1), so that the nuclei appear crowded. These last, as well as the cytoplasm, have greatly decreased in bulk, though otherwise they appear unchanged. At the periphery of the lobules a few endothelial cells along the capillaries may be somewhat swollen

[2] Ponfick, E., *Virchows Arch. path. Anat.*, 1895, cxxxviii, suppl., 81.

[3] Whipple, G. H., and Hooper, C. W., *Am. J. Physiol.*, 1917, xlii, 544.

[4] We wish to thank Dr. G. H. Whipple for sections illustrative of the Eck fistula liver.

with granules of a light brown, iron-containing pigment. Such pigmented Kupffer cells become more prominent as time goes on. There is no absolute increase in connective tissue.

Late Changes after Local Portal Occlusion.

The changes up to this point have been partially described by Steenhuis.[5] In his most advanced instance, an animal killed 4½ months after the portal ligation, a further moderate increase in pigmentation and atrophy was noted, but nothing more, a fact difficult to understand save on the assumption that portal collaterals to the main liver had developed, or that the animal was old or in poor condition, all of which factors largely affect the changes. For the atrophy goes further, and quickly too, resulting in a disappearance of all the parenchyma of the main liver, a process sometimes practically completed within 2 months, as we shall show.

Between the 12th and the 40th day after the portal ligation a circulatory readjustment occurs in the dwindling liver mass. Pale spots are no longer seen on its surface, which is of a brighter, more normal red, though tinged with brown. The organ cuts with difficulty, owing to the survival of all its ducts, vessels, and connective tissue, which are brought nearer together by the disappearance of parenchyma; and the tissue disclosed by the knife is more markedly spleen-like, with no trace of a lobular pattern. Histologically, the parenchyma may seem like the normal at first sight, except for the very small size of lobuli and cells, a marked irregularity in the arrangement of the former, and perhaps some irregular capillary widening. Fatty changes are entirely absent, and the atrophy is more evenly distributed. On close scrutiny one perceives here and there parenchymal elements almost without cytoplasm and with small pycnotic nucleus. These scattered cells in the last stages of disappearance are somewhat more numerous toward the center of the lobules. The cell cords in general may be especially atrophic here, and their capillaries wider than at the periphery, additional indications that the central parenchyma suffers most. Pigmented Kupffer cells, distended to a spherical or egg shape, are increased in number, but are found as before only near the periphery of the lobule. The interlobular tissue has nowhere invaded the parenchyma, is absolutely unincreased, and new formed bile ducts are not present. The ducts and vessels, unchanged from their original size, are bent into convolutions as the mass grows smaller, so that their number seems multiplied on cross-section (Fig. 5).

[5] Steenhuis, T. S., Experimenteel en kritisch onderzoek over de gevolgen van poortaderafsluitung, Proefschrift Rijks-Universiteit te Gröningen, 1911.

The period required for complete disappearance of the parenchyma varies with the individual (Table I). When the animal is opened the stomach is found to lie in the concavity of the diaphragm, and only on lifting it away is the insignificant remnant of the main liver discovered, with a gall bladder of normal bigness sessile upon it (Fig. 9). The compensating lobe, of great size, extends far down over the abdomen. On nearer inspection, the original lobes of the main liver are found to be represented by three little, flabby, pinkish brown tags (Fig. 4). Cultures from these are sterile. Their surface is roughened by numerous, close packed and tortuous vessels and ducts. Sometimes red varices stud the surface here and there. The hepatic veins, of almost the normal size, at once attract attention as distended cords, grossly disproportionate to the tissue out of which they spring. The hepatic artery, too, is still large. On section the tissue is extremely tough and shows no parenchyma, but everywhere the gaping mouths of vessels and ducts in a slight matrix of connective tissue. The blood immediately above the ligature on the portal trunk is usually fluid, and thrombi are always absent from the branches of the vein.

Microscopically, a few liver cells can be found even when the changes are most pronounced, for the reason that there exist in practically every case a few minute, collateral venules bringing portal blood to the tissue. The rapidity and completeness of the atrophy is in our experiments proportionate to the number of these little collaterals. Their influence may be directly seen where they enter the liver. For example, in Rabbit 27, killed 118 days after the ligation, 2 minute venules were found coursing to small masses of healthy parenchyma in the midst of the atrophy (Fig. 4).

The final changes have much interest. Little by little the lobular units grow smaller and more irregular in form, so that a central vein, when discoverable, may be far off to one side (Fig. 5). There is still no connective tissue invasion or proliferation, but Glisson's capsule becomes increasingly prominent in the picture, appearing to close in on the lobules and envelop them. As the parenchyma grows less, so do its attendant capillaries disappear, and they never survive when the liver cords are gone. Soon there remain only scattered islands consisting of a few small, but healthy looking liver cords with the characteristic capillaries, set in a matrix of connective tissue (Fig. 7). Here and there, near by, three or four parenchymal cells may perhaps be found as an isolated cord, not infrequently with a capillary along one side; and liver cells separated by the en-

veloping matrix of connective tissue may still be recognized. Many such isolated cells have lost their characteristic ground glass appearance, stain a clear pink with eosin, and may be of blunt spindle shape with a relatively large pycnotic nucleus (Fig. 8). Finally parenchymal elements become rare (Fig. 10). Their situation is sometimes indicated by the irregular zone of Kupffer cells distended with pigment that mark the border of the original lobule. As the atrophy increases such elements become prominent, and rounded nests or aggregations of thirty to forty are not infrequent (Fig. 6). Always they are confined to the region of the original periphery of the lobules and are separated from the parenchyma only by the disappearance of the latter. The total absence of invasive tendencies on the part of the connective tissue could not be more clearly shown than by this fact.

The final tag of ducts, vessels, and connective tissue (Fig. 10), representing 50 to 70 gm. of main liver, weighs, in the absence of coccidiosis, cirrhosis, or other intercurrent proliferative change, only 1 to 1.8 gm., which may perhaps be taken as nearly representing the original weight of the non-parenchymal elements. If a cirrhosis was originally present as shown by the caudate sections, the surviving tissue is of greater bulk.

Conditional Character of the Atrophy.

The liver atrophy in the dog and in man following diversion of the entire portal stream through an Eck fistula is never great. Hence we have questioned whether the complete atrophy observed on local portal diversion in rabbits is inevitable or dependent upon hypertrophy elsewhere. To test the matter hypertrophy has been largely prevented in some animals by tying the bile duct to the lobe mass of the liver after diverting the entire portal stream to it as usual. Under such circumstances the lobe mass undergoes some increase in size through cell proliferation, but combined with this is a continuous, scattered biliary necrosis, and by the end of 12 days a diffuse cirrhosis makes its appearance. After 25 to 30 days the tissue, though still of greater bulk than normal, is indurated and shows microscopically an almost complete replacement with connective tissue. The changes will be more fully described in a later paper. The fact to be emphasized here is that in the absence of hypertrophy of the lobe mass the main liver fails to undergo marked atrophy, although deprived of the portal stream. Such slight atrophy as occurs may be looked upon as inevitable to the circulatory change as such.

The rabbits used were kept under identical conditions and had approximately the same weight. In one series the portal blood was diverted from the main liver and the caudate lobe ablated as usual, while in the other ligation of the bile duct or ducts to the lobe mass was also performed. The local bile stasis had caused no jaundice, and the animals were in good health. The ducts to the posterior lobe, for there may be two or three, lie in an exposed position and can readily be isolated and tied off without damage to their surroundings. From this circumstance, taken with the differing results obtained in the two series of animals, it follows that direct nerve injury can be ruled out as a cause for the complete atrophy after simple portal occlusion. Animals with livers originally abnormal were discarded.

A complicating factor made necessary the early comparison of the series. The progressive cirrhosis occurring when the bile duct from the lobe mass is ligated brings about after a time an obstruction to the portal flow, with chronic passive congestion of the viscera. The spleen enlarges greatly, sometimes becoming cylindrical; and venous collaterals appear rapidly, as a rule preventing marked ascites, though this was once noted. None of the new venous channels had importance for us save such as might enable the portal blood to regain its old stream bed in the main liver; but unfortunately some of this character frequently developed within a few weeks. Usually they followed the course of the veins of Charpy, but sometimes found a way through adhesions. Portal diversion alone not infrequently led to their development in small number. The majority of the rabbits were killed and autopsied prior to their appearance; that is, 12 to 15 days after operation. Such small collaterals to the main liver as were then observed have found place in the general record (Table I). All the animals were killed soon after a feeding.

The weight of the entire liver was somewhat below the normal average in five animals killed 12 days after simple portal occlusion—3.22 per cent of the gross body weight as compared with a normal of 3.45 per cent. Every individual weight, though, was within the normal range of 2.18 to 5.28 per cent. In the five rabbits with local bile stasis added to portal ligation, whereby parenchymal destruction was superimposed upon hypertrophy, the livers weighed more, averaging 3.62 per cent of the gross weight. In the animal with simple atrophy, and its companion with bile stasis, killed after 15 days, the weights were 4.5 and 5.78 per cent of the gross, respectively. The average after longer periods was 3.73 per cent for ten rabbits killed from 21 to 68 days after portal diversion, and 3.69 per cent for three animals with an additional bile stasis, examined after from 21 to 30 days. It would seem that the reparative changes went beyond a mere replacement, as

TABLE I.

Liver Changes Following Diversion of the Portal Stream to the Lobe Mass.

Rabbit No.	Body weight.		Collateral veins to liver.	Liver weight.			Liver's per cent of body weight.			Condition of main liver.	Remarks.
	At operation.	Final weight.		Entire mass.	Main liver.	Lobe mass.	Entire mass.	Main liver.	Lobe mass.		
Duration of experiment, 12 days.											
	gm.	*gm.*		*gm.*	*gm.*	*gm.*					
1	2,200	2,475	None.	72.4	28.3	44.1	2.93	1.15	1.78	Marked atrophy; many pale spots.	
2*	2,050	2,175	One of 1½ mm.	78.6	43.3	35.3	3.62	1.99	1.63	Little atrophy; no spots.	
3	2,150	2,050	One of ¾ mm.	75.4	39.8	35.6	3.68	1.94	1.74	Marked atrophy; many spots.	
4	2,150	2,050	One of 2¼ mm.	76.6	48.0	28.6	3.74	2.34	1.4	Little atrophy; no spots.	
5	1,900	1,600	One of 3 mm.	46.4	21.7	24.7	2.9	1.36	1.54	Marked atrophy; no spots.	
6	1,925	1,600	Two of 1 mm.	65.2	30.2	32.8	4.07	1.89	2.05	Little atrophy; no spots.	Of total liver weight 2.2 gm. is caudate stump in simple hypertrophy.
7		1,525	One of 1 mm. and several smaller.	48.8	16.8	32.0	3.2	1.1	2.1	Marked atrophy; some spots.	Animal has lost little if any weight.
8	1,850	1,700	None.	55.0	29.9	25.1	3.24	1.76	1.48	Marked atrophy; many spots.	
9	1,550	1,275	One of 1½ mm.	43.1	23.2	19.9	3.38	1.83	1.55	Marked atrophy; many spots.	Animal grew thin after operation.
10	1,750	1,650	One of ½ mm.	56.4	38.3	18.1	3.42	2.32	1.1	Slight atrophy; some spots.	

Duration of experiment, 15 days.

11		1,425	1,525	One of 1 mm.	70.2	18.6	51.6	4.6	1.22	3.38	Marked atrophy; some spots.	
12		1,425	1,400	Two of 1 mm.	80.9	38.9	34.2	5.78	2.78	2.44	Slight atrophy; no spots.	Of total liver weight 7.8 gm. is caudate stump in simple hypertrophy.

Later periods.

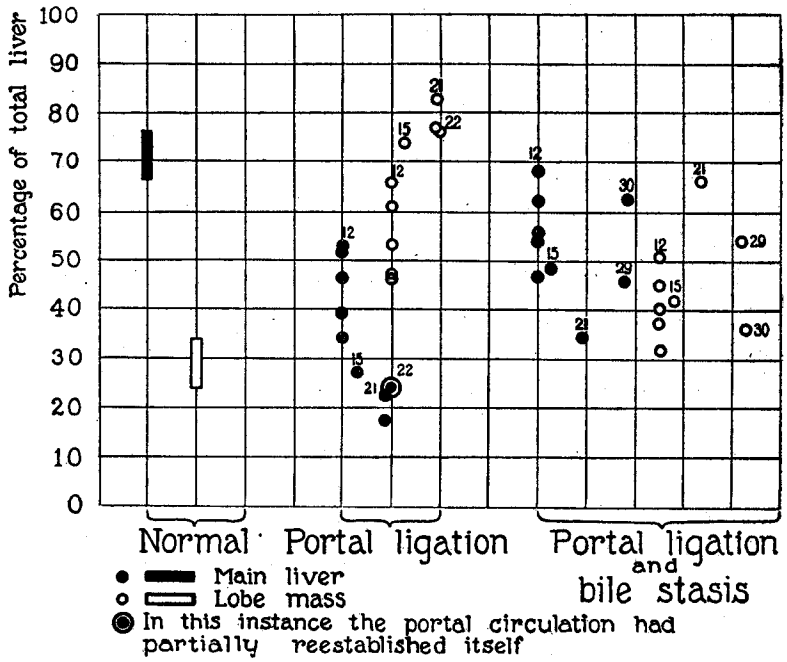
	days											
13	21	2,300	2,250	Only very fine ones.	73.5	17.0	56.5	3.27	0.76	2.51	Marked atrophy.	At least 2 gm. of main liver consists of coccidial change.
14	29	2,175	2,300	Only very fine ones.	78.5	37.0	41.5	3.42	1.61	1.81	Slight atrophy.	Marked chronic passive congestion. Spleen weight 4.1 gm.
15	30	2,275	2,275	Numerous very fine ones; also one of 1 mm. and of 2 mm.	69.1	44.0	16.4	3.02	1.94	0.72	No atrophy.	Caudate stump of 8.7 gm. in simple hypertrophy gives a by-pass for the blood. No passive congestion.
16	22	1,825	1,900	One of 5 mm.	122.7	30.5	92.2	6.47	1.61	4.86	Moderate atrophy.	Portal flow to main liver almost wholly reestablished.
17	21	1,875	1,375	One of 2 mm.	68.7	22.8	45.9	5.0	1.66	3.34	Moderate atrophy.	Chronic passive congestion; ascites; marked loss of weight.
18	21	1,575	1,750	None (?).	55.4	9.3	46.1	3.17	0.53	2.64	Marked atrophy.	Collaterals not sought for. No passive congestion.
19	21	1,675	1,950	None.	77.5	15.2	62.3	3.98	0.78	2.2	" "	No passive congestion.
20	25			Not noted.	73.5	19.5	54.0				" "	

* The findings in bold faced type relate to animals in which the bile duct of the lobe mass was also ligated.

TABLE I—*Concluded.*

Rabbit No.	Body weight.		Collateral veins to liver.	Liver weight.			Liver's per cent of body weight.			Condition of main liver.	Remarks.
	At operation.	Final weight.		Entire mass.	Main liver.	Lobe mass.	Entire mass.	Main liver.	Lobe mass.		
					Later periods.						
	days	*gm.*	*gm.*		*gm.*	*gm.*	*gm.*					
21	55	2,125	2,550	One of ½ mm.	84.3	5.0	79.3	3.31	0.2		Advanced atrophy.	
22	58	2,025	2,250	Two " 1 "	74.1	10.1	64.0	3.3	0.46		" "	
23	64		2,150	One " 1½ " " " 1 " several hair-like.	59.9	6.7	53.2	2.79	0.31		" "	
24	65		2,050	One hair-like.	70.9	1.8	69.1	3.46	0.09		Practically complete atrophy.	
25	68	2,025	2,050	" of 1 mm.	79.3	4.0	75.3	3.87	0.2		Almost complete atrophy.	
26	104	2,250	2,300	None.	82.4	9.4(!)	73.0	3.58	0.41		Advanced atrophy.	Unusual delay in atrophy.
27	118	1,825	2,375	Two of ½ mm.	99.0	1.4	97.6					Liver weighed with blood retained.
28	185		2,400	" " 1½ " and 1 mm. respectively.	71.1	1.6	69.5	2.96	0.07		Complete atrophy.	

with other tissues. The idea is borne out by the decrease in size of the liver occurring later. In seven animals killed 55 to 185 days after portal diversion the liver averaged only 3.22 per cent of the body weight.



TEXT-FIG. 1. The change in relative proportions of main liver and lobe mass after local portal diversion with and without ligation of the bile duct of the mass receiving the portal stream (see Table I). The range of the normal proportions as observed in thirteen rabbits, is given in the short columns. The caudate lobe had not been ablated in these instances as in the case of the operated individuals. The results in the latter are given in dots, and the number of days elapsing after operation is indicated in small numerals. When there is but one of these above a vertical row of dots it is supposed to apply to all.

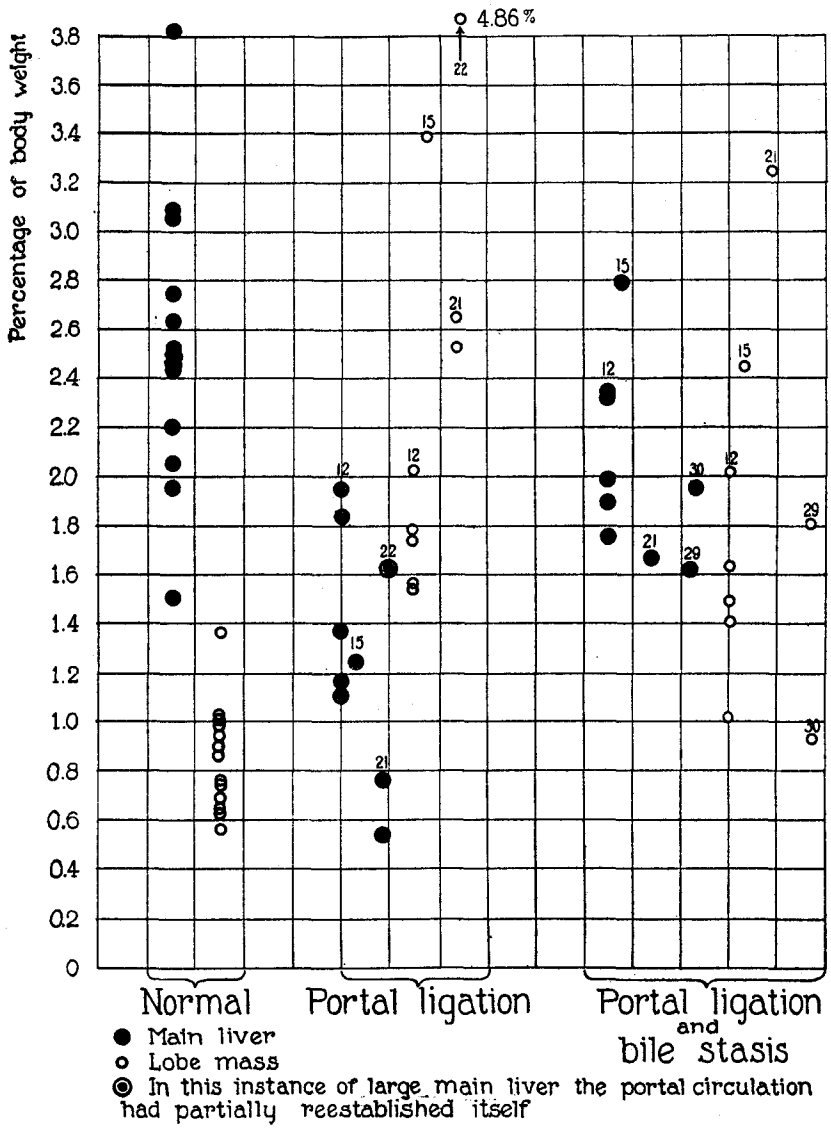
The distribution of the hepatic parenchyma was very different in the two series of animals (Text-fig. 1). Under normal conditions the relative size of the liver masses does not vary much, the larger ranging from 75.7 to 66.3 per cent and the smaller from 24.3 to 33.7 per cent of the whole. After operation not only did the general relations

change but the individual variations in the liver masses became greater. The latter alteration has no interest for us, however. The important point is that the main liver retained far more of its parenchyma after diversion of its portal blood if progressive hypertrophy of the lobe mass was prevented by biliary stasis (Text-fig. 2). The fact is illustrated by differences in both the proportional and actual weights of the liver masses; and the longer the period after operation the greater was the disparity noted, granting the absence of large hepatopetal collaterals. After 4 weeks of portal diversion plus bile stasis the main liver was sometimes three times as big as after but 3 weeks of uncomplicated portal diversion (compare Nos. 14 and 18, Table I, and see also Text-fig. 2).

The importance of portal venules measuring 1 to 2 mm. in diameter for the maintenance of the large mass of liver tissue that remains shortly after operation is negligible, as the general records show (Table I). The animal with the largest collaterals after 12 days, Rabbit 5, the subject of simple portal diversion, had a liver atrophy far greater than occurred in any of the controls with almost no collaterals but with bile stasis. Even at a late period of atrophy, when the liver is greatly shrunken, a collateral of 1 mm. diameter suffices to maintain but a small portion of parenchyma, as we have repeatedly found (Fig. 4). Yet the importance of very large collaterals is not to be gainsaid. It is well seen in the case of Rabbit 16, Table I.

A number of special instances excluded from the table and the text-figures for good cause might be quoted to illustrate the dependence of the pronounced liver atrophy on a compensating hypertrophy. One will suffice.

In a rabbit weighing 1,600 gm., killed 12 days after simple portal diversion, an unexpectedly large main liver was found. It weighed 33.2 gm., representing thus 2.1 per cent of the body weight of the animal, a proportion met with in other animals only when local bile stasis had prevented hypertrophy of the lobe mass. There were no collaterals to explain the condition, but in the lobe mass, which weighed only 22 gm., an atrophy of unknown cause was encountered, affecting at least half of its original tissue content, while the remainder was hypertrophied.



TEXT-FIG. 2. Changes in weight of the main liver and lobe mass, as expressed in percentages of the gross body weight. The number of days elapsing after operation is given in small numerals as in Text-fig. 1.

Functional Activities of the Atrophic Tissue.

The functional activities of an hepatic tissue deprived of portal blood and competing with a hypertrophic parenchyma that receives the entire portal stream have much interest. Asp[6] showed long ago that the immediate effect of a local portal occlusion in the rabbit is to lessen secretion from the affected parenchyma. In our animals the atrophic tissue still secreted bile in good quantity at a period when the liver mass possessing a monopoly of the portal stream was far advanced in compensatory hypertrophy.

The biliary secretion of the rabbit is thin and copious—5 cc. per kilo of animal in 1 hour according to Heidenhain,[7] or 169 gm. per kilo of liver. Krause[8] obtained an average of 115.7 gm. of bile per kilo of animal in 24 hours. The weight of his animals was taken after the intestinal contents had been removed, which entailed a reduction of some 20 per cent from the gross weight. The quantity of rabbit bile varies greatly from hour to hour; the pigments fail to give the ordinary color reactions in a satisfactory way; and neither they nor the other bile constituents have been sufficiently studied to establish a norm. For these reasons we have merely observed the amount and color of the secretion from liver masses in atrophy and submitted it to Pettenkofer's test, while well aware that the latter gives positive results with other substances than bile salts, notably with cholesterol.

Method.

Two operations were necessary, the first to ligate the portal vein to the main liver, and the second, weeks or months later, for the ligation of the bile duct to the atrophic mass and the production of a fistula. The duct was twice tied above the point of entrance of the branch from the compensating lobe mass; the gall bladder was slit at its tip; a fine, rubber-covered catheter was introduced; and this last was sewed to the lip of the abdominal wound in such fashion that the atrophic liver was left in its usual position. The gall bladder and larger bile passages above the ligatures were gently and repeatedly flushed with salt solution injected and withdrawn through the cannula. This was done to wash out all traces of the bile previously reaching the gall bladder from the hypertrophic tissue. The washing never caused even a temporary cessation of the bile flow so far as could be judged from cases in which this was abundant. The cannula was now connected with a thick walled, rubber tube that led to a sterile, flat bottle strapped to the abdomen with adhesive. Through the stopper an air-vent tube was carried around to the animal's back under a many tailed bandage. The

[6] Asp, G., *Arb. physiol. Anstalt Leipzig*, 1873, viii, 124.

[7] Heidenhain, R., in Hermann, L., Handbuch der Physiologie, Leipsic, 1883, v, pt. 1, 252.

[8] Krause, W., Die Anatomie des Kaninchens, Leipsic, 2nd edition, 1884.

bottle was adjusted at such an angle that the bile dropped into it from the end of the tube. The animals tolerated the arrangement well, and sometimes bile collection was continued for a period of 48 hours.

The several experiments in which bile collections were made from main livers in a state of moderate atrophy need not be cited in their entirety. In all an unexpectedly large amount of bile was obtained.

For example, 15 cc. of bright green bile giving a marked Pettenkofer reaction was obtained in 18 hours from an atrophic main liver weighing 19.5 gm., in the presence of a lobe mass of 54 gm. At the time when the bile fistula was produced, 25 days after portal closure, the original ligature on the vein was found to have relaxed, allowing a slight leak to the main liver, and accounting for the slightly delayed atrophy. A second, and completely occluding, ligature was laid on prior to the collection of bile. The latter was secreted at a rate much below the normal, though still considerable—43 cc. per hour per kilo of the atrophic tissue.

More interest attaches to instances in which the compensating mass approximated the whole original liver in size, and presumably in function, since the atrophic main liver had become very small.

Rabbit 24 had on the 65th day after operation a main liver weighing but 1.8 gm. and a compensating mass of 69.1 gm. On the day previous, while the animal was in excellent condition, the main bile duct was ligated and a fistula produced as usual. The ligature was placed above the entrance into the main duct of the branch from the left posterior lobe, and in consequence the secretion from only about two-thirds of the atrophic mass was obtained. At autopsy no portal collaterals to this fraction were found, nor was there the least biliary obstruction. The gall bladder was empty. From it 0.8 cc. of clear, watery fluid had come away in 23½ hours. This had a faint greenish tinge and gave a faint Pettenkofer reaction. The microscope later showed that definite islands of liver parenchyma were present in the tissue furnishing the bile.

A similar duct ligation with the branch from the left posterior lobe excluded was done in Rabbit 23 with a main liver of 6.7 gm., and 53.2 gm. of compensating tissue 64 days after operation. The atrophic tissue from which bile was collected, some two-fifths of the whole main liver, received a portal collateral 1.5 mm. in diameter. Nevertheless, there was secreted from it only 0.9 cc. of bile in 21 hours, though this was medium green in color and gave an outspoken Pettenkofer reaction. The tissue that was drained still consisted predominantly of parenchyma.

Rabbit 21 had a main liver of 5 gm. and a compensating mass of 79.3 gm. on the 55th day after operation. The main duct was ligated successfully, but a blood clot stopped the cannula, so the animal was killed 4 hours after the operation. During this period it had been lively. The stomach was full of food. Only 0.5 cc. of fluid, and this faintly green, was present in the collapsed gall bladder. No obstruction was found to the flow of bile through the ducts; and the

main liver mass was still predominantly parenchymal. A single hepatopetal portal collateral existed, 0.5 mm. in diameter.

The amount of parenchyma present in the atrophic main liver of Rabbit 24 was small. In the other two instances, though, where there was more of it, the amount of bile was far below that called for on calculation, had the conditions been normal, after allowing for 1.8 gm. of scaffolding, ducts, and vessels in the atrophic mass. Furthermore, the secretion in two of the three animals was markedly deficient in pigment, and in one gave but a faint Pettenkofer reaction. Yet there is no doubt that the hepatic tissue, even when extremely atrophic, does manufacture bile of a sort, and is not prevented from so doing by the presence of a compensatory liver mass of very large size. It should be remembered in this connection that the atrophic tissue receives through its large hepatic artery a liberal supply of blood.

Glycogen was sought with Best's carmine stain in three instances of far advanced atrophy. The method is subject to some errors, as Rusk[9] has brought out, yet it seemed preferable to a chemical analysis because of the greatly altered proportion of parenchyma in the tissue. The preparations showed a practically identical amount and distribution of glycogen in the hypertrophic and atrophic parenchyma of the same individual, even in cases as advanced as Nos. 24 and 25 (Table I). Neither the competition of the hypertrophic mass nor its favorable situation on the portal stream was sufficient to deprive the main liver of even relatively little glycogen. But this is scarcely surprising when one considers how widely the substance is distributed in the body, and that dextrose is normally present in the arterial blood. An interesting aspect of the findings is the evidence they give for the belief that such liver parenchyma as survives atrophy to a late period remains in remarkably good condition. For the glycogen content of unhealthy tissues is usually greatly altered.

DISCUSSION.

Conditional Atrophy in the Dog.

Recently one of us, with Dr. Philip D. McMaster, has ligated the portal trunk to the three upper lobes of the liver in a number of dogs. Changes ensued much more slowly than in the rabbit and are not yet

[9] Rusk, G. Y., *Univ. California Pub. Path.*, 1912, ii, 83.

complete, after 3 months, but the tissue deprived of portal blood has diminished to less than one-third of its original bulk through a simple atrophy, with a corresponding hypertrophy elsewhere.

Review of the Literature.

Previous work on the result of local portal occlusion has been well summarized by Winternitz,[10] who himself treats of the early changes in human livers. Though some observers, Solowieff[11] and others, have claimed that the occlusion of portal branches leads to cirrhosis, and Ehrhardt[12] stated that a moderate atrophy without cirrhosis ensues, the prevailing view, long since crystallized, is that no liver changes occur either in man or the laboratory animals unless pressure is abnormally low in the hepatic artery or high in the vena cava as the result of a disturbed systemic circulation. Under such contributing circumstances one finds within a few days the so called red infarct of Zahn in the region deprived of portal blood. Here the lobular capillaries are much distended, presumably from a venous stasis, and the liver cords somewhat atrophied. In the gross the liver portion is dark red and slightly sunken. The late changes have not been described, according to Winternitz, for the reason that such diseases as produce embolus or thrombosis in the portal system almost always end fatally within a brief period.

It is interesting to note here and there in the literature isolated statements that confirm our findings, and like them indicate that the prevailing view as just given is erroneous. Thus Frerichs[13] stated in 1858 on the basis of his own observations that local portal occlusion leads to parenchymal atrophy with liver scarring. According to Ehrhardt,[12] Nauwerck saw a case in which the left lobe of the liver was diminished to the size of the fist, with compensatory hypertrophy of the right lobe, as a result of long standing occlusion of the left portal branch. Ehrhardt himself produced a moderate atrophy with compensatory hypertrophy by local portal ligation in cats, but he did not follow the changes long.

As already mentioned, most authors state that the development of a red infarct of Zahn after local portal occlusion is conditional upon a general circulatory disturbance. The fact that Zahn[14] himself produced typical red infarcts by injecting mercury into a mesenteric vein of otherwise healthy dogs seems to have been forgotten, as has also his view that the condition is an atrophy from inactivity owing to the lack of portal blood, combined with a pressure atrophy

[10] Winternitz, M. C., *Bull. Johns Hopkins Hosp.*, 1911, xxii, 396.

[11] Solowieff, A., *Virchows Arch. path. Anat.*, 1875, lxii, 195.

[12] Ehrhardt, O., *Verhandl. deutsch. Ges. Chir., 31 Kong.*, 1902, xxxi, 544.

[13] Frerichs, F. T., Klinik der Leberkrankheiten, Brunswick, 1858 (Sydenham Society's translation, A clinical treatise on diseases of the liver, London, 1861).

[14] Zahn, F. W., *Verhandl. Ges. deutsch. Nâturforsch. u. Aerzte, 69 Versamml.*, 1897–98, ii, pt. 2, 10.

from stasis as the result of retrograde pressure in the hepatic veins. The drawing given by Chiari[15] shows a histological condition identical with that present in our rabbits 12 to 15 days after the ligation. There can be no doubt that a general circulatory derangement renders the atrophy more prominent, as was the case in some of our animals that fell sick. The widening toward the central vein of the lobular capillaries, when marked, is doubtles often the result of retrograde pressure; but it occurred in moderate degree in some of our well conditioned rabbits and would seem then to have been merely the consequence of rapid atrophy of the liver cords. That there may occur complete parenchymal atrophy which is conditional on hypertrophy of the remaining parenchyma has not been realized heretofore.

Since the completion of our work the paper of Steenhuis[5] has come to attention. It has attracted little notice among pathologists, owing perhaps to the fact that its author laid stress rather upon the surgical implications of his findings than upon the pathological. But Steenhuis ligated the portal trunk to the main liver of the rabbit, just as we have done, and observed an atrophy of medium grade thereafter, with the development of pigmented Kupffer cells. He did not follow the changes to even approximate completion, since in his most advanced instance a considerable bulk of liver tissue still remained, as the pictures and description clearly show. He noted the influence of portal collaterals to check the atrophy and drew the conclusion, since proved erroneous, that a direct portal stream is essential to liver survival.

Physiological Considerations.

Several reasons can be suggested for the changes which follow a local diversion of the portal stream. Among them are the following:

(*a*) *Direct Influence of the Altered Circulation.*—By the ligation of its portal trunk the main liver is supplied solely with arterial blood, which latter may be so unsuited to the liver cells that they can survive and function only in the absence of competition, as under the circumstances of an Eck fistula. The high oxygen content of the blood can scarcely be invoked as a cause of the hypothetical unfitness, since the atrophy is least at the periphery of the lobules where oxygenation is greatest.

(*b*) *Altered Functional Opportunities.*—By local portal obstruction one portion of liver tissue is deprived of its normal opportunity to obtain many substances and must compete with another receiving them in undue quantity. Functional atrophy and hypertrophy should follow as a matter of course. The extent and rapidity of the

[15] Chiari, H., *Z. Heilk.*, 1898, xix, 475.

changes alone are surprising. The hypertrophy goes on almost, perhaps quite, as rapidly as if the tissue deprived of portal blood had been ablated.

Few rabbits survive the abrupt removal of the main liver. Ponfick's instances do not enable one to judge when the compensating hypertrophy was complete. Von Meister[16] states that the right posterior lobe and caudate attain the weight of the whole liver in from 45 to 60 days. But this weight he puts at only 2.91 per cent of the gross body weight, whereas 3.45 per cent is nearer the truth and has been the basis of our calculations. In one of our cases such a proportion to the body weight was actually attained by the hypertrophied mass within 65 days and in another within 68, while the functional adequacy of the tissue was attested by complete atrophy of the main liver in one instance and approximately complete atrophy in the other. These results become more striking when one considers that our animals were adults weighing 2,000 gm., whereas von Meister's were young and of 900 to 1,400 gm., that is, far more favorable to hypertrophy, as he showed; and when the further fact is added that the caudate lobes were cut away in our cases so that there was less tissue capable of hypertrophy. Nasse[17] found that 4 months was required for the disappearance of the main liver mass of the rabbit after ligation of its bile duct.

If the rate of the hypertrophy is approximately the same after local portal deprivation as after local ablation, this might mean either that the tissue deprived of portal blood is useless to the organism or that hypertrophy goes on irrespective of its activities. The pros and cons cannot be profitably discussed, but both alternatives entail the assumption that the liver is wholly a portal organ, finding its reason for being in the substances carried to it on the portal blood and in them only. The biliary activity of the atrophic tissue does not constitute evidence against such a view, even granting that the substances from which bile pigment is produced come to the liver normally on the portal blood alone—an assumption yet to be proved. The small hepatic mass which receives the entire portal blood after local diversion of the stream must be thought of as unable to cope with its functional opportunities for some time, so that much material for liver activity passes through into the general circulation and reaches the atrophic competing mass. Later, as the compensating tissue attains the size and functional power of the whole original liver, less of the portal material may be supposed to escape through it. Yet

[16] von Meister, V., *Beitr. path. Anat. u. allg. Path.*, 1894, xv, 1.
[17] Nasse, *Verhandl. deutsch. Ges. Chir.*, 1894, xxiii, 525.

that a portion does pass through the normal liver has been shown by Van Slyke[18] for the amino-acids. It is perhaps a similar passage of material that enables a liver remnant wholly deprived of portal blood and advanced in atrophy to continue the formation of bile pigment, albeit in reduced quantity.

(*c*) *Food Deprivation.*—Though the main liver mass of our animals undoubtedly received relatively little of some at least of the substances upon which it normally acts, this need not have been the essential cause of its atrophy. Perhaps a special food is essential to liver maintenance. Whether this comes from a systemic or portal source, the tissue receiving the whole portal stream would have the best opportunity at it, and, possessing the superior powers of a growing, healthy tissue, would gradually increase its rival's deprivation. But were the source of the hypothetical food substance systemic, not portal, one would expect atrophy and hypertrophy to go on more slowly than is the actual case and perhaps not to reach completion. The question whether food substances can be distinguished from those utilized in function need not be entered upon.

Much of the foregoing incomplete analysis is only warranted in as far as it illustrates the vital importance for the liver tissue of a position on the portal stream. A situation there is not obligate, it is true. For the liver deprived of the direct portal stream by an Eck fistula still survives,—though perhaps only because it still receives the portal substances, at one remove, so to speak, by way of the systemic circulation.

Influence on Liver Development.

Toldt and Zuckerkandl[19] demonstrated in 1876 that the normal human liver undergoes notable changes in shape during the period from birth to adult life. In some portions of the organ atrophy occurs, while in others there is hypertrophy. The atrophy seems to be identical with that after portal diversion, while, when it is complete, as not infrequently happens, there are left behind the same large corded ducts and blood vessels. Toldt and Zuckerkandl attribute the changes to pressure from the surrounding organs and adduce

[18] Van Slyke, D. D., *Arch. Int. Med.*, 1917, xix, 56.

[19] Toldt and Zuckerkandl, *Sitzungsber. k. Akad. Wissensch. Wien., 3te Abt.*, 1876, lxxii, 241.

reasons for their belief. We would go a step further and suggest that the transmitted pressure may produce its effect in some instances through local alterations in the portal stream.

Mall,[20] who confirms the findings of Toldt and Zuckerkandl, points out in another connection that the distribution of the portal blood to the hepatic parenchyma is in general remarkably even, as can be demonstrated by injection methods. No hepatic region is specially favored. In the light of our observations the necessity for this is clear. For any enduring local irregularity in the portal flow will result in a shift of parenchyma. One of the commonest shifts observed by Toldt and Zuckerkandl entailed a complete atrophy of the left lobe. Herringham[21] found ten such cases in 3,000 autopsies. A reason for this is not far to seek, nor for the rarity of atrophy of the right lobe. In man the right branch of the portal vein is extremely short and thick, breaking up almost at once into many lesser vessels; whereas the left branch courses for a long distance through the parenchyma as a single slender trunk, much exposed to transmitted pressure.

Bearing on Liver Lesions.

Pathologists have long recognized that liver destruction frequently induces a local compensatory hypertrophy. From our observations it is evident that there exists, conversely, a type of destruction dependent upon compensatory hypertrophy. The knowledge should aid in an understanding of certain chronic liver lesions. The advanced local atrophy sometimes occurring in livers containing an echinococcus cyst, a gumma, slow growing tumor, or other limited process may well be the result of pressure upon portal radicles. In such instances there is present elsewhere in the organ an abundance of parenchyma capable of compensatory proliferation. The opportunities for marked changes are far less favorable in the atrophic cirrhosis of Laennec. The irregular stenosis and occlusion of portal branches which characterize the disease fail to lead to a complete atrophy of large liver portions because the parenchyma which under ordinary circumstances would proliferate in compensation is prevented from so

[20] Mall, F. P., *Am. J. Anat.*, 1906, v, 227.

[21] Herringham, W. P., *St. Bartholomew's Hosp. Rep. 1905*, 1906, xli, 15.

doing by a confining connective tissue. However, numerous small areas of partial hypertrophy and atrophy may and do exist.[22] In syphilitic livers with sharply localized scarring no such impediment is present; and we would suggest that local portal obstruction is a prime cause for the extreme atrophy and hypertrophy which in such cases frequently lead to great hepatic distortion. According to Sternberg[23] a whole lobe of the syphilitic hepar lobatum may be reduced to a connective tissue appendage.

The disappearance of large masses of liver tissue without the least connective tissue replacement may take place in the very old. According to MacCallum[24] whole layers of parenchyma may disappear, . . . "on the surface of the organ blood-vessels, bile-ducts, and the fibrous skeleton of the liver lie exposed." Not infrequently the atrophy is one of deprivation, and identical in its essentials with that resulting from local portal occlusion.

SUMMARY.

The occlusion of portal branches to a part of the liver of the rabbit leads to a progressive and ultimately complete atrophy of the parenchyma in the region deprived of portal blood, and to hypertrophy of the rest of the hepatic tissue which receives such blood in excess. Three-fourths of the liver may thus be reduced to a fibrous tag within 2 months, while the remaining fourth attains the bulk of the entire original organ. The atrophy is simple, unaccompanied by obvious degenerative changes or by any connective tissue replacement. More important, it is conditional in nature, failing to progress when the bile duct from the proliferating tissue is ligated and its hypertrophy checked in this way.

There are indications in the literature that an atrophy conditional on hypertrophy, such as is here described, occurs in man after local portal occlusion. And some experiments in our laboratory, not yet completed, show definitely its occurrence in the dog. The changes take place slowly in the canine liver. After 3 months the tissue de-

[22] MacCallum, W. G., *J. Am. Med. Assn.*, 1904, xliii, 649.

[23] Sternberg, C., in Aschoff, L., Pathologische Anatomie, Jena, 1911, ii, 855.

[24] MacCallum, W. G., Text-book of pathology, Philadelphia and New York, 2nd edition, 1914, 60.

prived of portal blood has diminished to about one-third of its original bulk. The conditional character of the atrophy is proven by its failure to occur to any similar degree in the absence of a compensating parenchyma, as when the portal stream is diverted from the whole liver by way of an Eck fistula.

Is the atrophy functional? If so, its completeness would indicate that the liver has no essential activity—none on which its maintenance depends—that it is not intimately connected with substances derived from organs drained by the portal system. Observations on the rate of hypertrophy after local diversion of the portal stream and on the character of the bile secreted by the atrophic tissue may be taken to favor such a view. The hypertrophy is nearly, perhaps quite, as rapid as if the tissue deprived of portal blood had been removed from the body. The bile secreted from a liver mass far advanced in atrophy and competing with a large bulk of parenchyma that receives the entire portal stream is almost colorless and may give but a weak Pettenkofer reaction. Glycogen, on the other hand, is present in the atrophic cells in approximately the same amount and distribution as in the hypertrophic liver tissue of the same animal.

The fact that a parenchymal shift follows local disturbances in the portal stream has a bearing on the cause of certain alterations in the shape of the normal liver that have been loosely attributed heretofore to pressure from the surrounding organs. It also has some interest in connection with pathological changes. Liver hypertrophy dependent on a preceding destruction has long been known to pathologists. Now a type of destruction dependent on compensatory hypertrophy must also be reckoned with. The occurrence of changes of the latter character will explain certain of the lesions observed in diseases that involve a disturbance of the portal flow to portions of the liver substance.

EXPLANATION OF PLATES.

PLATE 67.

FIGS. 1 and 2. Rabbit 7, Table I. Hepatic atrophy and hypertrophy, respectively, 12 days after diversion of the portal stream from the main liver. Three lobules of the main liver are barely equal in size to one of the hypertrophic lobe mass. The cells in atrophy are smaller and appear crowded together. Hematoxylin and eosin.

PLATE 68.

FIG. 3. Rabbit 9, Table I. Pale spots on the surface of a main liver 12 days after the ligation of its portal trunk. To the right is seen the corresponding hypertrophic lobe mass.

FIG. 4. Rabbit 27, Table I; 118 days. The effect of portal collaterals. The main liver is in complete atrophy save for a small, button-like area of healthy looking parenchyma, which receives at its center a portal venule from the lesser curvature of the stomach. Fig. 9 is a photograph of the entire specimen, and Fig. 10 shows the microscopic findings in the main liver.

PLATE 69.

FIG. 5. Rabbit 21, Table I; 55 days. Advanced atrophy of the main liver. The parenchyma is greatly diminished in amount, and the surviving lobules are extremely irregular. Bile ducts and blood vessels are prominent and numerous, and the intralobular capillaries are much widened in this special instance, but the lobules themselves are uninvaded by connective tissue which, however, is definitely increased. The increase was present prior to operation, as the liver fragment taken at the time shows. The dark rounded masses here and there are Kupffer cells distended with pigment. Hematoxylin and eosin.

FIG. 6. Rabbit 25, Table I; 68 days. Another instance of advanced atrophy of the main liver, but with pigmented Kupffer cells in unusual abundance. The peculiar appearance of the liver cells is due to the fixative. The great number of bile ducts relative to parenchyma should be noted, as also the characteristic absence of any increase in connective tissue, save for a slight thickening about the ducts, that was present prior to operation. Hematoxylin and eosin.

PLATE 70.

FIG. 7. Rabbit 24, Table I; 65 days. A late stage of parenchymal disappearance. Two small islands of liver cords with characteristic capillaries can be discerned. Many ovoid, pigmented Kupffer cells are present here and there. Methylene blue and eosin.

FIG. 8. A highly magnified parenchymal island from the same specimen. Near it are individual liver cords and cells isolated by the enveloping connective tissue. To the right and left lie Kupffer cells distended with pigment. Methylene blue and eosin.

PLATE 71.

FIG. 9. Rabbit 27, Table I; 118 days. Practically complete atrophy of the main liver, with compensatory hypertrophy of the lobe mass. In Fig. 4 a nearer view of the main liver is given.

FIG. 10. Condition of the main liver in the same rabbit. Save for an occasional cell, which cannot be discerned in the picture, the parenchyma is entirely gone. There remain arteries, veins, and bile ducts in a slight matrix of connective tissue, with some aggregations of round cells. Eosin and methylene blue.

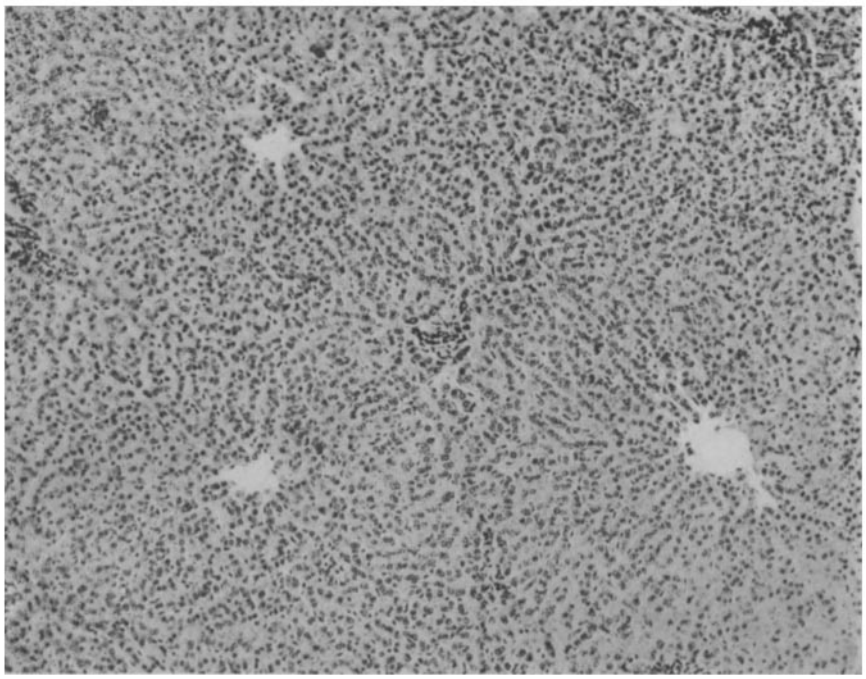


FIG. 1.

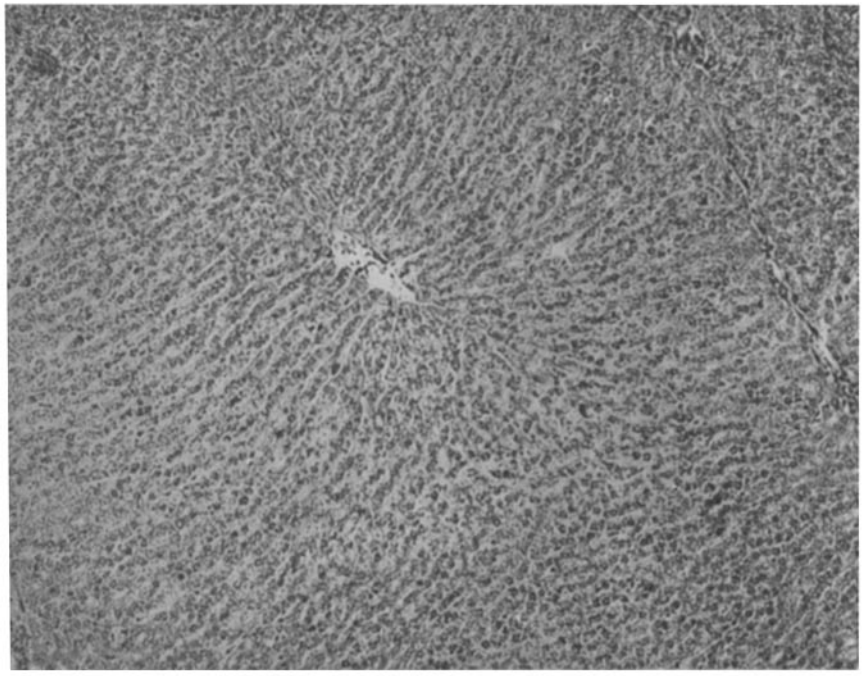


FIG. 2

(Rous and Larimore: Portal blood and liver maintenance.)

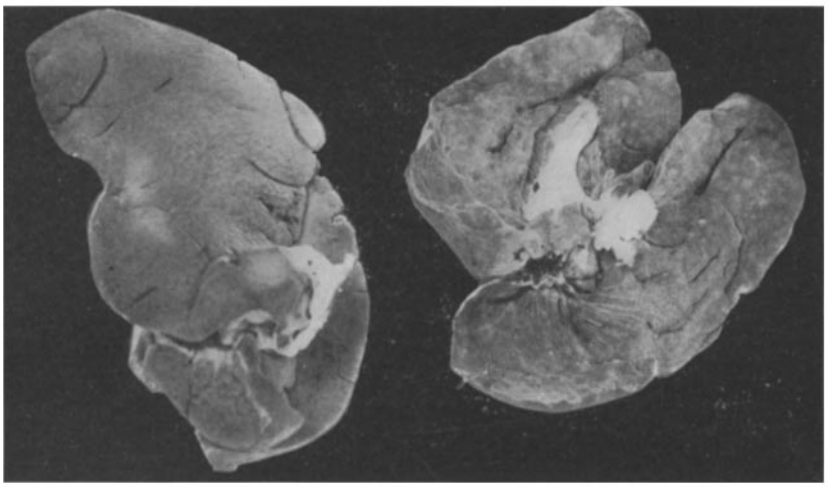


FIG. 3.

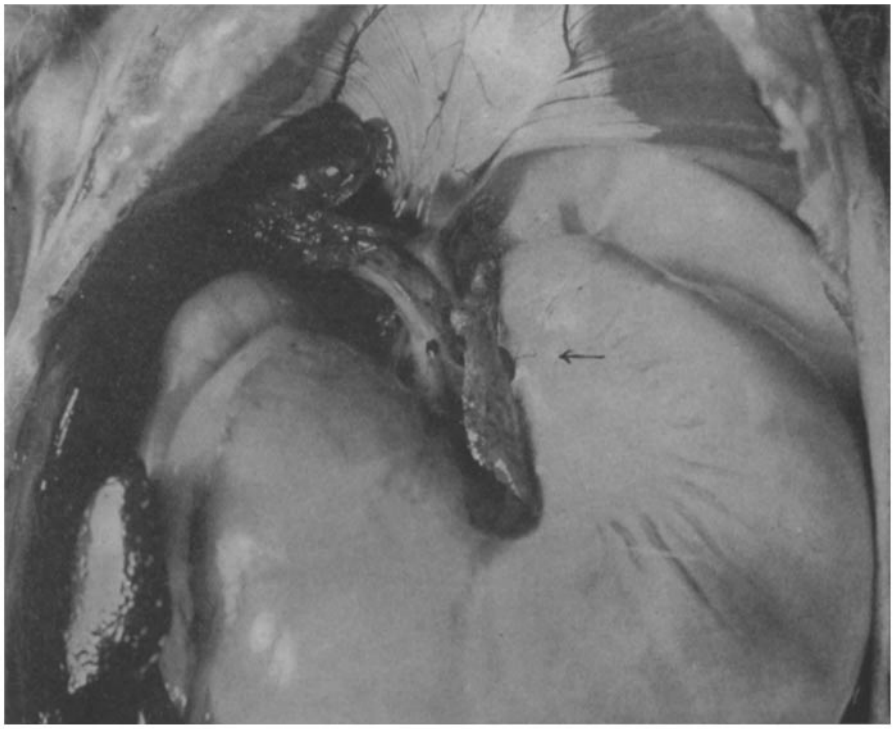


FIG. 4.

(Rous and Larimore: Portal blood and liver maintenance.)

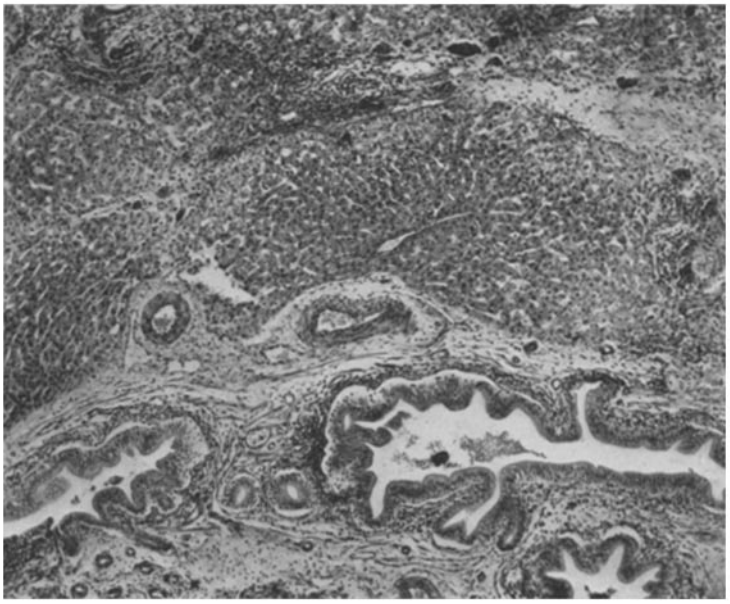


FIG. 5

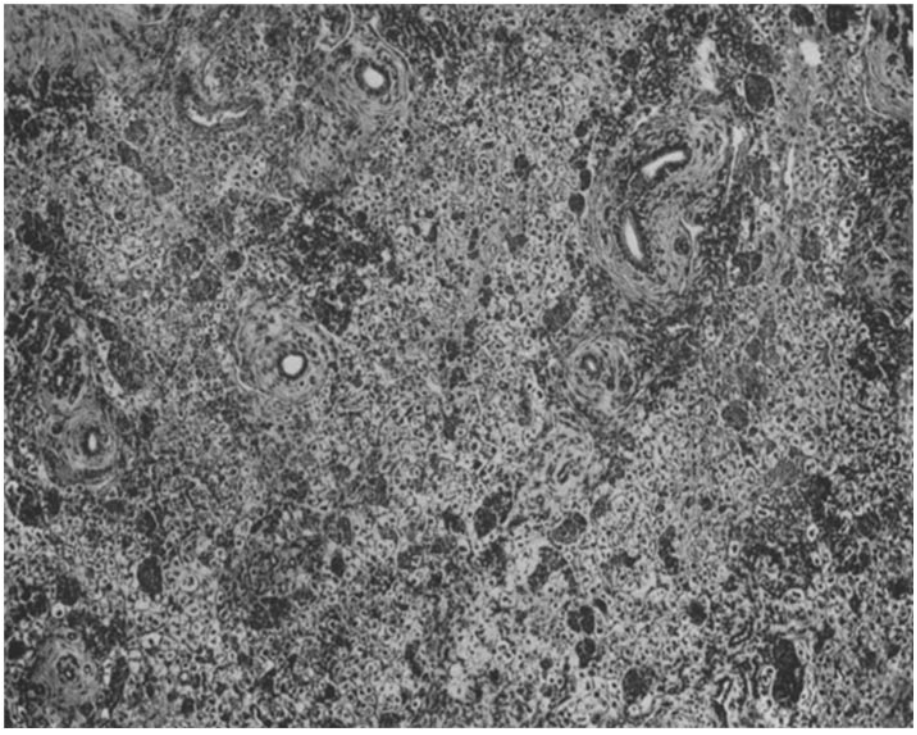


FIG. 6.

(Rous and Larimore: Portal blood and liver maintenance.)

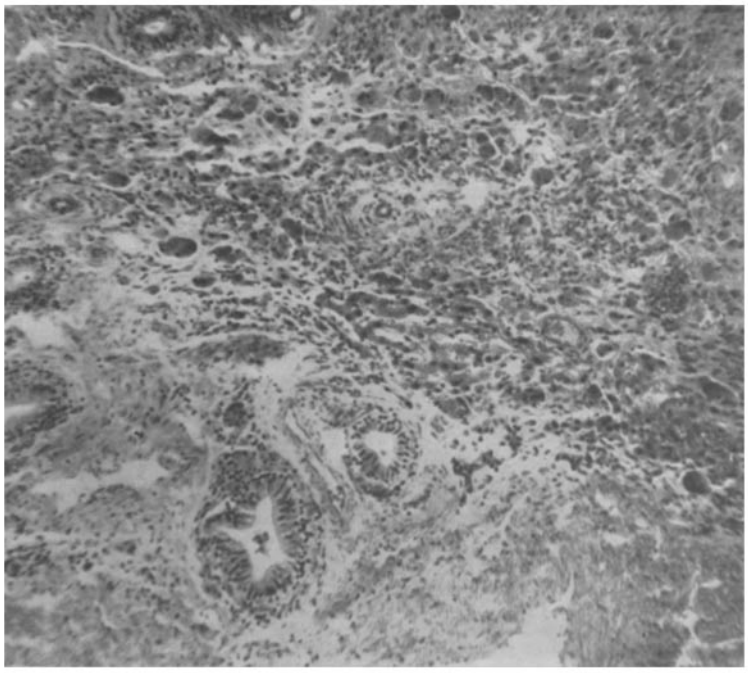


FIG. 7.

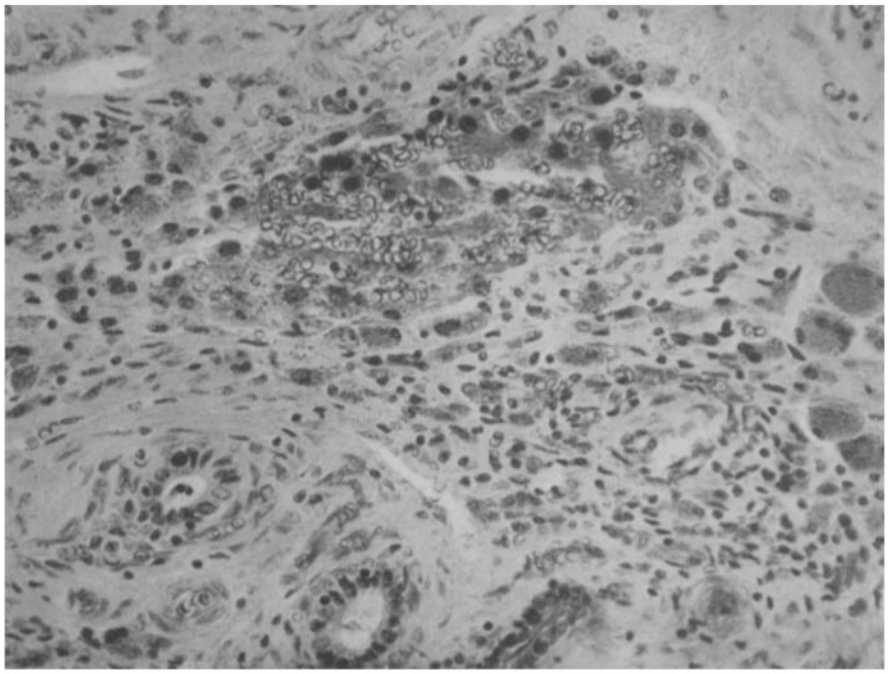


FIG. 8.

(Rous and Larimore: Portal blood and liver maintenance.)

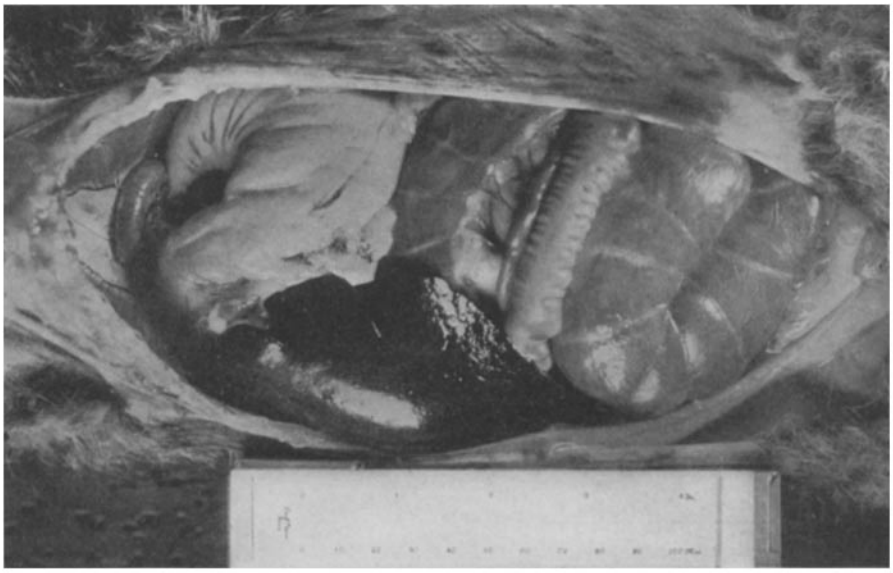


FIG. 9.

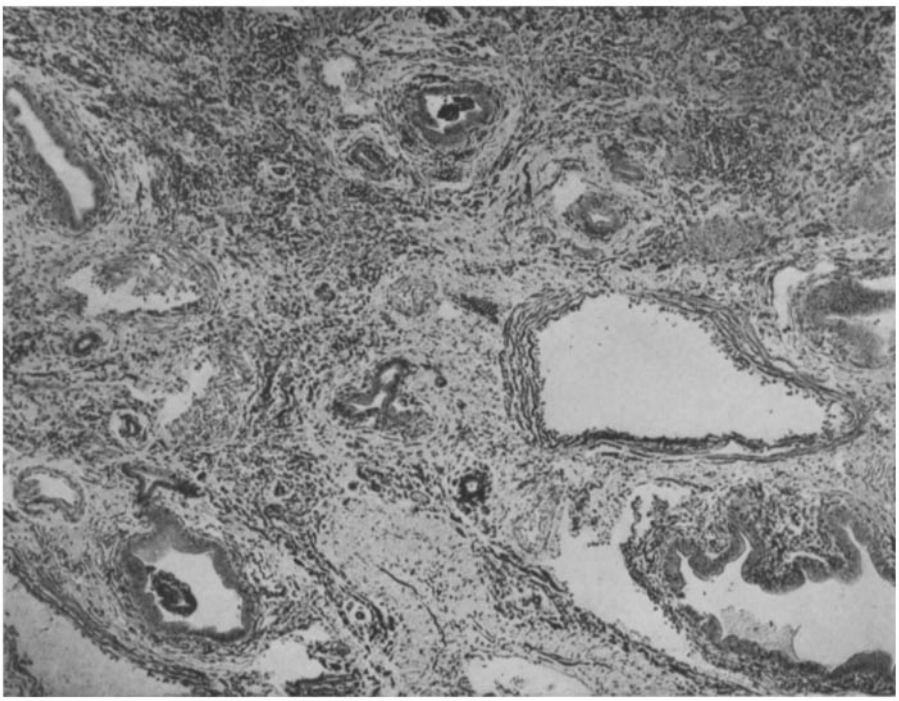


FIG. 10.

(Rous and Larimore: Portal blood and liver maintenance.)