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FUNCTIONAL MORPHOLOGY OF THE HEPATIC VASCULAR SYSTEM

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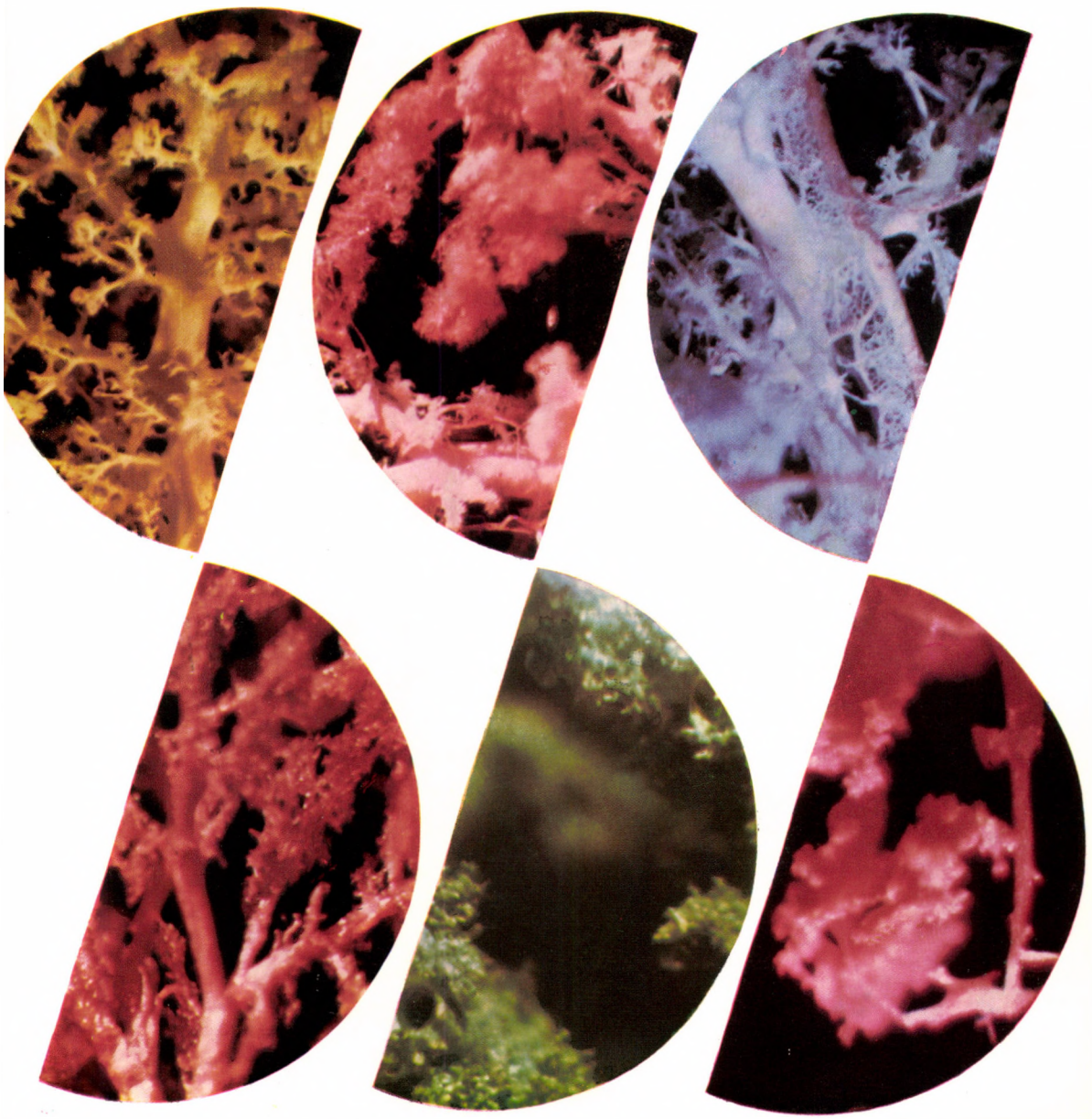

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Knowledge concerning the physiological and pathological activity of the liver has been accumulating rapidly, and at present, hepatology can already be regarded as an independent discipline of medical sciences.

This book is designed to systematize the functional–anatomical information about hepatic circulation and its regulation. The author's aim was to gain a deeper insight into the structure of the vascular system, blood flow, and the regulation of this blood flow, and into the histo-functional units that build up the liver. It has been studied in detail whether the histo-functional blood flow units (lobule, acinus-controlled system) of the liver can operate synchronously in the form of a more complex and larger structural–blood flow unit by means of a defined controlling system. A number of new findings, using a wide range of classical and up-to-date methods in the experimental investigations of both the controlled and controlling systems, are revealed.

Separate chapters focus on the segmentation of the liver, ontogenesis, and regeneration of the hepatic histo-functional units, extra- and intrahepatic vascular innervation, functional–anatomical bases of restrictive hepatic blood flow, and on certain vascular changes in some human and experimental liver injuries.

This richly illustrated volume will be valuable to clinicians and investigators interested in a deeper understanding of liver function.

AKADÉMIAI KIADÓ · BUDAPEST

Functional Morphology of the Hepatic Vascular System

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Contents

Foreword

Studies in microcirculation anatomy had long-standing traditions in the Ist Department of Anatomy at Budapest University Medical School, particularly during the chairmanship (1935–62) of Prof. F. Kiss; microcirculation of the eye bulb, meninges and choroid plexus, peripheral nerves, cardiac muscle and kidney having been the main topics of research. When taking over this Chair in 1963, I became immediately impressed by corrosion specimens of the human liver prepared by a junior assistant of this Department, Dr. György Ungváry. It would have been difficult not to realize the great clinical significance in liver surgery of a better understanding of the segmental anatomy of its vascular bed, so that I readily gave my consent and support for the continuation of these studies on a wider scale.

The studies conducted over the next ten years by Dr. Ungváry and a small group of dedicated co-workers gained rapidly in scope and soon surpassed the limited aims that we were able to envisage in 1963. By adding microcirculation anatomy of the smaller units of liver tissue and enlarging towards the fields of developmental anatomy and regeneration of tissue architecture the studies entered into new dimensions. However, the approach of Dr. Ungváry became truly interdisciplinary when investigations into the neural apparatus of the vascular bed and into the control of the blood flow were incorporated.

It is by no means usual that the reader can find a comprehensive treatment of the microcirculation of an important organ with an attempt at synthetizing tissue and vascular architectonics on the one hand, and a sophisticated analysis of its neural control systems on the other, using the whole repertory, at both the light and the electron microscopic levels, of modern techniques in neurohistology and histochemistry as well as physiological studies on blood flow.

This monograph summarizes a great wealth of information and offers a synthetic view of the functional architecture and control of liver microcirculation under both normal and pathological circumstances that – I am certain – will be of considerable novelty to everybody engaged or interested in the field of liver function and all kinds of surgical interventions with this organ.

J. Szentágothai

Introduction

Studies concerning the vasoarchitecture, blood circulation and regulation of the liver, the largest gland in the human and mammalian organism, seem to be of equal theoretical and practical importance. A more precise knowledge about the gross anatomy of the liver vasculature is substantiated by practical, surgical aspects, while research into hepatic circulation and its regulation is justified on a more theoretical basis. As it is the case with every organ, hepatic circulation is specific corresponding to the function of the liver. Measurement of the total blood flow of any organ does not meet the standards set up by modern research anymore. Therefore, in recent years attention has been focused upon the distribution of blood flow within the organs, the circulation of the smaller and larger histo-functional units. Circulation and especially its regulation within these units of the liver are not clearly understood yet.

The investigations are aimed at finding a system that can be divided into a controlling and a controlled part. The controlled part is the vascular system. The definition of the controlling part is not so simple, however. It includes the hepatic artery, which is a part of the controlled unit as well, and the neural and humoral organization of hepatic circulation. Naturally the interaction of these and possibly of other factors must be considered in the analysis of the control mechanism.

Vasculature of the liver is highly peculiar as it is derived from two systems, from that of the hepatic artery (vasa privata) and from that of the portal vein (vasa publica). The blood conveyed by the two afferent vessels is mixed in a special capillary system, the liver sinusoids. These sinusoids are lined with endothelial cells (without a basement membrane!) and are surrounded by a unicellular plate of hepatocytes. The sinusoids and the liver cell plates together form the histo-functional unit of the liver, which is defined as the acinus by Rappaport's concept, and as the lobule by Kiernan's view. Should we accept either of these two concepts, there is no apparent explanation, how the seemingly independent circulation of these histo-functional units fits into the complex circulation of a larger unit, e.g. the liver lobe. The persistence of these histo-functional units is another problem. It is apparent that the units developing during ontogenesis (whichever appears earlier) are not permanent, unless development, growth and perhaps regeneration of the liver take place exclusively via the formation of new units. Further studies on the macroscopic units of the controlled part have to elucidate whether these larger units possess structural features that enable them to give appropriate, integrated responses to experimental or pathologic stimuli.

The structure and function of the controlling system is even less known. Changes in the total hepatic blood flow are brought about primarily by changes in the quantity of blood delivered by the hepatic artery since portal venous blood flow is fundamentally determined by the extrahepatic splanchnic supply. It is not clear the way in which this regulatory function of the hepatic artery is realized along its terminal distribution in the histo-functional units. Likewise, it is not known which factors regulate the flow rate in the hepatic artery, the intrahepatic distribution of the arterial blood, how and at which level the humoral and neural regulation is exerted. Neural regulation of the liver is poorly understood, mainly due to the scarce morphological data on innervation.

A number of other questions can be raised ccncerning both controlling and controlled units in hepatic circulation. The present work can offer an answer only to some of the questions outlined above, since completeness would have meant the solution of tasks I had not been able to undertake.

1. Review of the literature

1.1. Topography of the hepatic vasculature Segmental subdivision of the human liver

Pathologists and clinicians have observed that certain diseases may inflict selective damage restricted to single lobes of the liver. The organ bears a close resemblance to the lungs in its development and functional morphology. Both organs develop from an entodermal diverticulum, both are supplied by separate afferent blood vessels – a nutritive and a functional one – and finally both have a central tubular system. It seemed, therefore, likely that the liver is built up of segments similar to the lungs.

Early observations on the vascular and biliary system of the liver date back to 1654, to the work of Glisson, whose descriptions and illustrations are acceptable even today. In 1888 Rex studied the hepatic vascular systems of different mammalian species on injection-corrosion preparations and developed the first nomenclature of the intrahepatic vascular system. In 1888 Rex, in 1898 Cantlie described a line, named after the authors the *Rex–Cantlie line*, that divides the liver into two main, the right and the left parts. This line runs along the *right sagittal fossa*, considerably to the right of the generally accepted boundary between the right and left lobes. The topography of the intrahepatic blood vessels was studied by Segall (1923) and Melnikoff (1924).

The first fundamental investigations on the distribution of the extra- and intrahepatic vessel systems, satisfying modern surgical standards (total right hepatic lobectomy, hemihepatectomy, major hepatic resection, etc. – Lortat-Jacob and Robert 1952, Quattlebaum 1953, Pack and Baker 1953, McDermott et al. 1963, Sapkin 1967, Ochsner et al. 1971) were carried out by Hjortsjö (1950–1951). Considering primarily the distribution of the portal venous and biliary systems, Hjorstjö divided the two main parts lying to the right and left of the Rex–Cantlie line, into three segments each. A clear-cut description of the topography of the hepatic vessel system was given by Elias and Petty (1952), who rejected the earlier nomenclature of Rex (1888) and Melnikoff (1924). Neither did they accept the so-called directional nomenclature of Hjorstjö (1948) and gave an impressive, comprehensive and concise description of the tributaries of the intrahepatic vessels. Based on the study of the biliary system, Healey and Schroy (1953) distinguished two segments in both the right and left main parts of the liver. Couinaud (1954), considering also the hepatic venous system, subdivided the right and left main parts into four sectors each. Koiss and Miletits (1958) distinguished 5 liver segments following the topography of the *Glisson's peduncles* (branches of the portal vein, hepatic artery and biliary ducts ensheathed by connective tissue).

All the foregoing subdivisions distinguished *portobiliary parts* (segments, areas, sectors, etc.) within the liver whose skeleton is formed by the branches of the portal vein, hepatic artery and bile ducts.

It is well known that the liver tissue continually proliferating around the vitelline veins undergoes early reorganization during its development into two lateral, sagittally oriented lobes and one central, horizontally situated lobe. Thereafter the liver develops from these three parts. It is also well established that the sinusoids empty their blood through three main hepatic venous trunks into the inferior vena cava. In view of these basic facts and the conflicting reports in the literature it is evident that further studies are necessary for the satisfactory clarification of the topography of the portobiliary segments and of their relationship to the hepatic venous system in the human liver. Furthermore, it has to be determined whether there is a correlation between the grossly different shapes of the livers and the intrahepatic distribution pattern of blood vessels.

1.2. Distribution of the portal vein, confluence of the hepatic vein. Acini, lobules segments, lobes of the liver

The extrahepatic portion of the primary divisions of the portal vein, proper hepatic artery (referred to as hepatic artery in the following) and hepatic ducts is short, only 0.5–2.0 cm long, in the human liver. They branch mainly within the liver where down at their terminal ramifications, or at their finest roots in case of the bile ducts, the three vessels are ensheathed by a layer of connective tissue, the *capsula fibrosa perivascularis hepatis*, or *Glisson's capsule* (Glisson 1654). The vessels with the enclosing fibrous capsule constitute the *Glisson's peduncles*, whose profiles correspond to the *Glisson's areas* or *Glisson's triads* in histological sections. These in turn run in the *portal channels*, formed by a one-cell-thick limiting plate of liver parenchyma cells, *membrana limitans* (Remak 1855, Elias 1949a, b, 1953, Bagley and Grafflin 1953).

Elias and Popper (1955) attached much importance to the *conducting veins* running in the portal channels in the distribution of the portal vein. In general, though there are species specific differences, the primary divisions of the portal vein, – *the trunks*, – the divisions of the trunks, – *the rami*, – the divisions of the rami, – *the ramuli*, – as well as the divisions of the latter which are still located in the portal channels and do not contribute directly to the blood supply of the liver parenchyma, are called conducting veins (Figs 1, 2). The conducting veins give rise by dichotomous division to terminal branches, the *axial veins*. These divide further in two ways: either they give rise to *peripheral sinusoids* from which *radial sinusoids* emerge (Figs 1, 2); or at one point they split to divergent, or parallel terminal branches which may anastomose with similar branches of another axial vein that course from the opposite direction. Side branches of the conducting veins are the smaller conducting veins, and the so-called *marginal veins* run either parallel with, or helically around the conducting vein in the portal channel (Figs 1, 2).

Fig. 1. Terminal distribution of the portal vein. 1 — conducting vein; 2 — perforans or ' inlet" vein; 3 — marginal vein; 4 — peripheral sinusoid; 5 — axial and paraxial sinusoids; 6 — radial sinusoids; 7 — axial vein. Regenerating rat liver injected with 8% gelatin in India ink. Spalteholz's thick preparation. ×130

Fig. 2. Terminal distribution of the portal vein. 1 — conducting vein; 2 — axial vein; 3 — perforans or "inlet" vein; 4 — peripheral sinusoid; 5 — radial sinusoid; 6 — marginal vein. Regenerating rat liver injected with 8% gelatin in India ink. Spalteholz's thick preparation. ×340

The *inlet veins*, the branches of the marginal veins penetrate the limiting plate and either terminate in the *peripheral sinusoids* and in their branches, the *radial sinusoids*, or ramify into the *axial* and *paraxial sinusoids* arranged parallel with their own course. From the axial veins the inlet veins arise directly (Figs 1, 2). In adult mammals the sinusoids are separated by one-cell-thick plates of hepatocytes (Elias 1949a, b). These laminae continue to form the limiting plates, not only around the portal triads, but also around the hepatic veins (Elias 1949b) and under the Glisson's capsule as well (Bagley and Grafflin 1953). According to this labyrinth conception (Elias 1949a, b), the liver is built up of a continuous laminar system of cell plates. The laminae surround spaces called the hepatic lacunae that communicate with each other and lodge the sinusoids. The sinusoids consist only of endothelial cells without basal lamina. There are only some exceptions, e.g. the endothelial cells of the sinusoids of adult sheep that are surrounded by a complete basal lamina (Gemmel and Heath 1972). The so-called Disse space is situated between the sinusoid endothelial cells and hepatocytes. In the Disse spaces presumably there is an endocapillary layer acting as a barrier between the intrasinusoidal blood stream and hepatocytes (Cossel 1971). As far as the shape of these lacunae is concerned the liver can be divided into saccular (man, cat), tubular (horse, rabbit), and transitional (dog) types. In mammals – a few weeks or years after birth – the majority of sinusoids are directed toward the first efferent vein, the central venule running perpendicular to the terminal portal vessels, the sinusoids. This arrangement underlies the structure of the hepatic lobule (Kiernan 1833), the axis of which is made up by the central venule (Figs 103 and 104, p. 188). The intralobular liver parenchyma around the central vein is called the centrolobular zone, the part at the periphery of the lobule (i.e. near the portal triad) is called the perilobular zone. There is an intermediate zone between these two areas. Starting from the point that the liver is an exocrine gland and thus the axial structure should be its efferent duct, in 1888 Brissaud and Sabourin described the biliary lobule. In 1906 Mall suggested the notion of the portal lobule; he considered the axis of the portal lobule to be the preterminal (interlobular) twig of the portal vein together with the accompanying twigs of the hepatic artery and bile duct.

On the basis of *in vivo* observations with transillumination microscope not the hexagonal Kiernan's lobule but a small mass of liver parenchyma, irregular in size and shape and located around the terminal branches of the portal vein, hepatic artery, bile duct and the ramifications of the latter (sinusoids and bile canaliculi that are devoid of wall) is considered to be the histo-functional unit of the mammalin and human liver as well (Fig. 104). Rappaport et al. (1954) and Rappaport (1958) called this unit, which at its periphery adjoins two neighbouring central venules, the *simple liver acinus*. One simple acinus constitutes one sixth of each of the two adjacent hexagonal Kiernan's lobules. Three simple acini around three terminal portal twigs (accompanied by a hepatic artery and bile duct) branching off from a single preterminal portal vein build up a *complex acinus*, a few of which (3 or more complex acini) comprise an *acinar agglomerate* (Rappaport 1958). The Rappaport model implies that moving from the centre of the simple liver acinus the area of the acinus

can be subdivided into three, – Z_1, Z_2, Z_3 – circulatory zones decreasing in sufficiency in the order of their mention.

No matter if we regard the Kiernan's lobule or the Rappaport's acinus as the unit of liver tissue, the ramification of the portal vein (that has already been discussed by Elias) is difficult to bring into harmony with the units so that we could also relate its exact topography either to the lobule or to the acinus. In this respect perhaps the Rappaport's simple, irregularly shaped liver acinus, with any portal vein entering at its axis, imposes less restrictions. A distribution pattern of axial and paraxial sinusoids is difficult to fit into a system built up of Kiernan's lobules.

Elias and Sokol (1953) put the problem of the liver lobule into new light. They concluded that under a physiological portacaval pressure gradient the Kiernan's lobule can be observed. At a decreased portacaval pressure gradient, however, the lobule undergoes rearrangement and the sinusoids will be reoriented toward the portal vein. This phenomenon was called the inversion of the lobule (Elias and Sokol 1953, Barone 1958).

The changes in the hepatic vascular network leading to the inversion of the lobule following portal obstruction were assigned by Rappaport (1958) to the residual blood circulation through the hepatic arterial system. Rappaport (1958) and Rappaport and Hiraki (1958a, b) could hardly accept the view that the common and frequent pressure changes in the veins would be able to turn a given system of the lobules into another.

It seems worth-while to analyze the matter of lobule and/or acinus together with the terminal portion of the portal and the initial portion of the hepatic venous system. The most likely localization of the hepatic histo-functional unit may be expected at the transition between the afferent and the efferent systems.

This transition is subject to changes during development and represents the morphological basis of liver function. More information could be obtained perhaps by studying this structure during ontogenesis.

Obviously, the structure that appears together with the most characteristic function of the liver can be regarded as a genuine histo-functional unit. The fetal liver does not function in the first trimester of pregnancy; it is in the state of physiological inactivity.

If we regard the liver as a principally exocrine gland, bile secretion should be considered its most characteristic function. The bile canaliculi differentiate already at the end of the first, whereas bile secretion starts in the third month of gestation (Streeter 1948); the differentiation of bile canaliculi still continues after birth, (De Wolf-Peeters et al. 1974). Accumulation of glycogen and fat in the liver can be observed in the third and between the third and fourth months of intrauterine life, respectively (Stieve and Kaps 1937). A number of hepatic functions, e.g. production of directly reacting bilirubin, prothrombin, fibrinogen and the detoxification of decomposition products from the gut and toxic substances are still insufficient at birth, when compared to the healthy adult. There are significant differences between the activities of enzymes of fetal and adult livers (Girard et al. 1973, Chiu and Phillips 1974), and the autonomic control of fetal and adult vascular systems (Nuwayhid et al. 1975), etc. The appearance of the final liver

structure is delayed – mainly by the presence of haematopoietic tissue – until after the seventh gestational month in the fetal liver. Definite functional units appear only after the cessation of the haematopoietic activity, their final structure is formed at the establishment of the mature liver function only (Ungváry 1971, Cutts et al. 1973).

The considerable capacity of the liver for regeneration is well known. The radical changes following partial hepatectomy result in an organ resembling much the fetal liver. In this model the development of mature liver structure is accelerated. Studies on liver regeneration offer therefore good opportunities for a better understanding of the relationship between the intrahepatic vasculature and the liver parenchyma and their interrelationship during regeneration.

Summing up, it seems worth to compare the macroscopy of the hepatic vasculature in the fetal and adult liver, further to investigate the appearance of smaller histo-functional units building up gross anatomical units and the changes of these structures during ontogenesis. Such studies should be extended also to liver regeneration. The results may elucidate whether anatomical or pathological changes in the glandular structure might influence blood flow through the vessels in the liver parenchyma.

1.3. Terminal distribution of the hepatic artery Relationship between the changes in arterial and portal blood flow

The contribution of the hepatic artery to the hepatic blood flow varies around 20 to 25%, though the reported values differ widely: Grindlay et al. (1941) measured 10 to 80% with thermostromuhr, Fischer et al. (1958) 14.4% with rotameter, Green et al. (1959) 20%, and Drapanas et al. (1960) 36%, Huet et al. (1972) 15%, all three applying an electromagnetic flowmeter; Huet et al. (1972) 14% using indicator dilution curves. An explanation for these divergent results was given by Fischer (1964). He has shown that if total hepatic blood flow equals or exceeds a value of 30 ml/min/kg in the dog, the arterial contribution is below 20%. At a lower rate of hepatic blood flow, however, the arterial contribution increases sharply at the expense of portal blood flow. These data show that, depending on the functional state, the arterial blood supply of the liver may differ considerably. The variability of the amount of blood conveyed to the liver through the hepatic artery may imply a variability of blood distribution at its terminal arborization.

The question of terminal distribution of the hepatic artery has been a challenge to morphologists for more than 100 years. Even nowadays many studies are published on the problem, and the great number of controversial results and interpretations clearly shows that there is no suitable method presently available for an unequivocal elucidation.

Until 1936, the year when Knisely first published his results obtained by the transillumination of the living liver, the interpretations had to rely on autopsy findings and on data obtained with injection–corrosion methods.

Kiernan reported (1833) that the bile ducts, the wall of the portal vein and the connective tissue of the portal tracts receive branches from the hepatic artery. He called the efferent vessels draining toward the portal vein the internal roots of the portal vein. Conheim and Litten (1876), Loeffler (1927), Cameron and Mayes (1930), Aunap (1931) and Kádár (1957) held essentially the same view and agreed that the liver cells are not supplied with arterial blood because the hepatic artery is related to the biliary system in its development and not to the liver parenchyma. Another group of researchers (Chrzonszczewsky 1866, Rindfleisch 1872, Elias 1949b and Elias and Petty 1953) argued this point. According to them, there are branches of the hepatic artery that directly supply the liver parenchyma. They claim that the central parts of the Kiernan's lobule are supplied by arterial, while the peripheral parts by portal venous blood, respectively, i.e the preterminal branches of the hepatic artery cross the periphery of the lobule. Olds and Stafford (1930) suggested that the hepatic artery is distributed mainly in the lobule, and that the sinusoids receive abundant arterial blood supply. This view was later corroborated by Lozano and Andrews (1966). Mall (1906) assumed that the arterial blood may reach the lobule through direct arterioportal shunts and through the internal roots of the portal vein. Andrews et al. (1949) suggested that primarily the periportal sinusoids but also the tracts in the portal channel would be supplied by the hepatic artery. Based on the microscopic studies of injection–corrosion preparations of the frog liver, Kratochvil et al. (1959) concluded that the portal and arterial systems unite in the sinusoids. Riedel and Morawec (1959) described that the arterioles take a short intralobular turn before entering the sinusoids; their findings reveal that the arterial blood enters the perilobular sinusoids. Mitra (1966) denied the existence of intralobular arterioles because the intralobular arterial ramifications are 6 to 9 μm in diameter. Kaman (1965) in pigs, Mitra (1966) in rats demonstrated that the terminal ramifications of the hepatic artery may be observed in the wall of blood vessels or of bile ducts, in arterioportal anastomoses and in the sinusoids of the lobule. The fine structure of the terminal branches of the hepatic arterial system of the rat was analyzed by Burkel (1970) in detail under the light and electron microscope using thick and thin serial sections. His results have confirmed those of Kaman (1965) and Mitra (1966) obtained by the microcorrosion method.

New perspectives in the elucidation of the terminal distribution of the hepatic artery were opened up by the introduction of the *in vivo* transillumination method. Fundamental advantage of the method is that passing light through the periphery of the liver lobe, the vasculature and blood circulation can be visualized under the microscope in vivo (Knisely 1936, Irwin and McDonald 1953). Transillumination studies have revealed that a part of the terminal branches of the hepatic artery anastomose with those of the portal vein in the perilobular area (Bloch 1940, 1955, 1970, Knisely et al. 1948, Debaker 1967), and others in the lobule enter directly into the sinusoids (Bloch 1955, McCuskey 1966, Rappaport et al. 1970). Unfortunately the results of transillumination studies are not unequivocal either; Kanbe

(1966) and Nakata (1967) had not been able to demonstrate arterial blood flow in the peri- and intralobular area after the ligation of the portal vein. Recently, after the ligation of the portal vein Ho (1972) was able to follow arterial blood flow and arteriovenous anastomoses in rat liver by means of a modified transillumination method.

Both physiological and morphological data offer a different image of the system of the hepatic artery. Perhaps this diversity has led the investigators to use indirect methods. Some authors attempted to reach conclusions as to one of the afferent blood vessels of the liver from the functional circulatory changes that occurred as a consequence of interventions either into the hepatic arterial or portal venous system. These studies revealed that neither the hepatic artery nor the portal vein is vital for the liver – at least transiently – provided that blood flow is undisturbed in either one of them (Fischer 1964). The hepatic artery turned out to be more responsive to experimental changes affecting the portal vein, while blood flow through the portal vein did not change even after the complete ligation of the hepatic artery (Fischer 1964). It should be noted, however, that using a method based on Fick's principle, Bollman and Grindlay (1953) later Horváth et al. (1957) did not find any change in total hepatic blood flow after the ligation of the hepatic artery. Although, the method applied was not sensitive enough, the results clearly indicated an increase in portal venous blood flow. It has also been reported that there is a significant decrease in the amount of oxygen available for the liver after the ligation of the hepatic artery (Cameron and Mayes 1930, McMichael 1934). According to Krarup and Larsen (1974), the main function of the hepatic artery is to supply the liver as a whole with oxygen and no other specific functions of the artery are demonstrable. Ternberg and Butcher (1965) have observed a decrease in portal venous blood flow simultaneously with the decrease of flow in the hepatic artery. If portal venous blood is passed through the femoral vein Fischer and Takács (1964) reported an increased blood flow in the hepatic artery and a rise in oxygen consumption. Similarly, an increase of liver's arterial blood flow has been observed after partial constriction of the portal vein (Popper et al. 1954a, b).

At the time of our first investigations (1961–63) concerning the hepatic artery one could think* that studies of injection–corrosion and injection–thick preparation performed with meticulous care could reveal the cause of the controversies about the terminal distribution of the hepatic artery. One way of answering this question was to investigate how the terminal ramifications of the two afferent systems join after experimental manipulations affecting one of them. Studies of that kind were performed by Kratochvil et al. (1957), who found a significant dilatation of the arterial system after the experimental reduction of portal venous inflow (Eck fistula, ligation of lobar portal venous trunks).

A further question to be answered was in which way the experimental manipulation of the hepatic artery or portal vein changed the capacity of the afferent vessels and the vasoarchitecture of the histo-functional units (acinus, lobule), where the systems of the hepatic artery and of the portal vein fuse.

* The transillumination methods perhaps due to their shortcomings were not used widespread; monochromatic light, image orthicon television systems, etc., were introduced only in the past two decades (Bloch 1964, 1965, McCuskey 1966, 1967, Ho 1972, Ho and Ma 1972).

1.4. Morphological basis of the neural regulation of the liver and hepatic blood vessels

Most detailed macroscopic studies on the innervation of the liver and biliary system were given by Latarjet et al. (1920), Raigorodsky (1928) and Kubo (1933). These descriptions are valid even today and only some particularities need completion. The nerve elements forming the *hepatic plexus* originate from both celiac ganglia, celiac plexus, vagus nerves and, as Bánfai et al. (1953) have shown, from the right phrenic nerve. Scattered nerve cell bodies can be found in the hepatic plexus along its course as far as the portal fissure (Mikhail and Saleh 1961, Sutherland 1964, Kerdivarenko 1965). Already at its origin, between the laminae of the lesser omentum, the hepatic plexus divides into two smaller, an *anterior* and a *posterior hepatic plexus*. The anterior hepatic plexus originates mainly from the left celiac ganglion and left vagus nerve and follows first the common then the left hepatic artery through the portal fissure, then it approaches the left part of the liver and disappears in the parenchyma through the portal channels. (Branches from the left vagus nerve reaching the lesser omentum bypass the celiac ganglion and enter the liver directly.) The posterior hepatic plexus originates primarily from the right celiac ganglion and from the right vagus nerve that passes through the ganglion. The plexus leaves the right celiac ganglion, turns downward and to the right, crosses the trunk of the portal vein from behind and it passes toward the portal fissure between the portal vein and the common bile duct where it anastomoses with the anterior hepatic plexus. The original fibres from the posterior hepatic plexus extend to the right main part of the liver along the right proper hepatic artery. In human liver the fibres reach the hepatocaval junction in the posterior part of the right sagittal fossa along the inferior vena cava, in the posterior part of the left sagittal fossa along the venous ligament. Fibres from the right phrenic nerve also reach this junction. It is rather of technical significance that the anterior hepatic plexus running along the hepatic artery is always divided into a few bundles, while the posterior hepatic plexus follows the portal vein as a single bundle. The fibre bundles proceed from the portal fissure in the main portal channel of each lobe of the multilobate liver or in those of the portobiliary lobes of the non-lobate human liver. Thus also in case of hepatic nerve supply, a segmental/lobar subdivision can be observed. The nerve plexus joining the trunks of the hepatic veins at the hepatocaval junction divides into smaller bundles following the course of the veins into the liver.

For long decades only the silver impregnation technique used to be available as the sole applicable method for the histological demonstration of the nerve fibres. Even today Bielschowsky's technique (1904) and its numerous modifications (Gros 1918, Jabonero 1948, 1951, Suzuki 1963, etc.) are the most widespread for the visualization of the terminal fibres of the autonomic nerve. The underlying chemical reaction is still not known, the staining is based on some kind of "silver affinity" (Richardson 1960). Due to methodological difficulties, some investigators, certainly not lacking imagination, aroused confusion concerning the very principles of the peripheral autonomic nervous system by misinterpreting

some structures seen or suspected. Some of these hypotheses, such as Stöhr's (1932, 1934, 1935) "terminal reticulum", Jabonero's (1952) "intraprotoplasmic nerve fibres", should be mentioned. The history of Cajal's interstitial cell (1904) is very interesting. First these cells were believed to be neurones (Meyling 1938, 1949, 1953, 1954, Jabonero 1952, 1953); later Szentágothai (1952) and Hillarp (1959) opposed to their being neurones. Recently, mainly on the basis of histochemical and electron microscopic investigations, the old hypothesis of Cajal's interstitial cells has been revived. These cells are neither neurones nor Schwann cells, nor typical connective tissue cells, nor muscle cells. The fact that there is a close relationship ("nexuses") between interstitial cells and smooth muscle suggests a specific function (Stach 1972).

By means of the degeneration method Lawrentjew (1931, 1934) and Schimert (1935, 1936, 1937, 1938) have shown that the nerve fibres of the vegetative ground plexus described by Boeke (1927, 1933) – who himself stood close to Stöhr's concept – are genuine axons. In spite of the formation of intraprotoplasmic plexuses with nerve fibres of different origin, even sensory type (Schimert 1936), they maintain their trophic autonomy independent of the neighbouring axons. They do not anastomose with other fibres, and after the destruction of the nerve cell body from which they originate, they degenerate in their entire length.

On the basis of these findings, Szentágothai (1952) described the autonomic ground plexus as follows: the autonomic ground plexus is a collective type nerve ending respecting neuronal subdivision, but at a low level of differentiation. It contains sensory elements, too, beside the parasympathetic and sympathetic fibres within the same plexus.

At the height of the impregnation era, the terminal reticulum concept of Stöhr was predominant. All the interpretations were based on this concept. Literature on the innervation of the liver is relatively scarce as compared to reports concerning other organs. In the last century Pflüger (1869) and MacCallum (1887) gave account of an abundant intraparenchymal innervation. Riegele (1928) supported the ideas of Retzius (1894) and Kölliker (1902) on the interlobular plexuses surrounding the interlobular bile ducts, arteries and veins in man and cat. He described that there are comparatively few, thin nerve fibres in the liver parenchyma and that these are neurofibrils. The fibres have no free endings but join and form a fine network. (This concept corresponds to Stöhr's terminal reticulum.) Riegele (1928) described neurofibrils which end with a minute reticulum in the cytoplasm of a liver cell. Stöhr (1957) completed Riegele's studies and noted in his monograph that in the liver, as it is the case with every exocrine gland, the terminal reticulum does not only supply the glandular parenchyma but the blood vessels and capillaries as well. In the wall of the capillaries the neurofibrils of the terminal reticulum are in cytoplasmic continuation with the Kupffer's cells where they can be demonstrated at the periphery of the cytoplasm. Riegele (1928) reported on a terminal reticulum in the bile duct where the fine network can be found below the epithelial layer and in the form of twisted intraepithelial neurofibrils. Nonidez (1936) challenged the existence of this aboundant terminal reticulum of the parenchyma and vascular network. He held the view that the dense network of nerve fibres is nothing else than interwoven fine argentophil fibres

of connective tissue. The presence of terminal reticulum in the liver was supported by Zanobio (1951) and Wang (1953), too. Suzuki (1963) went so far as to suggest that the Kupffer's cells were neuronal cells which through their processes might transmit impulses toward the liver cells. Tsai's (1958) studies on the efferent innervation confirmed the existence of a terminal reticulum. In addition, he described a great number of degenerated sensory endings in the vessels, bile ducts and parenchyma after the surgical ablation of spinal Th_5-L_1 and nodose ganglia, respectively. Godinov (1952) similarly found a great number of button-like receptors in the vicinity of liver cell cords. Godinov did not use the degeneration method in his work. In addition, it must be borne in mind that the buttons are very similar to the profiles of the bile canaliculi in cross-section. Only Stöhr (1957) and Tsai (1958) claimed the existence of neurons in the interlobular spaces of the liver.

Merely a few investigations using the silver impregnation methods have been reported on the innervation of the hepatic artery, the portal and hepatic veins. Azarova (1966) studied the hepatic venous, Mootz (1965) the portal venous system, while the hepatic artery has not been studied separately. Azarova (1966) demonstrated nerve fibres in the wall of the hepatic venous branches of every order of magnitude in silver-stained sections of the liver. Mootz, using Bodian's silver impregnation and the zinc-iodide-osmium techniques in his own modification (1965), described a nerve fibre plexus in the tunica adventitia of the portal vein at the margin of the muscle and connective tissue layers. From this plexus fine fibres reach the external part of the muscle layer of the tunica adventitia. The author found that the longitudinal muscle layer and the tunica media were free of nerves. Suyama (1940) and Dolgo-Saburow (1963) investigated the portal vein among many other venous vessels. Suyama (1940) gave account of the zonular innervation of the portal vein of Amphibia, birds, mammals and men. Dolgo-Saburow (1963) described a dense plexus made up of myelinated as well as unmylienated fibres extending from the adventitia to the intima of the human and feline portal vein.

Perhaps it can be ascribed to the shortcomings of the silver impregnation methods that investigations on the innervation of the liver were not satisfactory. It is not worth arguing against the concept of the terminal reticulum, or the Kupffer's cells as neurons because they were even in the era of the silver impregnation methods mere imagination or misinterpretation. Szentágothai (1957) expressed best this view. After a short description of the commonly observed histological picture he continued ... this is what we can see under the microscope. Everything else is the observer's mere speculation or interpretation... The neuronal concept of the vegetative ground plexus formulated by Szentágothai (1952) has by now gained general acceptance. Hillarp (1946, 1959) when giving the final criticism of the "terminal reticulum" fundamentally agreed with Szentágothai's new concept. Csillik (1970) expressed the view, that the use of already widely applied histochemical reactions for the investigation of peripheral autonomic fibre had significantly contributed to the emergence of the clear new concept. The same histochemical reactions were helpful in revealing that the three-dimensional peripheral autonomous ground plexus innervating the viscera contains or may contain cholinergic

as well as monoaminergic fibres (Hillarp 1959, Csillik and Koelle 1966). In the light of Burnstock's (1972) review I think we must complete the definition of the autonomic ground plexus with the possible presence of purinergic nerves. According to our present knowledge, in the mammals the elementary units of the nervous system, the neurons, and the neurons with the effector cells, respectively, are connected only with synapses working only with chemical trasmitter systems. Almost exclusively acetylcholine and noradrenaline and recently purine nucleotides are regarded as mediator substances in the synaptic transmission between the postganglionic neurons and effector cells. It should be noted that Beck (1964) described a histaminergic, a serotoninergic and a third, vegetative pre- and postganglionic terminal that functions only with an unknown, so far unidentified vasodilator transmitter. Champy and Champy-Hatem (1963) gave account of histaminergic fibres in malignant neoplastic tissue. According to Burnstock (1972), a variety of substances other than ATP have been explored as the possible transmitters released from non-adrenergic, non-cholinergic inhibitory nerves in the gut, including catecholamines, 5-hydroxytryptamine, cyclic AMP, histamine, prostaglandins, various amino acids and polypeptides. However, these substances were rejected as contenders by most workers on the ground that they proved either inactive or could not mimic the nerve-mediated responses. The specific blocking agents for these substances did not affect the nerve-mediated responses, or their action consisted in the stimulation of nerves and not in a direct action on the smooth muscle.

Acetylcholine, one of the two classical transmitters, cannot be detected by histochemical methods, nor is the cytochemical localization of the acetylcholine-synthetizing enzymes solved in spite of considerable efforts (Csillik 1970, Kása et al. 1970). Neither is the situation better with the identification of the structural changes of the acetylcholine-receptor protein of the postsynaptic membrane though some progress has been achieved (Zachs et al. 1962, Csillik 1963). The generally accepted routine of the visualization of cholinergic synaptic transmission is the demonstration of the acetylcholine-inactivating enzyme. This enzyme is the acetylcholinesterase (AChE), which can be detected by the classical procedure of Koelle and Friedenwald (1949) or by its many modifications, at both light and electron microscopic levels. For a number of reasons the localization of AChE is not necessarily identical with that of acetylcholine (Feldberg 1957). AChE may have another still unidentified substrate which is different from acetylcholine (Koelle 1955); one can assume that of the phylogenetically older cholinergic neurons some might have lost their acetylcholine or choline acetylase content but retained certain amount of AChE. In spite of all objections, one might agree with Csillik (1970) who argued that the nowadays often declared statement, that the AChE histochemistry is irrelevant as far as the mechanism of synaptic transmission is concerned, is a fundamentally wrong and negativistic point of view. There is no doubt that it is an acceptable effort to decide, whether the liver, hepatic artery, the portal and hepatic veins contain AChE-positive nerve terminals. Only a few papers have been reported on this subject. Mootz (1965) observed in rat the scarce occurrence of "cholinergic" fibres in the wall of the trunk of the portal vein. Perhaps it is more appropriate to use the term "acetylcholinesterase-positive". He observed that the longitudinal muscle layer of the adventitia gave a stronger, whereas the

circular muscle layer of the media yielded a weaker reaction. Sutherland (1964) studied the liver parenchyma (monkey, guinea-pig, rat) with the zinc-iodide-osmium technique, in his own modification and with Koelle's AChE reaction in Coupland-Holmes' modification. He described an abundant "cholinergic" network entering the liver parenchyma from beside the blood vessels and bile ducts. The strong background reaction observed is not surprising because he applied 10^{-6} M iso-octamethylpyrophosphoramid (iso-OMPA) as inhibitor during preincubation, and the drug in this low concentration does not effectively inhibit the large quantities of aspecific cholinesterase present in both the liver and Schwann's cells.

Noradrenaline is the other "classical" synaptic mediator of the mammalian autonomic postganglionic nerve terminals. The available histochemical methods are suitable for the direct detection of the synaptic mediator (Carlsson et al. 1961, Falck 1962, Falck et al. 1962, Corrodi and Hillarp 1963, 1964). With this procedure the noradrenergic, autonomic nerve fibres can be well visualized. The catecholamine-synthetizing enzymes cannot be demonstrated, while from the catecholamine-inactivating enzymes only the monoanime oxidase can be detected (Glenner et al. 1957) by histochemical methods. One should remember that the inactivation of monoamines is accomplished mainly by physical mechanisms (Csillik 1964, Malmfors 1965). Thus the identification of catecholamine-containing fibres is much more precise than that of the cholinergic neurons. This is further supported by the fact that the axons containing dense-core vesicles, of about 450 Å, were proven to be identical with the monoaminergic axons (Eränkö 1967, Csillik 1970). There are new possibilities to identify the monoaminergic nerves. There are three ways of replacing norepinephrine by false transmitters: 1. administration of amines acting as false transmitters themselves; 2. administration of false precursors; 3. by the blockade of certain steps in the synthesis or degradation of physiological amines (Thoenen and Tranzer 1971). The application of 5-OHDA and 6-OHDA is particularly important. The adrenergic axons can take up 5-OHDA and 6-OHDA and then these drugs will be accumulated in their granular vesicles which are visible electron microscopically. As far as the literature on the monoaminergic innervation of the hepatic artery or hepatic vein is concerned I am not aware of any reports except for our own (Ungváry and Donáth 1969). Only the trunk of the portal vein has been studied by Johansson et al. (1970) and Ljung (1970), using the histochemical fluorescence method of Falck et al. (1962). Their results corroborate our findings. Yamada (1965) studied the innervation of the liver of mice with the electron microscope. He saw axons without Schwann's cells reaching the liver cells at the border of the portal spaces. The axons contained mitochondria and dense-core vesicles. Recently Blouin and Côté (1973) have studied the hepatic innervation by means of electron microscopy. No other ultrastructural observations on the innervation of the liver have been published that we would be aware of. Even large monographs on the electron microscopic structure of the liver (Cossel 1964, David 1964) lack these data.

The purinergic nerves act with the third transmitter, purine nucleotides. In mammals the purinergic neurons are localized in the gut wall, probably only in the Auerbach's plexus. The terminal axons of these neurons supply the smooth

muscle of both longitudinal and circular muscle coats. The purinergic nerve profiles appear to be characterized by a predominance of large vesicles that differ from the large granular vesicles seen in small numbers in adrenergic and cholinergic nerves inasmuch as they are bigger (800–2000 Å) and do not have a prominent electron-translucent halo between the vesicle membrane and its granular core. They have been termed large opaque vesicles (Burnstock 1972). Concerning the localization of purine nucleotides, some information can be obtained by histochemical and electron-histochemical demonstration of ATPase and 5'-nucleotidase, too (Burnstock 1972, Wright et al. 1972). As far as I know purinergic nerves have not been demonstrated in the liver. Nevertheless, the possibility of their presence in the liver must not be excluded because of the strong evidence presented as regards the existence of non-adrenergic, non-cholinergic inhibitory fibres to the portal vein of the rabbit (Hughes and Vane 1970). The inhibitory responses induced either by electrical stimulation or nicotine are blocked by tetrodotoxin and mimicked by the direct action of ATP. In this way they appear to fit into the pattern already established for purinergic nerves in the gut.

As it has been mentioned earlier, a number of investigators have observed the presence of nerve cells in the portal fissure and even in the liver (Stöhr 1957, Tsai 1958, Mikhail and Saleh 1961, Kerdivarenko 1965, Sutherland 1964). The neurons here as elsewhere in the gastrointestinal tract and in other organs can be divided according to Dogiel (1896) into two groups: Dogiel type I neurons with many short dendrites and Dogiel type II neurons with less and longer dendrites and a not easily identifiable axon. Dogiel (1896), later Lawrentjew and Borowskaya (1936) suggested that type I neurons would have motor whereas type II neurons sensory function. Dogiel (1896) traced the processes of the cells into the vegetative ganglia. Lawrentjew and Borowskaya (1936) could find type I neurons only in the most oral and most caudal portions of the alimentary tract. From these data the authors tried to conclude on the function of cells. Schimert 1938, Szentágothai (1952, 1967) considered the Dogiel type II neurons to be less differentiated cell types that are able to build up reflexes without sufficient differentiation of the axon and dendrites and can carry out certain integrative function. These two cell types form large plexuses along the intestinal tract and its derivatives and underlie the local reflexes. Considering the large number especially of Dogiel type II cells in the local visceral plexus, it is reasonable to presume that apart from local reflex arcs within the plexus there might exist peripheral ones whose centre is situated in the large prevertebral ganglia. Such reflex connections are suggested by the electrophysiological observations of Siromyatnikov and Skok (1968) and Siromyatnikov and Korotchenko (1968). After the interruption of all pre- and postganglionic connections of the celiac ganglion, stimulation of one peripheral (postganglionic) stump evoked action potentials in the fibres of another stump with a latency well exceeding the time of synaptic delay.

The origin, terminal distribution, the motor or sensory nature and the histochemical features of the nerve fibres innervating the liver and its vascular systems await a more profound elucidation. Furthermore it has to be answered whether the processes of the nerve cell bodies located in the portal fissure and in other viscera of the splanchnic area may function as the afferent limbs of peripheral vegetative reflex arcs.

1.5. Intrahepatic–intralobar redistribution and control of local blood flow

The complexity of the liver vasculature and innervation prompted the search for such a regularity in this organ that is characteristic of the entire liver, and at the same time secures its most economic functioning. The segments or lobes of the liver can be removed surgically without fatal consequences, hence these are called surgical–anatomical units. About 30% of the original liver tissue is necessary for survival and the structural and functional restitution of the organ Pathologists observed that certain processes are localized to certain lobes of the liver. A possible explanation for this phenomenon is that a particular liver lobe is always supplied by the venous effluent of the same splanchnic area. One might cautiously suggest that the segments and lobes are pathological units as well. There is no need for the synchronized activity of the whole liver for its normal function. The average hepatic blood flow of the human liver is 1500 ml/min. In emergency conditions either less blood enters the liver or the same volume passes the liver more rapidly in order to assure the blood supply of other vital organs. One may wonder whether the circulating blood might temporarily bypass a liver segment with the consequent transitory decrease or cessation of its function. There is, however, no sign that the segments would be cut off from the circulation. Moreover, there is no apparent structure at the hilus of the segments either in the portal vein or in the hepatic artery which could block the inflow of the blood.

The problem outlined fits well into the current trends of modern circulation research which is focused on the inter- and intraorganic distribution of cardiac output (Mellander 1970). Fischer et al. (1960) found both the hepatic arterial and portal venous fractions of the cardiac output to be extremely low during severe hypoxaemia in dogs, indicating that hepatic blood flow does not necessarily change parallel with the increase in cardiac output. Takács (1963) called attention to an interesting phenomenon in nephrectomized rats. He observed that in nephrectomized rats the nephrectomy-induced rise in the splanchnic fraction of the cardiac output decreased in the first place together with the skin fraction after experimental bleeding. Thus the splanchnic region seemed to take over the role played by the kidney in the so-called circulatory redistribution.

Daniel and Prichard (1951a, b, c) observed two main types of blood flow distribution within the liver by means of serial portograms. In the majority of rats the portograms revealed the even distribution of the injected radioopaque material and the uniform filling of the sinusoids gave sharp contours to the liver (diffuse distribution of blood flow). In some animals the radioopaque material did not spread into the peripheral parts of the liver, the opacity was restricted to an area around the hilus (restricted distribution of blood flow). Measurements on corroded casts of the hepatic vascular tree showed that the distance between the portal and the hepatic veins is shorter near the hilus than more distally. They also observed that on stimulation of the hepatic plexus, or after intraportal injection of adrenaline, restricted distribution of blood flow can be seen more often. Brauer (1963) thought that the essential feature in the restrictive mechanism is an active

vasoconstriction in the portal system. In this connection the recent results on the innervation of the liver (Ungváry and Donáth 1969, Ungváry and Varga 1971c) are worth discussing. We have found that a strong catecholamine histofluorescence can be observed in the perilobular area at the periphery but not in the hilar central parts of the lobes. From the continuous innervation of the portal vein and hepatic artery we concluded that a vasoconstriction elicited by neural stimulation anywhere along the vessels would affect primarily the periphery of the liver lobe. Olerud (1953) studied hepatic circulation likewise by means of serial portograms in rabbits. He found that the elevation of intraabdominal pressure resulted in a restricted distribution of hepatic blood flow. Honig (1960) used oxygen micro-electrodes and heated thermocouples for measurements in dog liver. The fluctuations in local blood flow observed could perhaps correspond to the diffuse and restricted variations described in other species. Zöckler and Friedel (1970) measured hepatic blood flow in dogs by means of Hensel's thermoprobe. They could distinguish "individual parenchyma regions" which, as they suggested, may underlie the liver's reservoire function.

The question arises whether there is a difference between the vasoarchitecture of the central and peripheral parts of the lobe?

Further, could the administration of vasopressor, vasodilator substances or haemorrhagic hypotension evoke restricted distribution of blood flow in the liver?

An affirmative answer to the latter question, the circulatory effects of the stimulation of the hepatic plexus observed by Daniel and Prichard (1951 a, b, c), Brauers' (1963) analysis and our findings on hepatic innervation cited above together would support the view that the restriction of blood flow may be a reflex mechanism. From the innervation of the hepatic vasculature (Ungváry and Donáth 1969) it follows that such reflexes, if they exist, may affect not only the portal but also the hepatic arterial system. The splanchnic, vagus and right phrenic nerves may contain the preganglionic, while the hepatic plexus the postganglionic efferent fibres of the reflex arc. Further studies were aimed at the efferents of the hypothetical reflex.

1.6. Relationship between the changes in hepatic blood flow and certain diffuse liver injuries

The liver lobes (in man the corresponding portobiliary lobes) are the surgical anatomical units of the liver. In addition, we gave a tentative subdivision of the liver on the basis of the differences in the circulatory responses of the various parts. We distinguish a central core close to and a peripheral shell distal to the hilus in the liver. It is not clear whether subdivision of the liver into a central core and a peripheral shell might reflect differences in pathology, too. Experimental methods used in answering the earlier questions enabled a distinction only between the short circulatory responses of the two areas (central and peripheral) and the elucidation of the underlying reason of these differences. From these experiments it was concluded that the changes evoked by the applied stimuli – hypotension (normovolaemic, or hypovolaemic), electrical stimulation

of the splanchnic nerve, contraction of the diaphragm – elicited the intrahepatic redistribution of blood flow and that the "two parts" of the liver give different responses to the same stimulus. This phenomenon may reflect the pathophysiological differences between the two parts of the liver. If a pathophysiological differentiation could be proven, it would be justified to question whether or not there is any difference in the behaviour of the two parts (central and peripheral) under pathological conditions. Furthermore, is it possible that the differences in blood flow of the two parts could become so fixed as to cause considerable differences in the pathogenesis, the pace and extent of diseases. After the compilation of some relevant literary data we considered it warranted to study the question in detail.

Himsworth and Glynn, already in 1944, suggested that restriction of the intrahepatic circulation is an important predisposing factor of trophopathic hepatitis in man. Haranghy (1959) described in his Textbook of Pathology that common liver atrophy is a regular finding in starvation and marantic diseases. Senile atrophy may progress to such an extent that only the bile canaliculi remain in the sharp membranaceous edges of the liver. This means that first the peripheral shell of the liver undergoes atrophy. Perhaps the development of the fibrous appendix of the liver is also due to unfavourable changes in hepatic circulation. The atrophy of this part of the liver might arise when its circulation is switched from a favourable into a peripheral position caused by the changes in fetal circulation at birth. During the agonal impairment of circulation clay-yellowish spots with blurred margin penetrating more or less into the parenchyma may appear on the liver capsule, presumably due to the impression of adjacent ribs, bowels, etc. Pale yellowish spots with sharp, zigzag margins and frequent wedge-shaped extensions into the liver parenchyma are probably the result of defective blood supply and can be attributed to agonal vasoconstriction. These latter are rather of segmental localization but affect the periphery of the segments primarily. The same spots can be frequently seen in patients who died of septic diseases, peritonitis and cerebral processes, apparently because of the longer agony. Di Costanzo et al. (1974) have shown in the liver of patients suffering from irreversible coma numerous histological, enzyme histochemical and electron microscopic lesions that are the consequences of hypoxia due to circulatory disorders.

An interesting finding was reported by Rappaport et al. (1970) who induced toxic hepatitis by fulvine (*Crotalaria fulva*) in rats. In toxic hepatitis the sinusoidal blood flow must overcome increased resistance, because oedema of the hepatocytes develops early and narrows the sinusoids. At five hours after fulvine administration microthrombi block the sinusoids in the third circulatory zone of the Rappaport's acinus. Twenty-four hours after fulvine administration the oedema fully compresses the sinusoids and all acini along the edge of the liver become completely ischaemic. In spite of these dramatic changes, blood of the splanchnic area passed through the liver, although the portal venous pressure increased in the next 24 hours and reached a pressure of 260 mm H_2O on the third day. Unfortunately, with their transillumination method the authors could follow the changes in hepatic microcirculation only during the first 24 hours. Moreover, with this method only the peripheral shell, i. e. the edges of the liver can be studied, i. e. the parts that are injured earlier than the central area in experimental toxic, hepatitis.

Considering the above finding it seemed a worthwhile endeavour to study the behaviour of the central and peripheral parts of the liver in the pathogenesis of some diseases. The diffuse diseases of the liver such as acute infections, toxic injury, jaundice due to biliary obstruction may be considered in this respect. In chronic liver injury, e. g. in cirrhosis, the structure of the hepatic vasculature undergoes profound changes and presumably these livers differ from the normal ones with respect to their circulatory features as well (Popper et al. 1952, Hidayat and Wahid 1971). We tried to answer the question by studying the livers of patients who died of acute liver atrophy (fulminant hepatitis; Lucke and Mallory 1946, Popper and Schaffner 1957) following acute viral hepatitis. In addition, we examined animal livers after the ligation of the common bile duct (a model for obstructive icterus), or in experimental carbon tetrachloride intoxication.

2. Description of the experiments

2.1. Lobar subdivision and topography of intrahepatic vessels

The vascular architecture was analysed in livers obtained from fresh adult human cadavers in altogether 450 cases by means of single and combined injection corrosion (Ungváry and Faller 1963a, b, Faller and Ungváry 1964/65), X-ray and dye injection methods (Ungváry and Faller 1963a). The subdivision of the liver into portobiliary and hepatic venous lobes, their interrelationship and the correlation between the distribution pattern of hepatic vessels and the shape of the liver were studied. No sign of pathological changes were found in the liver and the patients had no previously diagnosed liver disease. In 50 human livers simultaneous injection–corrosion studies were performed so that the 3 main trunks, i. e. the right, intermediate and left trunks of the portal and hepatic veins were filled up with plastics of different colour. The main trunks were made accessible to cannulation by previous dissection (Faller and Ungváry 1964/65). The total weight and the weight of the right and left main parts of 50 adult human livers were also determined.

2.2. Fetal human and regenerating rat liver

2.2.1. The subdivision of the fetal liver into portobiliary lobes, the angle of divergence and convergence of the branching afferent and the joining efferent vessels, the vasculature of histo-functional units, the stage of development of the main right and left parts have been studied in 110 human fetuses between the 6th and 10th month of gestation, in 25 prematures, term newborns and infants by measuring organ weight and by injection–corrosion method (Munkácsi 1957). For the isolated injection–corrosion technique a ligature had to be placed on the venous duct of Arantius and the solution had to be injected through the umbilical vein or the inferior vena cava. The ontogenesis of sinusoids, hepatic plates and histofunctional units was further studied in 25 human fetuses, newborns and infants, 25 porcine, 25 rat fetuses and 25 newborn rats. The injection–corrosion technique (the livers of 5 animals in each group were injected through the portal vein, another 5 in each group through the hepatic vein), the Spalteholz's thick preparation technique (Romeis 1948) after injection of 8% gelatin in India ink (again 5 livers in each group, filled up through the portal, another 5 in each through the hepatic vein) and routine histology (the livers of 5 animals from each group were injected with 1% gelatin in India ink through the umbilical vein without the ligation of the venous duct of Arantius, formalin fixation, paraffin embedding,

haematoxylin and eosin staining) were applied. Benzidine reaction (Romeis 1948) was carried out on liver sections from further 5 rat fetuses, 5 newborn rats and 5 rats each, at 1, 2, or 3 weeks of age.

2.2.2. Changes of the histo-functional units during regeneration were studied in male rats weighing 150–200 g. In 130 rats partial hepatectomy was performed according to Higgins and Anderson (1931). The two large lobes (lobus magnus and lobus fissus), which amount to about 65–70% of the whole liver weight, were excised and the "estimated" liver weight was calculated from the weight of the measured two large lobes. Thirty rats served as sham-operated controls. Forty-five rats were reoperated three weeks after the first resection. In this case anterenal and retrorenal lobes located ventrally and cranially to the right kidney, amounting to about 70% of the regenerated liver mass, were removed. Twenty of these 45 animals were once more reoperated at the end of the third week following the second operation. This time the antiventricular lobe, amounting to about 50–60% of the second regenerate, was removed. As a result, only one of the original six lobes (two large end four small) was left in these animals. The mortality rates of the three successive resections were 2, 30 and 10% respectively. The body weight, the weight of the excised lobes and the weight of the liver at autopsy were accurately measured. Animals that had undergone only one resection were divided into groups of 25 each and sacrificed 1, 2, and 7 days, or 1 and 3 months after operation. The livers of 10 animals from each group, subjected to one resection only, were filled up through the portal, while 10 other animals from the same groups through the hepatic vein. Similarly, in one half of the cases the portal and in the other half the hepatic venous routes were used for filling up the livers of the animals in the groups undergone two or three resections. The livers were studied by our quantitative injection–corrosion technique. This was carried out as follows: 5% PVC (polyvinyl chloride) had been injected for 5 min via the portal or hepatic veins at a constant pressure of 40 or 20 mm Hg, respectively. The injection was started in anaesthetized, living animals. Organ weight was measured after injection in humans with 1.0 g and in rats with 0.01 g accuracy, while after the corrosion manipulations the vascular casts were measured to 0.01 g and 0.001 g, respectively. The cast/liver weight ratio shows the weight of blood vessel cast per unit weight of liver tissue. We call this ratio "vascular capacity" which is characteristic of the density and volume of the vascular network in the organ (Ungváry et al. 1969a, b.).

Further portograms were made in 5 rats of each group, sacrificed at different intervals after the first resection of the liver. The portograms were projected onto graph paper and the area covering the projected image was measured. In groups of 5 animals sacrificed 2 days, 1 week and 3 months after one resection, 8% gelatin in India ink was injected into the portal or hepatic vein and the vasculature was studied in sections made according to Spalteholz's thick preparation technique; the same, livers were studied also by conventional histological methods. In the livers of 5 animals with two resections benzidine reaction was performed.

2.3. Terminal distribution of the hepatic artery

The terminal distribution of the hepatic artery was investigated in about 20 human cadavers and in dogs, cats, guinea-pigs and rats. Spalteholz's thick section technique with the injection of 1, 6, or 8% gelatin in India ink and the injection–corrosion method were used. The hepatic artery and portal vein were injected with plastics at a constant pressure of 120–140, and 40 mm Hg, respectively. When the hepatic artery was in vivo separately filled a single ligature was placed on the portal vein.

Ligation of the hepatic artery was performed in 32 cats. Quantitative injection–corrosion studies of the portal venous system (Ungváry et al. 1969a, b) were carried out in 6 cats sacrificed after 1–2 hours, and in 12 cats, killed 1 week after the operation. The livers of 6 cats prepared in the same way were used as controls. Benzidine reaction and haematoxylin–eosin staining were performed in sections from the livers of controls as well as of 4 cats, sacrificed 1–2 hours, and 1 week after the ligation of the hepatic artery, respectively. In a group of 6 animals killed 3 weeks after the operation the hepatic arterial and portal venous systems were studied with the combined and simultaneous injection–corrosion technique.

In a further group of 6 cats the trunk of the portal vein was constricted to about the half of its original cross-section area by a silk thread tightened around the portal vein until the first signs of congestion became apparent in the intestinal tract. The external diameter of the vessels was measured during injection. It was 3.5–4.5 mm as opposed to the 5–6 mm found in the unoperated controls. Three weeks after operation the hepatic arterial and portal venous systems were studied by means of the combined and simultaneous injection–corrosion method.

2.4. Wall structure of the hepatic blood vessels and innervation of the liver

2.4.1. A systematic investigation of the wall structure of the portal vein, common hepatic artery, the junction of the hepatic vein and caudal vena cava (corresponding to the inferior vena cava in man) was carried out in guinea-pigs, cats and dogs. Serial sections from celloidin–paraffin wax embedded blocks were stained with Azan, Farkas–Mallory, Hornowsky and haematoxylin–eosin (Kiszely and Barka 1958).

2.4.2. The histochemical features of the nerve fibres were revealed by the catecholamine fluorescence method (Falck et al. 1962, Csillik and Kálmán 1967), the zinc–iodide–osmium staining (Champy 1913, Champy and Coujard 1941), and by the demonstration of acetylcholinesterase, non-specific cholinesterase (Coupland and Holmes 1957) and monoamine oxidase (Glenner et al. 1957) activity. Six dogs and groups of cats, guinea-pigs, rats and mice, 15 of each, were used in these studies.

The smaller animals were decapitated, the larger ones were killed under ether or hexobarbital anaesthesia by cutting the thorax open. Portions of the wall

of the portal vein, trunk of the hepatic artery, portal triad from the portal fissure, liver parenchyma from a peripheral and a central part of a lobe, and a strip from the junction of the hepatic venous trunk and the caudal vena cava were excised. An effort was made to excise the tissues rapidly. From all the above tissue pieces, about $4 \times 3 \times 2$ mm sections were made, as required, using the particular staining technique. Membrane preparation were made from the trunk of the portal vein of smaller animals. From the larger animals similar preparations were prepared from the branches of the first, second, and third order of the portal and hepatic veins, the falciform ligament and the Glisson's capsule.

2.4.3. The origin of nerves supplying the liver and hepatic blood vessels was investigated in organs of operated cats and dogs using the electron microscopic degeneration technique of Hámori et al. (1968). The following operations were performed in cats:

Group 1. Extirpation of both celiac ganglia of 5 cats, sacrificed 24–60 hrs later;

Group 2. Unilateral, right-sided extirpation of the spinal ganglia Th_5–L_3 (6 cats). Only 3 neighbouring ganglia were removed in each animal. The cats were sacrificed 24–48 hrs later;

Group 3. Transection of the left vagus nerve on the neck or at the cardia of 3 animals each, sacrificed 24–48 hrs later;

Group 4. Transection of the right phrenic nerve (3 animals). Similar transection was made in dogs – sacrificed 24–48 hrs later.

In Group 1 where the celiac ganglia had been removed the noradrenergic nerves were also investigated according to Falck et al. (1962).

2.4.4. For the demonstration of the hypothetical axon terminals of Dogiel type II neurons in the prevertebral ganglia the following operations were performed:

Group 1. Cholecystectomy;

Group 2. Resection of the right liver lobe + cholecystectomy;

Group 3. Resection of the left liver lobe;

Group 4. Resection of four-fifth of the jejunum;

Group 5. Removal of the celiac and superior mesenteric ganglia.

There were 3 cats in each experimental group. The animals belonging to Groups 1 to 4 were killed under hexobarbital anaesthesia 24–48 hrs after operation and the celiac and superior mesenteric ganglia were processed for electron microscopy. The animals of Group 5 were sacrificed 2 weeks after the operation under hexobarbital anaesthesia. The peripheral postganglionic branches of the removed prevertebral ganglia passing from the sympathetic ganglia to the portal fissure or along the superior mesenteric artery to the bowels were processed for electron microscopy. The blocks were fixed in paraformaldehyde solution, postfixed in osmic acid and embedded in Durcupan. Ultrathin sections were cut using an LKB or Reichert Ultrotome, and stained with uranyl acetate and lead citrate after Reynolds (1963a). The sections were studied under a Tesla BS 413 electron microscope. Axonal degeneration of the vegetative nerve fibres was evaluated according to the criteria established by Hámori et al. (1968).

2.5. Measurement of local blood flow in the liver lobes

The changes in local blood flow in the liver lobes and the underlying anatomical alterations were investigated in mongrel dogs of both sexes, weighing 10–16 kg.

2.5.1. Tissue samples from both the central and peripheral parts of the right medial lobe for the determination of the area occupied by the sinusoids per unit area of total liver tissue were excised from 5 dogs sacrificed by an overdose of hexobarbital. The excised samples in 8 μm thick sections were stained with haematoxylin and eosin. The sections were projected onto a plane together with a square grid with 10×10 intersections by means of a Palkovits–Csapó optical instrument used for caryometric investigations (Palkovits 1962). The number of sinusoids covering the grid points were counted in 100 visual fields from both the central and peripheral areas. The area occupied by the sinusoids was given in per cent of the total area analyzed.

The number of branchings of the portal and hepatic veins were counted in the central and peripheral area of one lobe in 5 dogs, given a lethal dose of hexobarbital (Ungváry and Varga 1971a).

2.5.2. Local blood flow in the central and peripheral parts of the same liver lobe was measured in 38 dogs anaesthetized by the intravenous administration of 0.075 g/kg chloralose + 0.75 g/kg Urethane. Local blood flow was simultaneously and continuously recorded measuring the local changes in heat conductivity by means of flexible thermocouples as described by Hensel (1953–54) using a two-channel Fluvograph. Pressure in the femoral artery and portal vein, respiration and pulse rates were converted into electric signals with Statham transducers, thermistors and a Hellige type pulse integrator and were recorded on a Hellige multiscriptor. In each animal three or four of the following treatments were carried out.

2.5.2.1. The following vasoactive agents were injected to 6–8 dogs: 10 μg/kg adrenaline (Tonogen, G. Richter, Budapest), 10 μg/kg noradrenaline (Noradrenalin, G. Richter, Budapest), 2 μg/kg isoproterenol (1-(3'4'-dihydroxyphenyl)-2-isopropylamine ethanol hydrochloride, – Propylon, G. Richter, Budapest), 20 μg/kg acetylcholine (Acetylcholine chloride, Berlin Chemie), and 20 μg/kg histamine (Peremin, G. Richter, Budapest). All the drugs were injected first intraportally through a cannula inserted into one branch of the superior mesenteric vein, then they were administered into the femoral vein.

2.5.2.2. Fifteen animals were exsanguinated until arterial blood pressure stabilized by the method of Engelking and Willig (1958) at 40–45 mm Hg.

2.5.2.3. The following nerves were electrically stimulated: hepatic plexus (8 dogs), the left splanchnic nerve (8 dogs), the left vagus nerve both on the neck and on the cardia (6 dogs; in these cases the thermocouples were in the left medial lobe), the left and right phrenic nerves on the neck, or in the latter case also in the mediastinum (6 dogs). The stimuli were generated with a Multistim (DISA) equipment using the following parameters: 5 V, 1 msec, 20 c/s, for 2 min.

2.5.2.4. In 6 animals thoracotomy was made and with a circular cut passing around the hepatic veins and caudal vena cava the diaphragm was cut open. Care was taken not to damage the branches of the right phrenic nerve that runs to the large hepatic veins. Ventilation was maintained by a respirator. Electric stimulus was applied to the right phrenic nerve before and after the incision of the diaphragm (Fig. 105, p. 189).

Routine methods were used for the statistical evaluation of data.

2.6. Pathologic human and experimentally altered animal livers

2.6.1. The cadaver livers were received from László Hospital, Budapest (the hospital for infectious diseases to which these pateints had been transferred with the diagnosis of acute yellow atrophy*). Altogether 32 livers originating from diagnosed acute virus hepatitis, were included. For comparison 20 cadaver livers devoid of any apparent liver disease were used. In 18 atrophied and 12 control livers the portal venous system was studied with our quantitative injection–corrosion method (Ungváry et al. 1969a). Vascular capacity (p. 30) was determined in the same livers; in the other cases single and combined simultaneous injection–corrosion technique, Spalteholz's thick preparation, following the injection of 8% gelatin in India ink, were used for the investigation of the portal and hepatic venous systems.

Before injecting the PVC solution or the gelatin–India ink mixture small pieces of the liver parenchyma had been excised and processed for routine histology. Only the histologically verified acute yellow atrophy cases* were included. The livers studied were derived from patients with fulminant virus hepatitis as described by Lucke and Mallory in 1946.

2.6.2. Carbon tetrachloride intoxication was brought about in rats by intraperitoneally injecting 0.2 ml/100 g/body weight of carbon tetrachloride and petrol-ether in 1 : 1. As maintenance doses, 0.1 ml/100 g body weight of the same mixture was used twice weekly not longer than 16 weeks. Twenty-two rats were sacrificed 2 and 24 hrs, 12 rats 3 and 7 days or 2, 4, and 16 weeks after the first injection. Ten livers from the first group of 22 rats were processed for histochemical investigations: succinic dehydrogenase (Nachlas et al. 1957), monoamine oxidase (Glenner et al. 1957), esterase (Bácsy et al. 1968), cholinesterase (Coupland and Holmes, 1957), alkaline and acid phosphatase (Burstone 1958a, b), which were detected both in the central and peripheral area of the liver lobe. The remaining rats were divided into further subgroups comprising 3 animals each. In these animals the vascular bed of the liver was filled through (*a*) the portal vein, (*b*) the caudal vena cava, hepatic veins, (*c*) the aorta, after the ligation of the portal

* The use of the term acute yellow atrophy is not very fortunate but generally accepted in Hungary. Here I wish to express my thanks to dr. Judith Temes who supported these studies by making the autopsy material available.

vein, with 6 or 8% gelatin in India ink. The livers were further processed according to Spalteholz's thick preparation technique. Benzidine staining was performed in both the central and peripheral areas of the lobes in 3 animals each.

2.6.3. Ligation of the common bile duct was carried out in guinea-pigs and rats. Groups of 15 animals were sacrificed 2 hrs, 1, 2, 3, 4 and 7 days after operation. Changes in the central and peripheral areas of the lobes were studied by histochemical stainings: succinic dehydrogenase, monoamine oxidase, nonspecific esterases, nonspecific cholinesterases, acid and alkaline phosphatases. The hepatic artery, the portal and hepatic venous systems were examined in Spalteholz's thick preparations after filling up the vessels with 6, or 8% gelatin in India ink.

Tissue samples from the central and peripheral area of a liver lobe were excised from 5 rats, killed one day after carbon tetrachloride administration, and from 5 guinea-pigs one day after ligation of the common bile duct. In these samples the changes in succinic dehydrogenase, monoamine oxidase and nonspecific esterase activities were analyzed with semiquantitative histological methods. Then the sections were projected onto a plane together with square grid with 10×10 intersections by means of a Palkovits–Csapó optical instrument used for karyometric investigations. The number of grid points covering areas with positive histological reaction or remaining unstained were counted in 100 visual fields and expressed as percentage of the total area investigated.

3. Vascular topography and lobar subdivision of the human liver

The three large vessels of the portobiliary system, the portal vein, hepatic artery and bile duct run together within the liver except for the area of the sinusoids. The intrahepatic topography of the portobiliary system may be best characterized by the description of the portal venous tree, the largest of the portobiliary vessel systems.

3.1. The portal venous system

The portal vein enters from the hepatoduodenal ligament behind the common bile duct and hepatic artery into the portal fissure where it generally splits into two main branches: left and common right trunks of the portal vein. The left trunk of the portal vein starts out from the portal vein at about a right or an obtuse angle, then it runs straight 2–4 cm to the left in the extension of the portal fissure where it bends with a convexity upwards and to the left. The convexity to the left is more pronounced and might correspond to a 2-cm long arch of a circle with a radius of 2 cm. This arc corresponds either to a plane placed through the falciform ligament and the left sagittal groove or lies to its left, deep in the groove, slightly above and in front of it. The end of the arc turns downward looking like a nose with a dead-end, for here the trunk emits only minute branches. Thus the left trunk of the portal vein in shape is very similar to the letter "J" (Figs 3, 4 and 5 A, Ungváry and Faller 1963a).

The following branches arise from the above-mentioned, most frequent variation of the left trunk (in 75% of 200 cases) rather regularly.

Branches originate from the straight part of the letter "J", coursing upward to the caudate lobe, downward, opposite to them to the quadrate lobe, forward and upward to the projections of these lobes on the convex surface (Ungváry and Faller 1963a).

In 80–90 % of the "J"-shaped variations the ramus superior of the left runk of the portal vein runs from the junction between the straight and curved portions of the "J" upward and to the left. It forms an angle of 130° with the straight part, opening upward and to the right (Figs 3, 4, 5 A).

The ramus intermedius of the left trunk of the portal vein, which in 80–90% the "J"-shaped variations springs from the left recess of the blind end of the "J", runs from the right to the left first transversally, then upwards following a downward convex curve (Figs 3 and 5 A).

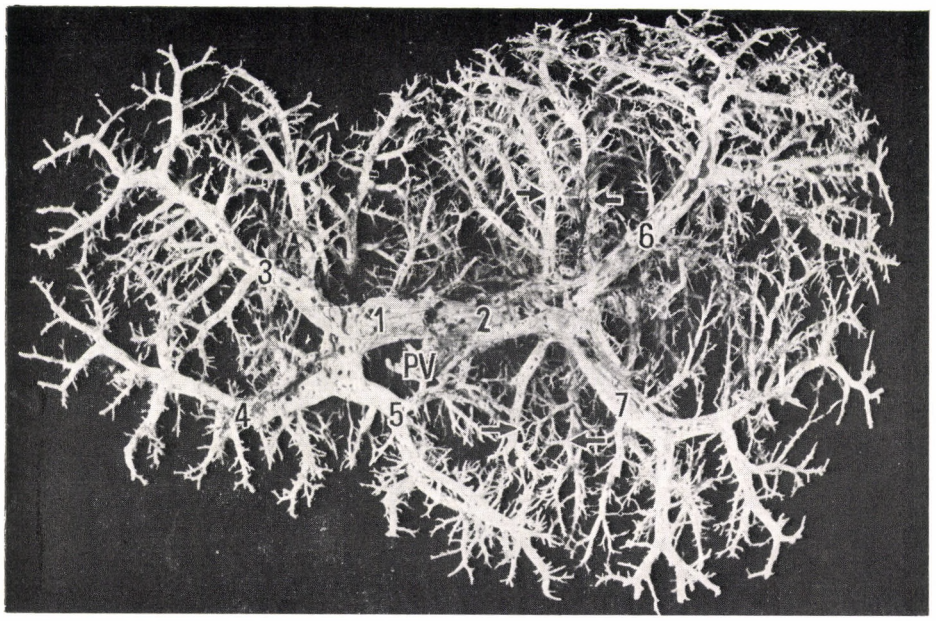


Fig. 3. PVC cast of the portal venous system of a human liver. PV — portal vein; 1 — left trunk of the portal vein; 2 — common right trunk of the portal vein; 3 — ramus superior of the left trunk of the portal vein; 4 — ramus intermedius of the left trunk of the portal vein; 5 — ramus inferior of the left trunk of the portal vein; 6 — ramus superior of the right trunk of the portal vein; 7 — ramus inferior of the right trunk of the portal vein. The arrows point at the branches of the middle trunk of the portal vein

The ramus inferior of the left trunk is present in 70 to 80% of the "J"-shaped variations. It emerges from the right lower recess of the closed, blind end of the "J"-shape and passes to the quadrate lobe. It often splits into smaller ramuli, in which case the right ramulus supplies the quadrate lobe (Figs 3, 4 and 5 A).

The rami arising left from the arc of the "J" and the ramuli of the superior, medius and partly of the inferior rami build up the portal tree of the "classical" left lobe (Ungváry and Faller 1963a).

Other, rather frequent variations of the vascular tree of the left portal trunk:

1. No "J"-shaped curvature is formed but the straight portion divides into many rami at a point left from the plane traversing through the falciform ligaments and the left sagittal groove. The latter might be designated a "radial", or "fan" type portal distribution of the left lobe (Fig. 5 B), as opposed to the "J"-shaped variation which may be called the magistral type distribution analogous with the distribution pattern of the renal artery (Ungváry and Faller 1962).

2. The left trunk of the portal vein divides into two larger rami to the left from the plane of the falciform ligament. Apart from these, smaller rami may branch off the trunk. This type can be regarded as an extreme case of "radial" distribution (Fig. 5 C).

Fig. 4. Portogram of the human liver. Radioopaque material: lead tetroxide suspended in PVC solution. 1 — left trunk of the portal vein; 2 — common right trunk of the portal vein; 3 — right trunk of the portal vein; x — origin of the middle trunk of the portal vein; portal vein (⟹); inflexion of the "J" shape (→); ramus inferior of the left trunk of the portal vein (o→)

3. Apart from a negligible twisting, the left trunk of the portal vein runs along the midline of the left lobe. Close to the visceral surface of the liver up- and downward rami, of about the same thickness, arise which run parallel to a plane connecting the attachment of the falciform ligament and the left sagittal groove (Fig. 5 D).

The common *right trunk*, the direct continuation of the portal vein. runs 1–2 cm to the right in the extension of the portal fissure where it divides into the truncus intermedius and dexter, respectively (in 65–75 % of the cases; Figs 3, 4, 6 B and 7b). In the remaining 25–35 % of the cases three, a left, a middle and a right trunk originate from the portal vein (Figs 6 A and 7 a).

In a few cases it was found that the left and right trunks of the portal vein arise from a common trunk and the middle trunk is separated. Similarly, in a negligible number of the cases the middle and left trunks emerge from a common trunk.

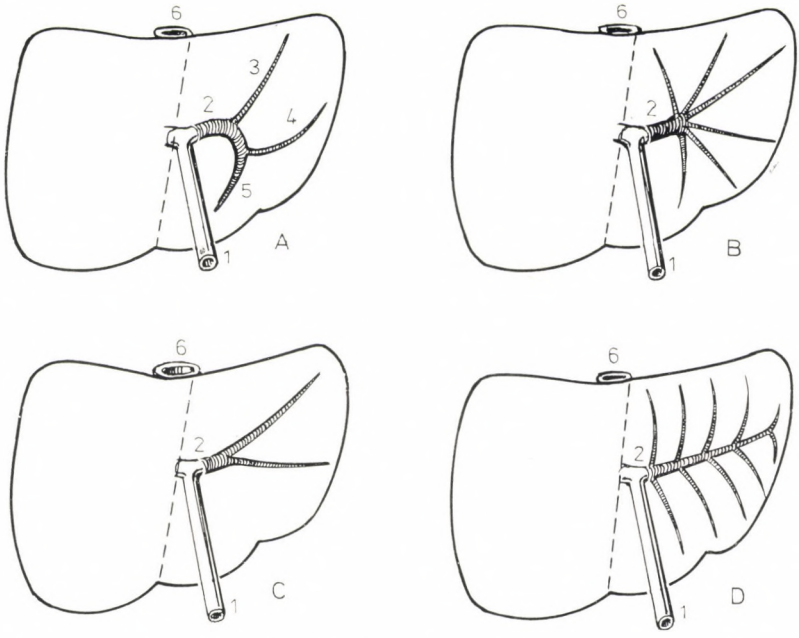


Fig. 5 A to D. More frequent variations of the branching of the left trunk of the portal vein. 1 — portal vein; 2 — left trunk of the portal vein; 3 — ramus superior of the left trunk of the portal vein; 4 — ramus intermedius of the left trunk of the portal vein; 5 — ramus inferior of the left trunk of the portal vein; 6 — inferior vena cava

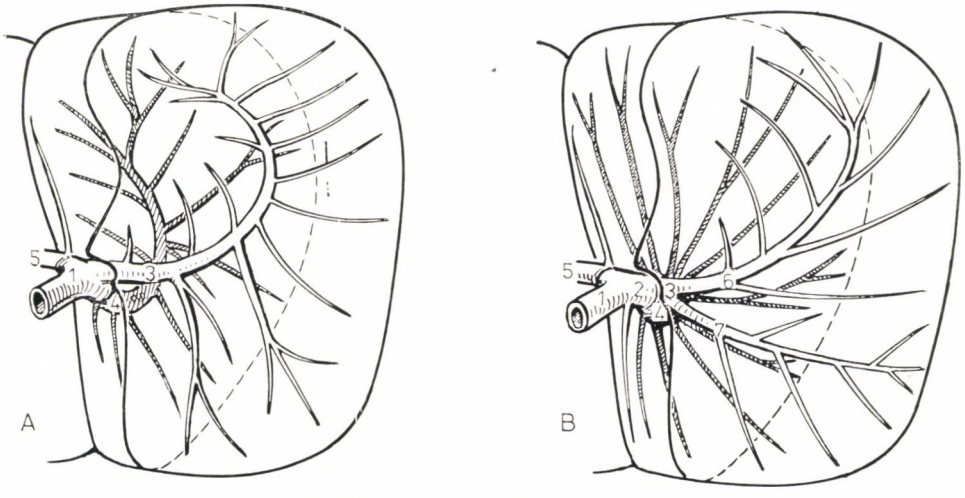


Fig. 6. The most frequent distribution patterns of the middle and right trunks of the portal vein. (A) both trunks curve along a "magistral type" arc. (B) radial (fan) type division of the middle trunk, the right trunk splits into two larger branches. 1 — portal vein; 2 — common right trunk of the portal vein; 3 — right trunk of the portal vein; 4 — middle trunk of the portal vein; 5 — left trunk of the portal vein; 6 — ramus superior of the right trunk of the portal vein; 7 — ramus inferior of the right trunk of the portal vein; the broken line indicates the border between the distribution of the middle and right trunks, projected onto the convex surface of the liver

In the majority of the cases the middle and right trunks arise with a common right trunk from the portal vein. The middle trunk makes a 1–2 cm long turn with a convexity downward, forward and to the right (Figs 4 and 6). The rami of the common right trunk run right from the Rex–Cantlie's line, parallel to the plane of fissure II (see later) in three directions: forward, downward, and upward (a part of the latter rami enter the caudate lobe). The rami of the middle trunk of the portal vein arise to the right from the ramifications of the common right trunk and downward, forward and upward filling the space just to the plane of fissure I (see later). There is no well-defined boundary or cleft between the branches (Figs 4 and 6). Larger branches, whose identification I have not found to be of importance are often present among the branches. The middle trunk divides according to the radial (fan) type and supplies the whole area available without giving off a segmental order tributary (Figs. 4 and 6 B). When the middle trunk arises separately (25–30%) at first it passes downward, forward and to the right, then it courses forward and finally upward, crossing from in front the right trunk of the portal vein. Several rami branch off the convexity of the arch running downward, forward and to the right. Others are emitted at the concave side and run upward, forward and to the right. This type we call the magistral type truncus intermedius venae portae (Fig. 6 A).

The common right trunk of the portal vein is present in 65–75% of the cases, when the most frequent (70–75%) variation of the course and distribution of the right trunk in case of a common right trunk is the following: after a short, 1–2 cm straight portion, the trunk bifurcates in a "V" shape, radial type (Figs. 3, 6 B). Short branches run to the right lobe (see later) from the trunk proximal to the bifurcation. One of the branches, the ramus superior, when passing upward takes a turn with a convexity downward and to the right; larger ramuli run from the convexity to the right toward the edge of the liver. Smaller ramuli, given off on the concave side, course to the left and upward to fissure I. The other branch, ramus inferior, passes to the right, downward and forward. The ramus inferior ramifies into ramuli in the posterior right lower part of the liver (Fig. 3).

The proportion of the liver tissue supplied by the superior and inferior rami of the right trunk varies widely. In 40% of the cases the tributaries of the ramus inferior, in another 40% of the cases the tributaries of the ramus superior alone supply two-third of the total mass of the right portobiliary lobe. In the remaining 20% of the cases, primarily in the absence of the right trunk, the contribution of the two tributaries equals 1 : 1 (Ungváry and Faller 1963a).

When the right trunk arises separately from the portal vein (25–35%), its course and distribution are in general of the magistral type, similarly to the separately emerging middle trunk. After its origin, the right trunk runs 3–4 cm long along the continuity of the portal fissure, then it takes a right turn down and forward, where it curves upward to reach the right upper posterior part of the liver. Radial, perpendicular, longer and shorter rami arise from the convexity toward the right lower and right edges of the liver. From the concavity of the magistral arc short rami start into the opposite direction (Figs 6 A, 8; Ungváry and Faller 1963 a).

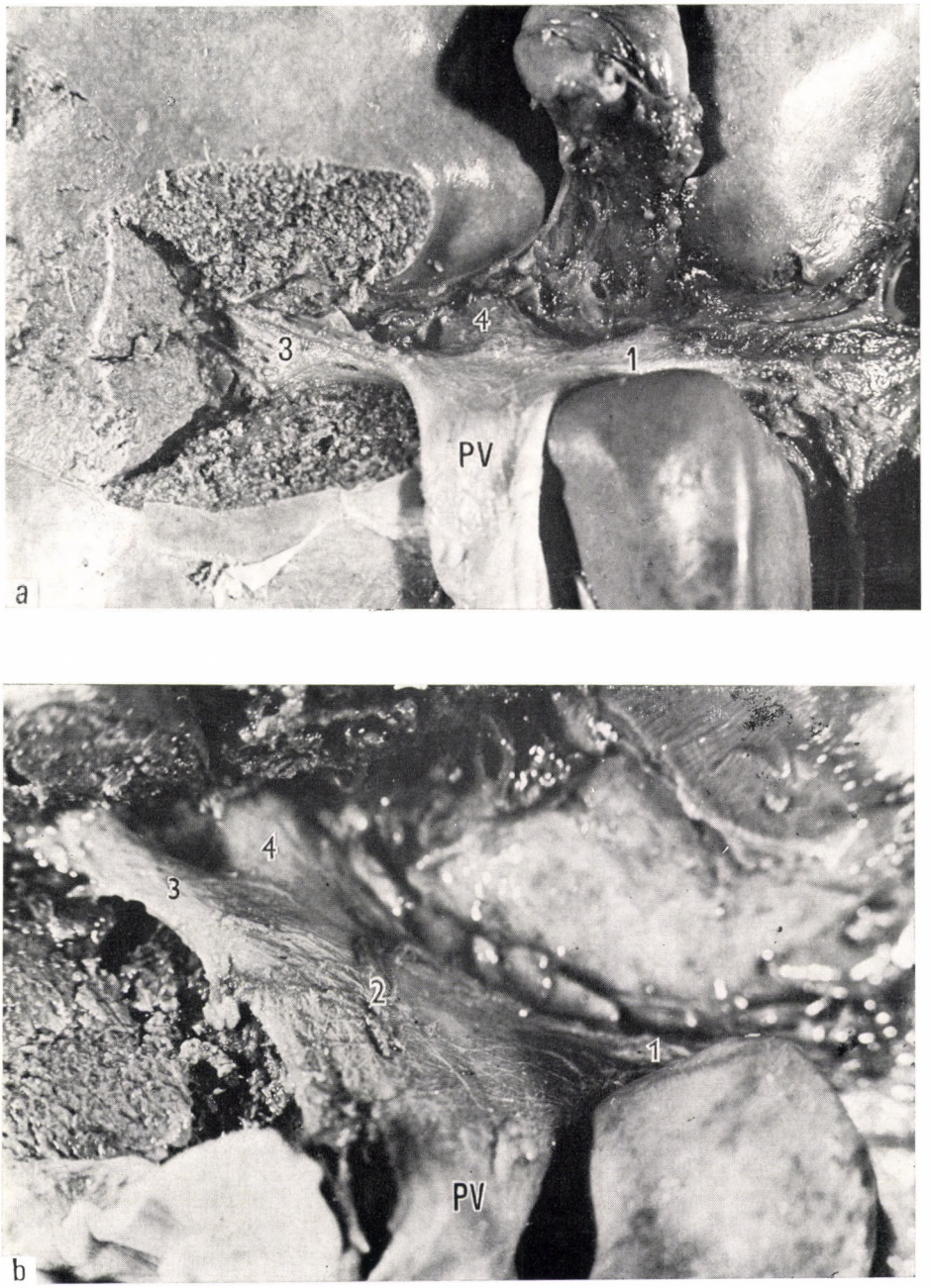


Fig. 7. Branching of the portal vein in the portal fissure. (a) — portal vein (PV) divides into three trunks (trifurcation); (b) — bifurcation of the portal vein (PV). 1 — left and 2 — common right trunks; 3 — right trunk of the portal vein; 4 — middle trunk of the portal vein. Human liver dissected after formalin fixation

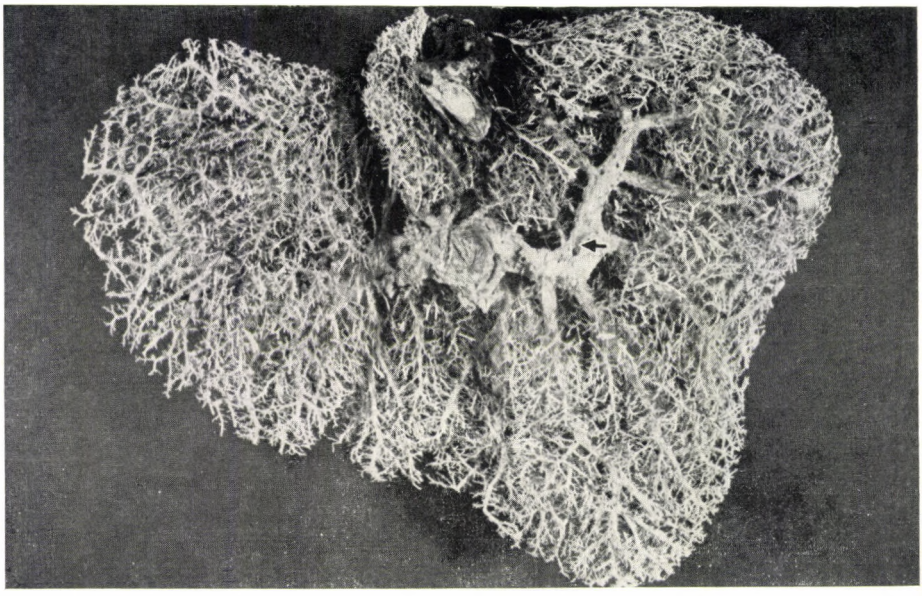


Fig. 8. PVC cast of the human portal venous system. The arrow points at the magistral arc in the right lobe

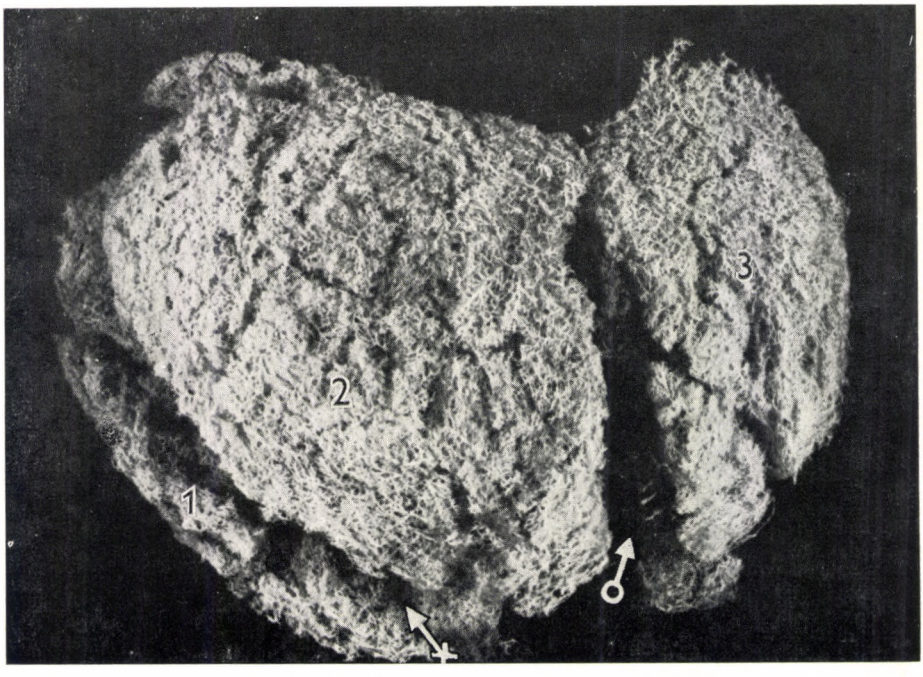


Fig. 9. PVC cast of the tributaries of the portal vein in an oval shaped human liver. Right (1), middle (2) and left (3) portobiliary lobes; interlobar fissure I (x→); interlobar fissure II (o→)

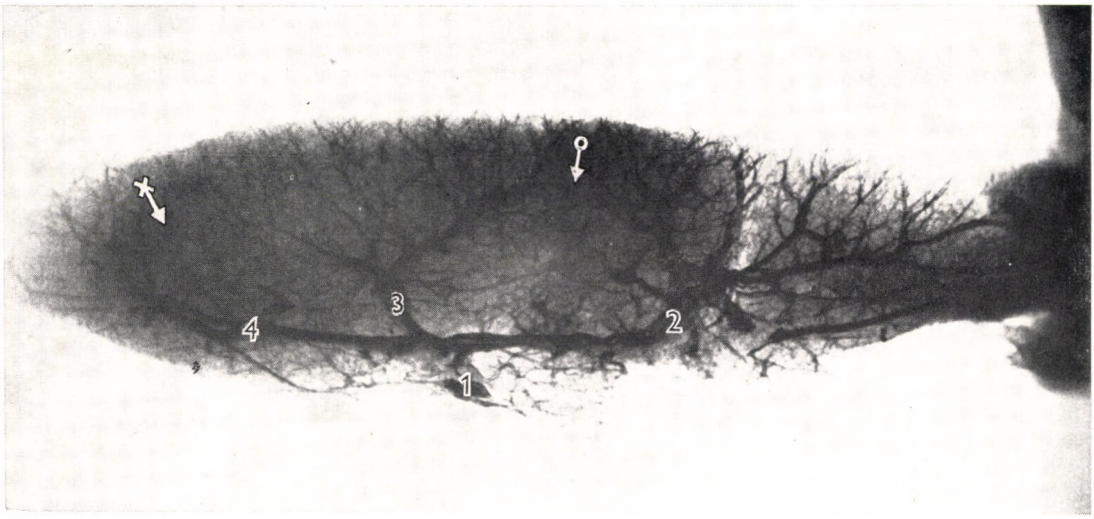


Fig. 10. Portogram of a human liver. The X-ray picture was taken by placing the liver on its anterior edge. 1 — portal vein; 2 — left trunk of the portal vein; 3 — middle trunk of the portal vein; 4 — right trunk of the portal vein; interlobar fissure I (x→); interlobar fissure II (o→)

Earlier injection studies with well-diffusing dyes have shown that to all three (left, middle and right) trunks arising from the portal vein belongs a separate individual system; these systems do not anastomose with each other at the periphery. The boundaries between the liver parts supplied by the three trunks are well marked, the colours do not mix. The three portal venous trunks (in fact the three portobiliary stems) to which belong the three independent parts of the liver that are called the left, middle and right lobes, respectively. The left of the two lines, intersecting the convex surface of the two planes that divide the liver into three parts, corresponds to the Rex–Cantlie's line, while the right line is situated 4–5 cm to the left of the right margin of the liver. (Fig. 106, p. 190; Ungváry and Faller 1963a).

Our corroded vascular casts of the portobiliary system have furnished evidence as to the trilobate structure of the liver. The individual lobes are separated and the position of the fissures dividing them can be well determined (Fig. 9; Ungváry and Faller 1963a).

The stereo view of the radiogram revealed that the branchings of the three main trunks underlie three independent systems which, due to superposition, cannot be discerned on the usual radiogram (Fig. 4). However, on the radiogram of the liver placed on its edge the three separate lobes can be well distinguished (Fig. 10; Ungváry and Faller 1963a).

We call the cleft separating the right and middle lobes, fissure I, and its projection on the surface of the liver, contour I. Similarly, the cleft between the left and middle lobes and its projection on the surface we call fissure II, and contour II,

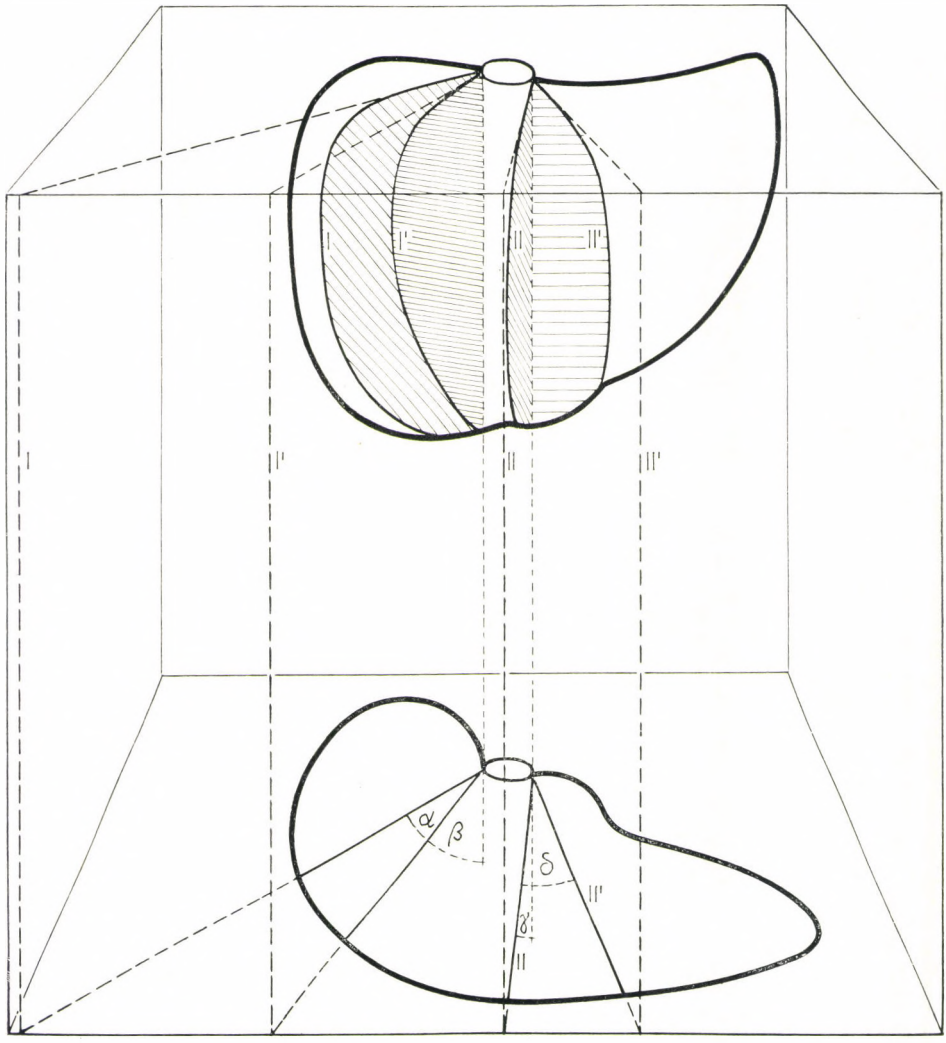


Fig. 11. Top spatial arrangement of the portobiliary and hepatic venous lobes and of the fissures separating them. Bottom: projection of the liver, lobes and fissures separating the lobes onto the horizontal plane. $\alpha + \beta = 50°-65°$; $\beta = 25°-45°$; $\gamma = 5°$ to the left or to the right; $\delta = 5°-25°$; I: right, II left portobiliary, I' right, II' left hepatic venous fissures

respectively (Figs 11, 19, Ungváry and Faller 1963a, Faller and Ungváry 1964/65). The position of the fissures has been determined by the careful dissection of the liver along the colouration following the injection of dyes or India ink or by the separation on the corroded portal casts of the rami and ramuli belonging to the individual trunks that supply the lobes. The position of these contours and fissures is the following.

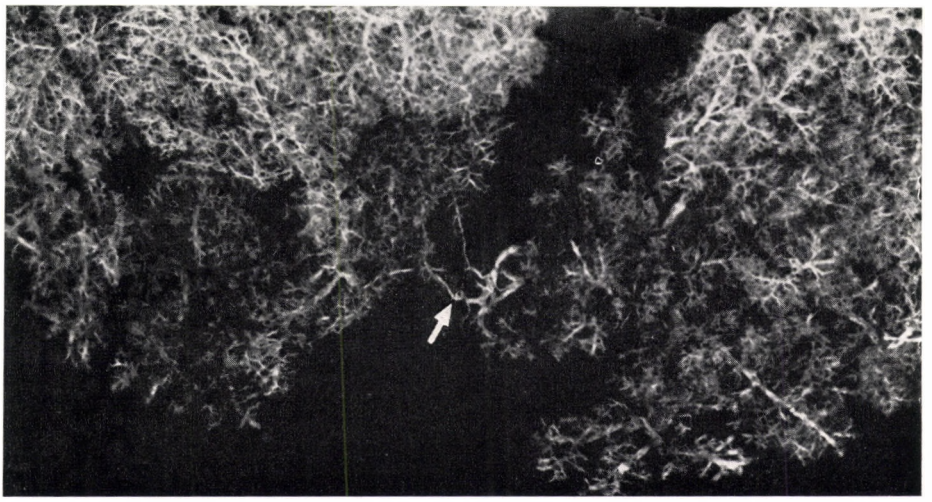


Fig. 12. PVC vascular cast of the human portal venous system. The arrow points at the portal anastomosis crossing the Rex–Cantlie's line

Contour I starts at the right side of the inferior vena cava. The first portion and the wall of the inferior vena cava in contact with the liver surface form an angle of 150°. This section extends to the margin of the upper surface where it ends 4–5 cm to the left from the right margin. Then the contour bends to the anterior surface and follows a straight line to a point located 2–3 cm from the inferior (anterior) and 2–6 cm from the right margin of the liver. Here it turns to the left, the previous and the new directions form an angle of 140° and after a course of 3–4 cm it meets the anterior margin at the right end of the gall bladder's groove. Turning down to the visceral surface the contour runs along the right margin of the gall bladder's groove to the right end of the portal fissure, then upward to the right of the right border of the caudate lobe following the right side of the inferior vena cava, back to the origin (Fig. 19).

Contour II starts at the left side of the inferior vena cava. The initial portion on the upper surface of the liver and the wall of the inferior vena cava facing the liver form an obtuse angle of 115–145°. The initial and the next portion of about the same length form an angle of 130–150°, opening downward and to the right. The following 4–8 cm long part runs 3–4 cm to the right of and parallel to the falciform ligament then it turns to the right and runs to the right and downward 3–4 cm long so that the former and the latter portion meet at an upward facing open angle of about 150°. There, after a short course parallel to the attachment of the falciform ligament it meets the anterior margin around the centre of the gall bladder groove. On the visceral surface the contour runs toward the left margin of the groove of the gall bladder and reaches the centre of the portal fissure from where it returns to the left side of the inferior vena cava. Often a curvature to the left, extending as far as the midline of the caudate lobe, is included in contour II (Fig. 19).

Fissure I, which separates the right and middle lobes, i.e. the plane connecting contour I on the convexity with that on the visceral surface, forms with the sagittal plane an angle of about 50–65° opening forward and to the right as measured in a horizontal plane (Fig. 11).

Fissure II, which separates the middle and left lobes (Rex–Cantlie's line), i.e. the plane connecting the points of contour II, forms with the sagittal plane an angle of 5°, opening either to the right or to the left as measured in a horizontal plane (Fig. 11).

The middle lobe is a backward narrowing, wedge-shaped part of the liver which covers the major part of the right lobe, when looked at from ventral aspect (Fig. 107, p. 191; Ungváry and Faller 1963a, Faller and Ungváry 1964/1965).

The proper place of the caudate lobe in this classification is variable. Most often one part of it belongs to the left, while the other one to the middle lobe.

On the basis of these results we divided the liver into three lobes. Due to the broad variability we do not think it would be justified to distinguish segments within the lobes. We mention, however, that in general the left lobe can be divided into two parts, one to the right and the other to the left from the arc of the left trunk. The so-called major liver resection is performed along the margin of the two parts of the left portobiliary lobe (McDermott 1970). The left one of the two parts is the classical left liver lobe located to the left of the falciform ligament. The subdivision of the middle lobe seems quite unreasonable. In the right lobe an upper and a lower segment can be distinguished in 85% of the cases, but their volume ratio is widely variable (Ungváry and Faller 1963a, Faller and Ungváry 1964/65).

It should be stressed that we did not find any anastomosing system that would pass the interlobar fissures in our rather big material. We encountered an anastomosing branch traversing through the Rex–Cantlie's line (fissure II) merely on three occasions. It is probable, however, that these twigs reach the other lobe through the wall of the gall bladder. No pathological changes have been found in the gross anatomy of these livers (Fig. 12, Ungváry and Faller 1963a).

3.2. The hepatic artery

The hepatic artery is the tributary of the common hepatic artery. From the origin of the right gastric artery the hepatic artery runs on the left side of the hepatoduodenal ligament and in the portal fissure; after giving off the cystic artery most often it divides (70–75%) into two branches (Fig. 108, p 192). The arteries are located in front of the portal venous trunks in the hilus. (We do not dwell upon the numerous variations in the topography of the arteries.) The right hepatic artery ascends behind the common hepatic duct and then it crosses the Calot's triangle; the left hepatic artery ascends on the left side of the common hepatic duct. The right hepatic artery divides in or before the triangle into the ramus intermedius and ramus dexter. The ramus dexter crosses the right proper hepatic duct dorsally or sometimes ventrally (Fig. 108, p. 192). The ramus intermedius enters fissure I' that separates the right and middle hepatic venous lobes (Fig. 108, p. 192). The ramus intermedius, ramus dexter and the left

hepatic artery provide the arterial tree of the middle, right and left portobiliary lobes, respectively. Rather frequently (20–25%) the hepatic artery divides into three branches in which case each enters a portobiliary lobe. The arteries follow the portal venous ramifications in the portal channels all along their intrahepatic course. As far as the intralobar distribution of the arteries is concerned we refer to the description of the intralobar course of the portal vein. It should be pointed out that the arteries conveying arterial supply to the portobiliary lobes respect the portobiliary fissures I and II (Fig. 107, p. 191). Regarding only the distribution of the hepatic artery the liver can be subdivided into three lobes coinciding with the right, middle and left portobiliary lobes (Ungváry and Faller 1963a).

3.3. The biliary system

The common hepatic duct comprises two (in 70–75% of the cases), or three (in 20–25%) proper lobar hepatic ducts. If two ducts fuse to form the common hepatic duct, one of them, the common right hepatic duct arrives from the right,

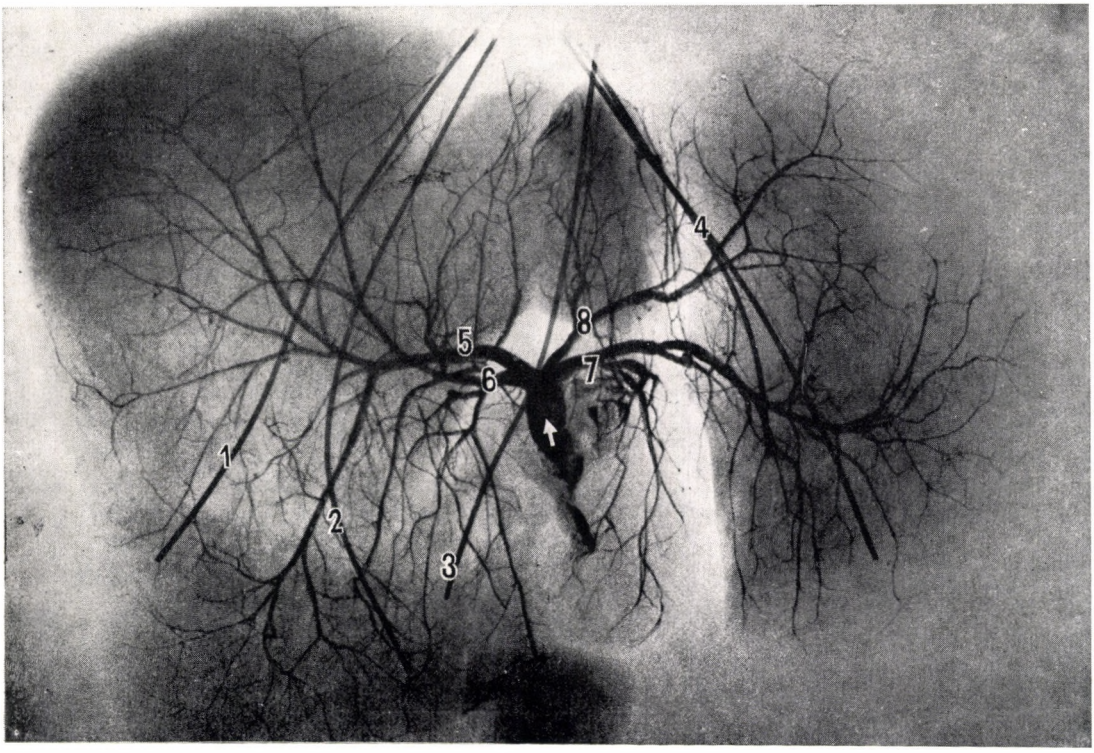


Fig. 13. Cholangiogram of a human liver. Radioopaque material injected: Triopac 400. The common hepatic duct (→) is formed by the union of the right (5), the middle (6) and two left (7, 8) proper hepatic ducts. Ureter catheters in the right hepatic vein (1, 2) in the middle (3) and left (4) hepatic veins

the other, the left proper hepatic duct, comes from the left to the junction. In this case the common right hepatic duct, arises near this junction by the confluence of the right and middle proper hepatic ducts that course from the right backward and right forward directions. The region drained by the right, middle and left proper hepatic ducts corresponds to the right, middle and left portobiliary lobes (Fig. 107, p. 191) and Fig. 20). The terminal roots of the biliary channels draining the individual lobes respect the portobiliary fissures I and II separating the portobiliary lobes, they do not pass from one lobe to another. Though numerous variations of the biliary tree occur (Fig. 13), in general the tributaries of the biliary system and of the portal vein run together within the liver. Therefore, as far as the intrahepatic ramification of the biliary tree is concerned, we refer to the intrahepatic distribution of the portal vein described above (Ungváry and Faller 1963a).

3.4. The hepatic vein

The blood conveyed by the afferent vasculature to the liver is carried away by three main hepatic venous trunks into the inferior vena cava (Fig. 14). The main trunks are: the right, middle and left hepatic veins.

Using the nomenclature introduced by Elias and Petty (1952) and Elias (1953) for the hepatic venous system, we call the vessels that open into the trunks rami and their roots ramuli. We do not use the directional nomenclature in the identification of the branches, for in the hepatic venous system variations are even more numerous than in the portal system. In our original paper, however, we still used the directional nomenclature for the designation of the hepatic veins (Ungváry and Faller 1963b).

The left hepatic vein arises in general from the junction of three rami and drains the blood from the liver mass lying to the left of the falciform ligament and the left sagittal groove, i.e. the classical left lobe. The ramus superior arises at the upper lateral end of the left lobe (classical left lobe), near the fibrous appendix of the liver forms a slightly bent cranially concave arc and it follows a nearly parallel course with the upper contour of the liver from the left to the right (Fig. 14). The ramus intermedius is formed by the junction of a dorsal and a ventral ramulus collecting blood from the veinlets and sinusoids of the left lower and middle portions of the left classical liver lobe. The ramus intermedius runs from the lower left ventral edge backward and cranially to the right and joins the ramus superior at an angle of 20–40°, opening to the left. The trunk formed by the two rami proceeds for a short length where the ramus inferior joins it at an angle of 30–50° opening to the left. The ramus inferior arises with a dorsal and ventral ramulus at the lower edge of the liver. Both ramuli run in the same sagittal plane and form a larger or smaller angle depending on whether they unite after a shorter or longer course. The ramuli and the rami run upward either in a plane connecting the attachment of the falciform ligament and the left sagittal groove, or 3–4 cm from it on the left forming an angle with the latter. These vessels drain the blood into the left hepatic

Fig. 14. X-ray picture of the human liver taken after the injection of lead tetroxide suspended in a 5% PVC solution into the hepatic venous system. VC — inferior vena cava; 1 — left hepatic vein; 2 — middle hepatic vein; 3 — right hepatic vein; a — ramus superior of the left hepatic vein; b — ramus intermedius of the left hepatic vein; c — ramus inferior of the left hepatic vein; d — ramus dexter of the middle hepatic vein: e — ramus intermedius of the middle hepatic vein; f — ramus sinister of the middle hepatic vein; g — ramus superior of the right hepatic vein

vein from the liver mass located just to the left of the above plane. The common trunk formed by the ramus superior and intermedius proximal to the junction of the ramus inferior is called the left hepatic vein. The left hepatic vein is about 2.5–3.5 cm long. It runs below the upper contour of the liver, and after uniting with the middle hepatic vein it empties into the inferior vena cava on the left side just below the upper surface of the liver (Fig. 14). The three rami forming the left hepatic vein widely vary in calibre. Most often the ramus inferior (35%) and intermedius (45%) are the largest, while in 20% of the cases the ramus superior is the biggest root of the left hepatic vein.

The tributaries to the middle hepatic vein drain blood from the middle part of the liver. Most frequently they are formed by three branches, the ramus dexter, intermedius and sinister (Fig. 14).

In general, the ramus sinister is the smallest and shortest among the three and may often be replaced by a few smaller rami. It may join the ramus dexter or the ramus intermedius, but it may also empty into the middle and left hepatic veins at their confluence. It drains the liver mass lying to the right of the attachment of the falciform ligament.

The ramus intermedius ascends along the Rex–Cantlie's line arising from the vicinity of the groove of the gall bladder, nearer the convex surface. Frequently, the middle hepatic vein forms its direct upward continuation.

Similar to the ramus sinister, the ramus dexter is also located nearer the visceral surface than the ramus intermedius. The ramus dexter runs upwards and backwards after its origin.

After the confluence of the three branches (the adjacent branches join at an angle of about 30–40°), the arising middle hepatic vein runs first parallel with the inferior vena cava, then forms an arc with a convexity upward and forward. Finally it empties into the left side of the inferior vena cava, in 85% of the cases together with the left hepatic vein just below the upper surface of the liver (Fig. 14). About 1–2 cm below its confluence with the inferior vena cava a larger ramus may join the middle hepatic vein either from the left or from the right at an angle of 20–30°, when measured in the frontal and sagittal planes. This ramus arises in the lower middle third of the liver as indicated by its projection onto the convex surface of the organ.

The tributaries of the right hepatic vein collect blood from the liver mass located to the right of a line drawn parallel, 1 or 1½ finger breadth to the right from the right sagittal groove. The right hepatic vein arises from the junction of rami varying in number in every individual. The most common patterns:

The ramus superior of the right hepatic vein begins in the right upper region of the liver from the union of the ramulus anterior and posterior (Fig. 14). The two ramuli join at an angle of 30°. The posterior ramulus is longer, it runs nearly parallel with the upper contour of the liver to its orifice into the right hepatic vein, taking up underway the ramulus anterior. It unites with the right hepatic vein about 2–3 cm from the inferior vena cava. The frontal projections of the ramulus anterior and posterior usually coincide.

The right hepatic vein arises in the right lower region of the liver from the union of two or more rami (Fig. 14). The emerging ramus ascends nearly in a vertical plane, usually forming a right convex arc, then proceeds to join the ramus superior (Fig. 14). Up to this point the vein receives 2–4 larger rami of variable calibre and course from the right. A great number of small rami join from the left (Fig. 14). In 60–70% of the cases only one, in the other 30% two parallel veins, but far narrower than the main trunk, join the inferior vena cava below the right hepatic vein.

The venous drainage of the caudate lobe is highly variable. Its venous blood may be conveyed into all three hepatic veins, or most often directly into the inferior vena cava. The branches from the caudate lobe are divergent with little regularity.

It is apparent on radiograms (Fig. 14) and on corroded vascular casts (Figs 15, 16) that the liver can be subdivided into three distinct, well-separated lobes, also with regard to the hepatic venous system. Most of our corroded casts of the

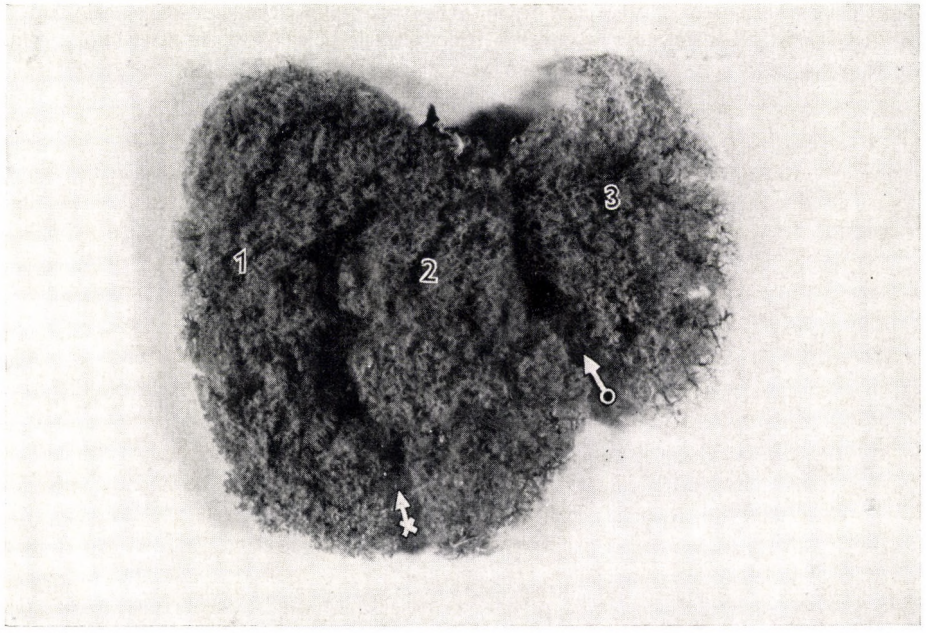


Fig. 15. PVC cast of the hepatic venous system in human liver. Convex surface. 1 — right hepatic venous lobe; 2 — middle hepatic venous lobe; 3 — left hepatic venous lobe. Fissure I' (x→); fissure II' (o→)

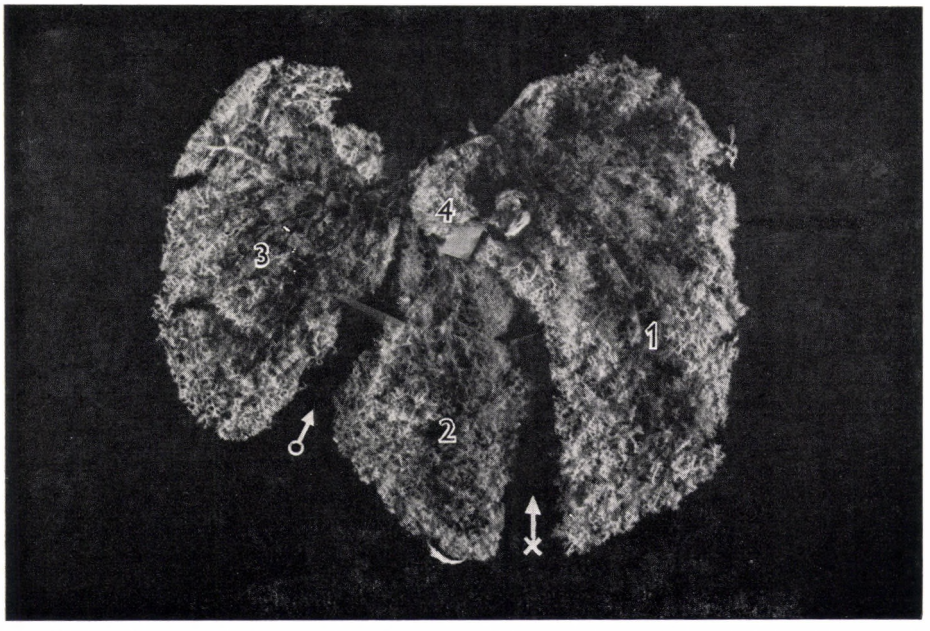


Fig. 16. PVC cast of the hepatic venous system in human liver. Visceral surface. 1 — right hepatic venous lobe; 2 — middle hepatic venous lobe; 3 — left hepatic venous lobe; 4 — caudate lobe. Fissure I' (x→); fissure II' (o→)

hepatic venous system fell apart into three completely distinct parts connected only by the inferior vena cava via the three hepatic veins. This finding shows that the three hepatic veins described can be regarded as lobar veins.

The three lobes are separated by two clefts – fissures I' and II' i. e., the right and left interlobar fissures of the hepatic venous lobes (Figs 15, 16). The plane of the left interlobar fissure (fissure II') starts at the umbilical incisure on the anterior edge and forms an angle of 5–25°, opening forward and to the left (measured in the horizontal plane) with a sagittal plane running along the left side of the inferior vena cava in situ (Fig. 11; Ungváry and Faller 1963b).

The plane of the right interlobar fissure (fissure I') starts to the right from the right margin of the gall bladder's groove. It forms an angle of 25–45° opening forward and to the right (measured in the horizontal plane), with a sagittal plane passing along the right side of the inferior vena cava in situ (Fig. 11). The parts of the liver located to the left of the left fissure, to the right of the right fissure and that between the left and right fissures we called left, right and middle lobes, respectively (Figs 17, 19, 21; Ungváry and Faller 1963b).

The caudate lobe does not belong to any of the three lobes as it is clear from the above data. However, it seems most reasonable to include it into the middle lobe (Fig. 16).

The more or less variable rami and ramuli form the skeleton of the hepatic venous lobes. This skeleton is supplemented and rendered more bulky by the "perforating" hepatic veins, which run perpendicularly to both the rami and ramuli on the one hand, and to the surface of the liver, on the other hand. These perforating hepatic veins emerge at the centre of the star- or spider-shaped veinlets located parallel with and near the surface. They descend from there between the branches of the portal vein (Ungváry and Faller 1963b).

Our preparations injected with India ink (Fig. 17) show that in the majority of cases there are no significant anastomoses between the hepatic venous lobes. In 5–6% of the cases anastomoses can be observed mainly at the margins of the fissures. These shunts are formed by 2–3 twigs and are located in about the centre of the depth of the fissure (Fig. 18, Ungváry and Faller 1963b).

When we compare the lobar subdivision of the liver based on the portobiliary system, with that based on the hepatic venous system, it is immediately obvious that they do not correspond exactly, the two fissures of the two systems are not located in the same position. In other words, the hepatic venous lobes are "shifted to the left" as compared to the portobiliary system. Consequently, the lobes of the two systems partly overlap each other (Figs 11, 19, 109, p. 192, 110, p. 193; Ungváry and Faller 1964, Faller and Ungváry 1964/65).

The right hepatic venous lobe includes the whole right portobiliary lobe and the right half of the middle portobiliary lobe. The middle hepatic venous lobe includes the left half of the middle portobiliary lobe and that part of the left portobiliary lobe which lies to the right of the falciform ligament. The left hepatic venous lobe includes the remaining part of the left portobiliary lobe which lies to the left from the attachment of the falciform ligament. It follows, that while in the portobiliary system the right lobe is usually smaller in size than the middle and left lobes, in the hepatic venous system the right lobe is the largest and the

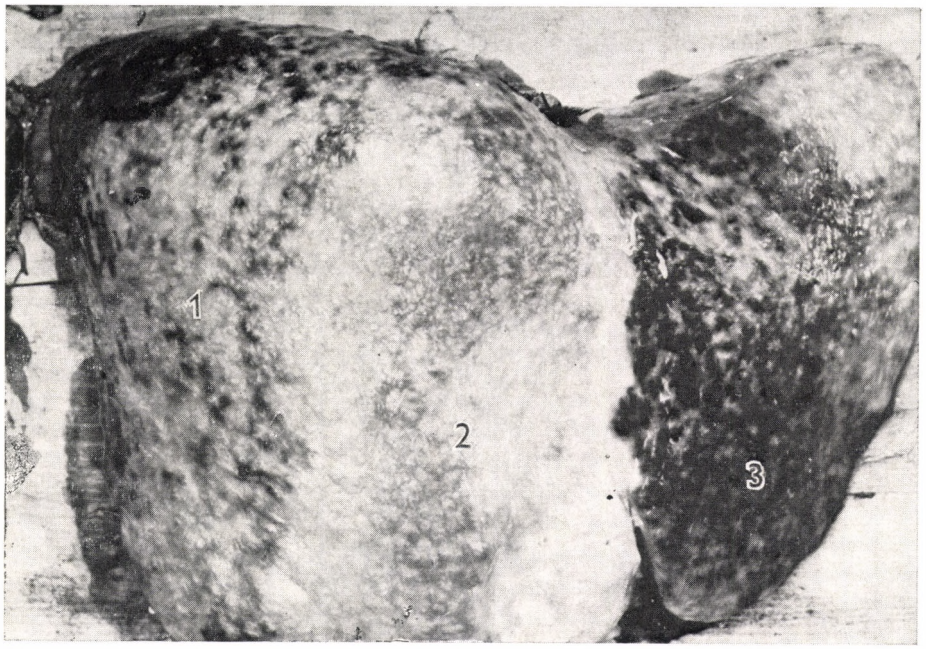


Fig. 17. Hepatic venous lobes in the human liver. Convex surface. 1 — right hepatic venous lobe; 2— middle hepatic venous lobe; 3 — left hepatic venous lobe; 8% gelatin in India ink was injected into the left and right hepatic venous systems

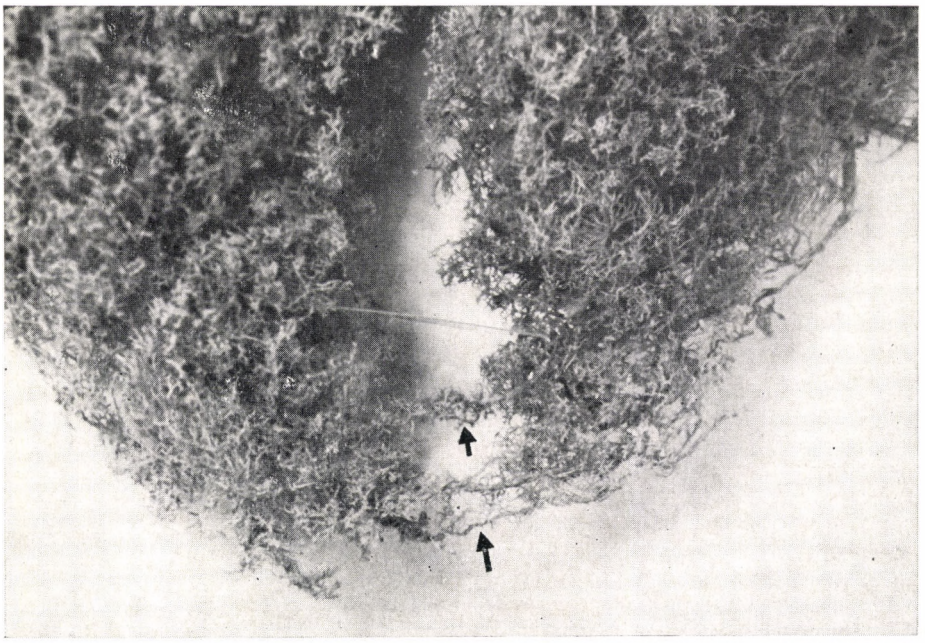


Fig. 18. PVC cast of the hepatic venous system in human liver. The arrows point at the veno–venous anastomoses bridging the right interlobar fissure (I')

left one is the smallest. All the venous blood from the right portobiliary lobe is drained through the right hepatic venous lobe. The blood from the right half of the middle portobiliary lobe is drained by the veins that empty from in front and to the left into the right hepatic vein. The left half of the lobe is drained by the main trunk of the middle hepatic vein by its ramus intermedius and dexter as well as by the anterior and right ramuli of the latter rami. The part of the left portobiliary lobe which lies between the attachment of the falciform ligament and the Rex–Cantlie's line (fissure II) is drained by the middle hepatic vein, by its ramus intermedius, sinister and also by the ramus visceralis (if the latter enters the main trunk from the left) and by their ramuli that join the rami from the left, frontal and dorsal directions. The rest of the left portobiliary lobe located to the left from the attachment of the falciform ligament is drained by the vessels of the left hepatic venous lobe (Figs 19, 109, p. 192; Fig: 110, p. 193; Ungváry and Faller 1964, Faller and Ungváry 1964/65).

As outlined above, there are four interlobar fissures radiating in the shape of a fan from the "H"-shaped grooved system of the liver surface. The fissures from right to left are the following: right portobiliary fissure (I), right hepatic venous fissure (I'), left portobiliary fissure (II), left hepatic venous fissure (II') (Figs 11, 19). It is very important that the fissures separating the individual lobes contain some of the main trunks of the other system (hepatic veins between the porto-

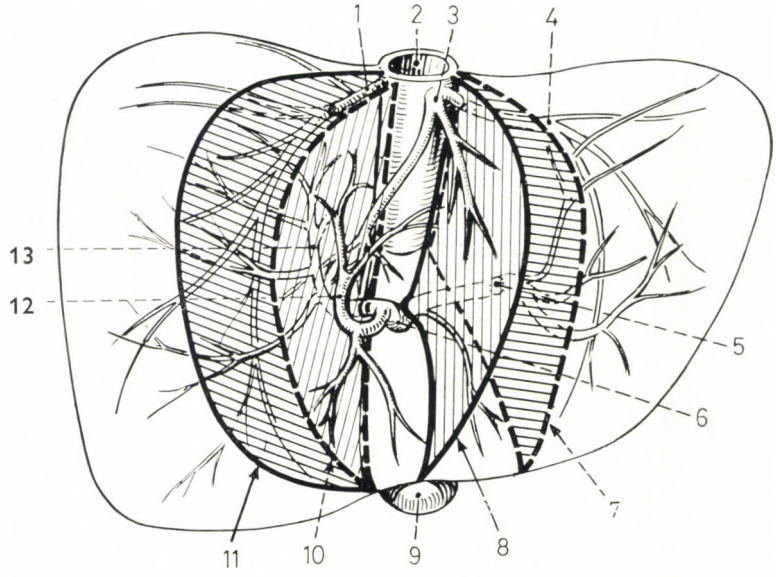


Fig. 19. Schematic illustration of the portal and hepatic venous systems and the relation of portobiliary and hepatic venous lobes. 1 — right hepatic vein; 2 — inferior vena cava; 3 — middle hepatic vein; 4 — left hepatic vein; 5 — left trunk of the portal vein; 6 — portal vein; 7 — left (II') interlobar fissure of the hepatic venous system; 8 — left (II) interlobar fissure of the portobiliary system; 9 — gall bladder; 10 — right (I') interlobar fissure of the hepatic venous system; 11 — right (I) interlobar fissure of the portobiliary system; 12 — middle trunk of the portal vein; 13 — right trunk of the portal vein

Fig. 20. Cholangiogram of a human liver. The arrow points to the common hepatic duct. I — ureter catheter in the right hepatic vein lodged in the right (I) interlobar portobiliary fissure: II — ureter catheter in the middle hepatic vein running in the left (II) interlobar portobiliary fissure; III — ureter catheter in the left hepatic vein; 1 — left proper hepatic duct; 2 — middle proper hepatic duct; 3 — right proper hepatic duct. X-ray was taken of the liver placed on its anterior edge

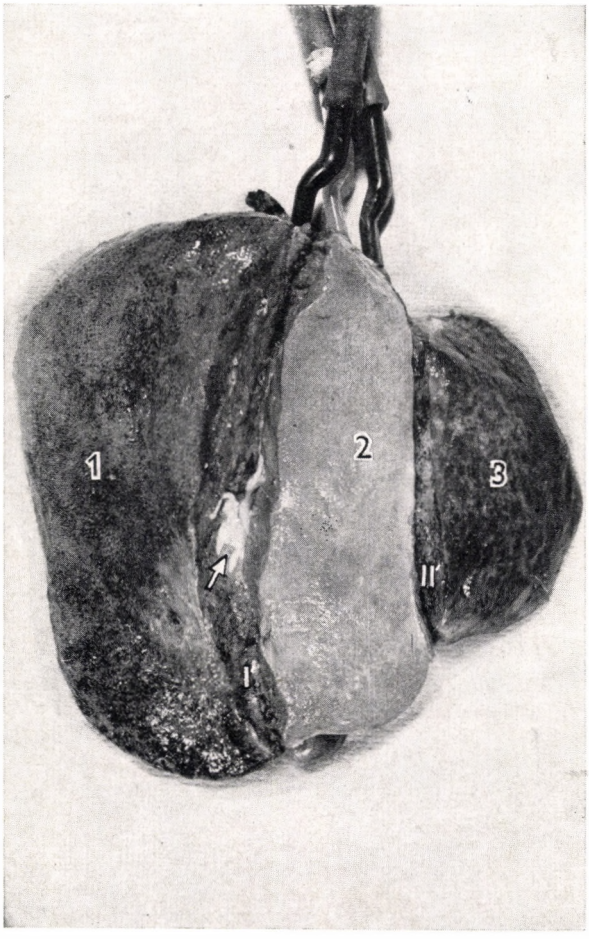


Fig. 21. The left and right hepatic venous systems were injected with 8% gelatin in India ink. Fissure I' separating the right (1) and middle (2) hepatic venous lobes and fissure II', separating the middle (2) and left (3) hepatic venous lobes had been exposed. The arrow in fissure I' points at the middle trunk of the portal vein

biliary lobes and portobiliary vessels between the hepatic venous lobes). In this way it is possible, when resection in the fissures is necessary, to find the main trunk of the other system, and to spare or ligate the afferent or efferent blood vessels in the lobar part that can be kept or must be removed (Fig. 19; Faller and Ungváry 1964/65).

The right portobiliary fissure (fissure I) contains the main trunk of the right hepatic vein (Fig. 20) and the major rami entering the trunk from the right. Approaching the fissure from the convex surface, we can expose the side branches, first the uppermost, then those emptying lower and lower into the right hepatic vein, and finally we find the main trunk itself deep in the fissure. The deeper lies the main trunk in the fissure the wider is its calibre and the larger is the right part of the liver (triangle-shaped liver, see later). Apart from the careful ligation of the side branches, one should spare the main trunk when manipulating in the fissure because it drains the blood from the right half of the middle portobiliary lobe, too! This is very important, because there are usually no significant anastomoses between the hepatic venous lobes.

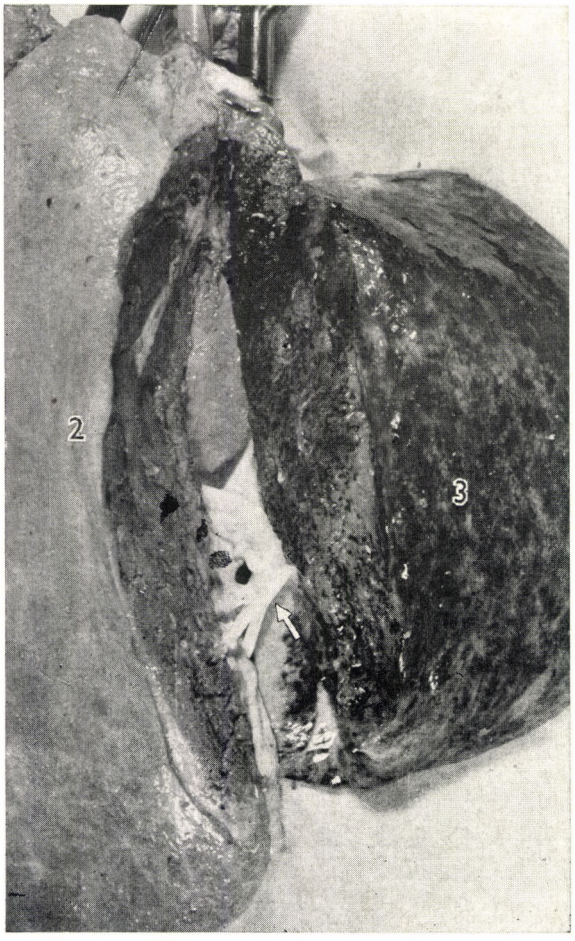


Fig. 22. The arrow in the exposed fissure II' points at the "J"-shaped arc of the left trunk of the portal vein. 2 — middle hepatic venous lobe; 3 — left hepatic venous lobe

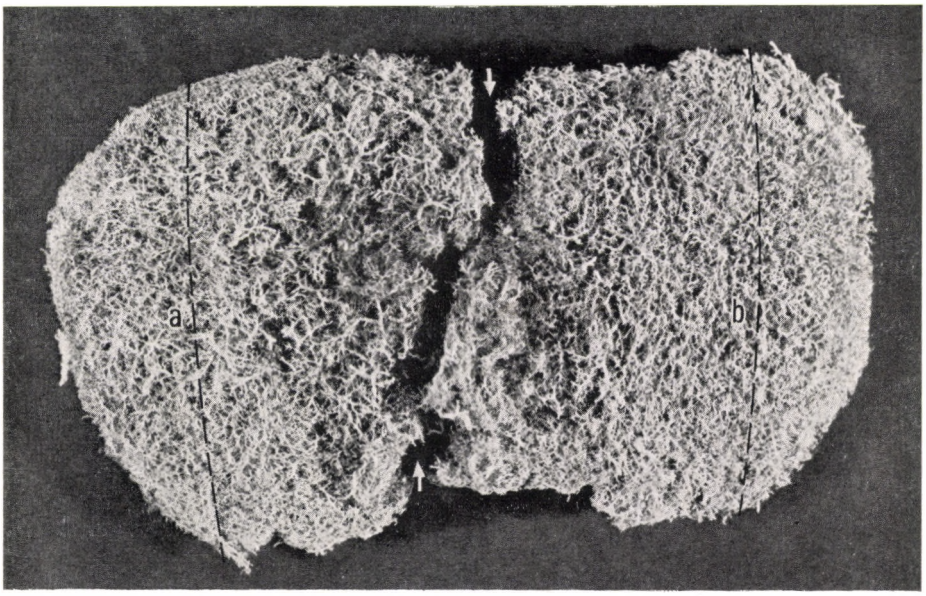


Fig. 23. Corroded cast of an extremely oval-shaped human liver narrower in the centre. The portal venous and the right and left hepatic venous vessels were filled with plastics. The arrows point at the left portobiliary fissure; (a) the height of the liver at the right portobiliary fissure; (b) height of the liver in the midline of the left hepatic venous lobe; a = b

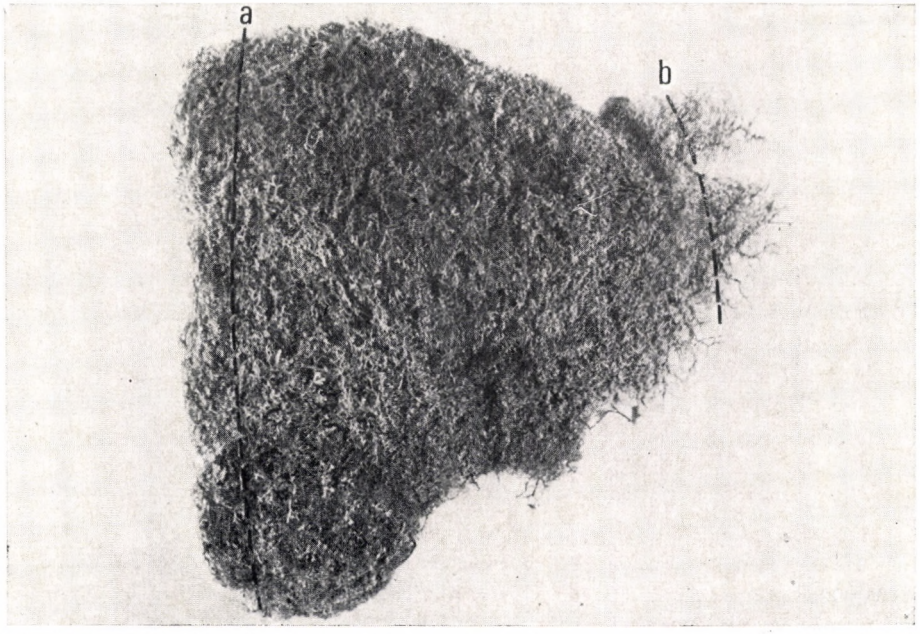


Fig. 24. An extremely triangle-shaped human liver. Corroded vascular cast. 5 % PVC solution was injected into the portal vein, middle and right hepatic veins. (a) Height of the liver at the right portobiliary fissure; (b) height of the liver in the midline of the left hepatic venous lobe; a > b

The left portobiliary fissure (fissure II) lodges the main trunk of the middle hepatic vein (Fig. 20) as well as one, usually the middle one, of the three rami forming the main trunk distal to the porta hepatis. The main trunk approaches first the visceral later the convex surface. When resecting along the fissure, care must be taken to spare the main trunk, because it drains the left half of the middle and the right half of the left portobiliary lobe!

Into the right fissure of the hepatic venous system (fissure I') enters the middle Glisson's peduncle from the portal fissure. The tracts of the peduncle run toward the convex surface from the depth of the fissure, then they split into a large number of small branches characteristic of the trunk. One larger branch runs upward another downward in the fissure at about half the thickness of the liver. Very often the right and middle Glisson's peduncles arise from the main trunk at a point in the extension of the porta hepatis, where the visceral surface and the fissure meet. When operating in the fissure the Glisson's peduncle containing the middle trunk of the portal vein, the proper hepatic artery and the proper hepatic duct must be spared, because their branches running to the left supply the rest of the left half of the middle portobiliary lobe (Fig. 21).

The left fissure of the hepatic venous system (fissure II') – in case of the typical left-side division – lodges the characteristic "J"-shaped blind pouch of the portal vein. All the other tracts of the Glisson's peduncle run uninterrupted through the fissure. When resection is performed here – as it is quite often the case – it is advisable to spare the blind pouch, because it gives off the ramus inferior to the liver mass, which lies to the right of the fissure (risk of postoperative necrosis and bile leakage) (Fig. 22; Ungváry and Faller 1963a, Faller and Ungváry 1964/65)!

3.5. The types of livers according to shape

We observed, that according to shape, the livers can be divided into two groups, with transitional forms in between. To the first group belong the livers of an approximately oval shape (projection onto the frontal plane) with a transverse long axis, where the height of the liver is about the same at the right margin and at the midline of the left hepatic venous lobe (Fig. 23). This type may be called the oval-shaped liver. To the other group belong livers resembling a triangle with rounded off angles. In this type the height of the liver measured at the right portobiliary fissure is about 1½ times the height measured in the midline of the classical left lobe. This type is called the triangle-shaped liver (Fig. 24). The thickness slightly varies in the oval types, while in the triangle-shaped liver the part lying to the left of the Rex–Cantlie's line is much thinner than that to the right. In our material 30–40% of the livers was of the oval, another 30–40% of the triangle and the remaining 20–30% of the transitory shape.

We observed a correlation between the shape of the liver and the division of the hepatic vascular system. In the oval-shaped livers a radial, fan-type distribution and usually two distinct segments can be observed in the right portobiliary lobe (Fig. 6 B). Usually in the triangle-shaped livers the framework of the right portobiliary lobe is given by a magistral arc together with the branches arising from it.

Consequently, no further segments can be distinguished (Figs 6 A, 8). In the a transitory form both division types may occur. In the case of a threefold division a magistral arc is usually found in the oval-shaped livers, too (Faller and Ungváry 1964/65).

No correlation has been found between the shape of the liver and the vascular pattern in the two other lobes.

Comparison of the shape of the hepatic venous lobes with the shape of the liver as a whole revealed that in the triangle-shaped livers the right hepatic venous lobe is much larger than the two other main venous lobes. In the oval-shaped livers the size of the hepatic venous lobes is approximately the same. The size relation of the portobiliary lobes to the shape of the whole liver is the opposite of that observed about the venous lobes. The portobiliary lobes are approximately of the same size in the triangle-shaped livers, while in the oval-shaped livers the left lobe (left main part) is larger than the two other lobes (Ungváry and Faller 1964, Faller and Ungváry 1964/65).

3.6. Interdigitation of the intrahepatic blood vessels

The trilobate subdivision of the liver becomes conspicuous during contrast filling either through the portal vein or the hepatic venous system only. After the simultaneous filling of both systems the liver cannot be broken up any more (Fig. 111, p. 193). It is a known fact that a great number of animal phyla (pisces, amphibia, reptilia and the majority of mammals) have multilobate livers (Fig. 25). In the human liver the portal and hepatic venous branches cross at acute or right angles (Fig. 112, p. 194), while in the multilobate livers the twigs of the two systems run parallel (Fig. 113, p. 194).

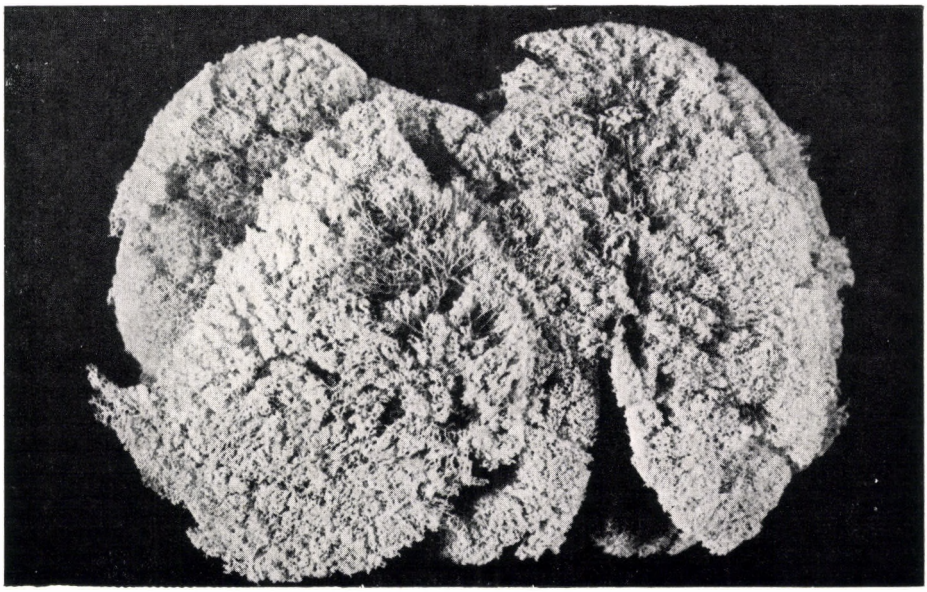


Fig. 25. Vascular cast of a canine liver. Multilobate liver

3.7. Topography of the portal and hepatic venous systems. Surgical significance of the liver segments

Our results show that a generally acceptable, uniformly valid subdivision of the liver is possible only on the basis of the above-outlined scheme. Data in recent reports corroborate our results and support our view. For example, according to Platzer and Maurer (1966), the segmental borders in both the left and right main parts of the liver are variable to such an extent that no general scheme can be given.

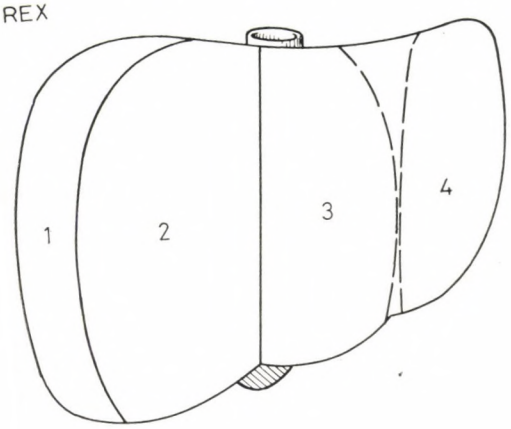
Healey (1970) pointed out that it would be highly desirable to standardize the nomenclature of the larger intrahepatic vessels and liver segments in international usage. The present wide variability, ambiguities in terminology hinder the clinical application of our knowledge on intrahepatic topography. Our classification can be applied to all livers only if we do not use it rigidly. The shape and size of the lobes vary with the shape and vascular pattern of the liver, but the number of lobes and the content of the interlobar fissures are constant. The demonstration of the latter in radiograms, feasible even during operation by filling up the intrahepatic bile ducts, and the simultaneous visualization of hepatic veins by means of a heart catheter enable us in the specific case to determine the position of the fissures and thus the shape and size of the lobes can be recognized (Ungváry and Faller 1964, Faller and Ungváry 1964/65).

There is no doubt that a resection performed along a fissure reduces haemorrhage and postoperative complications. The afferent and efferent vessels of the remaining liver parenchyma will suffer less damage in this case and postoperative liver necrosis, bile leakage and related problems can be prevented (Ungváry and Faller 1964, Faller and Ungváry 1964/65). In view of the powerful capacity of the liver for regeneration, as well as of the fact that a relatively small portion of the liver can meet temporarily the functional requirements of the organism (Monaco et al. 1964, McDermott 1970), it may seem reasonable to sacrifice larger portions of liver tissue and to devote more attention to the exact localization of the fissures in order to diminish surgical stress and risks involved (Elias 1970, McDermott 1970, Ochsner et al. 1971, Trenti et al. 1971, Miller 1972, McPeak and Bowden 1972, Mizukami et al. 1972, Bengmark et al. 1972, Cady 1973, Lin 1973).

→

Fig. 26. Portobiliary segments of the liver; classifications from different authors.
Rex (1888): 1 — area of the arcuate and descending branches; 2 — area of the ascending branch; 3 — tributaries on the right side; 4 — tributaries on the left side;
Hjortsjö (1950/51): 1 — dorsocaudal segment; 2 — intermediate segment; 3 — ventrocranial segment; 4 — medial portion; 5 — ventrolateral segment; 6 — dorsolateral segment;
Healey et al. (1953): 1 — upper posterior area; 2 — upper anterior area; 3 — upper medial area; 4 — upper lateral area; 5 — lower lateral area; 6 — lower medial area; 7 — lower anterior area; 8 — lower posterior area;
Couinaud (1954): Roman numerals indicate the sectors in Couinaud's classification;
Koiss and Miletits (1958): 1 — right lateral posterior segment; 2 — right medial anterior segment; 3 — left medial anterior segment; 4 — left lateral upper segment; 5 — left lateral lower segment;
Ungváry and Faller (1963): 1 — right portobiliary lobe; 2 — middle portobiliary lobe; 3 — left portobiliary lobe

REX



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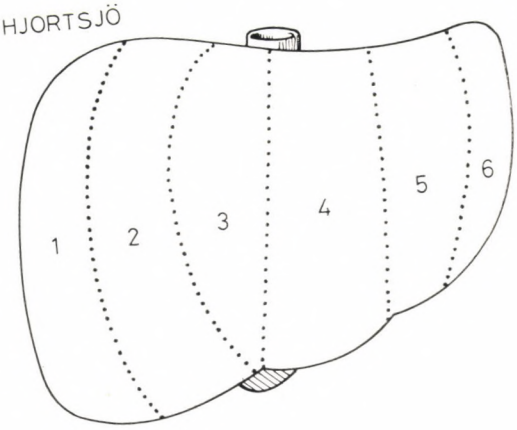
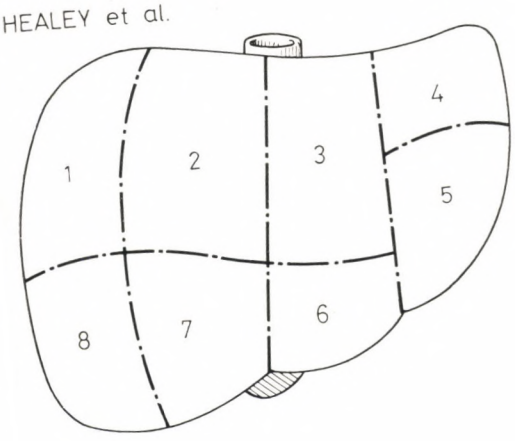
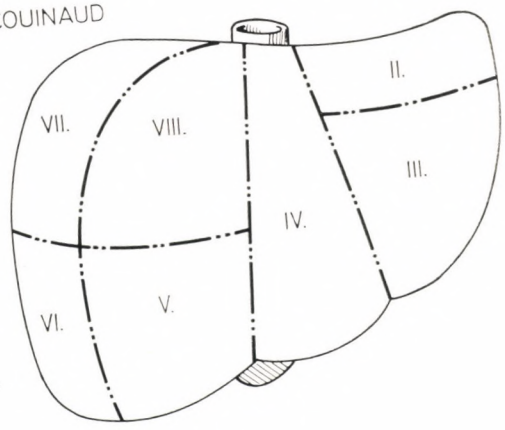


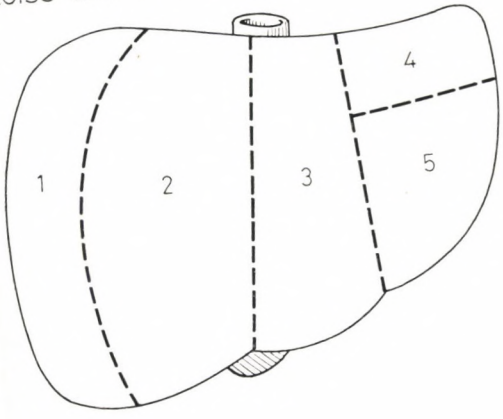
HEALEY et al.



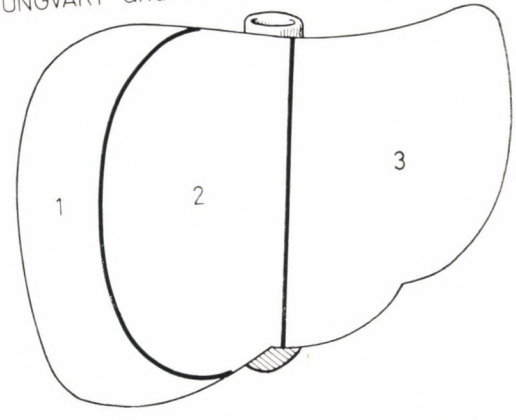
COUINAUD



KOISS and MILETITS



UNGVÁRY and FALLER



When comparing our results on the segmental subdivision of the liver with literary data, the discrepancies turn out to be seeming contradictions only.

Figure 26 shows the schematic illustration of the portobiliary liver segments from the works of Rex (1888), Hjortsjö (1950/51), Healey et al. (1953), Couinaud (1954, 1955) Koiss and Miletits (1958). By projecting, after careful scale adjustment, all segmental margins described onto a single figure a composite image is obtained which supports our classification. At the site of our portobiliary fissure I only Healey et al. (1953) did not find intersegmental fissure, nevertheless they outlined an intersegmental fissure which is not far to the left from portobiliary fissure I. Portobiliary fissure II (Rex–Cantlie's line) has been indicated by each author. All the other intersegmental fissures indicated were drawn in only by one or two of the authors (Fig. 27). The figure shows that the authors often regarded the less frequently present and thus less characteristic segments as individual components of the liver. This aspect becomes even more apparent when we fit also the likewise widely variable hepatic venous system into the schemes.

The only segment indicated by each author excepting us (Ungváry and Faller 1963a, Faller and Ungváry 1964/65) is the part of the liver which lies to the left of the plane passing through the attachment of the falciform ligament and the left sagittal groove, i.e. the classical left lobe. The resection of this lobe does not interfere with the hepatic venous system, whereas this part overlaps the part termed by us the left hepatic venous lobe (Ungváry and Faller 1963b). Considering the variations in the vascular pattern in the left portobiliary lobe and that of the lo-

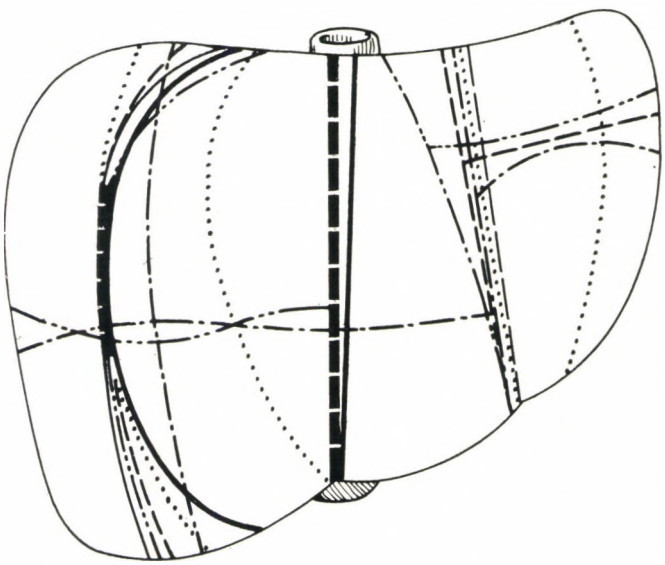


Fig. 27. Superimposed projection of the liver segments described by the same authors. ————: Rex (1888); ·····: Hjortsjö (1950/51); —·—·—: Healey et al. (1953); —··—··—: Couinaud (1954); — — —: Koiss and Miletits (1958); ————: Ungváry and Faller (1963); ▬ ▬ ▬: boundaries indicated by all the authors

calization of the "J"-shaped arc of the left portal vein, together with the regularity with which the ramus inferior emerges from its part arcing to the left of the left sagittal groove a strong branch (ramus inferior) runs downward to the right to the quadrate lobe, one might expect significant postoperative liver necrosis in a certain number of cases. The ramus inferior was present in 70% in our material (Ungváry and Faller 1963a). One should spare by all means the "J"-shaped arc of the left portal vein, when resection is performed in spite of the fact that the arc is often localized within the liver parenchyma to be resected.

Our segment scheme of the liver as regards the arrangement of the hepatic venous system agrees with those of other authors (Ungváry and Faller 1963b, Esbolov 1973, Ryncki 1974).

The "classical" left lobe which corresponds to the left venous lobe cannot be considered to be an independent portobiliary lobe. Its surgical significance is great as it can be relatively easily resected. Moreover, in case of a "large lobe resection" when only this part is left, its activity is sufficient for saving the patient's life. Later, due to its rapid regeneration, it will adequately perform the normal function of the liver (McDermott 1970).

3.8. Haemodynamic aspects of the intrahepatic vascular distribution pattern

The above discussion has been centred only upon the surgical significance of the topography and distribution pattern of the intrahepatic vessel systems. Now we will very shortly refer to the functional significance of the interdigitations of the hepatic and portal systems, the lobar division and the vascular arborization, as factors controlling local blood flow. The interdigitation of the hepatic and portal veins was already observed by Glisson (1654). As we have mentioned earlier, in the non-lobate human liver the portal and hepatic branches cross each other, while in the majority of animal species the trunks and branches of the two systems have a parallel course. It is conceivable that the difference in the vascular tree might reflect differences in blood flow. Differences in hydrodynamics may arise from the differences in terminal distribution of the afferent and efferent vessels and from the differences in the angles of division. It is a known phenomenon that local differences in blood flow can arise due to the difference in the angularity of distribution. The division at acute angles is a more favourable condition than the division at right or obtuse angles. The course of blood vessels seems to be more harmonic, the distribution of blood flow seems to be more even in human (non-lobate) livers.

The difference in the angularity of distribution may offer an acceptable explanation for the differences in liver shape (Faller and Ungváry 1964/65, Smirnova 1970). When we agree with the view of Mall (1906) and Elias and Petty (1952) that the more favourable angles of division and, consequently, more abundant umbilical supply would be the reason why that part of the liver which lies to the left of the Rex–Cantlie's line is larger than the right main part, then it is

conceivable that in case of portal trifurcation the right and middle portobiliary lobes are larger than the average. The magistral arc of the right lobe may be associated with a relatively large right lobe (triangle-shaped liver) because this arch is the direct continuation of the common right trunk of the portal vein and the branches are given off at acute angles.

The exact knowledge of hydrodynamics perhaps would enable us to elucidate the reason why certain pathological processes have consistently the same localization in the liver. Also, this knowledge might help to decide whether the portal vessels convey the blood of circumscribed splanchnic areas preferentially to the left or right territory of the liver parenchyma (Himsworth and Glynn 1944).

4. Histo-functional units in the ontogenesis and regeneration of the liver

4.1. The size and shape of fetal livers Gross anatomy of the vasculature

In fetuses the left hypochondrium and epigastrium are occupied by the liver nearly to the same extent as the right hypochondrium (Fig. 114, p. 195). The liver to body weight ratio therefore is significantly higher in fetuses than in adults. In the 8th–10th months of gestation the mean liver weight of fetuses was 120 g, mean body weight 2500 g, thus the weight of the liver represented 4.8% of the body weight. In neonates the average liver weight was 131 g, the mean body weight 3200 g, with a liver to body weight ratio of 4.1%. The average weight of adult livers (male) amounted to 1524 g, the mean body weight amounted the last time still alive to 74 kg, thus the liver to body weight ratio calculated was 2.06%. In porcine fetuses in the last third of gestation the mean liver weight amounted to 5.9% of the whole body weight.

In human fetuses of the 8th–10th months of gestation the mean weight of the liver parts right and left of the Rex–Cantlie's line was 48 g and 72 g, 40 and 60%, respectively. In adult cadaver livers the mean weight of the same two parts was found to be 915 g and 609 g, respectively. In percentage the right and middle portobiliary lobes amounted to 60, the left lobe to 40% of the total liver weight. Thus the fetal proportion of the weight of the left and right main liver parts on the two sides of the Rex–Cantlie's line is the reciprocal of the adult one (Ungváry 1967, 1971).

An important feature of the gross anatomy of the fetal liver vasculature is, that while the common portal vein and the left trunk of the portal vein form an angle of 80°, the common right trunk is the direct, arching continuation of the common portal vein. This division may explain that the blood of the common portal vein enters primarily the right main part of the liver. The umbilical vein continues into the arc of the left half of the trunk (pars umbilicalis; Elias and Petty 1952) and thus the blood from the umbilical vein runs against the blood coming from the common portal vein through the left trunk. Therefore, the left trunk of the portal vein that forms a shunt in the fetus between the umbilical and common portal veins, widely varies in calibre and length as was reported by Elias and Petty (1952). The direction of blood flow in the left trunk is determined by the pressure ratio between the common portal and umbilical veins (Fig. 115, p. 196).

The umbilical vein has a considerable share in providing a more favourable blood supply to the left main part of the liver as compared to the right one. Also the drainage of the left main territory seems to be more advantageous. In the adult liver the right and left hepatic veins join the inferior vena cava at an angle of 45°

and 90°, respectively. The drainage of the venous blood is further complicated by the fact that the middle hepatic vein joins the left trunk at about a right angle. In the fetal liver the right hepatic vein and the inferior vena cava unite at the same angle as in adults, but the left hepatic vein enters the vena cava at an angle of 30–80°, and provides in this way a streamlined hydrodynamics in the venous drainage (Ungváry 1967, 1971).

It is striking that both the portal and the hepatic venous vascular casts are more bulky to the left than to the right of the Rex–Cantlie's line. The branches of the left trunk are more numerous than in the adult liver. This may have a favourable influence on the venous drainage from the left main part of the fetal liver (Elias and Petty 1952, Ungváry 1967).

In the first 3–4 years after birth the growth and development of the portal and hepatic venous tree of the left main part lags behind that of the right part. Certain branches become completely obliterated (fibrous appendix of the liver).

In this connection it is interesting to note that in porcine fetuses where there is no or only a narrow, convoluted intrahepatic venous duct of Arantius, the left part of the liver is enormously developed.

4.2. Vasculature of the histo-functional units in fetal liver

Counting the number of divisions along the longest possible course, i.e. from the hilum to the periphery of the lobe, on portal casts of fetal livers between the 6th–10th months of gestation, it was found that the sinusoids corresponded to the 6th–7th divisions of the portal vessels. A thorough examination of histological sections revealed that the sinusoids are irregular with alternate narrowings and dilatations. In the perisinusoidal spaces of Disse i.e. between the endothelium of the sinusoids and the hepatocytes, haematopoietic foci can be observed (Dvorak 1964).

The formation of new portal vessels does not stop at birth, but continues afterwards. New branches develop and the number of divisions preceding the sinusoid will increase. After birth within 3–4 years the development of the portal tree reaches a stage characteristic already of the adult liver, when the sinusoids represent the 8th–10th divisions of the portal vein. The preterminal and terminal portions of the portal divisions do not follow a rigid pattern, beside quite irregular branchings, clusters of sinusoids with regular spatial orientation, resembling portal lobules, occur (Fig. 28). The portal lobule (here the portal lobule is not used in the sense of Mall) or acinus of the corroded vascular casts corresponds to the first (Z_1) zone of Rappaport's simple liver acinus in the adult liver. On corroded casts of the hepatic venous system characteristic distributions resembling the Kiernan's lobule can be observed only. These hepatic venous lobules in the adult are composed of the third (Z_3) zones of adjacent Rappaport's simple liver acini. It is obvious already from these casts, but especially from those which were filled up either with combined injection or with injection

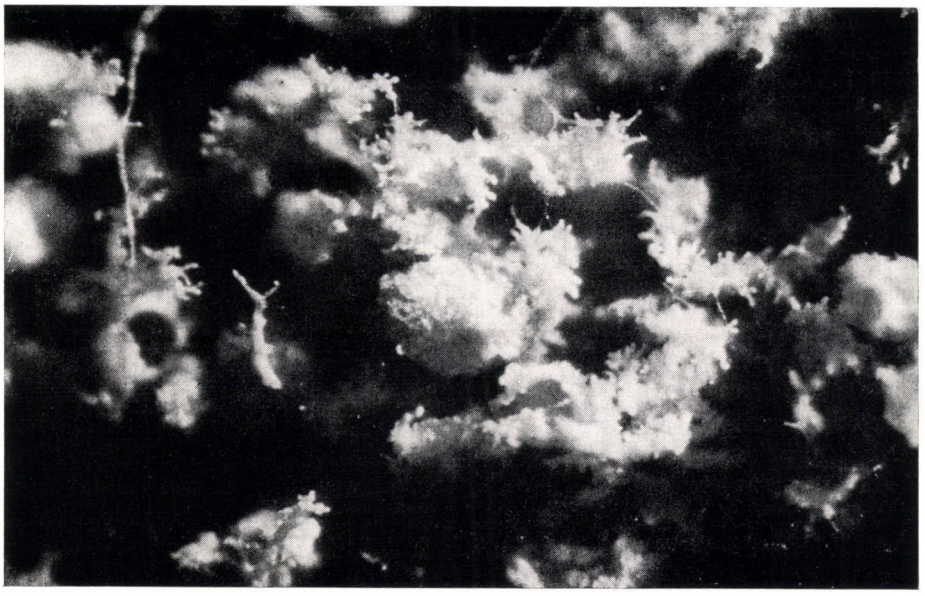


Fig. 28. PVC cast of the portal venous system of a human fetus; portal lobules or portal acini — the sinusoids of the irregular portal tufts run in every direction in the space and do not correspond to the portal lobules of Mall. × 35

Fig. 29. PVC cast of the hepatic venous system of a human fetus; the sinusoids enter every branch of the hepatic vein directly. × 60

through the umbilical vein without the ligation of the venous duct of Arantius, that the efferent vessel system of the fetal liver differs qualitatively from the hepatic venous system of the adults. While in the adult liver the sinusoids join the central venule only, in the fetus they may enter even larger hepatic veins too (Fig. 29). This type of junction can be found in the rat among adult mammals (Ungváry 1967).

4.3. Fetal acinus and the appearance of the Kiernan's lobule in ontogenesis

Histological examination of the haematoxylin–eosin stained fetal livers revealed that the majority of the hepatocytes are arranged in double layers: 300 visual fields in the liver sections of each of the 5 fetuses differing in gestational ages (6–10 months) were counted. Parenchyma cross sections of two cell-thickness amounted to 70%, while the one-cell-thick plates to 30% of all formations (Ungváry 1967). The 3–10 cell long and wide formations had not been included because these cannot be distinguished from the profiles of the one-cell-thick plates, cut in a plane parallel to that of the plate.

In the sections prepared from the liver of a 4-year-old child, similar to adult livers, only plates of one-cell and sometimes of several-cell thickness could be observed (Fig. 30).

If one reconstructs a region of the fetal liver in which the radial arrangement of the sinusoids around a hepatic venous twig is similar to the structure of a later lobule then one obtains a model like that seen in Fig. 31. It was indicated in the Figure that the sinusoids enter not only the initial, smallest but also larger hepatic venous branches near the inferior vena cava. The endothelial layer and the haematopoietic foci that lie between the endothelial cells and hepatocytes and cause the considerable irregularity of the sinusoid lumen had not been shown. The one-cell-thick hepatic plates which are already present (Ungváry 1967, 1971) were not indicated in the Figure either.

The two-cell-thick hepatic plates are regularly seen in the livers of premature infants and neonates (50 or 30%, respectively) and disappear only 3 or 4 years after birth. In the liver of newborn rats in the 3rd postnatal week, the Kiernan's lobules can already be well discerned. At this time no thicker hepatic plates than those of one-cell thickness are present in this species. The Kiernan's lobules appear in the histological sections at the time, when already the one-cell-thick hepatic plates dominate the picture. In the human fetuses, the tufts of the portal and hepatic veins which can be demonstrated by means of the injection–corrosion methods do not get arranged into Kiernan's lobules (Figs 28 and 29). The formation of the Kiernan's lobules and the arrangement of the sinusoids ensue only when the one-cell-thick hepatic plates become a predominant general feature. The liver of the human fetus is thus built up of modified acini (pre-acini) whose axis is formed by a portal twig from where the fetal sinusoids arise in every direction. On the margin of the

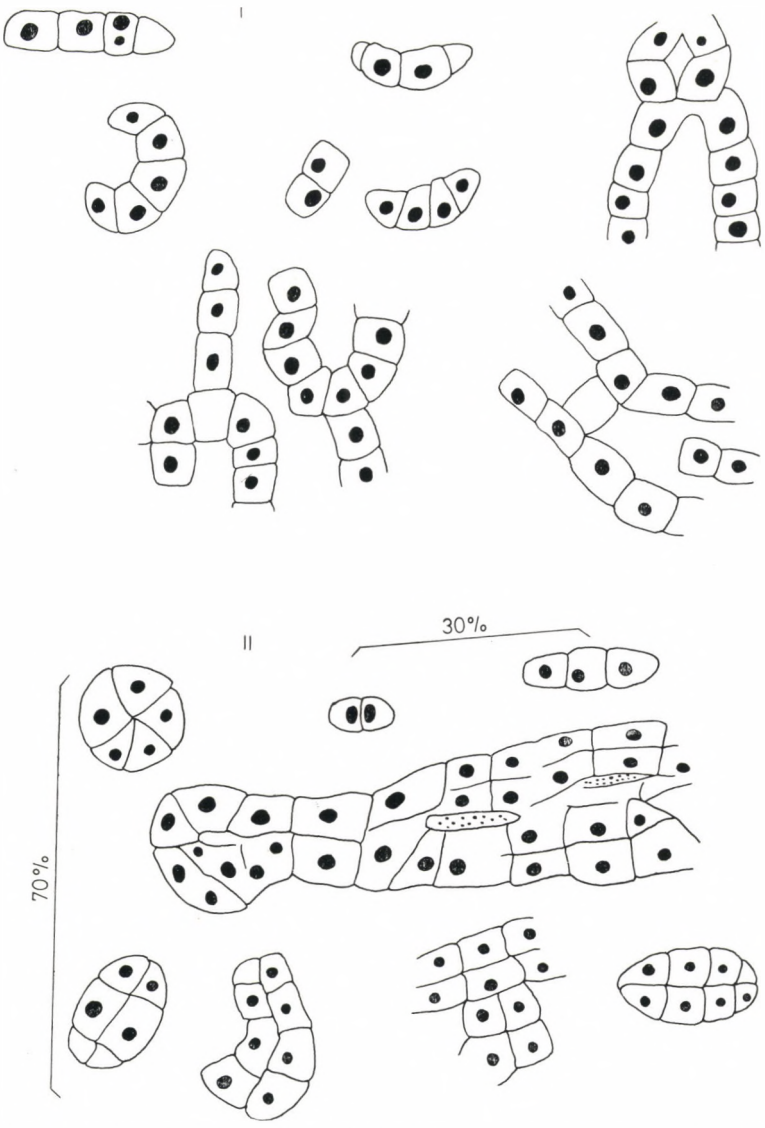


Fig. 30. Part I: cell groups occurring in the adult human and mammalian liver as seen in 6—8 μm thick sections, haematoxylin–eosin staining; part II: cell groups occurring in the liver of a human fetus. The dotted area corresponds to the "fetal sinusoids"

portal tuft, 2–4 central or larger hepatic (postinitial) veinlets run at a right or acute angle with the tuft. The fetal sinusoids enter into these veinlets. The sinusoids entering the postinitial venous branches frequently change already into preterminal or terminal portal veins and thus can be regarded also as fetal portohepatic anastomoses (Ungváry 1967, 1971).

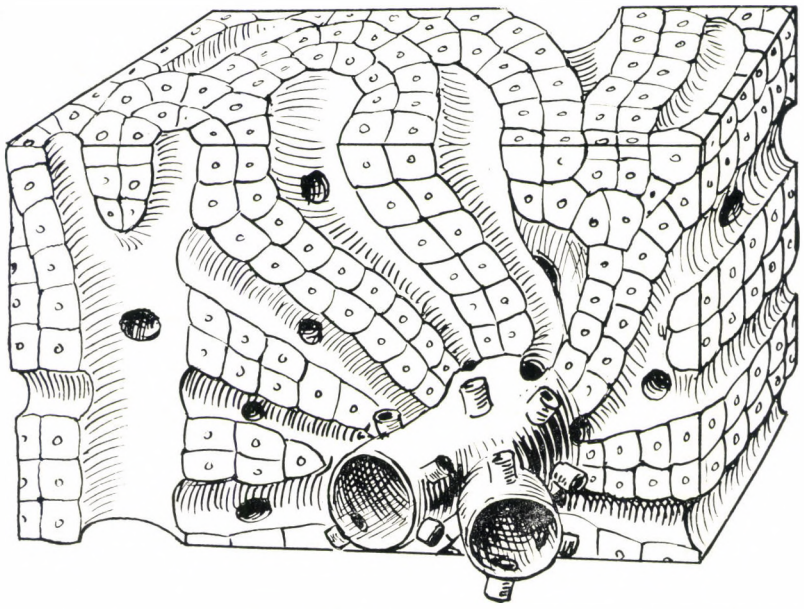


Fig. 31. Block section of a part of a human fetal liver resembling a Kiernan's lobule developing later. The sinusoids are limited by two-cell-thick hepatocyte plates and they may join larger efferent blood vessels also. Endothelial layer and haematopoietic foci are not indicated.

4.4. Rate of liver regeneration after partial hepatectomy in rats

4.4.1. The radiogram of the liver from a control rat shows the outlines of the lobes after the injection of 1 ml radioopaque material into the mesenteric vein (Fig. 32 a). On the X-ray taken one week after the resection of the two large lobes, the four remaining enlarged lobes can be observed (Fig. 32 b). A radiographic follow-up showed that, while the rate of regeneration had been rapid until the end of the first week, a slight decrease followed therafter (Ungváry et al. 1969b).

There was a significant increase in the wet weight of liver during the first week after partial hepatectomy that was followed by a significant decrease up to the first postoperative month (Fig. 33; for experimental details see Section 2.2.2.). The weight of the corroded casts of the hepatic venous system was significantly higher on the 7th than on the 2nd day after partial hepatectomy (Fig. 33), and a slight tendency for further increase had been found even thereafter. The average weight of the corroded casts of the portal vein (Fig. 33) was similarly higher at 1 week than 2 days after operation. This increase was followed by a slight but not significant decrease (Ungváry et al. 1969b).

The mean weight of the four remaining lobes after the 1st week roughly approached and after 3 months following resection considerably exceeded (by 20 %) the estimated weight of the whole liver (6 lobes) at the time of operation.

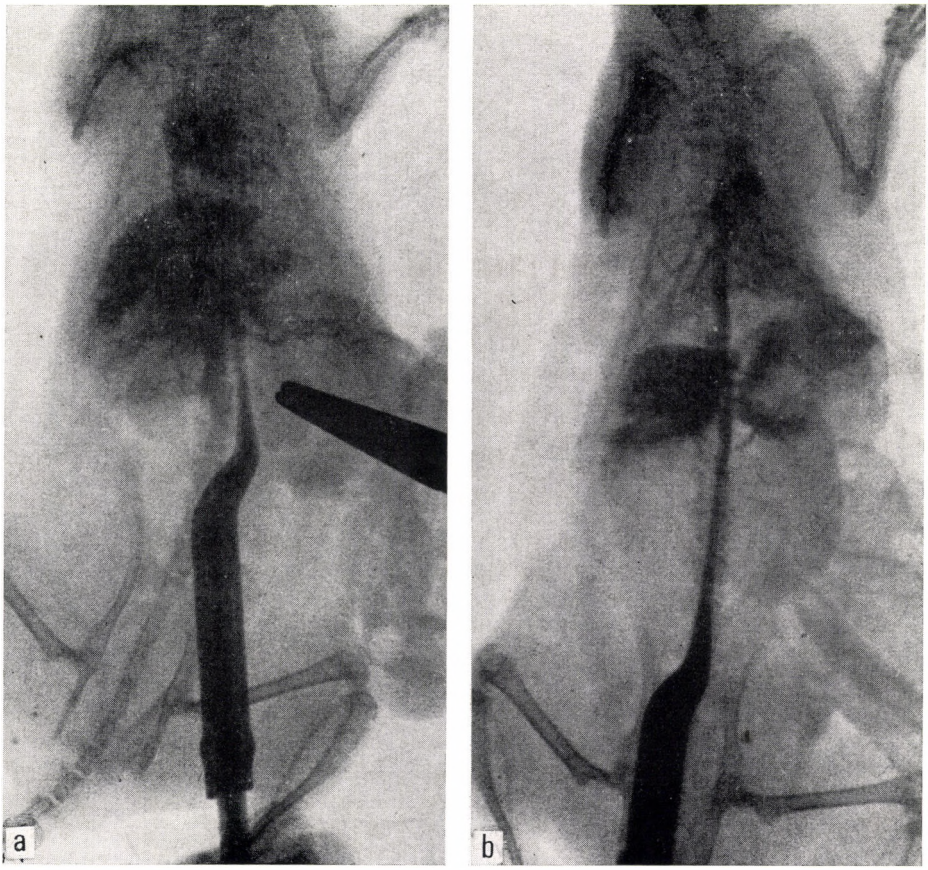


Fig. 32. (a) portogram taken from a control rat; (b) portogram one week after partial hepatectomy

The liver to body weight ratio was significantly higher 1 week after resection, while after 1 and 3 months it roughly equalled that of the controls (Ungváry et al. 1969b).

The changes in vascular capacity are interesting. The corroded hepatic venous cast to liver weight ratio reached a minimum at 1 week after resection, thereafter it increased and stabilized at a value only slightly less than that of the controls. Both the absolute and relative weight of the corroded portal venous casts were found to be the lowest 1 and 2 days after resection. [The weight of the portal venous cast of the four smaller lobes left was less than that of the controls (absolute value); on the contrary, their wet weight was higher in the operated than in the control animals. Accordingly, the portal cast to liver weight ratio (relative value) was also less in the operated group 1 and 2 days after resection.] There was a significant increase in the mean weight of the portal venous casts 1 week after resection, and with a further increase the value approached the original level at the end of the experiment (Fig. 34; Ungváry et al. 1969b).

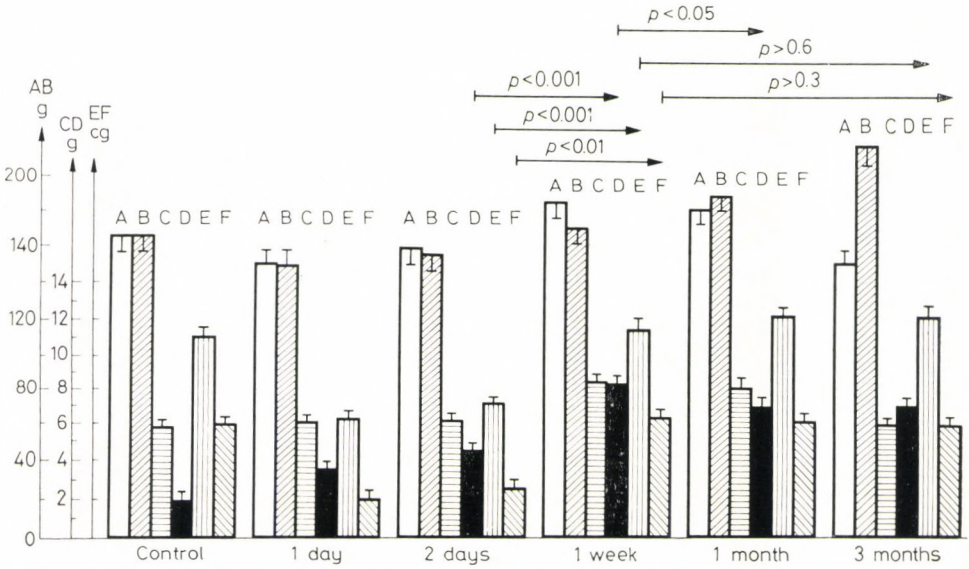


Fig. 33. The changes found during liver regeneration in (A) body weight of the animals at the time of operation; (B) body weight of the animals at the time of autopsy; (C) calculated liver weight; (D) the weight of the four small lobes referring to the regenerated lobes in experimental and to the original ones in the control animals; (E) weight of the hepatic venous casts; (F) weight of the portal venous casts. The number of animals was 20 in groups A through D, and 10 in E and F. The time after operation is shown on the abscissa. The columns indicate $\bar{x} \pm$ SD

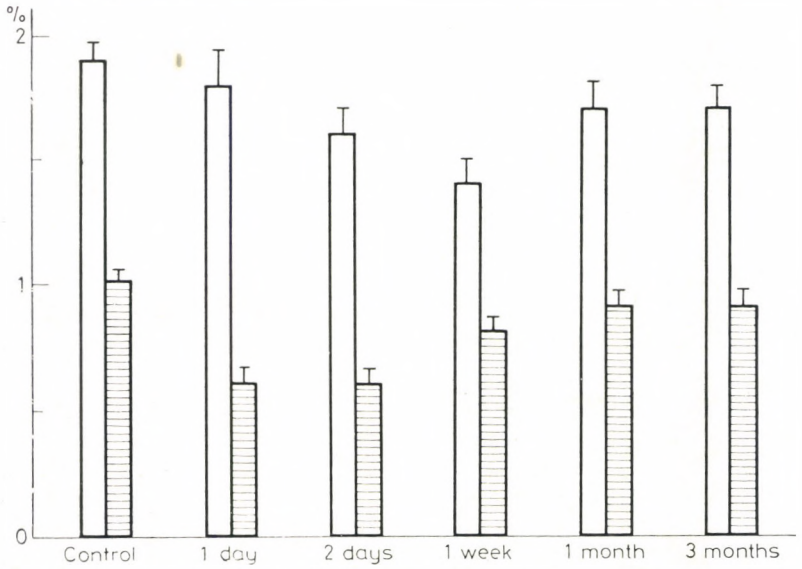
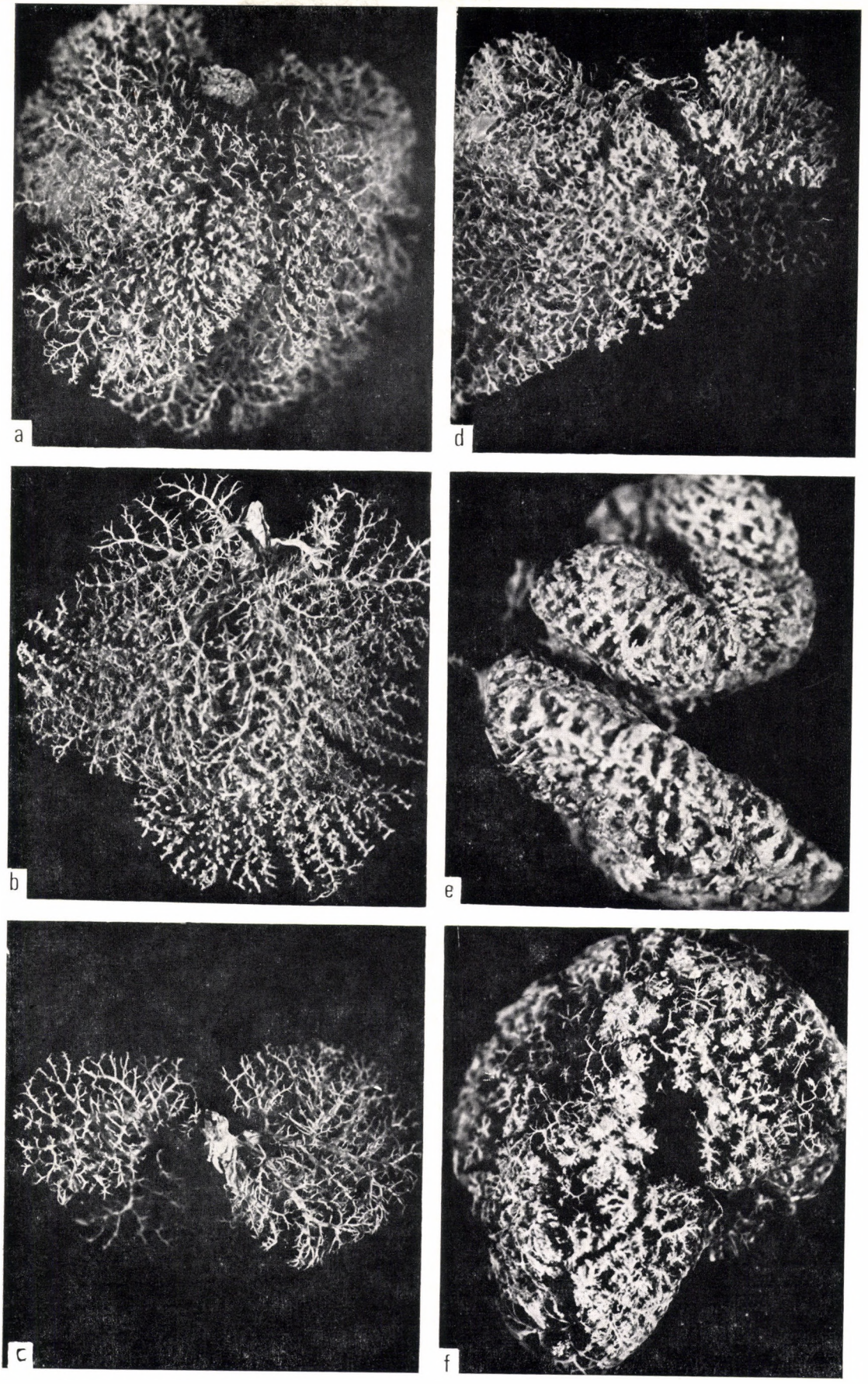


Fig. 34. The weight of the vascular casts expressed as percent of the whole liver weight (vascular capacity). The columns indicate the vascular cast/liver weight ratio in percent for the hepatic (empty bar) and portal (shaded bar) venous systems, respectively. The time elapsed between operation and sacrifice is shown on the abscissa. Each column indicates $\bar{x} \pm$ SD of 10 measurements

Fig. 35. (a) PVC cast of the portal vein of the liver of a control rat; (b) PVC cast of the portal venous system of the two large lobes to be resected first; (c) PVC cast of the portal venous system of the four smaller lobes remaining after the first resection; (d) portal cast of the four regenerated smaller lobes of a rat liver subjected to one resection 4 weeks earlier; (e) portal venous cast of the remaining, regenerated smaller lobes of a rat liver subjected to two resections 8 and 4 weeks earlier; (f) portal venous cast of the remaining regenerated lobe of a rat liver subjected to three resections 12, 8 and 4 weeks earlier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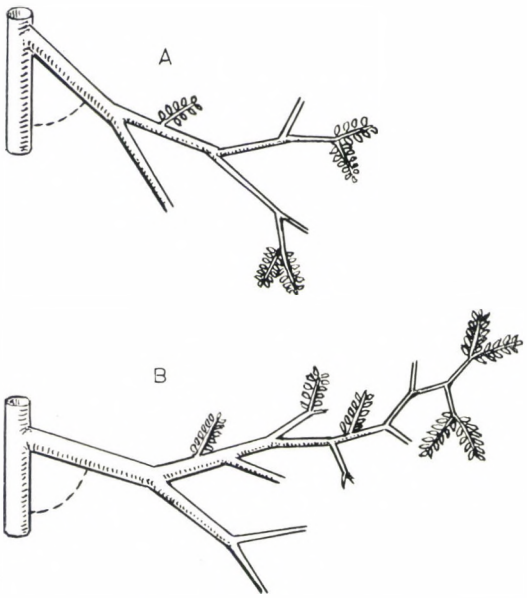


Fig. 36. Confluence of the caudal vena cava and lobar hepatic vein; the number of divisions of the lobar hepatic vein in control (A) and regenerating (B) rat livers

Characteristic changes in the shape of the liver were observed during regeneration. Figure 35 shows the relatively scarce branches of the corroded portal venous cast of a control liver (a), of the two large lobes to be resected (b) and of the remaining four smaller lobes (c). The lobes are thin and have sharp edges. The remaining four smaller lobes of the rats subjected to one resection had still sharp edges but their portal casts were bulkier with more abundant ramifications (d) 3–4 weeks after operation. The corroded portal venous casts of the livers from animals subjected to two (two lobes remain), or three (only one lobe remains) resections became dense 3–4 weeks after the last resection. The weight of the remaining lobes roughly approached in these cases the initial estimated weight of the whole liver, the lobes had blunt edges and the shape of the original lobe was no longer identifiable (e,f).

The length, width and thickness of the lobes were also changing during regeneration. It is a characteristic phenomenon, that the angle of confluence of the hepatic vein with the inferior vena cava and the angle formed by the first dividing trunks of the portal vein are larger in the regenerating liver (Ungváry et al. 1969b).

On the portal vein along the longest possible course down to the sinusoids 6–7 divisions were found in the control group, while 9–10 divisions were observed in animals 3 months after one liver resection. The number of side branches joining the hepatic vein from the sinusoids to the inferior vena cava is similarly higher in regenerating than in control livers (Fig. 36). In other words, not only the length and calibre of the vessels increased during regeneration, but also the number of divisions. At the same time the sinusoids emerge not only at the 9th to 10th division as usual, but near the hilum branches of the 3rd to 4th order or at the periphery of 5th to 8th order will already divide into sinusoids.

The number of the Rappaport's simple liver acini increased (Ungváry et al. 1969a, b).

4.5. Changes in the histo-functional units of the liver during regeneration

Stereomicrophotographs of the portal venous and hepatic venous casts of livers from animals subjected to one or two resections are shown in Fig. 37 with the same magnification. Figures a through c show the tufts of the portal venous system, which become bigger with increasing number of resections (portal lobule = zone Z_1 of the Rappaport's simple liver acinus, when a 5% PVC solution is injected). Figures d through f demonstrate the hepatic venous system. The expansion of the region of the central and sublobular veinlets is conspicuous (under the region of central and sublobular veinlets the particular vessels and all the entering sinusoids are meant, the region corresponds to the zones Z_3 of a few Rappaport's simple liver acini, when a 5% PVC solution is injected). The hypertrophy and the rising number of acini, or lobules during regeneration means at the same time that the simple liver acini develop into complex ones. The vascular casts and the intrahepatic vascular distribution pattern visualized by means of benzidine reaction (the extremely long sinusoids – Fig. 38) of the livers from animals undergone two or three successive resections (Fig 37 c, f) resemble the hepatic vasculature of animals (fish, frog, lizard, chicken) standing at a lower level of phylogenesis (Figs 116, p. 197, 117, p. 197, 118, p. 198). Figure 39 shows the region of the central vein in the hepatic venous cast of a rat subjected to three successive resections. This region corresponds to the centrolobular area of the Kiernan's lobule. The elongation of the sinusoids is conspicuous, some of the elongated sinusoids are able to form later a central or sublobular vein (Ungváry et al. 1969a, b).

The portal venous and hepatic venous casts of the regenerating lobes showed only slight qualitative changes in spite of the gross quantitative changes. Vascular casts or thick preparations injected with a mixture of India ink and gelatin in case of mature regenerates hardly revealed that the preparation was derived from a regenerating liver. It is remarkable, however, that areas intersected by conducting veins and supplied by perforating twigs of the marginal vessels (inlet veins) from adjacent regions can more often be observed. The difference between control and experimental pictures is much more striking in the early stages of regeneration when hepatic cell plates with two or more cell layers resembling the embryonic structure can be observed.

At some places the extensive proliferation of the hepatocytes may result in the production of nodules, into which blood vessels do not enter. Except for these hyperplastic nodules the Rappaport's acini can be found everywhere in the regenerating liver, though irregularity and complexity may increase. The presence of Kiernan's lobules is characteristic of the completion of regeneration only in the final stage when the one-cell-thick hepatic plates are present again and the vasculature has already completed its development. One should add that the Kiernan's lobules are considerably distorted and much larger than in the controls. The acinus is the universal, regular unit present during regeneration in the same way as in embryonic life (Ungváry et al. 1969a).

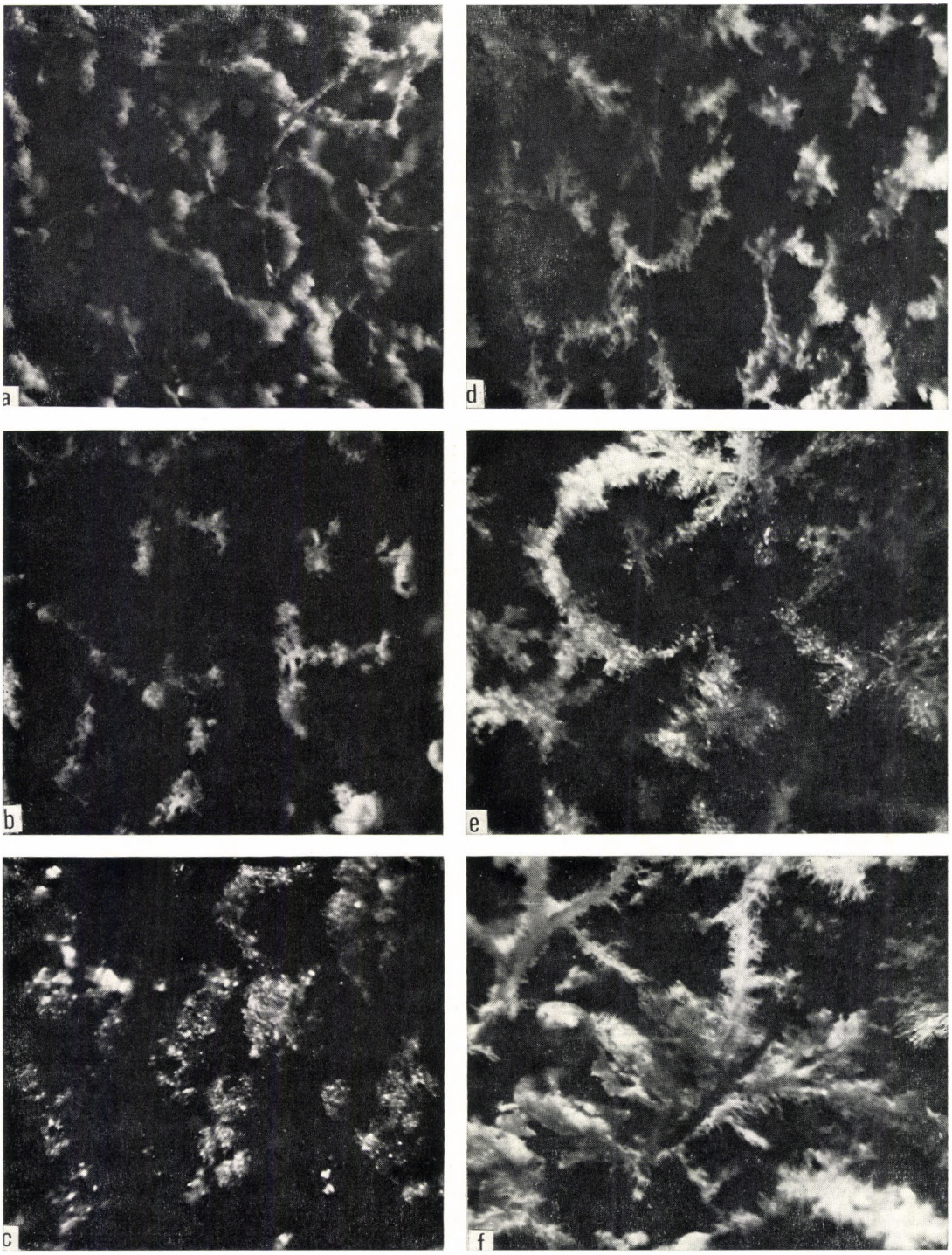


Fig. 37. Stereophotomicrograms of the portal (a, b, c) and hepatic venous casts (d, e, f) of the livers of rats subjected to no, one, or two resections, respectively. Each $\times 50$

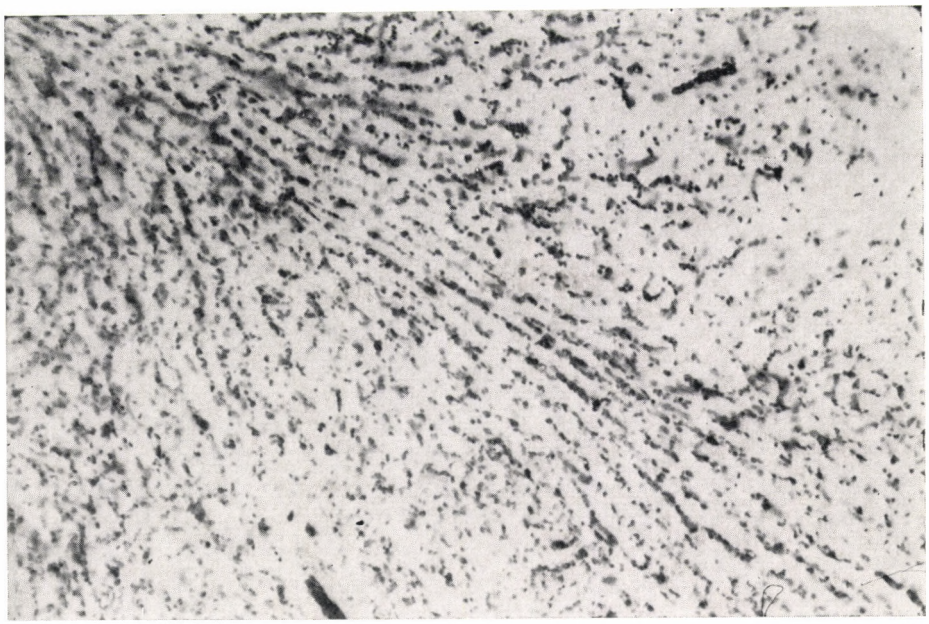


Fig. 38. Benzidine reaction in a rat liver subjected to two resections. Extremely long sinusoids are shown along the diagonal. ×140

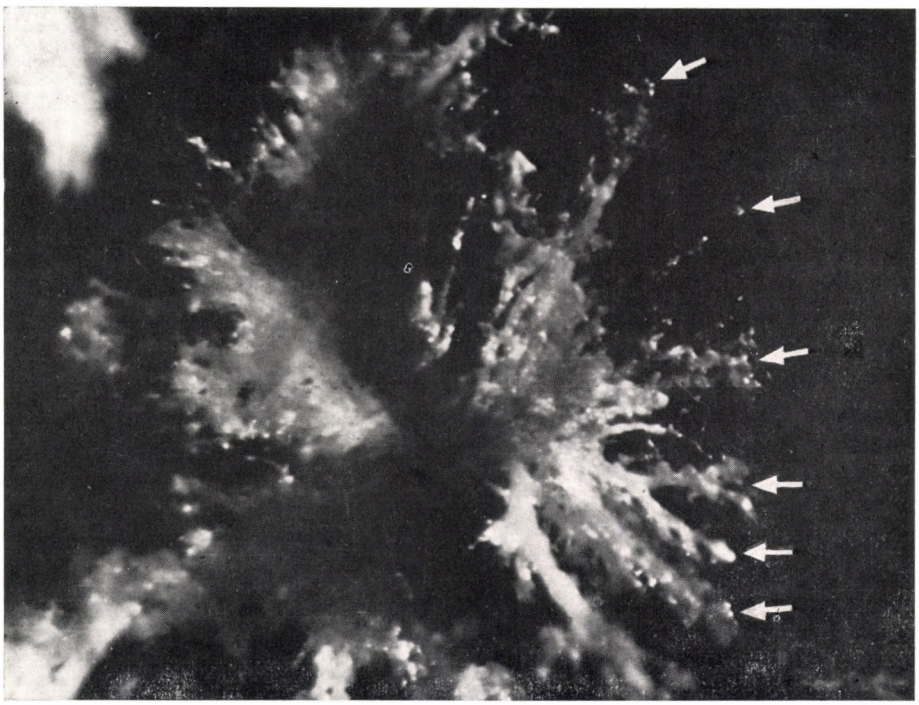


Fig. 39. PVC cast of the hepatic venous system of the regenerated liver of a rat subjected to three successive resections. The region shown corresponds to the centrolobular area of a Kiernan's lobule. The arrows indicate the branching and elongation of the sinusoids. ×88

4.6. Development of the histo-functional units of the liver

Histologists and pathologists regard even nowadays the Kiernan's lobule as the structural unit of the liver in spite of the fact that the knowledge of the Rappaport's liver acinus may offer a good explanation for the localization of a number of pathological changes actually or presumably connected with hepatic circulation. The reason may lie in the regular geometry of the Kiernan's lobule by means of which one can always easily find orientation in the histological sections. One should emphasize, however, that this statement is only true for the histological sections, because by in vivo transillumination only acini and no Kiernan's lobule can be observed (Wakim and Mann 1942, Knisely et al. 1948, Irwin and MacDonald 1953, Rappaport et al. 1954, Rappaport and Hiraki 1958a, b, Bloch 1970, Rappaport et al. 1970). In the same way Rappaport's simple liver acini cannot be seen either in normal histological sections (Rappaport el al. 1954, Rappaport 1958, Barone 1958, Rappaport and Hiraki 1958a, b). Recently, Ho and Ma (1972) showed that the hexagonal lobular pattern of intrahepatic structure, suggested in histological sections, could be seen in the transilluminated liver in situ; however, as far as we know their results have not been confirmed so far. On stereomicrophotographs taken of corroded portal venous casts, the terminal portal branch forming the axis of Rappaport's simple liver acinus together with the best supplied Z_1 and part of the Z_2 zones can be observed. Thus, the portal tufts correspond to zones Z_1 and Z_2 Rappaport's acinus. The empty spaces between the tufts correspond to the abaxial half of zone Z_2 and to zone Z_3 where the central veins and the larger efferent vessels run. The tufts of the hepatic venous casts represent zones Z_2 and Z_3 of at least 4 to 6 adjacent acini. The adaxial half of zone Z_2, zone Z_1 and the portal vessel are located between the empty spaces of the hepatic venous tufts. All the above findings can be well illustrated on the casts corroded after double filling (Figs 103 and 104, p. 188). From the definition of Rappaport's simple liver acinus it follows that it amounts to $2\times{}^1/_6$ of the Kiernan's lobule. This is, however, true only when the conditions are given for the formation of the Kiernan's lobule. It is a generally accepted view that the sucking effect of the negative intrapleural pressure is an important factor in the development of the lobular structure of the liver, as it begins to develop only when respiration has already started (Braus 1924, Pfuhl 1939, etc.). Nevertheless, this factor cannot be the only cause. Our studies have shown that neither in the fetal nor during a shorter or longer postnatal period is the presence of the Kiernan's lobule a general feature (Ungváry 1967). Toldt and Zuckerkandl (1932) could not find Kiernan's lobules even in the liver of porcine fetuses, in which species the lobules become ensheathed later by a capsule of connective tissue. It is not easy to understand how the sucking effect of the vena cava could affect the liver structure since the pressure in the vena cava varies between $+2$ and -2 mm Hg. This means that at a pressure of $+2$ mm Hg the clamping of the portal vein and hepatic artery (the pressure in the afferent vessels will equal zero) would result in the reversal of blood flow, i.e. the blood of the inferior vena cava would enter

the central veins and sinusoids (Barone 1958). According to Elias and Sokol (1953), the structure of the Kiernan's lobule is maintained by the normal pressure difference between the portal vein and the hepatic vein–inferior vena cava. Its decrease results in the inversion of the lobule, described by them. The investigations of Barone (1958), Barone and Batolo (1958) support the role of the portacaval pressure gradient. In adult mammals and in man the portal venous pressure amounts to 8–10 mm Hg (Demling 1963, Nakata 1967, Ungváry et al. 1969c), the portacaval pressure gradient to 6–12 mm Hg, respectively. The venous pressure in the inferior vena cava of the fetus is about 0 mm Hg and is no subject to respiratory fluctuations. The pressure in the umbilical vein of the fetuses was found to be 6–15 mm Hg (Mann 1970) which means that the umbilicocaval pressure gradient in the fetus does not differ much from the portacaval pressure gradient of the adults. Thus the portacaval pressure gradient in itself does not seem to be the factor of unique, crucial importance in the development of the structure of the Kiernan's lobules. Our investigations of both fetal and regenerating livers indicate that the appearance of the lobules coincides with the completion of the development of the terminal acini. At that time only sinusoids arise from the axial vein of the acinus, which is usually the circumlobular portal vein, and the axial veins have already outlined the hexagonal structure. The preterminal portal vessels divide at a single point into three terminal branches at angles of 120°. Perhaps the most important fact is that at the time of the appearance and increasing prevalence of the Kiernan's lobules only the one-cell-thick hepatic plates are present. Presumably the more rigid, two- or more-cell-thick hepatic plates cannot be arranged into lobules under the influence of the otherwise similar portacaval pressure gradient. On the other hand, the same pressure gradient is capable of arranging the more malleable, only one-cell-thick hepatic plates. From all these one can conclude, that the acinus is the real permanent unit of the liver and that the presence of the Kiernan's lobule indicates only a functional state, which is characteristic of the histology of a liver with normal circulation (Ungváry 1967, 1971).

4.7. Correlation between the regeneration of the intrahepatic vessels and the liver parenchyma

The disorders of liver function following partial hepatectomy do not interfere with the animal's survival. The most important results of the studies on liver regeneration are the recognition of its mighty capability for regeneration, its great functional reserves and some observations of general biological importance. The pioneers in this field investigated the capacity of the liver for regeneration. First Cruveilhier (1829–1833) and later Podwyssozki (1886) gave account of liver regeneration. Ponfick (1890a, b), Meister (1894), Flöck (1895), Milne (1909) already performed partial hepatectomy. The most informative on the capacity of the liver for regeneration were the works of Mann (1921), Bollman and Mann (1936) who had removed a liver lobe in every 10th day in dogs. At the end of the experiment the weight of the remaining lobe exceeded that of the original whole liver. Recent works analysed mainly the rate of regeneration (Weinbren

1955, Czeizel et al. 1964, Jatropulos 1965, Preda et al. 1972, Karoń 1974), the factors influencing and regulating regeneration (Christensen and Jakobsen 1949, Bucher and Glinos 1950, Weinbren 1955, Fachet et al. 1963, Fisher et al. 1963, MacDonald et al. 1963, Fischer 1964, Bullough and Rytömaa 1965, Menyhárt 1971, Takata 1974, Weinbren et al. 1975), and fine ultrastructural and histochemical changes of the liver cells during regeneration (Bartók 1964, Bartók and Virágh 1965).

The investigation of vascular regeneration following partial hepatectomy was made possible by our quantitative injection–corrosion method, which enabled us to compare the rate of regeneration of the parenchyma with that of the vascular capacity, i.e. vascular regeneration (Ungváry et al. 1969b).

The change of wet liver weight in our study roughly agreed with that described in the literature. The rapid increase in weight as it is in every fast growing organ, tissue – e.g. in the kidney (Jerusalem 1963), muscle (Wendt 1952) during the development of hypertrophy – is probably due at least in part to an increase in the water content. Within 48 hrs (Zaki 1954), or 72 hrs (Harkness 1952) after resection, the remaining part of the liver contains a large amount of water.

Bartók and Virágh (1965) concluded that from the dark and light liver cells, seen electronmicroscopically during regeneration, the decrease in electron density of the latter is due to their greater water content.

Three weeks after operation the water content of the resected liver reaches the normal value and regeneration is completed (Harkness 1952, Zaki 1954, Czeizel et al. 1964). Our data are in accordance with these findings (Ungváry et al. 1969a, b).

Until the 7th day a rapid then later a further, slower increase in the vascular capacity of the hepatic venous system was observed. When comparing these changes with the changes in liver weight, it becomes apparent that there is a relative insufficiency, the most pronounced on the 7th day, of the hepatic venous system during the first days after resection.

A slower, a faster and again a slower increase of the portal venous capacity were seen during the first two days, between days three and seven and thereafter, respectively. In spite of the relatively increased blood supply at the beginning, the resulting portal venous capacity of the remaining small four lobes seems to be even less than in normal, a maladaptation probably due to the high water content of the surrounding parenchyma and vessel walls. It is interesting to compare our data with those of Menyhárt and Simon (1966). They had shown that the liver weight was 55 and 75%, 24 and 72 hours after resection, while at the same time the increase in vascular resistance amounted to 65 and 55%, respectively. The increase in weight was not followed by a corresponding change in resistance, a phenomenon which can be well explained by the slower increase of vascular capacity. (There are no sinusoids between the layers of the two- or several cell-thick hepatic plates.)

There are a number of hypotheses to explain the homeostasis of the liver weight and the regulation of liver regeneration (Mann's "circulation" hypothesis – 1944; the feed-back regulation mechanism by Glinos – 1960; chalon theory by Bullough and Rytömaa – 1965). According to Mann's (1944) idea, multiplication of the liver cells is due to the passage of portal blood through a narrowed intrahepatic

space that would stimulate regeneration of the intrahepatic portal vessels resulting in the regeneration of the parenchyma. To the contrary, Child et al. (1953) and Weinbren (1955) have shown that regeneration proceeds also in the liver deprived of the portal venous supply. Of course one should not ignore the importance of the vasculature in the regeneration process. In our studies the nodules could never be filled up with plastics, which finding well explains the frequent presence of the necrotic areas in the regenerating liver. There is no doubt about the necessity of a qualitatively and quantitatively adequate vasculature during regeneration. Disorders in local blood flow would result in the necrosis of the hepatocytes. The results show that regeneration of the hepatic vessels and parenchyma cells is completed at the same time. The regeneration of the hepatic arterial system (Figs 46, 125, p. 202) was investigated by our team recently. Partial hepatectomy was performed in rats, cats and dogs. It was conspicuous that irrespective of whether the arterial or portal system of the regenerating liver was filled up with plastics of different colours, the spatial arrangement of the casts was the same indicating that the sinusoids in the acini were accessible by the portal or arterial approach alike. Predominance of the arterial system to such an extent can be termed as "regeneration arterialization". It can be assumed that the arterialization is attributable to the large number of arterioportal anastomoses present. Besides the steady function of the hepatic artery in controlling local blood flow of the acini and lobules in normal liver, the hepatic artery also controls segmental blood flow during liver regeneration via the dilated pre-existing and newly formed arterioportal anastomoses. In the casts of the mature regenerated hepatic vessels we cou'd not find more arterioportal anastomoses than in those of the controls (Ungváry et al. 1974a). During the "maturation" period of regeneration the blood vessels play an important role in the establishment of a dynamic equilibrium between the vasculature and the hepatocyte plates. Naturally, the new equilibrium may differ from the previous one (Ungváry et al. 1974a, b).

The characteristic changes in the shape of the lobes following single and multiple resections imply changes in the angularity of confluence and division of the hepatic blood vessels, with a concomitant change in blood flow (Ungváry et al. 1969a, b, Aronsen et al. 1970, Karoń 1974).

It has been shown by means of our injection–corrosion technique that the growth of liver tissue during regeneration consists of two components: 1. the formation of new acini, and 2. the hypertrophy of the existing ones (Ungváry et al. 1969b). Photographs of the hepatic vascular casts, especially those from the livers subjected to two successive resections, illustrate well the hypertrophy of the portal venous and hepatic venous lobules. The hypertrophy results in the significant elongation of the sinusoids which means that in larger portions of the liver the local blood flow became equivalent with the worst supplied third zone (Z_3) of the Rappaport's simple liver acinus. Zone Z_3 forms the outer shell of an ellipsoid or irregular body around the preterminal portal venule; under physiological conditions all the three zones are of about the same width; the volume of zone Z_3 is larger than that of the inner zone Z_1. In the regenerating liver the distance of a hepatocyte located on the shell farthest from the axis is much larger than in the normal simple liver acinus due to the longer sinusoid. For this reason it is

an open question whether from the point of view of metabolism and resistance to intoxications, etc., the situation of a liver cell in zone Z_3 of a regenerate is equivalent to a hepatocyte in zone Z_3 of a normal simple liver acinus. Only further experiments can decide the question. At any rate, during regeneration the liver responds to a functional load or vasoactive substances with altered reactions as compared to the control conditions. Drugs, such as hexobarbital, chlorpromazine, pethidine, etc., are significantly less well metabolized by the microsomal enzymes of the regenerating livers than by the livers of the control rats (Kaltiala 1970). While the infusion of noradrenaline (stepwise increasing the doses into the portal or femoral vein) decreases local blood flow in the liver of control rats, it increases local blood flow in the regenerating liver of rats 7 days after partial hepatectomy (Ungváry et al. 1975). The changed effect of vasoacting substances on local blood flow of regenerating liver will have disappeared by the time the regeneration of the parenchymal, vascular and neural structure is completed (Ungváry et al. 1969b, 1974a, b, 1975). One can assume, however, that the heterogeneity of the functional capacity of the hepatocytes in the different zones of a mature regenerate is greater than in a normal liver. Jatropulos (1965) showed by exact measurements that most frequently the distance between the Glisson's triad and central venule in normal livers varied between 370–420 μm. In liver regenerates this value was 460 μm and 490 μm on the 2nd and 10th postoperative weeks, respectively. Although Jatropulos observed a decrease in the diameter after the 20th week following operation due to the inadequacy of the methods used, he refrained to postulate that this decrease corresponded to the formation of the new lobules. Hyperplasia of the existing lobules had already been observed by a number of authors in earlier investigations (e.g. Bollman and Mann 1936). Our results show that the number of divisions along the portal vessel is significantly larger than in the normal controls. The first ramification along a portal vein which forms a lobule, i.e. which divides into sinusoids, is of the third or fourth order. Thus at the end of regeneration in a liver subjected to one resection a portal vein along its course has about 12–14 branches forming individual lobules. The corresponding value was 8 to 10 in normal controls. The counting of all portal lobules, complex lobules and acini was not performed, but we do not think it necessary for the unambiguous demonstration of the increase in the number of the portal lobules, acini (Kiernan's lobules, complex acini) (Ungváry et al. 1969a, b).

This conclusion was confirmed by the results of repeated resections. Figure 39 shows part of a growing Kiernan's lobule. A few sinusoids are longer than the adjacent ones, moreover, they have already given off a few twigs. Presumably, the new central venules are formed later from these veinlets, their branches becoming the sinusoids. The formation of the new liver structure which is similar to the original one with respect to the general presence of one-cell-thick hepatic plates and Kiernan's lobules in histological sections is connected with the regeneration of the hepatic vasculature. Besides the development of vasculature, the other factor of decisive importance in the intralobar distribution and drainage of blood in the regenerating liver is the multiplication and distribution of the new liver cells. With other words, the spatial distribution of the elements building up the liver has a major influence on intrahepatic local blood flow.

5. Terminal distribution of the hepatic artery in relation to the histo-functional units of the liver

One part of the hepatic arterial system supplies the tracts of the portal channel. Fine branches form an abundant, densely anastomosing capillary network around the biliary vessels (Figs 40, 119, p. 198), which is most pronounced in guinea-pigs. Other branches provide the less prominent vasa vasorum of portal and hepatic veins, which is substantially similar in all species (Figs 41, 42). The small veins arising in the portal channel drain into the portal vein, forming the internal roots of the portal vein. In another part, some terminal branches of the hepatic artery extend to the Glisson's capsule (Fig. 120, p. 199) and after supplying it, the arising small veins empty into the portal system. Most of the preterminal and terminal twigs of the artery (the third part of the hepatic arterial system) enter either directly the terminal portal venules surrounding the hepatic lobules or directly the sinusoids (Figs 120, p. 199, 121, p. 199).

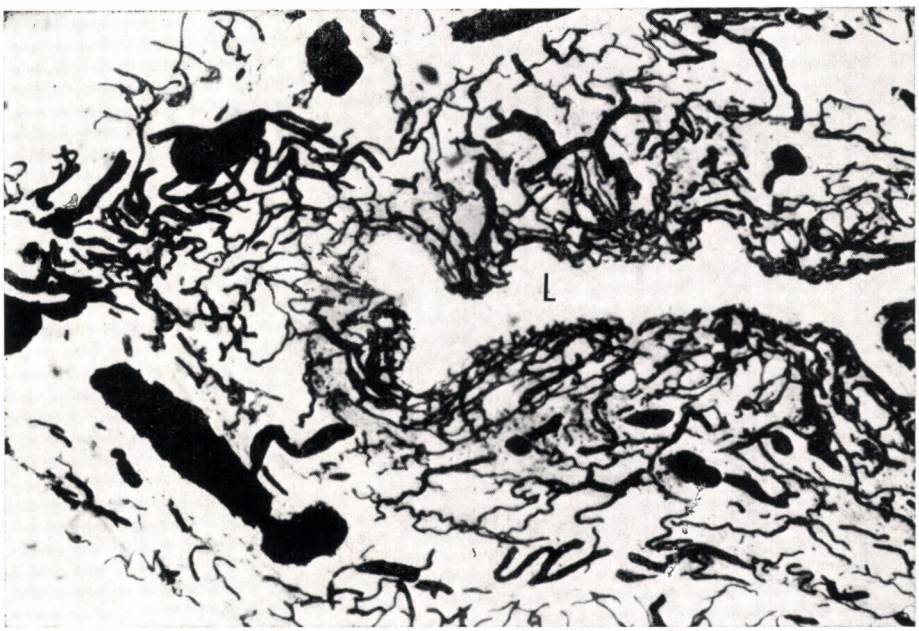


Fig. 40. Vasculature of the common hepatic duct. A dense capillary network can be found in the mucosa. 6% gelatin in India ink was injected through the hepatic artery. L — lumen. Rat. ×140

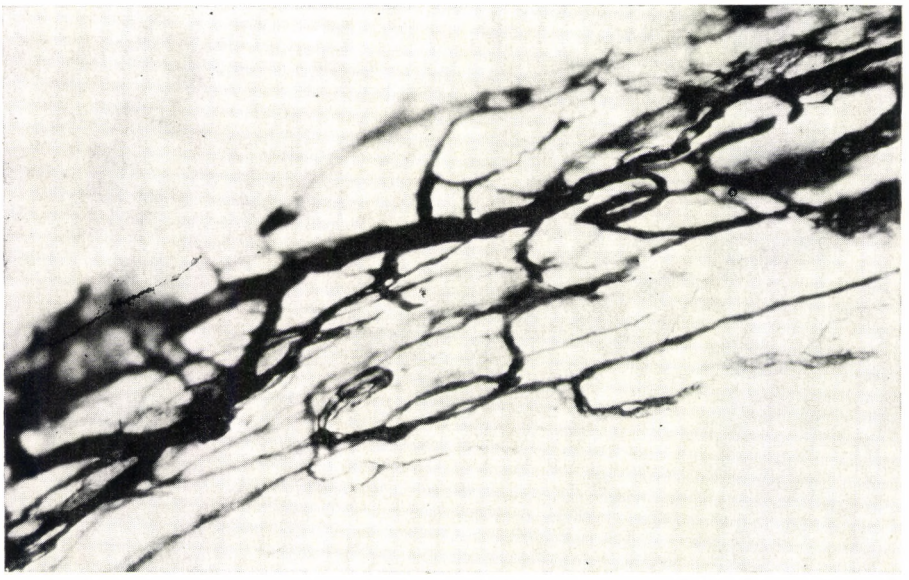


Fig. 41. Surface view of the vasa vasorum of the portal vein. Membrane preparation. Guinea-pig. 6% gelatin in India ink was injected through the hepatic artery. ×140

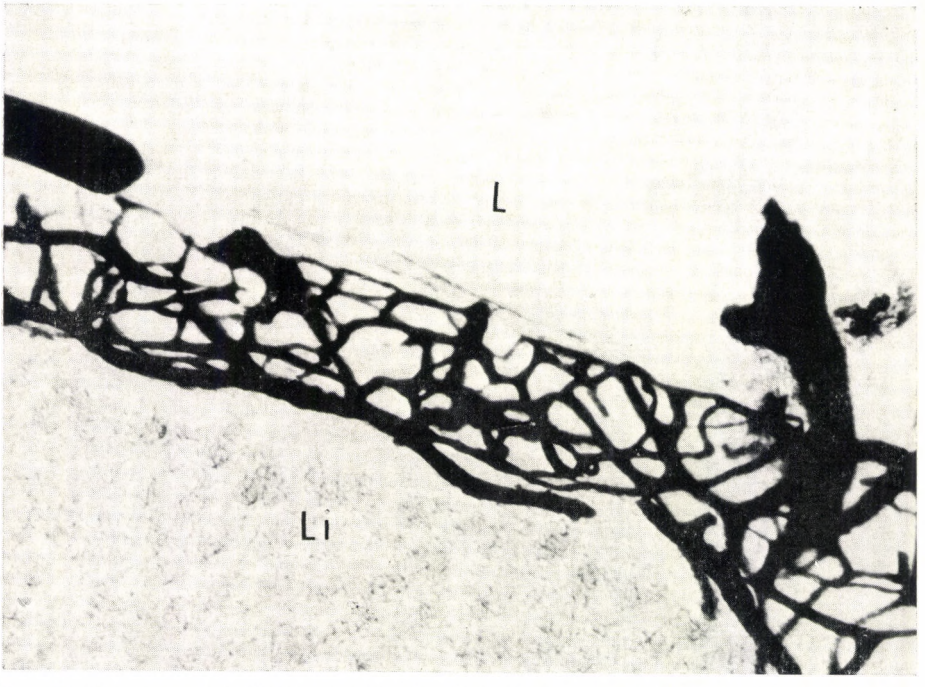


Fig. 42. Vasa vasorum of the hepatic vein. 6% gelatin in India ink was injected through the hepatic artery. L — lumen; Li — liver parenchyma; Cat. ×350

The arterial twigs join the portal venules at acute, right, or obtuse angles. Filling up the sinusoids through the arterial system results in a spotty distribution of the plastic, the spots comprise most often at least one simple or one complex liver acinus as a whole. Some of the acini are filled via the portal vein, while others via the hepatic artery (Fig. 121, p. 199). Filling up (inflow) from the arterial side is most often determined (controlled) within the inter- or circumlobular space. Preterminal branches of the hepatic artery may join the interlobular, seldom even larger portal branches forming thus the arterioportal anastomoses (Fig. 122, p. 200). We have observed two arterial twigs anastomosing in human material (arterio-arterial shunt). However, no direct anastomoses between the branches of the hepatic artery and hepatic vein (arteriohepatic shunt) could be demonstrated. The vascular pattern in the peri- and intralobular space is identical regardless whether the injection was given through the portal vein or the hepatic artery (Ungváry 1967).

5.1. Effect of hepatic artery ligature on the portal vascular capacity and on the histo-functional units of the liver

The portal casts of cats with ligated hepatic artery differs from that of the control one. In normal animals the vascular network is dense, the majority, about 60–80%, of the sinusoids are filled up (Fig. 43 a). In the portal casts of cats prepared 1 week after the ligation of the hepatic artery less, only about 25–45% of the sinusoids were filled up (Fig. 43 b). In some areas of the cast the presinusoidal blockade of the injected plastics, corresponding to the inlet sphincters, could distinctly be recognized (Nagy and Ungváry 1971).

In spite of the lack of a significant difference in the mean weight of livers or vascular casts the cast/liver weight ratio in the operated animals was significantly higher ($p < 0.05$) 1–2 hrs and significantly smaller ($p < 0.05$) 1 week after the ligation of the hepatic artery than in the controls (Fig. 44). Hence, there is a change in the number or in the volume of blood vessels filled per unit weight of liver tissue after the ligation of the hepatic artery, which means that an initial increase is later followed by a decrease in capacity (Nagy and Ungváry 1971).

Benzidine reaction revealed the regular Kiernan's lobules in the liver of a control cat (Fig. 45 a). With this reaction the lobule can be well divided into the circulatory zones of Rappaport's acinus. The benzidine reaction in the liver of a cat killed 1 hr after the ligation of the hepatic artery is astonishingly intensive. The sinusoids are dilated and the stain can be followed further in a section of the same thickness than in the controls. The regular lobular structure can be well recognized (Fig. 45 b), the sinusoids show radial arrangement around the central hepatic venule. The circulatory zones of the liver acinus, described by Rappaport, are levelled up and become indistinct (Nagy and Ungváry 1971).

Three weeks after the ligation of the hepatic artery a number of collateral arteries reach the liver through the falciform and hepatoduodenal ligaments or through the adhesions (Fig. 123, p. 200; Nagy and Ungváry 1971).

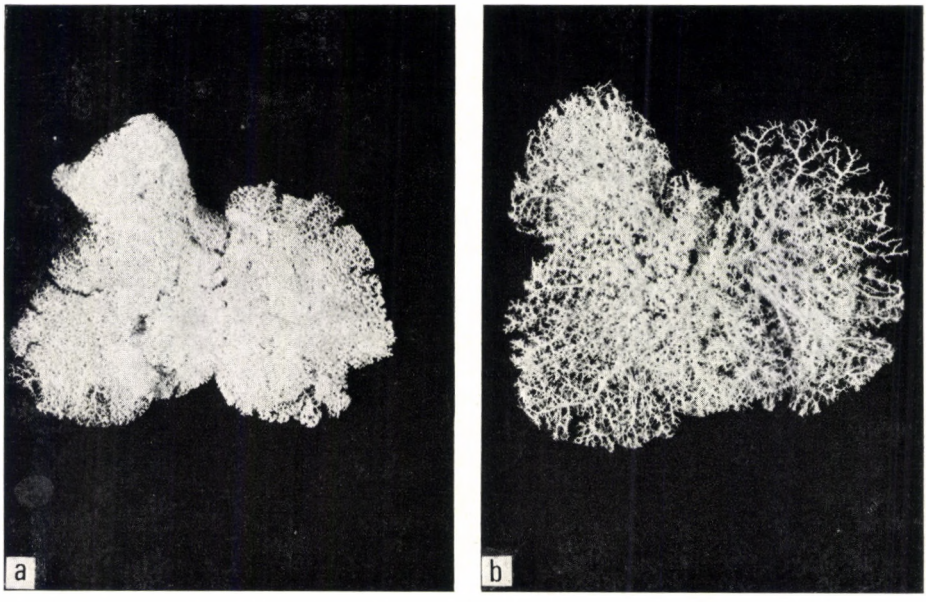


Fig. 43. Corroded vascular cast. Cast of the portal venous system from the liver of a control cat (a); cast of the cat portal venous system made one week after the ligature of the hepatic artery (b)

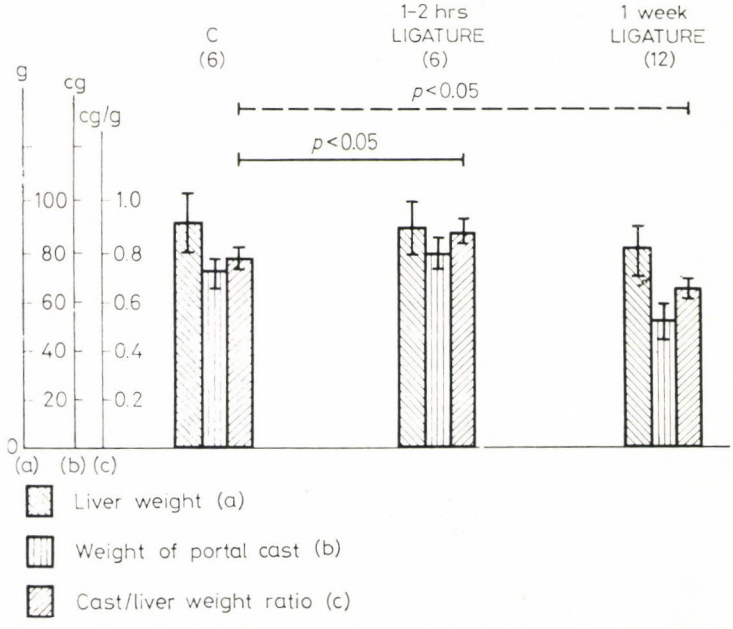


Fig. 44. The time elapsed after ligation of the hepatic artery is shown on the top. The liver weight (g), the weight of the portal cast (cg), the cast/liver weight ratio (cg/g) are scaled on the ordinate. The number of animals used in the experimental groups are shown in parentheses. Columns represent $\pm$SEM

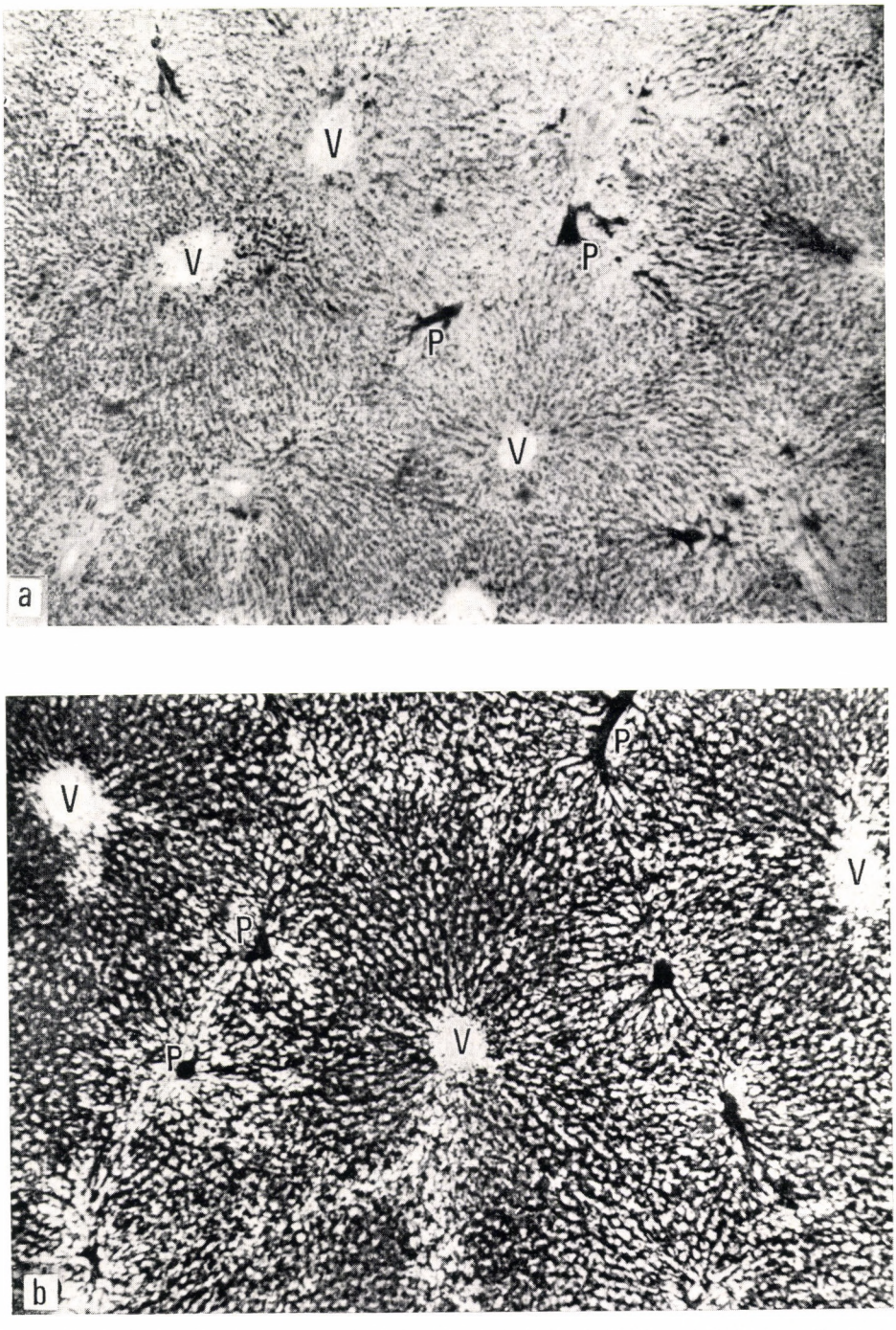


Fig. 45. (a) Liver of a control cat. (b) Liver of a cat subjected to ligation of the hepatic artery 1 hr earlier. Central venule (V); portal venous twigs (P). Benzidine reaction. × 50

5.2. The effect of portal constriction on the terminal division of the hepatic artery

Injection of red plastic through the hepatic artery and blue PVC through the portal vein, following the prior constriction of the portal vein, results in strikingly more red details on the cast (Fig. 124, p. 201).These red details correspond to bulky tortuous arterial branches under the stereomiscroscope (Figs 124 a, b, p. 201), a finding similar to that seen in cirrhotic livers. Following the pattern of ramification of the arteries, from the first branch on the hepatic artery in a lobe along its longest possible course down to the sinusoids, one can observe that no new twigs arise, but the already existing arteries become considerably dilated. Thus, filling of the sinusoids through the artery can be achieved much more often than in the control material. The sinusoids through the artery can be filled not only near the liver surface but in the deeper regions as well.

5.3. *The intermittent function and regulatory role of the terminal branches of the hepatic artery*

Injection technique alone is not sufficient for the complete description of the termination of the hepatic artery. Contradictory results in the earlier literature are partly due to the shortcomings of the method and partly to the lack of sufficient information until recently. Up to the second half of the 1960s, when a number of vital microscopic observations on hepatic circulation were published, most authors did not count with the presence of inlet sphincters of inlet venules, with the inlet and outlet sphincters of sinusoids at their portal and central endings, respectively, as well as with the sphincters of arterial twigs entering the sinusoids or portal venules (Irwin and MacDonald 1953, McCuskey 1966, Bloch 1970, Rappaport et al. 1970). The open or closed state of the sphincters naturally affects the outcome of injected preparations (Fig. 125, p. 202). It is reasonable to ask how could the presence of sphincters have escaped recognition for such a long time? The answer is very simple on the one hand, but it raises many further still unsolved questions, on the other. Namely, the endothelium and Kupffer's or stellate cells, present in the liver sinusoids, are unsuitable for sphincter function as far as their morphology is concerned. Simone (1965) proposed that the endothelium and Kupffer's cells are not different. On the basis of electron microscopic investigations Schmidt (1960) dinstinguished 3 and Schaffner et al. (1961) 5 types of these cells, but neither mentioned contractile cells. The presently more and more accepted view is that there is only one type of endothelial cells in the liver. These endothelial cells may contain different materials in varying quantity but they lack contractile elements. Furthermore, the cells at either end of the sinusoid are similar to those located in the centre (David 1964, Cossel 1964). The sphincters must have escaped attention because in the hepatic sinusoid they lack the usual morphological features of a sphincter.

Cossel (1968) suggested that circumscribed changes in the calibre of the sinusoids might arise from an active mobility and passive deformability of the endothelial cells, as well as from changes in volume of both the endothelial and parenchymal cells due to resorption and secretion. All these movements and changes are thought to be sufficient for evoking the changes in the sinusoid calibre, which seems to be rather random and irregular. Cossel (1968) did not see entirely closed sinusoids either in his own material or in other studies under the electron microscope. In his opinion all these data do not support the results of vital transillumination microscopy according to which 75% of the sinusoids do not function under physiological conditions (Wakim and Mann 1942). If this were true, he argues, one should see the distinct morphological correlate of the closed sphincters. Burkel (1970), when analysing the terminal hepatic arterial twigs, has found that the capillaries arising from larger arterioles have well-developed precapillary sphincters at their origin, whereas those arising from terminal arterioles have less prominent smooth muscle cuffs. He has pointed out that there are no smooth muscle sphincters at the terminal ends of the capillaries where they join the branches of the portal vein or sinusoids but large endothelial cells usually guard these junctions and frequently their nuclei bulge into the lumina of the vessels and may close them off. Though Knisely et al. (1948) as well as Seneviratne (1949/50) thought Wakim and Mann's value (1942) to be overestimated, they agreed that there is a significant fluctuation in the function of the sinusoids during openings and closures. It is a fact that has also been corroborated by a whole series of up-to-date transillumination studies made in vivo, that the activity of the arterioles and the endothelial inlet and outlet gates of the sinusoids is intermittent. The differences between the portal venous casts of unoperated controls and of animals subjected to hepatic artery ligation suggest a quantitative difference in the intermittent function of the sinusoids. For obvious reasons the sinusoids do not become filled when the inlet sphincter is closed and therefore the number of tufts seen becomes less (Ungváry 1967, Nagy and Ungváry 1971).

Considering the data obtained with intravital microscopy we can conclude that our results on the terminal distribution of the hepatic artery are valid only with a few reservations. We cannot determine whether the PVC or India ink used for injecting the vessel system has arrived into the specific sinusoid through an arterial twig directly, or from an arterioportal anastomosis through a portal venous twig, or from a dilated arterial capillary (internal root) also through the portal vein. The injection–corrosion, and the India ink injected thick preparations are capable of fixing and preserving only the actual functional state of the hepatic vasculature, but do not reveal all the possible intrahepatic routes of blood flow at the same time. This is the reason why the individual casts differ from each other even under standardized conditions.

There is no remarkable difference between the terminal distribution of the hepatic artery of the mammals studied. Our results obtained by means of the injection–corrosion and gelatin–India ink injected thick preparations support earlier results, that terminal branches of the hepatic artery enter either into the inter- or circumlobular portal venous twigs through arterioportal anastomoses resulting in a mixed arterioportal venous blood supply of the sinusoids, or enter

directly into the sinusoids. The closed or opened state of the arterioportal anastomoses and that of the precapillary sphincters determines the composition of the blood flowing or stagnating in the sinusoids. One can assume that the angularity of the arterioportal junctions may influence the proportion in which the arterial and portal venous blood are mixed. Kamenev (1938) calculated that mixing of the entering streams in a tube system with rigid walls is proportional to the cosinus of the angles formed between the two joining and the efferent tubes, respectively. All these data help to understand the result of Rees et al. (1964), or Hollenberg and Dougherty (1966) obtained by means of the radioisotope washout technique using ^{133}Xe and ^{85}Kr, respectively. ^{133}Xe and ^{85}Kr were introduced by infusion into the hepatic artery or portal vein and the disappearance rate of radioactivity was measured. Both isotopes were found to be washed out faster when given into the hepatic artery than after the injection into the portal vein. The authors concluded that the blood from the two vessel systems does not pass through the same sinusoid bed, thus there were at least two different routes for blood flow. On the basis of Bloch's (1970) in vivo observations and our findings showing that the casts of the terminal branches of the arteries do not always continue into sinusoids but fill up the sinusoids in a randomly occurring, "spotty" way, we can suggest that arterial blood does not pass through all the sinusoids of the liver at the same time, but only a part of it, depending on the open or closed state of the arterioportal and arteriosinusoidal (precapillary) sphincters (Fig. 125, p. 202). It might be possible that the ratio of sinusoids receiving to those not receiving arterial blood is about the same, but it is not at all probable that always the same sinusoids receive the arterial supply. Presumably, arterial blood flows in always different sinusoid spaces depending on the actual requirement. As regards the open or closed state of the sinusoids and terminal arterial branches, McCuskey (1966) attributed importance to metabolites formed during hypoxia or glycogenolysis. We are of the opinion, however, that beside the above factors the large number of autonomous catecholaminergic nerve fibres around the preterminal and terminal arteries as well as preterminal portal venous branches may be of importance in regulating the intermittent function of the acini and sinusoids and thus local hepatic blood flow (Ungváry and Donáth 1969).

Along the bile ducts there is a substantial arterial precapillary and capillary system, the plexiform network of which gives the impression that it has a regulating influence on the amount of bile secreted. This notion has been supported by Scholtholt and Shiraishi (1968) who showed that a prolonged infusion of acetylcholine and bradykinin will increase terminal pressure in the common bile duct only if injected into the hepatic artery. Presumably acetylcholine injection into the hepatic artery increases portal venous pressure through its branches to the wall of the hepatic and portal veins because no similar effect could be observed after a direct injection into the portal vein (Scholtholt and Shiraishi 1968).

The degree of arterial filling is much more pronounced after the double injection of the liver of animals with a previously constricted portal vein. We call the phenomenon arterialization after Hulten (1966) but here, in contrast to the cirrhotic as well as regenerating arterialization, no new arteries are formed (Fig. 46). The vascular pattern and the number of twigs along a branch of the hepatic artery

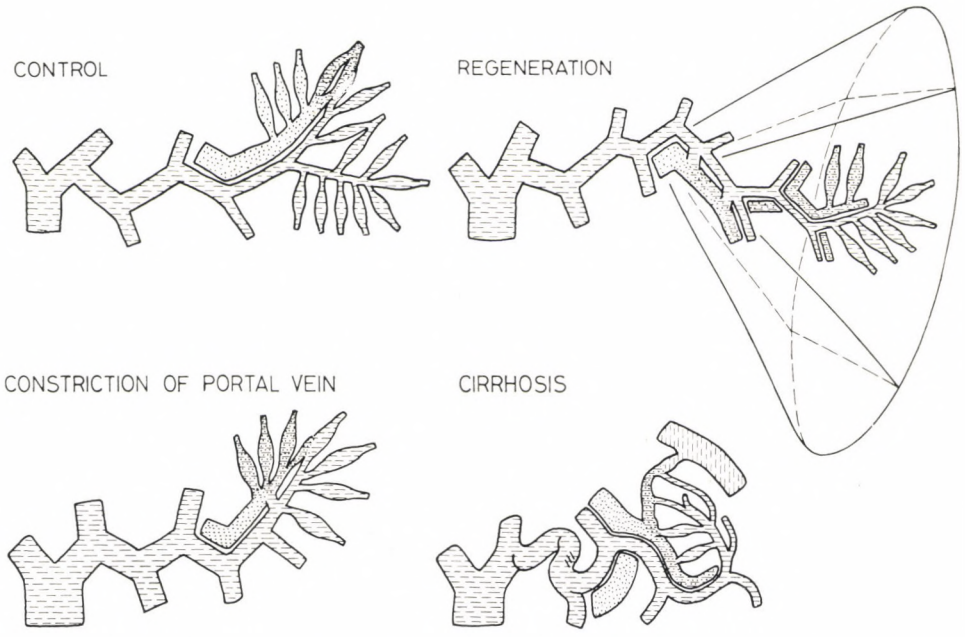


Fig. 46. Forms of the junction between the portal vein and hepatic artery under various conditions. Under control and regenerating conditions the distribution pattern of the portal venous and hepatic arterial systems are elucidated in detail in Fig. 125. Following the constriction of the portal vein the hepatic arterial system is dilated but there are no newly formed arterial twigs as in the regenerating liver. In the cirrhotic liver tortuous hepatic arteries are visible; some of the hepatic arterial twigs are newly formed. During regeneration, cirrhosis and constriction of the portal vein there are so-called arterialization, however, their mechanism and distribution pattern are different. Broken line area: — hepatic artery; dotted area: – portal vein; Broken line + dotted area: – joining of portal venous and hepatic arterial twigs

on its longest possible course down to the sinusoids varied between 6–8, similar to controls. The probable cause of arterialization is the dilatation of the arterial system; the arterial casts are bulkier and much more sinusoids can be filled from the arterial system than in the controls. The latter finding can be attributed to the opening of more arterioportal and arteriosinusoidal (precapillary) sphincters. It seems that larger portions of the liver are supplied by arterial blood after constriction of the portal vein than otherwise. The terminal distribution of the hepatic artery becomes more pronounced and better accessible to investigation after constriction of the portal vein (Nagy and Ungváry 1971). The possibility of the increase in the vascular capacity of the arterial tree offers a good explanation for the physiological phenomenon that in spite of a decrease in total hepatic blood flow the arterial contribution is increased (Fischer and Takács 1964).

The interrelationship of the hepatic artery and portal venous system and the mutual interdependence of their function deserves attention, too. For a long time species-specific differences had been supposed in the quality and quantity of the territories supplied by the hepatic artery. Fraser et al. (1951) were the first who succeeded in keeping dogs alive after the ligation of the hepatic artery. It became

clear that the dogs of earlier experiments subjected to the ligation of the hepatic artery died of septicaemia caused by anaerobic bacteria due to the lack of protecting antibiotics. The rat, cat and monkey usually survive the ligation of the hepatic artery without antibiotics, too. It is true, however, that oxygen concentration in the portal venous blood of the latter animals is normally higher than that of the dogs (Karn and Vars 1951, Wiles et al. 1952, McFadzean and Cook 1953, Payer et al. 1958). The ligation of the hepatic artery results always in hypoxaemia, which is not surprising since the main function of the hepatic artery is thought to be the maintenance of a satisfactory oxygen tension (Karsner and Ash 1912/13, Cameron and Mayes 1930, Krarup and Larsen 1974). We should start out from the phenomenon of hypoxaemia when we try to explain the increase and the decrease in portal venous capacity a few hours or one week after the ligation of the hepatic artery, According to the generally accepted view of physiologists, there is no increase in portal blood flow following the occlusion of the hepatic artery (Fischer and Takács 1964, Fischer 1964). Shoemaker and Itallie (1958) in dogs, Feruglio et al. (1966) and Hultman (1966) in man described a pronounced increase in hepatic blood flow after the administration of glucagon. Sutherland and Rall (1960), McCuskey (1966), Bloch (1970) have pointed out that upon administration of substances with glycogenolytic effect (glucagon, isopropyl noradrenaline, etc. and during glycogenolysis the adenosine molecule and potassium ions given off by the hepatocytes are capable of causing dilatation of the portal venules and sinusoids. Adenosine and potassium may leave the hepatocytes also due to hypoxaemic damage of the liver cells. The 20–40% oxygen deficit after the ligation of the hepatic artery (McMichael 1934) might cause vasodilatation in the portal venous system, at least shortly after the ligation of the artery. Our results with the benzidine reaction have demonstrated vasodilatation in the histological sections but this alone does not increase portal venous inflow. One can anticipate that blood flow in the hepatic artery not only supplies oxygenated arterial blood for maintaining necessary oxygen tension but it may also use its kinetic energy for accelerating blood flow in the portal vein and mainly in the sinusoids. This view is supported by the finding of Ternberg and Butcher (1965) who noted that a decrease in portal venous blood flow was followed by an increase in the blood flow of the hepatic artery, but a decrease of the hepatic arterial flow resulted in a concomitant decrease in the portal blood circulation. The authors explain this relationship between the two vessel systems by the mechanical resistance exerted by the slower stream in the way of the faster one. The occlusion of the hepatic artery results thus in a decrease in local blood flow which may later cause a decrease in portal capacity by directly damaging the portal system (Nagy and Ungváry 1971).

All the above data indicate that the hepatic artery because of its terminal distribution pattern may be one of the most important factors in the regulation of local blood flow in the liver. The changes in the calibre of the hepatic artery, in the anastomoses between the portal venous and hepatic arterial system, and in the precapillary sphincters of the hepatic artery, as it has already been mentioned above, may be regulated either by tissue metabolites (McCuskey 1966), or by direct neural influences.

6. Innervation of the liver and hepatic blood vessels

6.1. The wall structure of the largest hepatic blood vessels

6.1.1. The wall structure is different in the trunk of the portal vein, at the confluence of the common mesenteric and splenic veins, at the portal vein's division into primary trunks, and in the primary trunks (Fig. 47). The circular muscle fibres of the media at the confluence of the lienal and common mesenteric veins and at the division of the common trunk into primary trunks are surrounded by a layer of longitudinal muscle bundles running parallel with the axis of the portal vein in the inner zone of the adventitia. These longitudinal bundles are absent in the middle segment between the confluence and bifurcation on the ventral side of the trunk and are not present at all in the primary trunks (Ungváry et al. 1971b). The absence of the longitudinal muscle layer in the adventitia is much less extensive in cats and dogs than in guinea-pigs.

6.1.2. The histology of the wall structure of the common hepatic artery and its primary divisions shows no difference when compared to that of other arteries supplying other viscera, elsewhere in the organism. A great number of nerve fibre profiles can be observed in the connective tissue of the adventitia. Species-specific differences are only as regards the size of the artery.

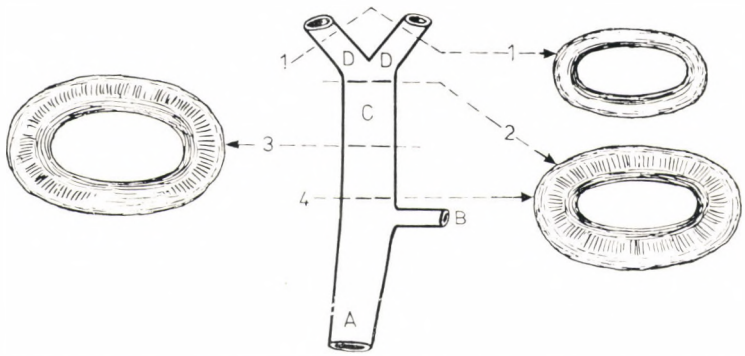


Fig. 47. Schematic layout of the wall structure of the portal vein in guinea-pigs. Common mesenteric vein (A); splenic vein (B); portal vein (C); primary trunks of the portal vein (D). The ventral sector of the vessels looks downward in the drawings. In cross section 1 there is only connective tissue in the adventitia and the media consists of a circular smooth muscle layer; in cross sections 2 and 4 there is a longitudinal smooth muscle layer of considerable thickness in the deeper layer of the adventitia; in cross section 3 the longitudinal smooth muscle layer is absent in the ventral part of the vessel wall

Fig. 48. Corroded PVC vascular cast of the hepatic venous system of a dog. 5% PVC was injected 3 min after the intravenous administration of 10 μg/kg b.w. histamine. A conspicuous helical impression is seen on the cast. ×22

6.1.3. There is a circular smooth muscle layer in the media all along the vessels of the hepatic venous system up to the junction with the inferior vena cava except for the central venules in which only a few muscle cells can be seen at random. In the adventitia powerful smooth muscle bundles in spiral or longitudinal arrangement can be observed. The musculature, first of all in dogs, is capable of functioning as a sphincter, and is affected by histamine for example (Fig. 48). Perhaps not only the large hepatic venous trunks joining the inferior vena cava but also the smaller branches of the hepatic venous system participate, in varying degrees, in this sphincter function depending on the species. The external layer of the adventitia consists of connective tissue.

6.2. Innervation of the portal vein and the trunks of the portal vein

The following observations were made on the trunk of the portal vein: positive acetylcholinesterase reaction was found only in a few nerve bundles containing preterminal fibres that run in the connective tissue of the adventitia (Fig. 49a, b). With the Coupland–Holmes (1957) acetylcholinesterase reaction no positive nerve fibres could be shown in the musculature even in guinea-pigs, who are known to have many acetylcholinesterase-positive fibres in the liver. Both muscle layers stain well by the reaction for non-specific cholinesterases (Ungváry et al. 1971b).

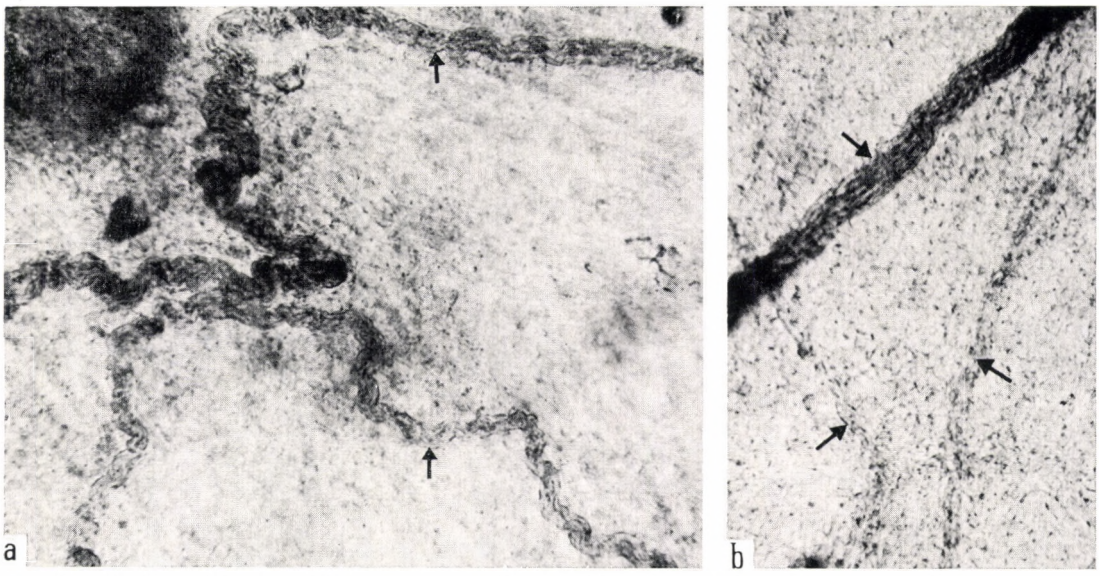


Fig. 49. (a and b). Acetylcholinesterase-positive bundles of nerve fibres in the wall of the portal vein of the guinea-pig; arrows indicate bundles of nerve fibres of different thickness in the adventitia. Stretched membrane specimen; Coupland–Holmes reaction; incubation for 6 hrs after 30 min preincubation with 10^{-5} M Iso-OMPA; pH 5.2; ×140

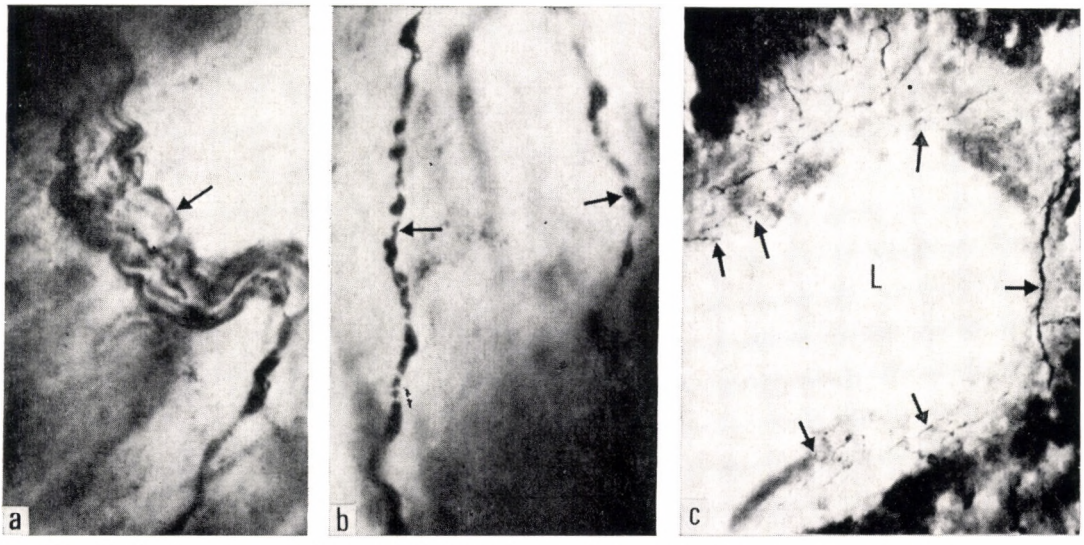


Fig. 50. Surface view of the zinc-iodide-osmium-positive nerve fibres in the wall of the portal vein of the guinea-pig. a (×500) and b (×800) arrows indicate the nerve fibres in the adventitia. Stretched membrane specimens. (c) arrows indicate the nerve fibres extending to the intima. L — lumen of the vein; Champy's method ×140.

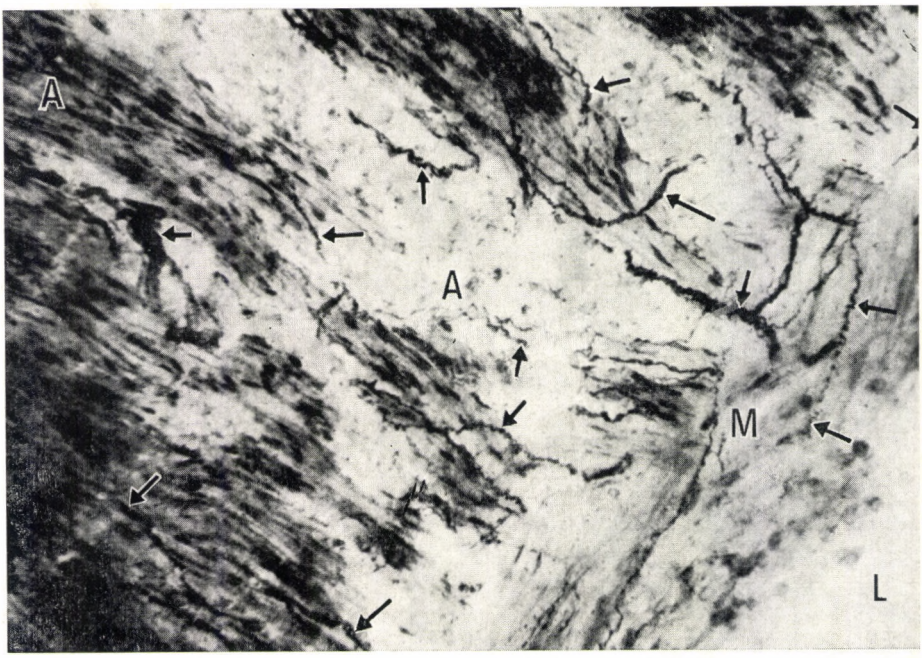


Fig. 51. Zinc-iodide-osmium-positive nerve fibres in the wall of the portal vein of the guinea-pig. L – lumen; M — media; A — adventitia; arrows indicate the zinc-iodide-osmium-positive fibres. Champy's method. ×350

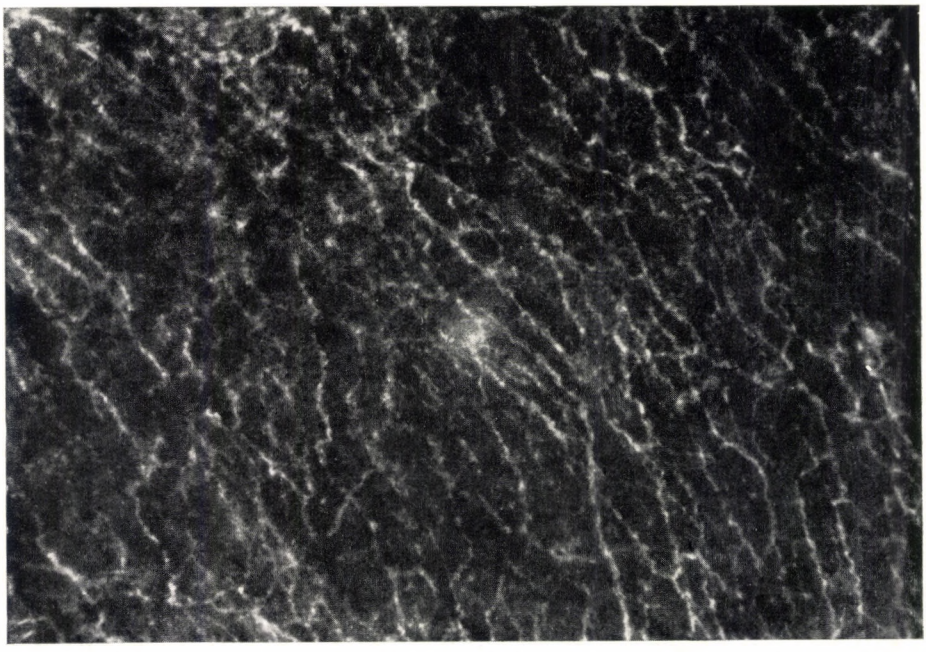


Fig. 52. Surface view of the almost entirely two-dimensionally oriented dense monoaminergic network of nerve fibres in the wall of the portal vein of the guinea-pig. Stretched membrane preparation. Paraformaldehyde reaction of Falck et al. ×180

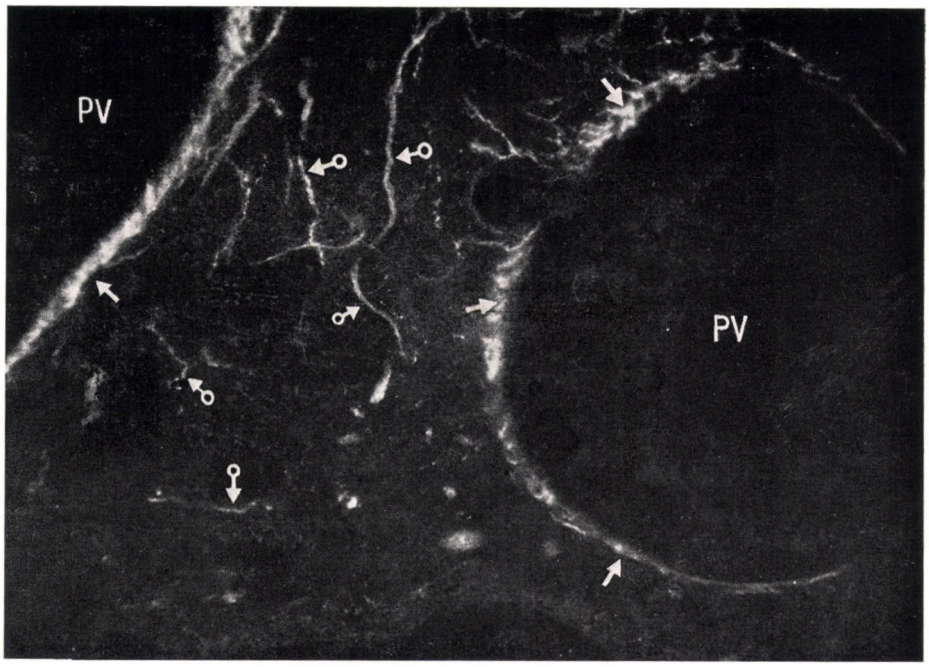


Fig. 53. Monoaminergic nerve fibres showing intensive fluorescence (→) at the margin of the media and adventitia of the portal vein of the guinea-pig; there are "free" monoaminergic nerve fibres (o→) between the two trunks of the portal vein (PV); cross section above the primary division of the vessel. Reaction of Falck et al. ×250

Some of the bundles and fibres detaching from larger nerve bundles can be stained with the zinc-iodide-osmium reaction (Fig. 50 a, b). These bundles and fibres run in the adventitia and give off only a few terminal fibres which pass further along the longitudinal muscle bundles of the adventitia. The majority of the fibres enter the longitudinal muscle layer and some of them even into the deeper zones of the media and reach almost the intima (Figs 50 c and 51). A great number of nerve fibres can be seen at the bifurcation of the portal vein (Ungváry et al. 1971b).

Detection of monoaminergic (noradrenergic) fibres by the method of Falck et al. (1962) calls attention to a remarkably rich monoaminergic innervation. The abundance of nerve terminals with characteristic fluorescence particularly at the origin and bifurcation of the portal trunk is comparable to that found in the iris (Fig. 52). The sections just at the division clearly show that the monaminergic fibres lie close on the media, between the media and adventitia and that only a few fibres lie "free" between the primary trunks (Fig. 53; Ungváry et al. 1971b).

Histochemical localization of the monoamine oxidase activity and of nerve terminals with catecholamine fluorescence overlap only within broader limits. An intensive monoamine oxidase reaction has been detected in the outer longitudinal muscle layer of the adventitia, while it was practically absent in the con-

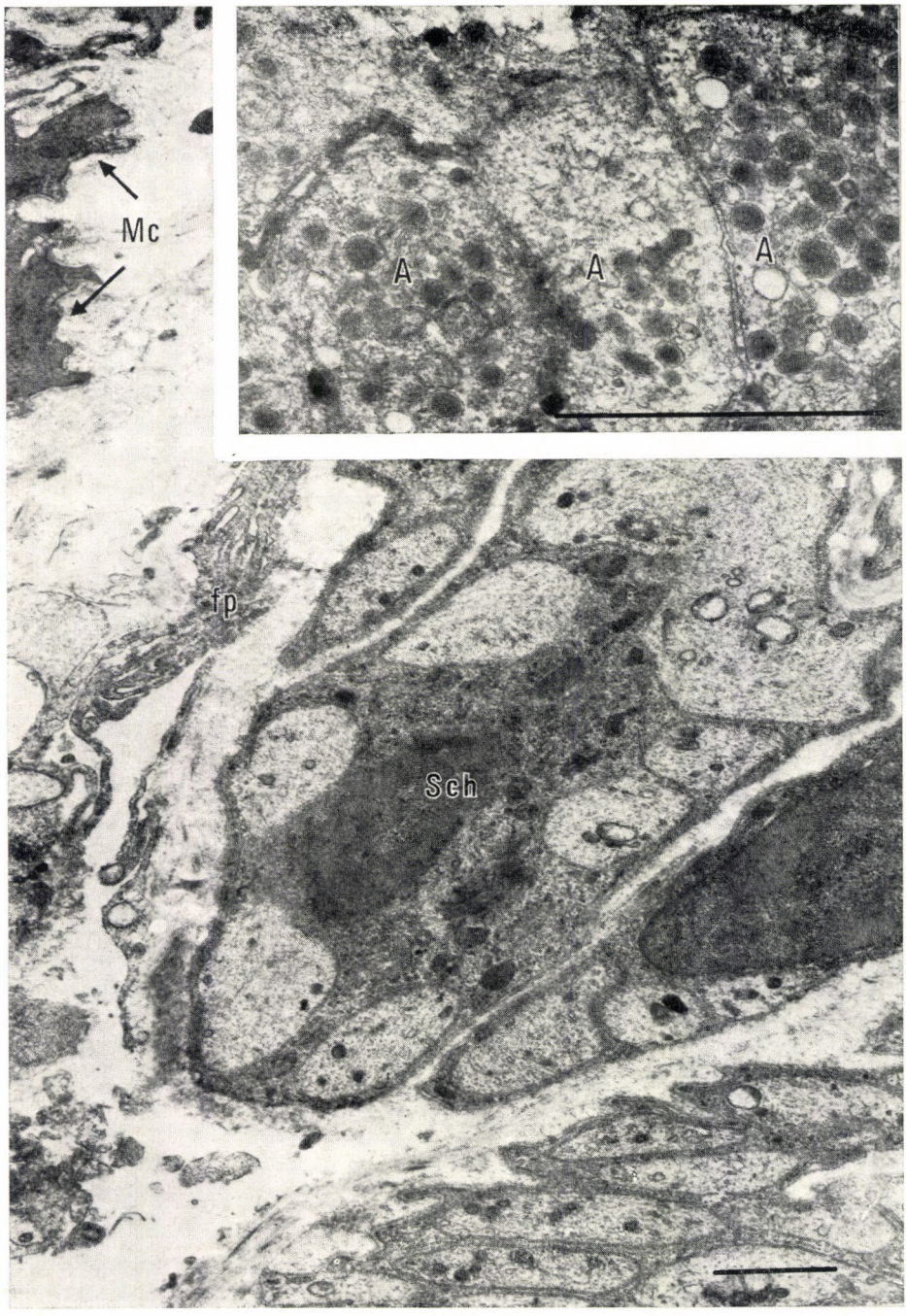


Fig. 54. Electron micrograph of the adventitia of the portal vein. Guinea-pig. Numerous axons are located in the cytoplasm of the Schwann cell (Sch). In the left upper corner a smooth muscle cell (Mc) is seen. The process of a fibrocyte (fp) penetrates between the muscle cell and Schwann cell containing the axons. Inset: Axons (A) with dense-core vesicles from another part of the adventitia. Both scales indicate 1 μm

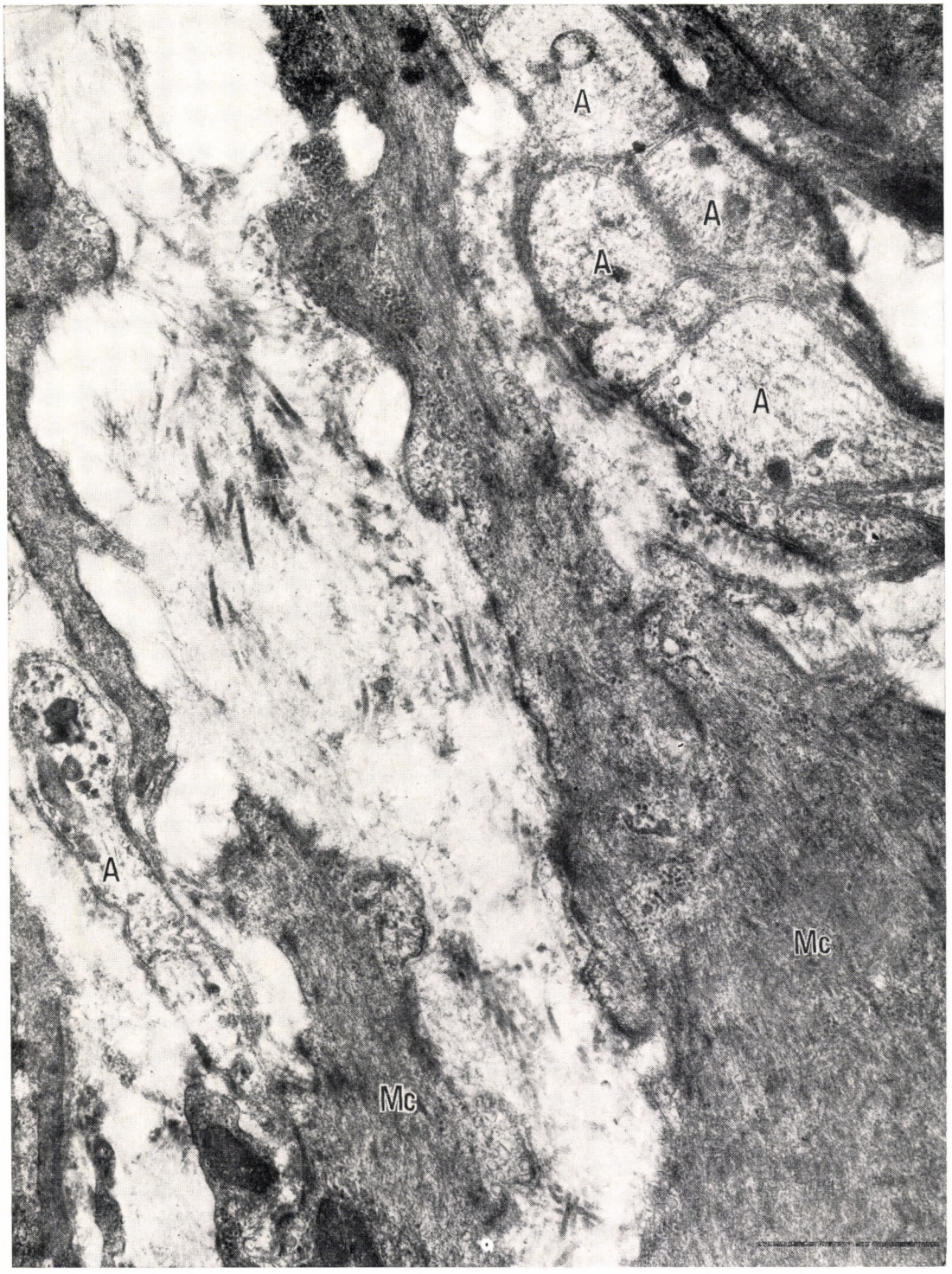


Fig. 55. Electron microscopic appearance of a part of the media of the portal vein of a cat. The axons (A) are contained within the Schwann cells between the smooth muscle cells (Mc). Axons in the upper right corner are in loose contact with the smooth muscle cells. The axon terminal in the left lower corner is only partly covered with Schwann cell processes. Scale 1 μm

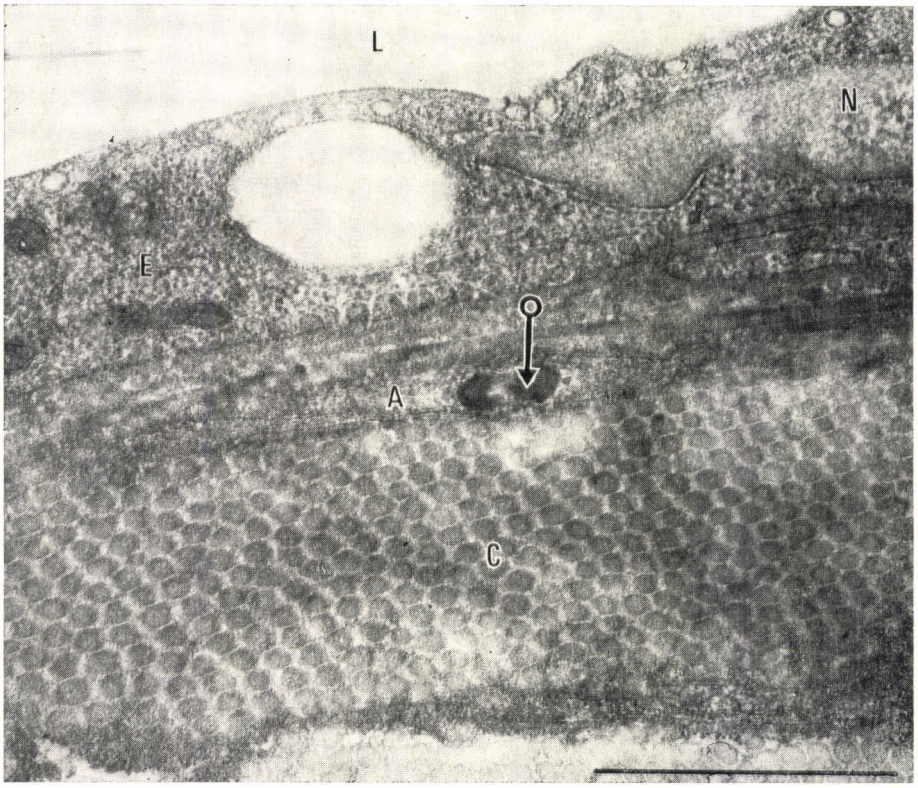


Fig. 56. Electron micrograph from the intima of the portal vein of a cat. There is an autophagous cytolysome (o→) in an axon (A) 48 hrs after extirpation of the spinal ganglia Th_6-L_2 on the right side. E — endothelial cell; N — nucleus of the endothelial cell; L — lumen; C — collagen space. Scale 1 μm

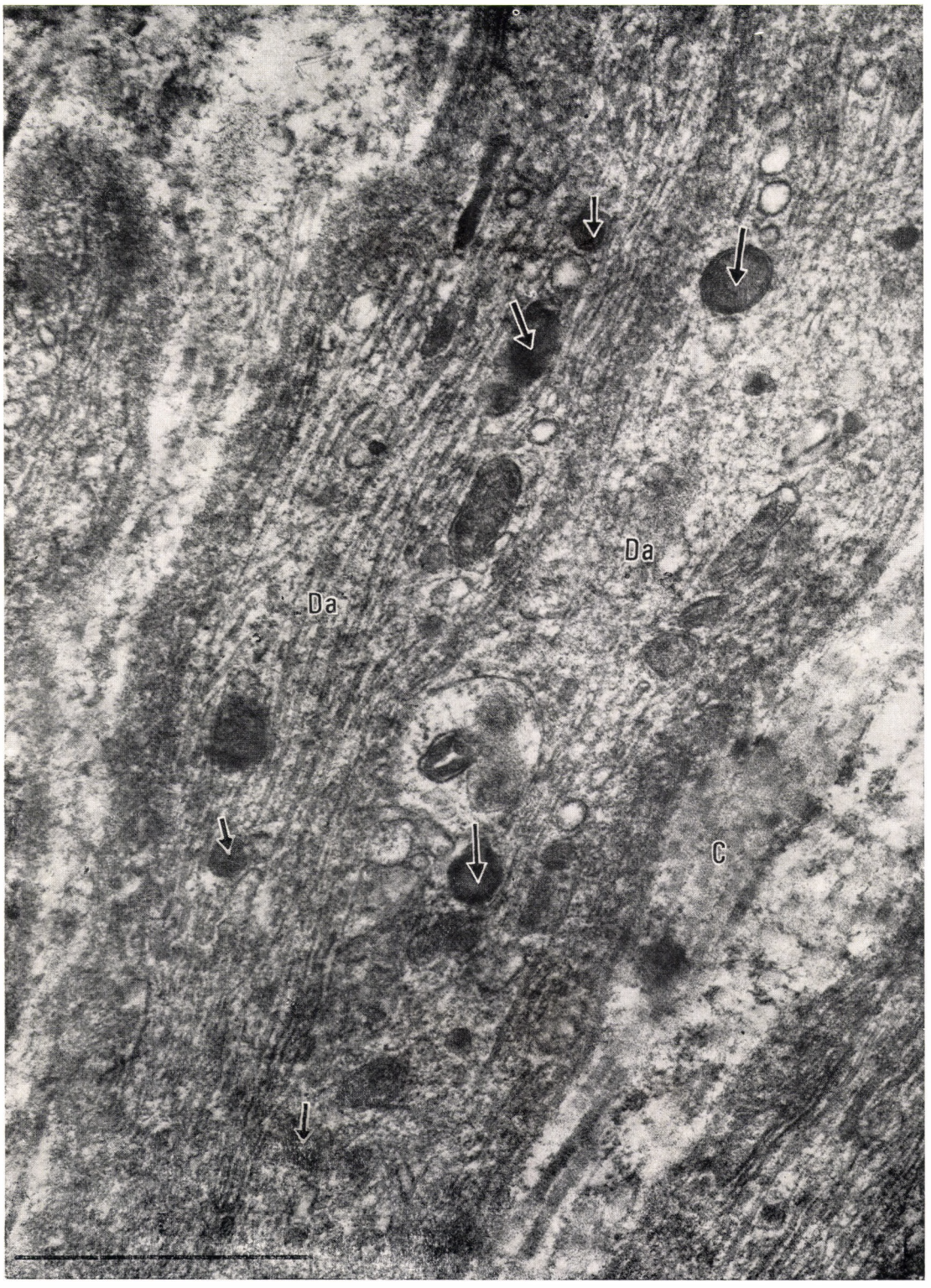
nective tissue, circular muscle layer of the media and in the intima. No fibre-like localization was found, the reaction product was localized outside the neurons.

Electron microscopic investigation revealed nerve fibres in all three layers of the portal venous trunk. Several axons are ensheathed in a common Schwann cell in the adventitia (Fig. 54) and a few of them contain dense-core vesicles (Ungváry et al. 1971b).

In the media between the muscle fibres there are axons in close connection with smooth muscle cells. Some of them are coated while others are not coated by the Schwann cell processes (Fig. 55; Ungváry et al. 1971b).

Axon terminals have also been found in the intima partly ensheathed by Schwann cell processes and partly already devoid of them (Ungváry et al. 1971b).

Fig. 57. Electron micrograph from the media of the portal vein of a cat 48 hrs after extirpation of the spinal ganglia Th_6-L_2 on the right side. Da — degenerating axon; C — collagen. Arrows indicate the autophagous cytolysomes. Scale 1 μm


Da
Da
C

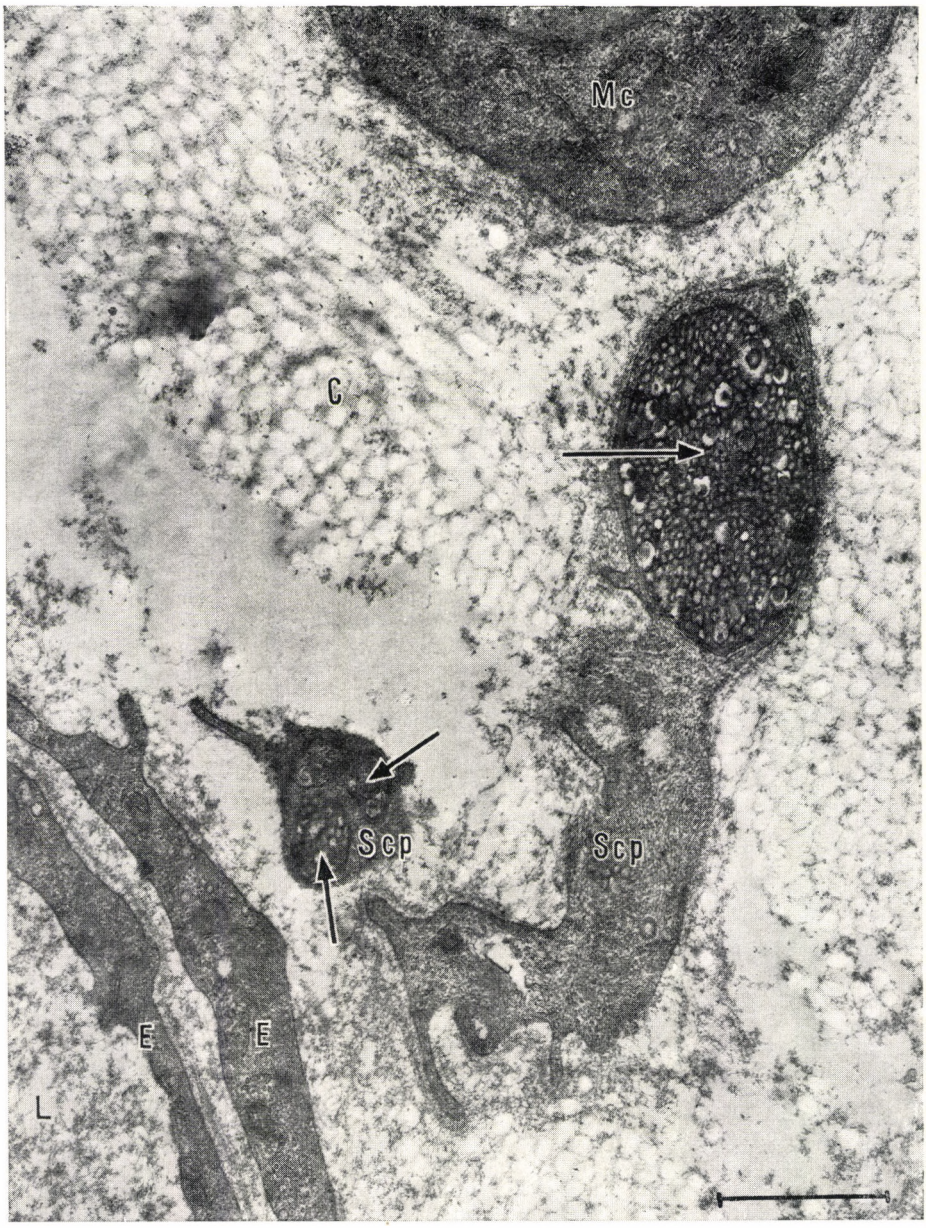


Fig. 58. Electron micrograph from the border between media and adventitia in the hepatic artery of a cat 48 hrs after extirpation of the celiac ganglion. Mc — smooth muscle cell; C — collagen; L — lumen of a vessel of the vasa vasorum; E — endothelial cell; Scp — Schwann cell process. Arrows indicate the degenerating axons. Scale 1 μm

Forty-eight hours after the extirpation of the spinal ganglia Th_6-L_2 on the right side autophagous cytolysomes have been observed in the electron photomicrographs of the portal vein indicating axonal degeneration in the media and intima (Figs 56 and 57). Catecholaminergic nerve fibres were scarcely seen in the wall of the portal vein after the extirpation of the celiac ganglia. Electron microscopically the signs of axonal degeneration were seen to occur 24–48 hrs after extirpation of the celiac ganglia. No degenerating axons were found after the transection of the vagus nerve either on the neck or at the cardia (Ungváry et al. 1972).

6.3. Innervation of the common and proper hepatic arteries

Nerve terminals with intensive catecholamine fluorescence have been found at the margin of the media and adventitia of the common as well as proper hepatic arteries. In the same region a monoamino oxidase reaction of medium intensity was found. There were preterminal nerve bundles showing pale catecholamine fluorescence in the adventitia, while no such fibres could be detected in the media with the method applied.

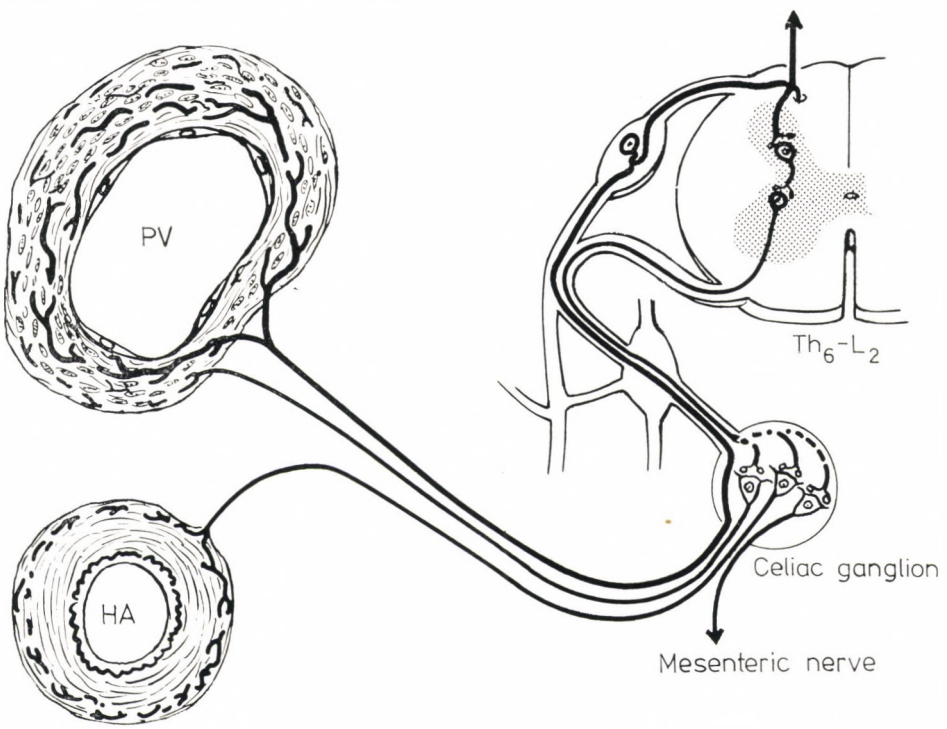


Fig. 59. Schematic representation of a possible reflex arc with the receptors in the wall of the portal vein and effectors in the wall of the portal vein (PV) and hepatic artery (HA)

No degenerating axons were seen in the arterial wall 40–48 hrs after extirpation of the right spinal ganglia Th_6-L_2, or after the transection of the vagus nerve (Ungváry et al. 1972).

Degenerating axons at the border between the media and adventitia of the hepatic artery were however found 24–48 hrs after the extirpation of the celiac ganglia (Fig. 58; Ungváry et al. 1972).

Innervation of the hepatic artery and portal vein and an anticipated reflex arc are shown in Fig. 59.

6.4. Intrahepatic nerve fibres

Fine varicose monoaminergic fibres, parallel to the axis of the vessel, are encountered in abundance along the walls of the intrahepatic portal vessels of first, second and third order (Fig. 60 a). Most fibres run longitudinally, while some transversally and obliquely, forming together a closed, intricate network around the vessels (Ungváry and Donáth 1969).

Much fewer monoaminergic fibres are present in the walls of the hepatic veins of the same order of division. The meshes of this network are much larger and the plexus itself does not seem to be so powerful as that along the portal vein (Fig. 60 b, c; Ungváry and Donáth 1969).

The vasa vasorum of the larger hepatic veins are also well supplied with noradrenergic fibres (Fig. 60 d). Acetylcholinesterase-positive fibres were only scarcely seen in the vessel walls.

In the portal channels components of the portal triad, the portal vein, hepatic artery and bile duct can be readily distinguished and easily studied with the method of Falck et al. (1962) (Fig. 61 a).

The larger nerve bundles, entering the liver through the portal fissure, follow the course of the hepatic artery. These bundles give a moderate fluorescence only and run parallel to the axis of the artery (Fig. 61 a, c; Ungváry and Donáth 1969).

Longitudinal and transverse preterminal and terminal noradrenergic fibres innervating the hepatic artery yield a strong catecholamine reaction. The dense network with intense fluorescence is located at the border between the media and adventitia. It is most abundant in cats (Fig. 61 a, c), dogs (Fig. 61 d), guinea-pigs (Fig. 61 b) and somewhat less pronounced in rats (Fig. 61 e); especially if compared with that of the neighbouring portal veins. The strong autofluorescence of the internal elastic lamina is conspicuous in the sections of the arteries. No nerve fibres in any species studied have ever been observed inside the media between the internal elastic lamina and the above-described network with strong catecholamine reaction (Ungváry and Donáth 1969).

Noradrenergic innervation of the bile ducts appears to be sparse. Nerve fibres yielding catecholamine fluorescence can be noted at random in all species studied (Ungváry and Donáth 1969).

The noradrenergic nerve fibres supplying the portal vein, the third component of the portal triad, can be well observed. Catecholamine reaction in the larger

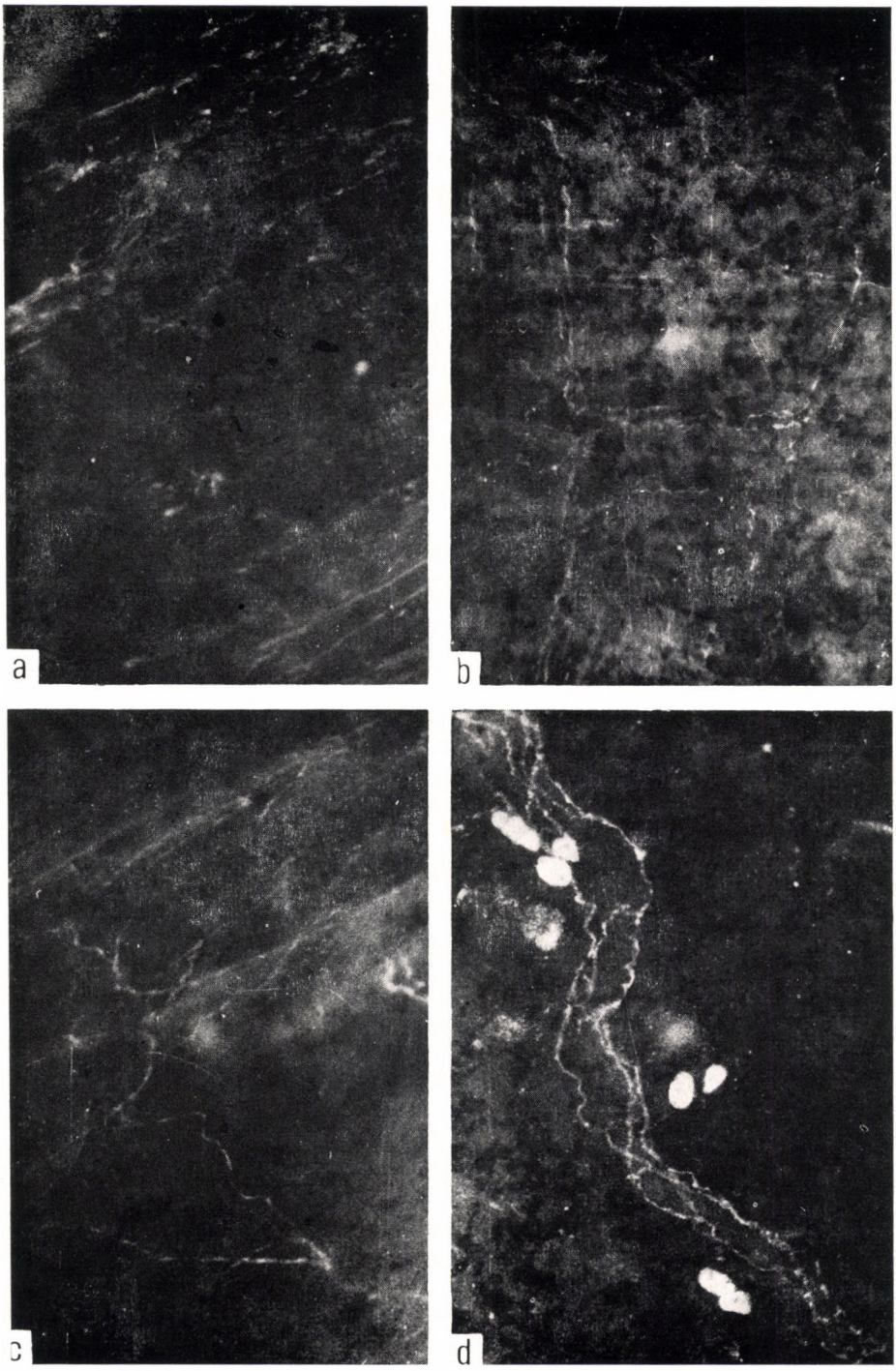


Fig. 60. Rat. (a) Surface view of the monoaminergic plexus in a portal branch arising at a division of the third order. (b) Surface view of the monoaminergic plexus in a branch of third order division of the hepatic vein. (c) Monoaminergic fibres of a branch of second order division of the hepatic vein. (d) Perivascular monoaminergic fibres with intensive fluorescence in the vasa vasorum of a large hepatic venous trunk. Mast cells can be recognized on the basis of strong yellow fluorescence beside the vasa vasorum. Rat. Membrane preparation. Catecholamine reaction of Falck et al. ×160

portal areas of rat liver are shown in Figs 61 e, 62 b and c. The catecholamine reaction at the border between the media and adventitia is the strongest in the wall of the portal vein (Fig. 61 e). In Fig. 62 b the longitudinal section of a large portal vein reveals a rich noradrenergic innervation. The fibres at both ends of the section penetrate also the parenchyma for a short distance. In Fig. 62 c abundant monoaminergic connections are seen between two neighbouring portal channels. The innervation of the walls of the portal vein is similar to that seen in Fig. 61 e. In a tangential section of the wall of the portal vein (Fig. 62 a) a rich network of densely interwoven varicose nerve fibres is shown, from which axons project into the liver parenchyma. The larger portal vessels in cats and dogs give a weaker catecholamine reaction (Figs 61 a, d). There is a striking similarity between rat and guinea-pig liver as far as the catecholamine reaction is concerned. Quite frequently monoaminergic nerve fibres enter the parenchyma far from the vessels (Figs 63 a, c). Nerve fibres penetrating between the hepatic plates were found also in dogs at the same places (Fig. 63 b; Ungváry and Donáth 1969).

Guinea-pig was the only species studied that possess a rich acetylcholinesterase-positive fibre system attached mainly to the bile ducts. These actylcholinesterase-positive fibres can be traced in some places deep into the parenchyma (Fig. 64 a).

Intensive catecholamine reaction, especially in the rat liver, was observed in the preterminal portion of the portal channels, in the inter- and circumlobular areas where the interlobular vessels divide to form circumlobular twigs (Fig. 63 d). Similarly, more fibres yielding specific catecholamine fluorescence can be found in the same region in guinea-pigs. Nerve fibres from the inter- and circumlobular area enter the outer third of the lobule (Fig. 63 c) and a positive reaction can be seen even around the central venules (Fig. 65 f). In cats and dogs, too, a catecholamine fluorescence of higher intensity can be observed in the inter- and perilobular areas showing an abundant monoaminergic innervation. This stronger fluorescence of the inter- and circumlobular spaces was seen rather at the periphery of the liver lobes (Figs 65 a, b, c, d; Ungváry and Donáth 1969).

Acetylcholinesterase-positive nerve fibres in the perilobular area have been found only in guinea-pigs (Fig. 64 b).

Except for cats in the other three species studied a few short, not characteristic nerve fibres enter from the inter- and circumlobular vessels of the portal channels into the lobule and run between the hepatocyte plates (Ungváry and Donáth 1969).

In histological sections of the guinea-pig liver, prepared with the freezing-drying equipment of fine intraparenchymal monoaminergic nerve terminals could be frequently encountered in the Disse spaces, i.e. between the liver cells and the wall of the sinusoids. No such fibres could be seen after reserpine pretreatment. Many acetylcholinesterase-positive fibres enter the lobules in the guinea-pig liver. So far, we have not been able to verify these findings with the electron microscope.

The liver parenchyma cells appear as regular hexagonal cells with clearly delineated borders and green fluorescence when studied with the Falck–Hillarp method. Scattered in the liver parenchyma, but particularly around the vessels

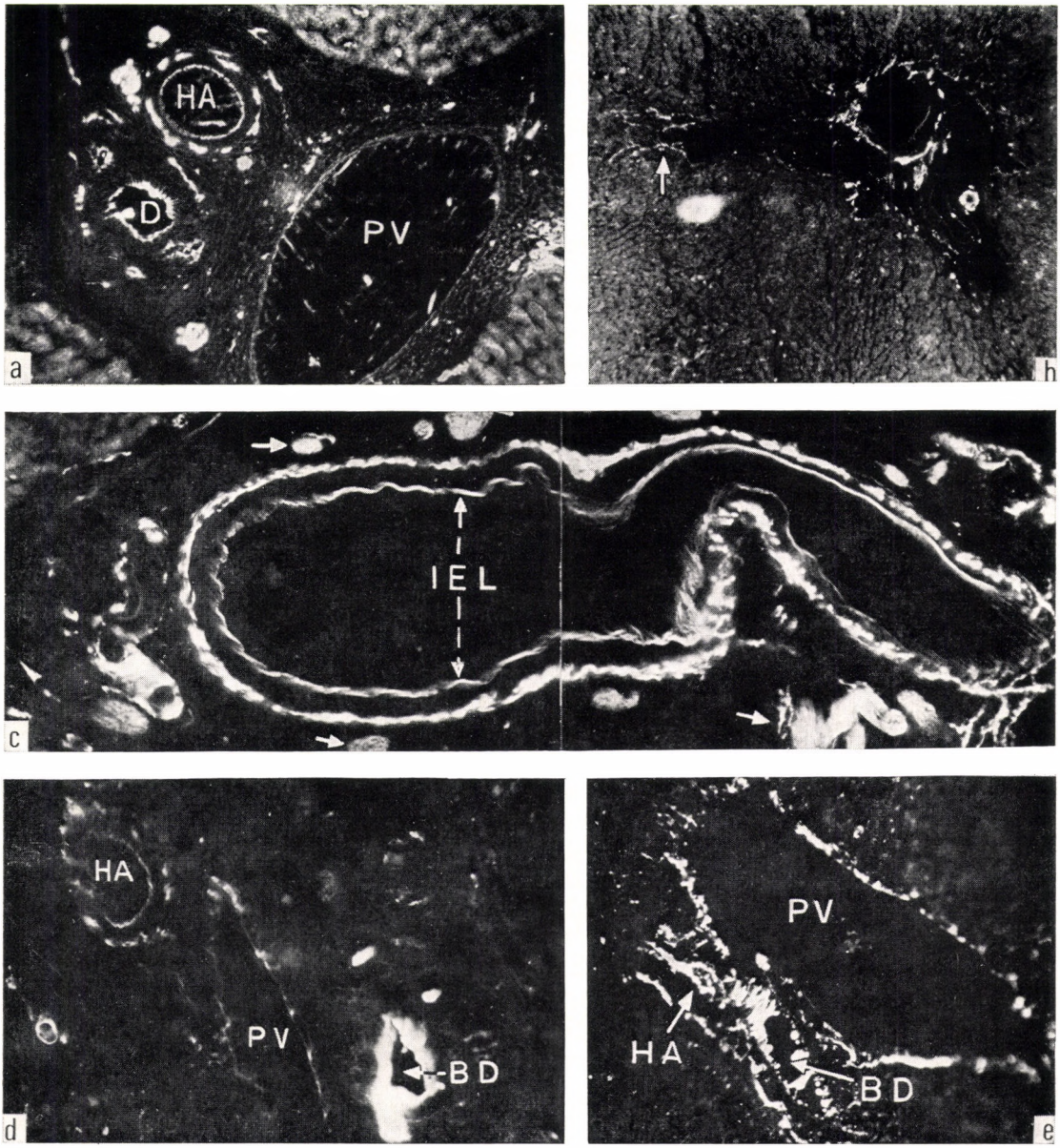


Fig. 61. (a) Adrenergic nerve elements around the portal triad in the portal channel of a cat. Most monoaminergic fibres are found around the hepatic artery (HA). PV — portal vein; D — bile duct. ×140. (b) Portal space. The adrenergic fibres penetrate the peripheral part of the lobule (→). Nerve fibres with intensive fluorescence are seen around the artery. Guinea-pig. ×80. (c) Larger branch of the hepatic artery surrounded by bundles of nerve fibres showing moderate fluorescence (→). The terminal plexus between the media and adventitia yields very strong fluorescence. There is no fluorescence in the media. The internal elastic lamina (IEL) can be recognized by the strong yellow autofluorescence. Cat. Reaction ×140. (d) Portal space. The strongest catecholamine reaction can be seen around the hepatic artery (HA). The smudged bile around the bile duct gives a strong yellow autofluorescence. BD — bile duct; PV — portal vein. Dog. ×140. (e) Portal triad. There is a most pronounced catecholamine reaction of the nerve fibres around the portal vein (PV). HA — hepatic artery; BD — bile duct. Rat. Reaction of Falck et al. ×140

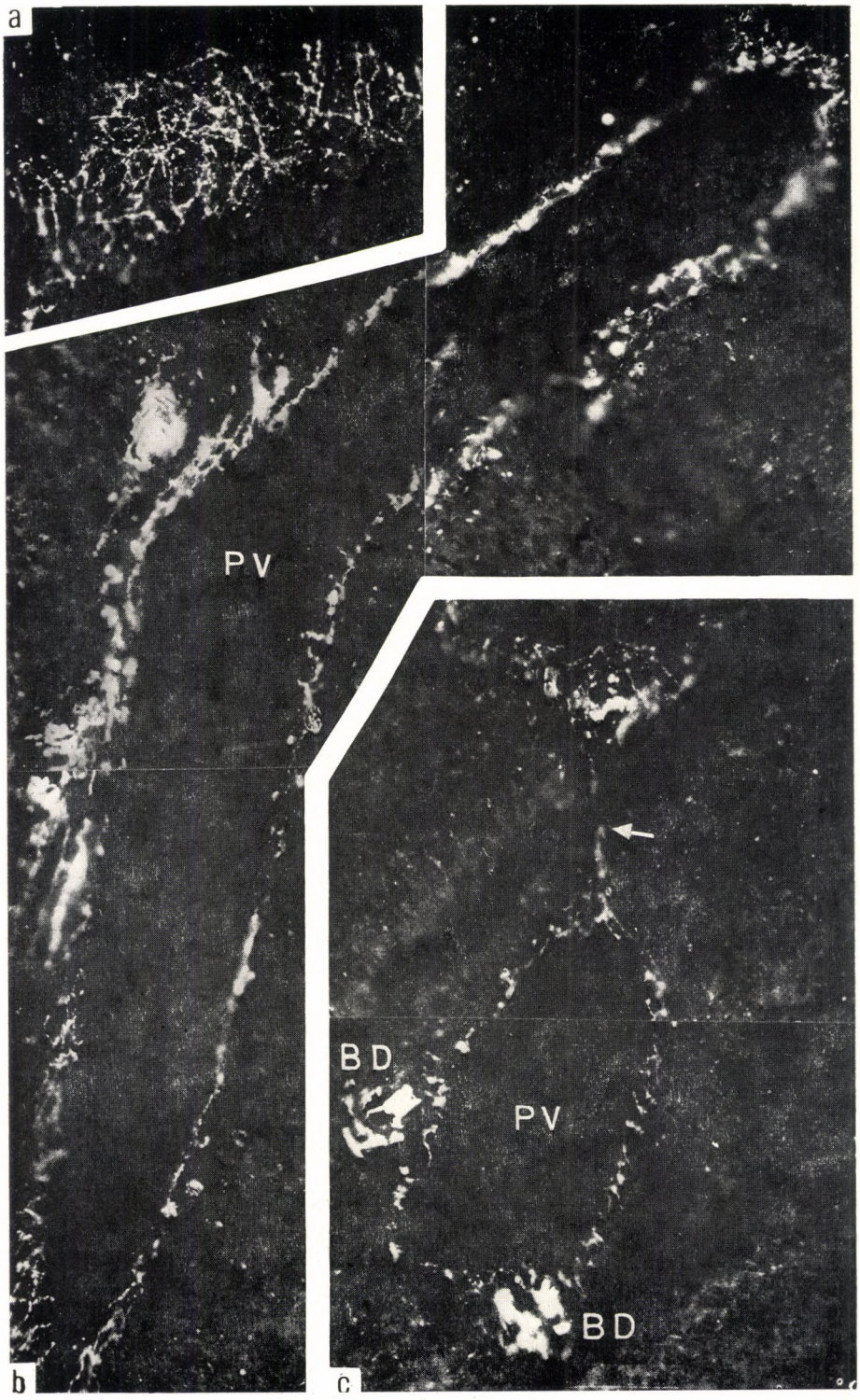


Fig. 62. (a) Tangential section of a portal venous branch; the adrenergic plexus appears to be mainly circular. (b) Longitudinal section of a portal venous branch PV. A few fibres from the perivascular plexus project toward the parenchyma. (c) Cross section of a major portal vein (PV, lower part) and the tangentional section of an interlobular vein (upper part). Monoaminergic fibres connect the two vessels (→). Beside the portal vein yellow autofluorescence of the bile is seen. BD – bile duct. Rat. Reaction of Falck et al. × 140

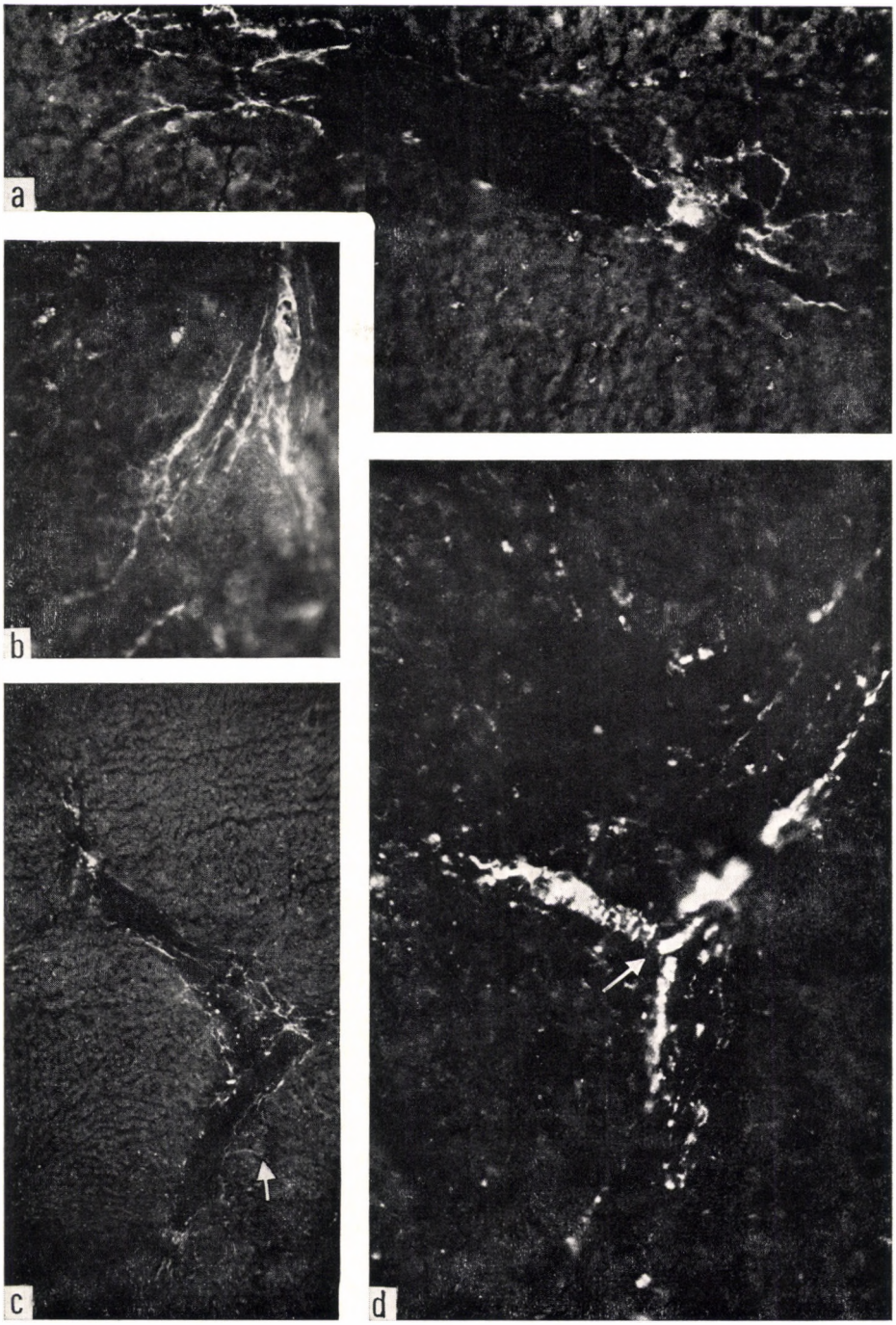


Fig. 63. (a) Adrenergic nerve fibres entering the parenchyma from the portal space. Guinea-pig. (b) Adrenergic nerve fibres entering the parenchyma from the portal space. Dog. ×140. (c) Delicate monoaminergic nerve fibres (→) from the portal space entering between the hepatocyte plates. Guinea-pig. ×80. (d) Adrenergic fibres in the portal space surrounding a hepatic artery branch showing greater density at the site of the branching of the vessel (→). Rat. Reaction of Falck et al. ×140.

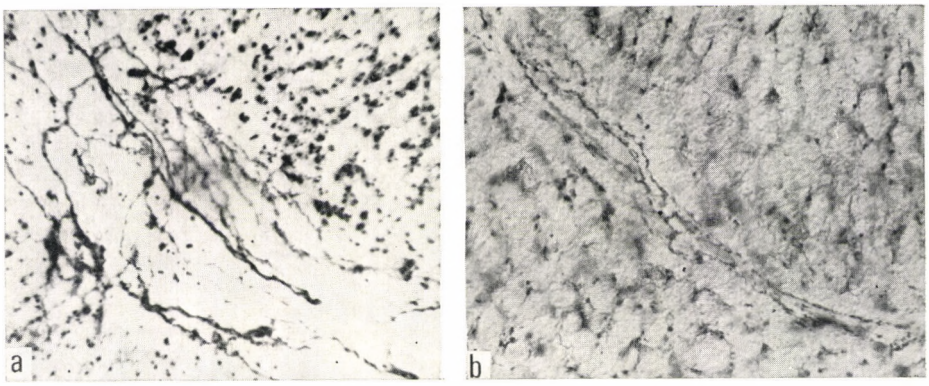
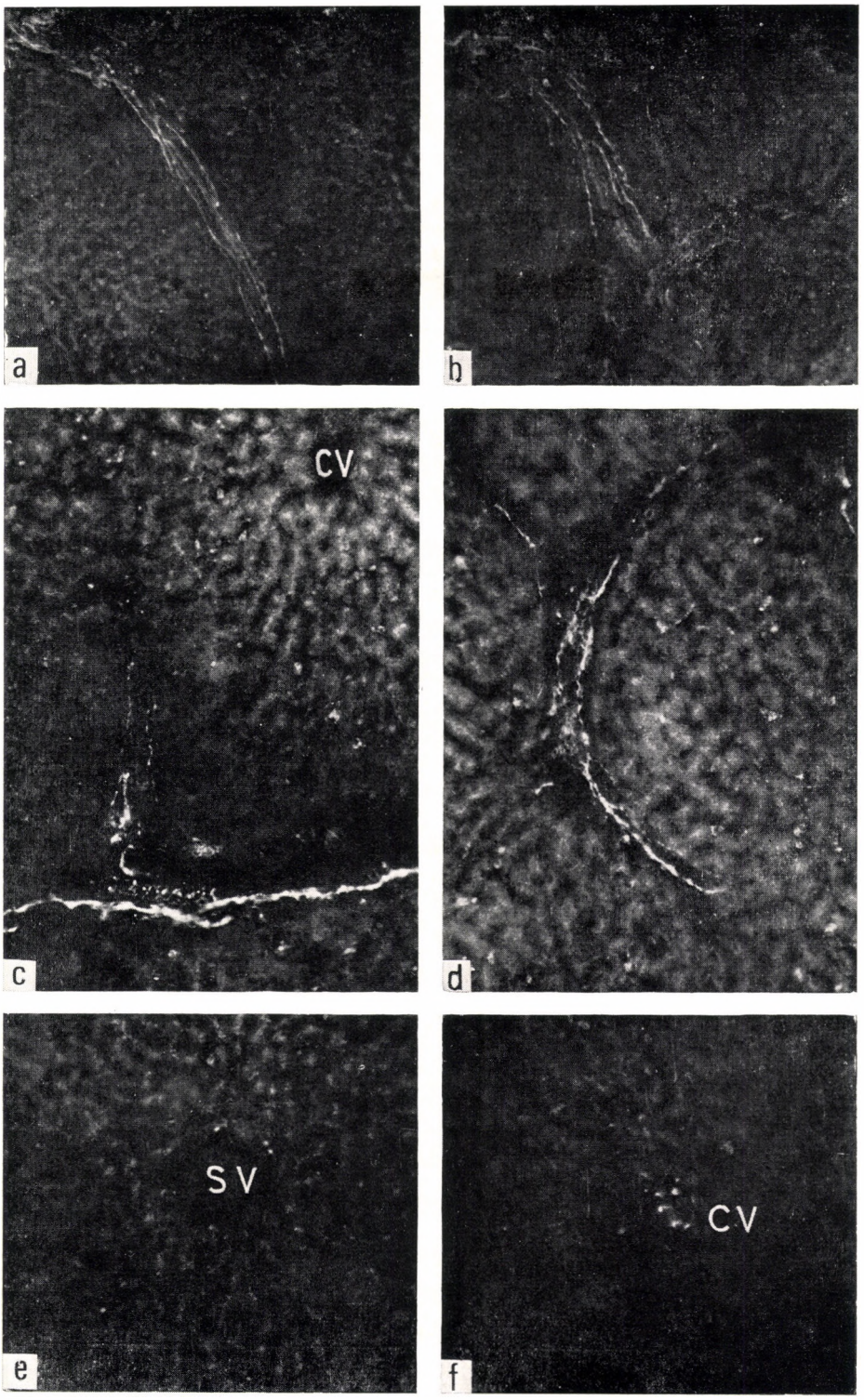


Fig. 64. (a) Acetylcholinesterase-positive nerve fibres from a portal space entering the liver parenchyma. × 100. (b) Acetylcholinesterase-positive nerve fibres in the circumlobular area. × 140. Guinea-pig. Coupland-Holmes reaction. 30 min preincubation with 10^{-5} M Iso-OMPA, 6 hrs incubation; pH 5.4

mast cells with strong yellow fluorescence (serotonine) can be identified (Fig. 60 d). In the sinusoids the star-like Kupffer's cells are conspicuous due to their orange-coloured fluorescence. The smaller processes of the Kupffer's cells could not be observed and no connection between these cells and the noradrenergic nerve fibres could be found. The liver cells exhibit a strong nonspecific cholinesterase and monoamine oxidase reaction (Ungváry and Donáth 1969).

Catecholamine reaction around the central veinlets could not be seen everywhere. Figure 65 f shows the profile of a few noradrenergic nerve fibres around the central venule, however, no catecholamine reaction could be discerned around the central venule in Fig. 65 c. Some of the smaller hepatic veins were followed by monoaminergic nerves (Fig. 65 e), while others were not (Fig. 66 a). In larger branches of the hepatic vein in general noradrenergic nerve fibres are located in the vessel wall at the border between the media and adventitia. The reaction is more intense at the ramification of the hepatic vein. Here more fibres are present in the vessel walls than before and after the junctions (Fig. 66 b; Ungváry and Donáth 1969).

Fig. 65. (a) Strong catecholamine reaction in the interlobular space at the periphery of the liver lobe. The fibres do not seem to enter the lobule. × 100. (b) Monoaminergic nerve elements in the portal channels. The parenchyma is entirely devoid of the reaction. × 100. (c) Intensive reaction in the nerve fibres running in the inter- and circumlobular spaces; no reaction in the parenchyma. A moderate yellow autofluorescence can be seen along the biliary vessels. × 140. (d) Intensive catecholamine reaction of circumlobular nerves; macrophages giving autofluorescence can be distinguished in the parenchyma. × 140. (e) A few dots around the sublobular vein (SV) give the catecholamine fluorescence. They might correspond to the cross section of adrenergic nerve fibres. × 140. (f) Cross section of a few adrenergic nerves around the central vein. × 140. Cat. Reaction of Falck et al. CV — central vein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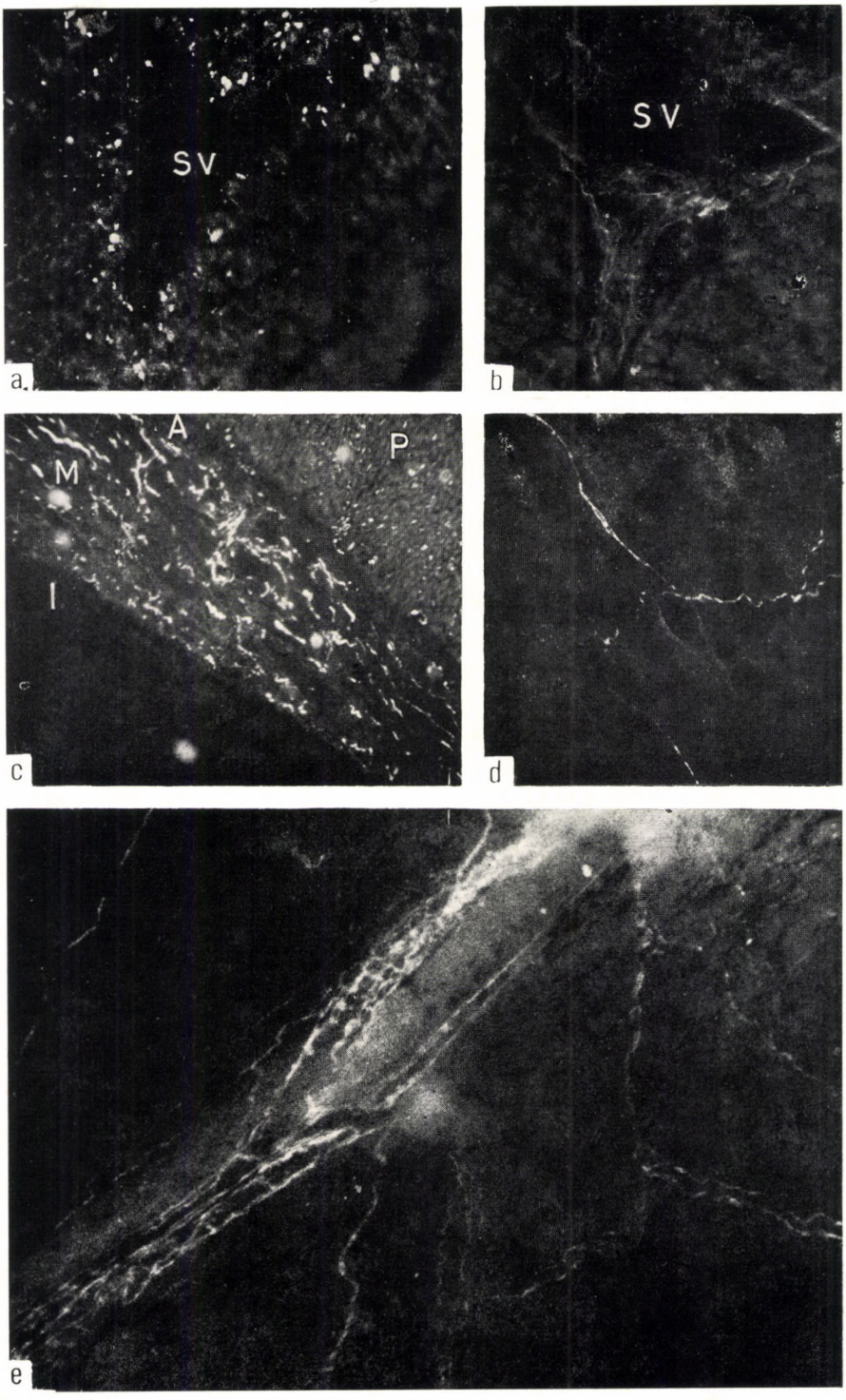
SV
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In the falciform ligament near the liver as well as in membrane preparations made from the Glisson's capsule many fine varicose noradrenergic fibres with intense fluorescence could be observed. They are usually attached to vessels in the Glisson's capsule (Fig. 66 e), while no such association was found in the falciform ligament (Fig. 66 d; Ungváry and Donáth 1969).

6.5. Innervation of the hepatic venous system and its sphincters

By means of the catecholamine fluorescence method of Falck et al. (1962) relatively few monaminergic nerve fibres could be seen in the connective tissue of the adventitia of the hepatic veins. However, a great abundance of noradrenergic nerve fibres were found between the bundles of smooth muscle cells in the muscular layer both of the adventitia and media with some fibres approaching the intima (Figs 66 c and 67 a; Ungváry and Donáth 1969).

After a number of modifications of the Coupland–Holmes (1957) reaction in order to suppress the strong activity of nonspecific cholinesterases in the smooth muscle cells (Fig. 67 b), we succeeded in demonstrating larger nerve bundles with moderate acetylcholinesterase activity in the outer part of the adventitia of the hepatic veins (Fig. 67 c, d). In tangential sections of the vessel wall thin nerve terminals arising from the acetylcholinesterase-positive bundles could be traced to the muscle layers of the adventitia and media (Fig. 67 e; Ungváry and Léránth 1970a, Ungváry and Léránth 1972).

By means of the zinc-iodide-osmium technique nerve fibres could be demonstrated between the bundles of the longitudinal and circular smooth muscle layers of the adventitia and media (Fig. 67 f) a few of which may approach (or enter) the intima (Fig. 67 g; Ungváry and Léránth 1970a, Ungváry and Léránth 1972).

The above light microscopic findings were verified in normal livers electron microscopically as well. Single axons and groups of axons could be found both between longitudinal (outer) and circular (inner) muscle cells. The axons are partly or completely embedded into the Schwann cell processes (Fig. 68 a). Some of the axons are thin and contain only neurotubules, while others which presumably correspond to varicose thickenings, contain clear (empty) or dense-core vesicles. All axons, found in the muscle layers, are in contact at least with a part of their surface with Schwann cell processes. However, the axons that enter the intima

←

Fig. 66. (a) Environment of a sublobular vein (SV) with many granules giving yellow autofluorescence. Rat. × 140. (b) Nerve plexus around the sublobular vein (SV), more dense at the site of the branching of the vessel. Cat. × 140. (c) Portion of the hepatic vein joining directly the inferior vena cava. There is no catecholamine reaction in the intima (I). An abundant adrenergic plexus with strong catecholamine fluorescence is localized between the bundles of muscles in the media (M) and adventitia (A). P — parenchyma. Dog. × 80. (d) Free nerve fibres in the falciform ligament. Surface view of the stretched membrane preparation. Cat. × 140. (e) Perivascular adrenergic nerve fibres in the Glisson's capsule. Surface view. Membrane preparation. Rat. Reaction of Falck et al. × 140

are always in lose contact with the Schwann cell processes either entirely or partially along their surface facing the endothelium. The terminal thickenings of these naked axons can be found immediately beneath the vascular endothelium. They might contain dense-core vesicles, 450–800 Å in diameter, characteristic of the adrenergic nerve terminals (Fig. 68 b). Myelinated fibres were found in the outer zone of the adventitia (Ungváry and Léránth 1970a, Ungváry and Léránth 1972).

After the transection of the right phrenic nerve secondary degeneration was confined to the utmost outer layer of the adventitia. No degenerated fragments could be detected between the smooth muscle cells (Ungváry and Léránth 1970a, 1972).

After the removal of the celiac ganglia a great number of degenerating axons can be found between the longitudinal and circular smooth muscle cells. At 24–60 hrs after operation a considerable number of intact axons were present (Fig. 69). Extirpation of both celiac ganglia results in a nearly complete disappearance of the catecholamine fluorescence in this region of the vascular tree. As everywhere in the terminal autonomous plexus degeneration produces two different types of changes. Some of the axonal fragments appear as dark cytolysome-type bodies with an amorphous structure (Fig. 69, inset), in which the remnants of synaptic vesicles can be recognized only occasionally. Remnants of other axons can be identified as large, light "blown up" vacuoles containing irregular precipitates or sometimes small dark bodies (Fig. 69). The actual appearance of the axonal degeneration probably varies depending on which part of the degenerated fragment has been included into the ultrathin section. Already in the earlier light microscopic descriptions of secondary degeneration of the terminal autonomous plexus it was observed that the degenerated axon fragments consist of dark argentophilic and light vacuolar parts [Schimert (Szentágothai) 1935, 1936, 1937, 1938]. Degenerated axons could be traced as far as the close vicinity of the endothelial cells (Fig. 70; Ungváry and Léránth 1970a, 1972).

After extirpating the right spinal ganglia Th_9–L_2 degenerating axonal fragments, identifiable beyond doubt, were detected between the cells of both muscle layers and in the intima. The degenerating axon terminals are in a relatively close contact with the endothelium (Fig. 70, inset). Degenerating axons originating from the spinal ganglia were encountered even in the walls of rather small tertiary branches of the hepatic vein (Fig. 71; Ungváry and Léránth 1970a, 1972).

No signs of axonal degeneration were found in the walls of the hepatic vein after the transection of the left vagus nerve either on the neck or at the cardia (Ungváry and Léránth 1970a, 1972).

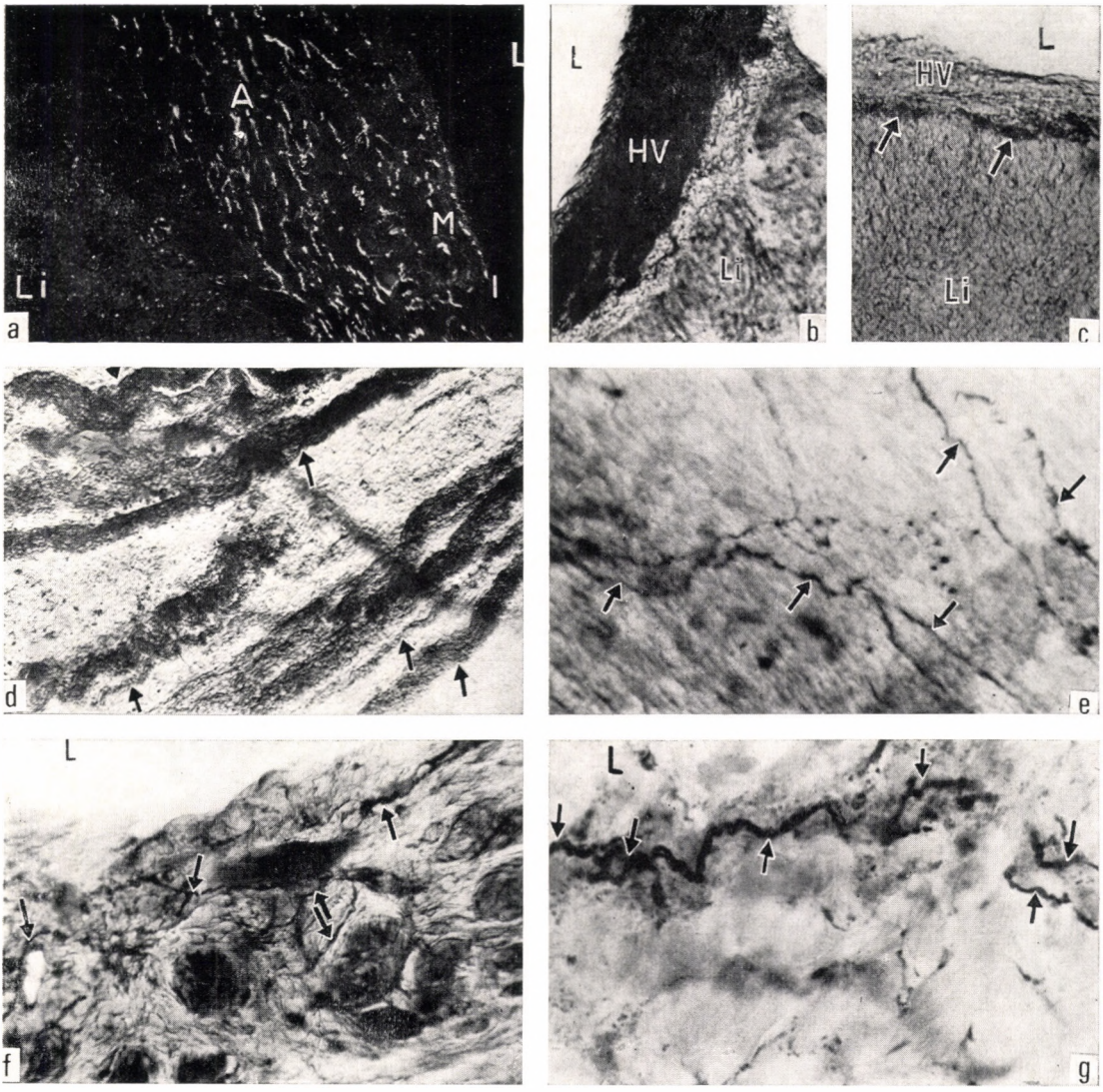


Fig. 67. (a) Monoaminergic nerve fibres at the junction of the hepatic venous trunk and caudal vena cava. Nerve fibres can be observed in the adventitia (A), media (M) and some fibres enter even the intima (I); Dog. Catecholamine reaction of Falck et al. ×80. (b) Strong nonspecific cholinesterase reaction in the muscle layer of the hepatic venous trunk (HV). Coupland-Holmes reaction. 6 hrs of incubation without preincubation with an inhibitor of nonspecific cholinesterases. ×80. (c) Acetylcholinesterase reaction of the cross section of a few bundles of nerve fibres in the adventitia of the hepatic venous trunk. Arrows indicate the cross section of the acetylcholinesterase-positive nerve fibres. Cat. Coupland–Holmes reaction. Preincubation for 30 min with 10^{-5} M Iso-OMPA, incubation for 6 hrs; pH 5.4; ×80. (d) Stretched membrane preparation of the wall of the hepatic vein, containing acetylcholinesterase-positive bundles of nerve fibres. Presumably the cross section of the latter corresponds to the cross sections of the bundles of nerve fibres in Fig. 67 c. Arrows indicate the acetylcholinesterase-positive nerve fibres. Cat. Coupland-Holmes reaction. Preincubation for 30 min with 10^{-5} M Iso-OMPA; Incubation for 6 hrs; pH 5.4; ×120. (e) Acetylcholinesterase-positive nerve fibres (→) entering the media in the wall of the hepatic vein. Cat. Coupland–Holmes reaction. Preincubation for 30 min with 10^{-5} M Iso-OMPA; incubation for 6 hrs; pH 5.4; ×350. (f) Wall of a proximal hepatic vein trunk. There are zinc-iodide-osmium-positive nerve fibres (→) in the media between the bundles of smooth muscle (→). Cat. Champy's method. × 120. (g) Zinc-iodide-osmium-positive nerve fibres (→) approaching (and perhaps entering) the intima of the hepatic vein. Cat. Champy's method. ×350. L — lumen; Li — liver parenchyma;

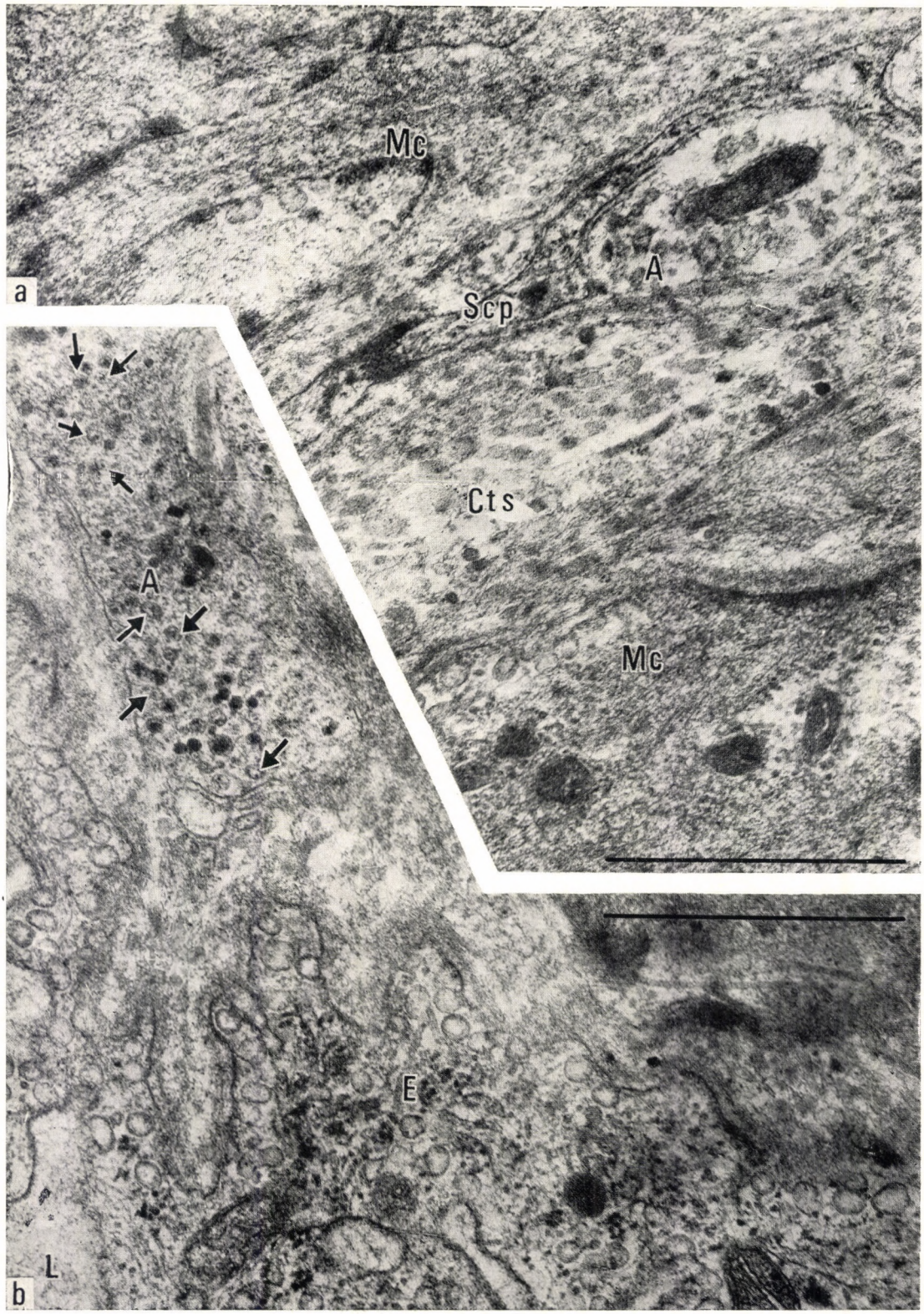


Fig. 68. Electron micrograph (a) from the media of the hepatic vein of a cat. Preterminal axons (A) containing synaptic vesicles enveloped by Schwann cell processes (Scp) are present between the smooh muscle cells (Mc) of the media. Axons and smooth muscle cells are separated by a Schwann cell process evten at the point where the distance is the smallest between them. Cts — connective tissue space with collagen fibres; (b) from the intima of the hepatic vein of a cat. The subendothelial axon terminal (A) contains numerous dense-core vesicles (arrows) and a few larger osmiophylic vesicles. E — endothelial cell with a number of pinocytotic vesicles; L — lumen. Scales 1 μm

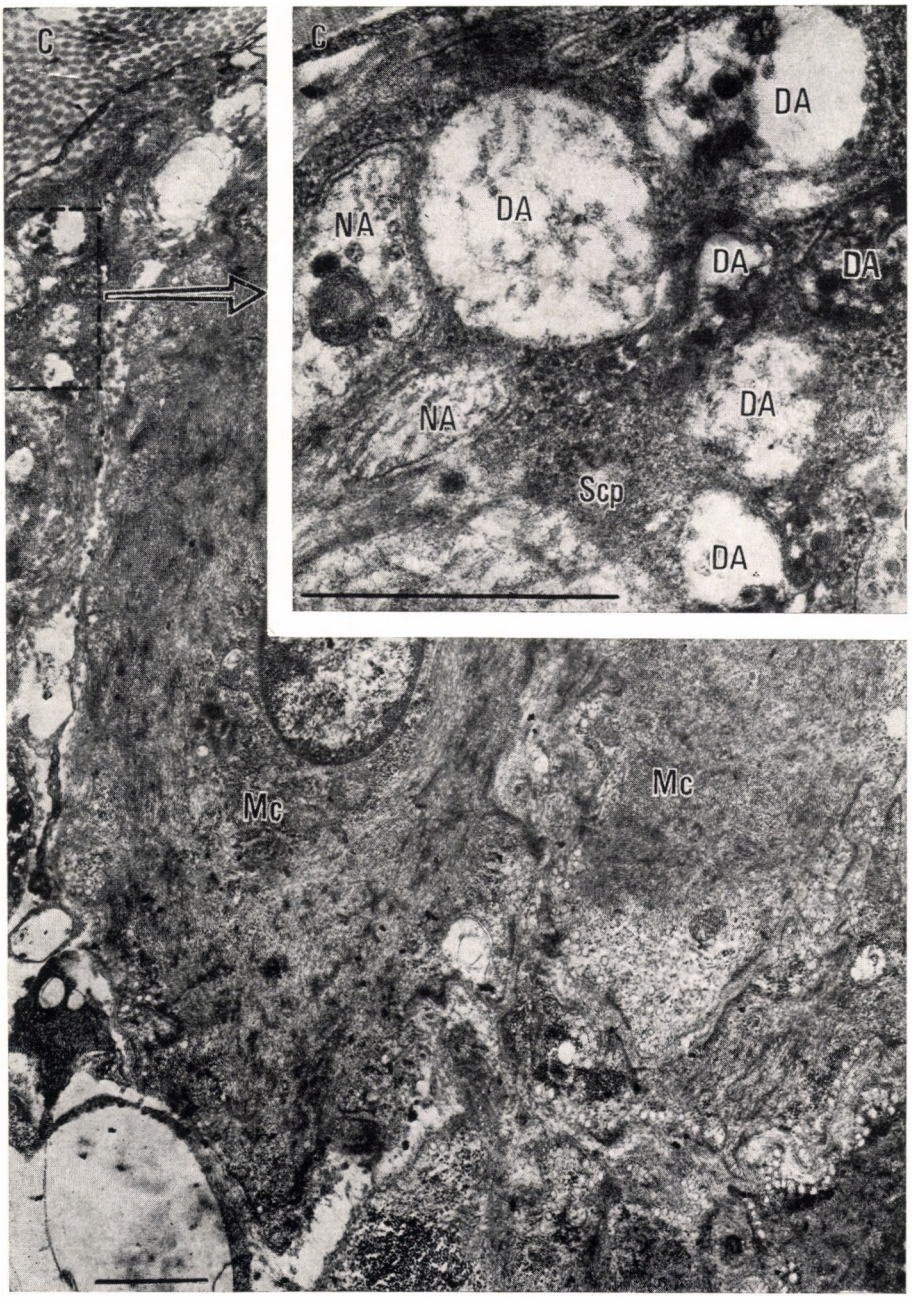


Fig. 69. Degeneration of the terminal nerve plexus in the media of the hepatic vein of a cat 60 hrs after extirpation of the celiac ganglion. Two smooth muscle cells (Mc) cover the main part of the Figure. The area indicated by the broken lines can be seen enlarged in the inset. The degenerated axons (DA) may appear light as well as dark; NA — normal axon; C — collagen. Scp — Schwann cell process. Electron micrograph; Scales 1 μm

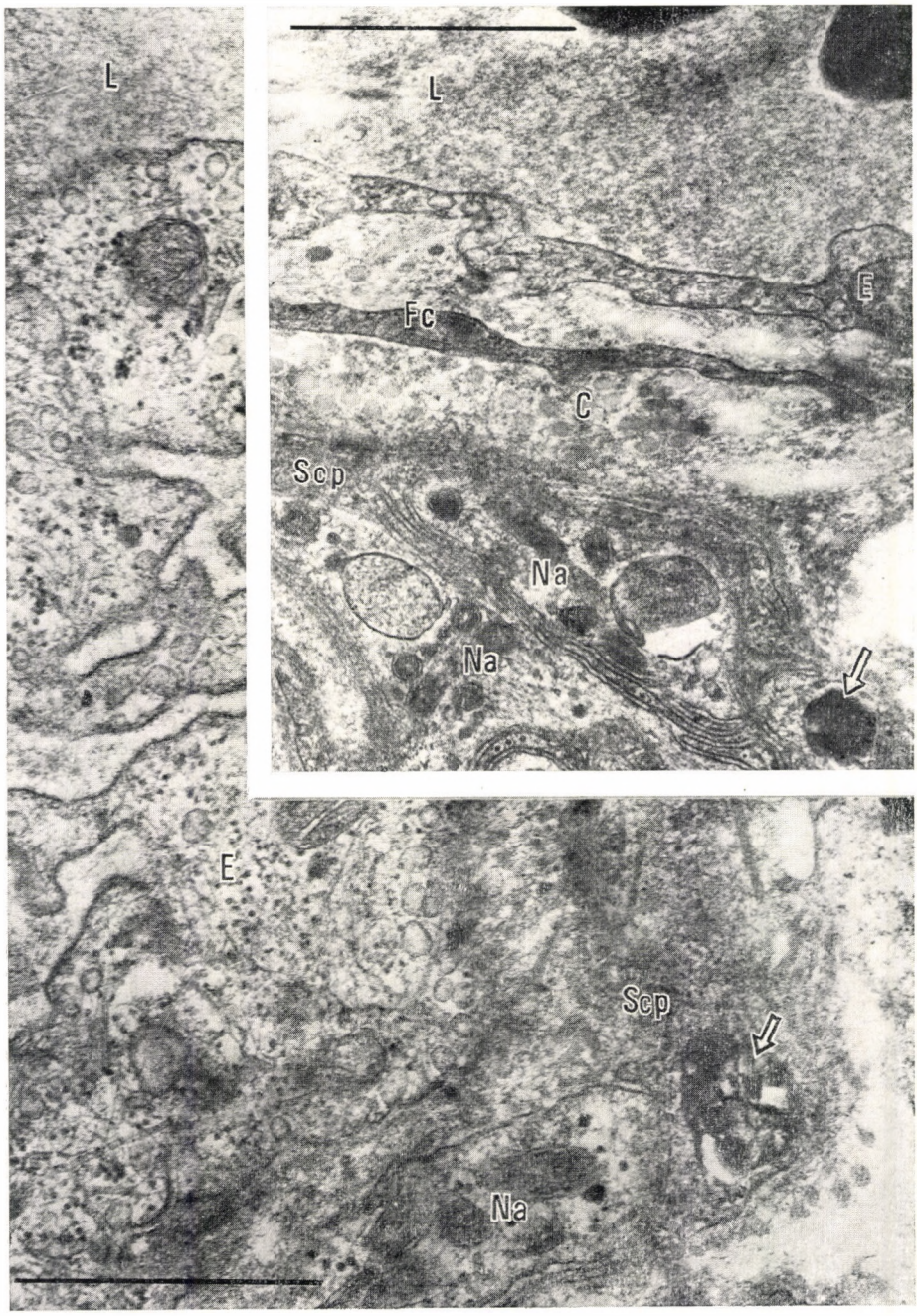


Fig. 70. Electron micrograph of degenerated terminal axons in the subendothelial layer of the intima in the hepatic vein of a cat 48 hrs after extirpation of the celiac ganglion. Inset: degenerated sensory nerve terminal after extirpation of spinal ganglia Th_9L_2 on the right side. E — endothelial cell; L — lumen. Arrows indicate degenerated axons. Scp — Schwann cell process; Na — normal axon; C — space with connective tissue with a process of a fibriocyte (Fc) entering from the left. Electron micrograph; scales 1 μm

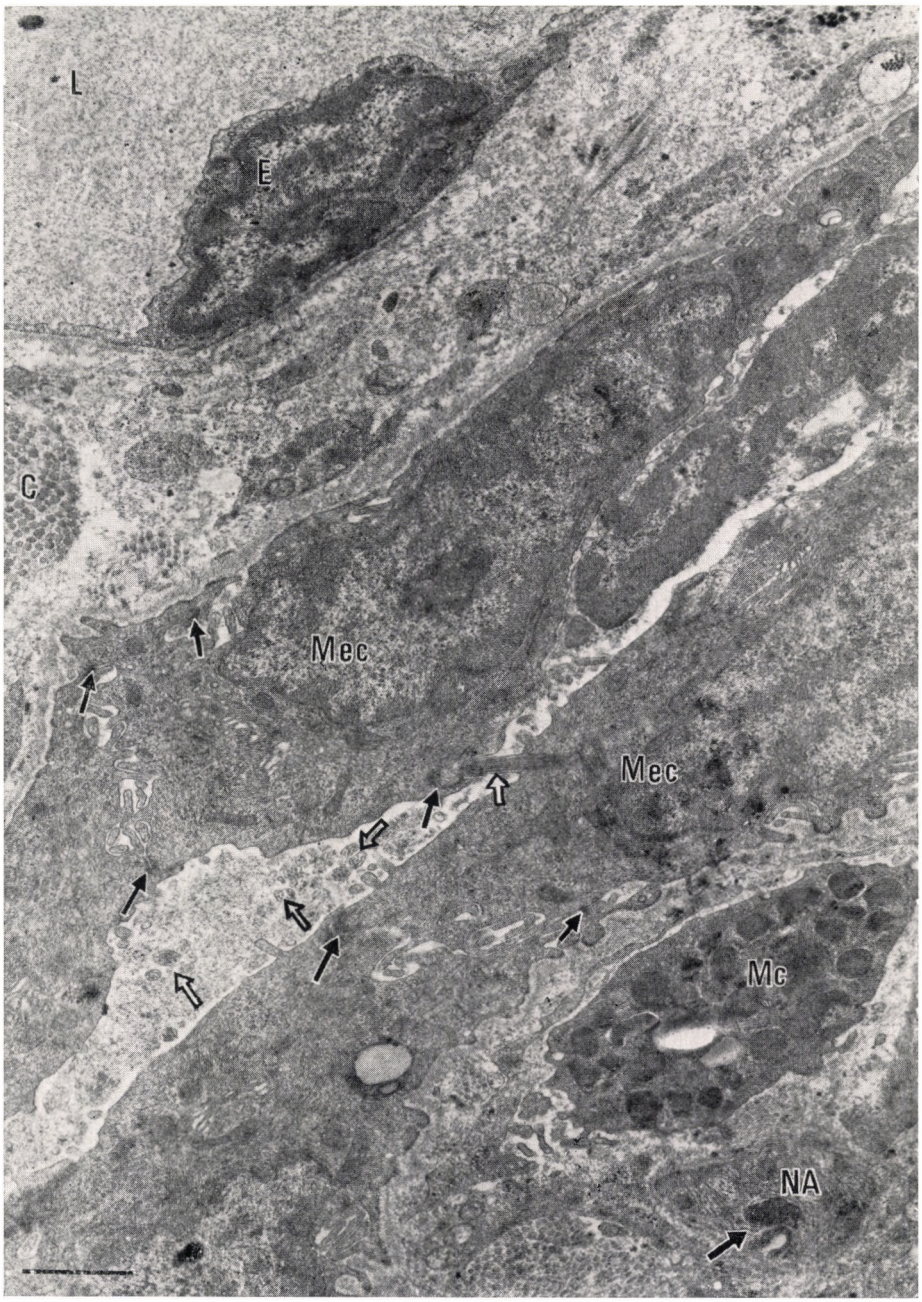


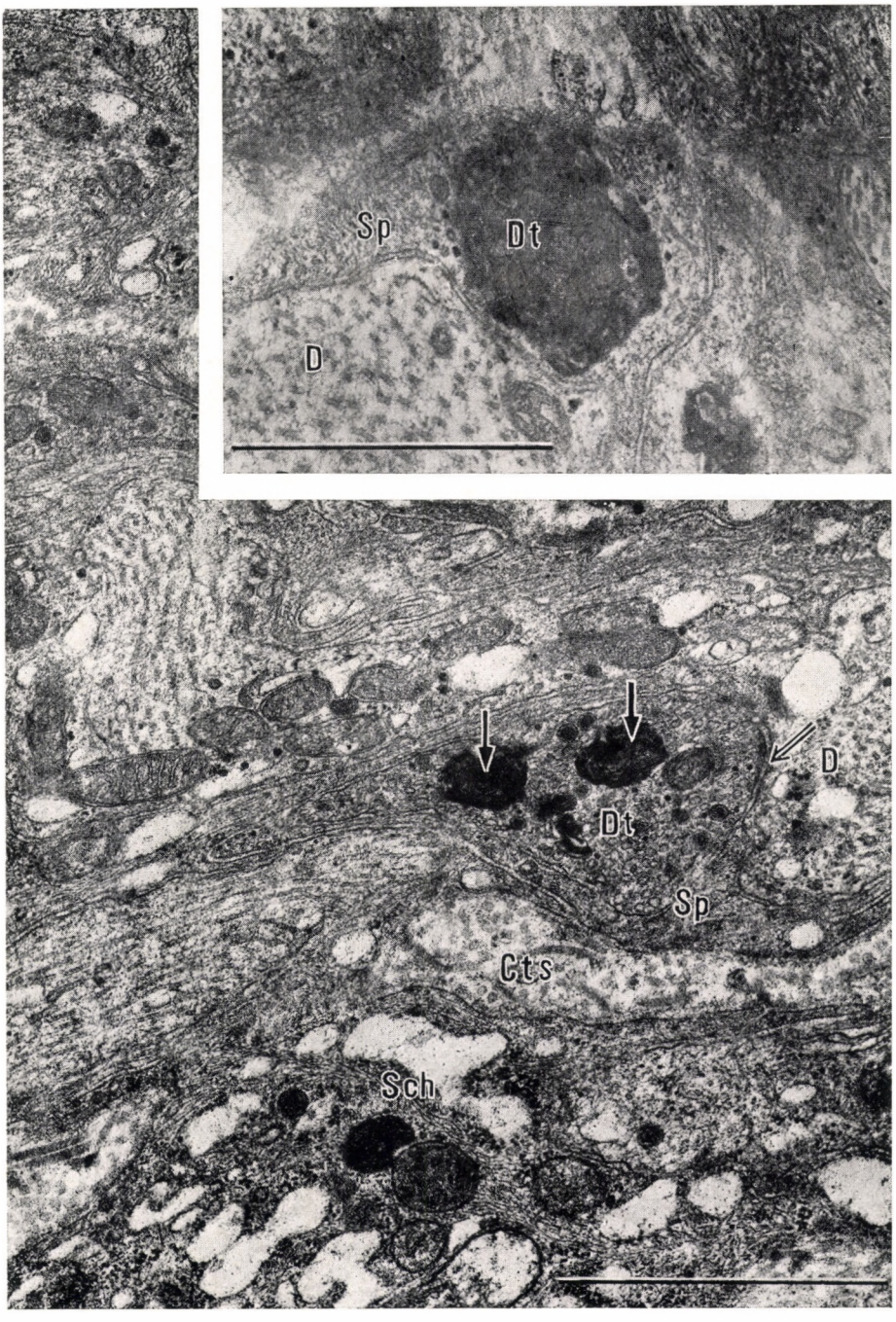
Fig. 71. Electron micrograph of a small branch of the hepatic vein of a cat 48 hrs after extirpation of the spinal ganglia Th_9-L_2 on the right side. L — lumen; E — endothelial cell with nucleus, C — collagen fibres in the connective tissue space; Mec — (myoepithelial cell) connected by desmosomes (→); there are cilia (⟹) between two myoepithelial cells; Mc — mast cell, there is a bundle of nerve fibres containing a few intact and a degenerating axon in the right lower corner (indicated by heavy arrow). Scale 1 μm

6.6. Termination of the Dogiel type II cell processes in the prevertebral ganglia

Forty-eight hours after cholecystectomy alone or combined with the surgical removal of the right liver lobes or after the resection of the left liver lobes alone, autophagous cytolysomes that proved to be axonal degeneration have been observed in several axons in the celiac ganglion. Figure 72, inset shows a larger fragment of an axon in an advanced stage of degeneration with some of the original dense-core vesicles still visible. In a few cases the synaptic attachment of dendritic profiles to degenerating axon terminals containing typical autophagous cytolysome can be observed (Fig. 72). After resection of four-fifth of the jejunum, axonal degeneration in the celiac and superior mesenteric ganglia was even more frequently seen than after liver resection or cholecystectomy (Ungváry and Léránth 1970b).

Two weeks after the removal of the prevertebral ganglia the empty spots in places of the degenerated axons are clearly visible in the peripheral stump of the visceral nerve running from the ganglia to the viscera. Figure 73 b clearly indicates that certain central spaces are filled with a light non-cellular material, probably tissue fluid, while others contain cytoplasmic material and mitochondria. It is uncertain, however, whether these larger profiles are persisting nerve fibres, regenerating cones, or something else. At the same time very thin persisting axons can be clearly recognized mainly at the periphery of the Schwann's tubes. This becomes quite clear if a normal peripheral branch of the prevertebral ganglia (Fig. 73a) is compared with that of a degenerating one (Fig. 73 b). In the control nerve branch the small axons are similarly situated mainly at the periphery of the Schwann's cells. The minimal difference of the small axons in the two figures can probably be attributed to the shrinkage during degeneration (Ungváry and Léránth 1970b).

Fig. 72. Electron micrograph of cat celiac ganglion 40 hrs after cholecystectomy. Autophagous cytolysomes (→) can be seen in a degenerated axon terminal (Dt) forming a synapse (⟹) with a dendrite (D). Below the cytoplasm of a Schwann cell (Sch) is seen; the dark profile is not the product of degeneration but a normal lysosome. The connective tissue space (Cts) between Schwann cell (Sch) and its processes (Sp) contains the cross section of collagen fibrils. Inset: celiac ganglion of a cat 40 hrs after the removal of the gall bladder and of the right liver lobe. Terminal axons can be seen in an advanced stage of degeneration (Dt). Dendritic profiles (D) with characteristic tubules are enveloped by the same Schwann cell process (Sp). Scales 1 μm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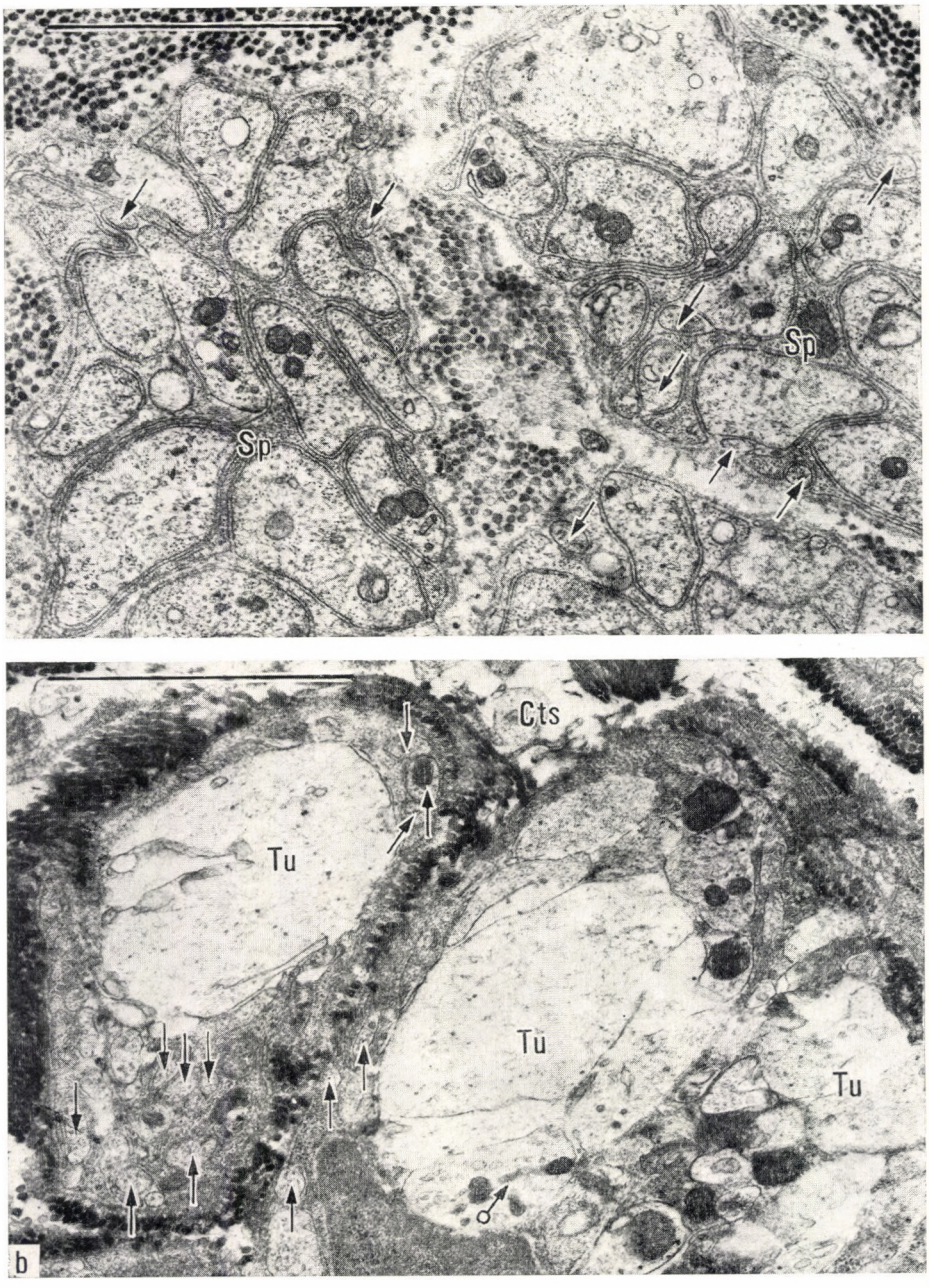


Fig. 73. Electron micrograph of a visceral (postganglionic) branch of the celiac ganglion in (a) control cat. Typical unmyelinated nerve with numerous axon profiles, varying in diameter, ensheathed by Schwann cell processes (Sp). Extremely delicate axon profiles are indicated by arrows at the periphery of the Schwann cell processes; (b) visceral (postganglionic) branch of the celiac ganglion of a cat two weeks after extirpation of both celiac ganglia. Arrows indicate (→) the profiles of small persisting axons arranged into bundles in the walls of the empty Schwann tubes (Tu). Occasionally cellular products of unknown origin (o→) are found in the tubes. Schwann cell processes are surrounded by dark collagen fibrils of the connective tissue spaces (Cts). Scales 1 μm

6.7. The functional–morphological basis of the neural regulation

The usual structure of the portal vein of the guinea-pig, cat and dog is similar to the human portal vein, well known from pathology (Köhn and Richter 1959) and to the rat portal vein used often for studies on the neural and myogenic control mechanism of the vascular neuroeffector system (Funaki 1967, Ljung 1970, Johansson et al. 1970). In 1963 Brauer wrote that the portal vein itself is a collapsible reservoir, placed between two larger reservoirs. In this reservoir the pressure fluctuations are the function of the changes in abdominal pressure which in turn depends on the diaphragmatic movements. The observations of Brauer (1963) on the pressure fluctuation in the portal vein depending on the changes in the intraabdominal pressure are substantiated (Olerud 1953). The conception of the portal vein as a passive vessel portion is less acceptable. As revealed by our studies, the powerful double muscle layer of the portal vein characteristic only of the main trunk but not of the mesenteric and lienal veins and the branches of the portal vein, may indicate that the portal vein is an active independent vascular segment capable of individual function. This hypothesis is supported by the observation of Köhn and Richter (1959), according to which in portal hypertension of any origin the wall of the portal vein (mainly the outer longitudinal muscle layer) becomes thicker, independent of the splanchnic or intrahepatic blood vessels. It is a matter of interest that the wall of the portal vein of rodents showing more powerful spontaneous phasic contractions (Booz 1964, Ljung 1970) may be devoid of the outer longitudinal muscle layer along a wider portion than the wall of the portal vein of cats and dogs, showing less spontaneous activity (Ungváry et al. 1971b).

In his monograph on the innervation of heart and blood vessels, Ábrahám (1969) expressed the view that the innervation of veins is about the same as that of the arteries. Larger nerve trunks can be seen in the adventitia; these decrease in number and in diameter toward the media. The nerve fibres in the media approach the muscle cells, where they terminate.* The majority of workers hold the view that nerve fibres do not penetrate deeper than the media. Our results obtained by light microscopy only partly agree with those of Mootz (1965) who studied the innervation of the portal vein in detail. His results obtained by the histochemical detection of acetylcholinesterase and silver impregnation are similar to ours. Different results were obtained, however, with the zinc-iodide-osmium method. When using Champy's method in his own modification Mootz (1965) failed to demonstrate nerve fibres between the bundles of muscle cells even in the adventitia. With the same technique we have shown that there are zinc-iodide-osmium-positive nerve fibres both in the adventitia and media near the intima. The same nerve fibres did not stain either with the method of Falck et al. (1962), specific for catecholamines, or with the method of Coupland and Holmes (1957) which is specific for acetylcholinesterase. The result may merit some attention, because earlier it was thought that Champy's method detects adrenergic nerve fibres, while Akert and

* The majority of authors treat the muscle layer of the adventitia together with that of the media.

Sandri (1968) found the precipitate of the zinc-iodide-osmium reaction in the synaptic vesicles of cholinergic junctions. Csillik (1970) since then showed that both cholinergic and adrenergic nerve fibres in the abundant double autonomous nerve supply of the iris stain readily with the zinc-iodide-osmium method. Our result might allow the cautious conclusion that the zinc-iodide-osmium staining correlated neither with the catecholamine nor with the acetylcholine content of the nerve fibres but perhaps was bound to some "common" structure in both nerve fibres.

The noradrenergic innervation of the trunk of the portal vein is strikingly abundant. The richness and density of the two-dimensional plexus is comparable to that of the noradrenergic plexus of the iris (Ungváry and Donáth 1969, Ungváry et al. 1971b). Johansson et al. (1970) and Ljung (1970) gave account of similar results.

Forty-eight hours or two weeks after the extirpation of both celiac ganglia monoaminergic nerve fibres were not found in the trunk of the portal vein. Similarly zinc-iodide-osmium-stained fibres also disappeared two weeks after operation (they were examined only at that time). The nerve fibres of the hepatic artery could not be demonstrated by the reaction of Falck et al. (1962), when the celiac ganglion had been excised earlier. The majority of the cell bodies where the monoaminergic and zinc-iodide-osmium-positive fibres originate may be located in the celiac ganglia. (This finding excludes the possibility that the zinc-iodide-osmium-positive nerves would be purinergic.) Extirpation of the celiac ganglion results in the transection of fibres both originating and passing through the ganglion (e.g. fibres from the right vagus nerve pass through the right celiac ganglion toward the hepatic plexus).

On the basis of our electron micrographs it can be stated that the nerve fibres ensheathed by Schwann's cells or their processes that emerge from them only occasionally, reach all the layers of the portal vein. Two types of axons can be distinguished according to the vesicles: 1. axons containing empty vesicles, and 2. axons with dense-core vesicles. The first type of axons could be found in all the layers; axons with dense-core vesicles were located mainly at the border between media and adventitia. The noraderenergic plexus demonstrated by the Falck–Hillarp technique is localized mainly in the latter area, while the main histochemical localization of the monoamine oxidase corresponds to the longitudinal muscle layer (Ungváry et al. 1971b). This is in agreement with the observation of Radymska-Wawrzyniak (1968) who found the most intense monoamine oxidase reaction in the same layer of several vein segments from different species. Lukas and Cech (1966) have shown that there is only a gross overlap between the localization of monoamine oxidase and adrenergic nerves in the iris.

We have found axonal degeneration with the electron microscope in the walls of both portal vein and hepatic artery 24–48 hrs after the excision of the celiac ganglion. Axon degeneration was found in the intima of the portal vein after excision of the right Th_6–L_2 spinal ganglia indicating undoubtedly the sensory innervation of the segment. At the same time no nerve fibres originating from the spinal ganglia could be detected in the hepatic artery. It is known that changes in the portal venous blood flow are followed in general by changes in the blood flow of the hepatic artery. Based on our results we can suggest that the informa-

tion obtained by the intramural receptors of the portal vein may result in reflex changes in the blood flow of the hepatic artery (Fig. 59). The presence of such a reflex arc does not exclude the possibility of autoregulation, humoral or any other kind of regulation (Ungváry et al. 1972). No degenerated nerve fibres have been found in the portal vein after the transection of the vagus nerve. This finding is not very surprising, because to our best knowledge there are no nerve cells in the wall of the portal vein, consequently the presence of preganglionic nerve fibres is also ruled out. (Postganglionic vagus fibres would probably originate distal to the cardia.) Centripetal sensory fibres running toward higher centres could have shown the signs of degeneration, but we have not been able to observe any (Ungváry et al. 1972). The presence of vagus fibres innervating the portal vein or hepatic artery would be surprising because experimental manipulation of the nerve had no effect on the vessels (Bradley 1963b, Ungváry and Varga 1971c).

In the light of its highly organized wall structure and rich sensory and motor innervation the portal vein can be considered a venous segment of considerable independence. It is well known from neurophysiology that a small change in the frequency of spikes, used for stimulation of different sympathetic efferent fibres, may evoke considerable changes in the blood flow of the region supplied (Löfving 1961). The noradrenaline released from the nerve endings during stimulation causes vasoconstriction. The vascular reaction depends not only on the frequency of spikes but also on the mural structure and the number of axon terminals in the vessel (Khayutin 1964, Fedina 1967). Electrical stimulation of the splanchnic nerve or hepatic plexus is known to decrease total hepatic blood flow to its one-third or one-fourth by increasing the vasoconstrictor tone. Similarly, most functions of the organ are affected by changes in sympathetic influence.

In view of the above considerations and Yamada's (1965) demonstration of nerve fibres with dense-core vesicles in the liver, our observation of the large number of nerve fibres containing noradrenaline in the liver is not so much surprising. These fibres, as already described, join primarily the vessels of the portal channel and branches of the hepatic vein (Ungváry and Donáth 1969). Detached from the blood vessels and bile ducts "free" nerve fibres, yielding catecholamine fluorescence, were found only in the falciform ligament. All nerve fibres in the vessel walls are thin axon terminals along which at regular distances 0.5–1 μm thick, 1–2 μm long varicose thickenings can be seen with formaldehyde-induced green fluorescence. Not regarding the media reactions that correspond to the hepatic sphincters, the axons form a two-dimensional plexus along the border between the media and adventitia. No nerve ending-type terminations could be demonstrated in the network. This localization characteristic of the autonomic plexus agrees well with the electron microscopic observations of Brettschneider (1962). He showed that in the arteries and arterioles the axon bundles formed from the preterminal plexuses in the adventitia run toward the outer part of the media.

As it has already been mentioned, by the description of the noraderenergic innervation of intralobular areas, we saw nerve fibres entering only from the peri- and circumlobular areas into the lobules. Only sympathetic stimulation, i.e. the

stimulation of the splanchnic nerves or the sympathetic centres in the hypothalamus could influence liver functions: e.g. an increase in glycogen metabolism, glycogen phosphorylase and glucose-6-phosphatase activities, a change in bile secretion (Ban 1965). Hence, if the neurones affected cell function directly, then these effects would be realized via the adrenergic axon terminals that run to the liver cells. However, we could detect noradrenergic nerve fibres in the Disse's spaces only in the guinea-pig applying an improved freezing–drying technique. In other species the presence of the innervation of parenchyma cells can be excluded with almost absolute certainty (Ungváry and Donáth 1969). As far as the results of Ban (1965) are concerned, Celander (1954) has earlier shown that the sympathetic nervous system controls directly only the vascular smooth muscle, while the sympathetic regulation of metabolic processes is realized via the hormones of the adrenal medulla. The existence of these mechanisms seems to be supported by the results of Wurtman (1975).

It is beyond doubt, however, that noradrenergic nerve fibres enter the periphery of the lobules.

Localization of the nerve fibres corresponds to that of the arterial sinusoids and arterial twigs described by Elias and Petty (1952), Bloch (1970) and others. The nerve fibres do not penetrate deeper than the level where these enter the portal sinusoids. The function of the nerve fibres may be connected with the regulation of the junction between arterial and portal sinusoids (Ungváry and Donáth 1969, Holzbauer and Sharman 1972, Blouin and Côté 1973).

There is an abundance of noradrenergic nerve fibres in the inter- and circumlobular area. One can assume that the mixing of arterial and portal blood in the lobules or rather in the acini may be under neural control at least under certain circumstances. In these areas, as known from the works of Bloch (1970), Rappaport et al. (1970) and others, there is an abundance of arterioportal connections even in normal livers. It is of some interest that the intense reaction of the inter- and circumlobular areas is characteristic mainly of the peripheral part of the liver, while it is rarely seen in the central parts of the lobes near the hilum. This might imply a more pronounced vasoconstriction in response to sympathetic stimulation at the periphery than in the perihilar region of the liver lobe (Ungváry and Varga 1971a, b).

The rich noradrenergic nerve fibre supply of larger portal vessels may be similarly involved in the regulation of redistribution of blood within the organ. The liver assumes a passive role and it does not alter the volume of the blood that flows in through the portal vein. The volume of blood from the splanchnic area that by all means perfuses the liver is determined distally to the portal vessels. Therefore, there is only one explanation at hand, namely that the nerve bundles that are situated along the portal system might be in different functional states along the different portal branches. Accordingly, blood flow in certain parts of the organ may be more abundant, faster or else poorer and slower than in other regions.

Most probably the nerve plexus along the hepatic artery which is very pronounced in cats, dogs and guinea-pigs might participate in the arterial compensation when portal blood flow is altered (Ungváry and Donáth 1969).

There are only a few noradrenergic nerve fibres along the bile ducts. This would support the physiological observations according to which the biliary tree is mainly under parasympathetic control.

The nerve fibres found in the Glisson's capsule were always running along the blood vessels and for this reason they can be regarded as vasomotor nerve fibres. Free nerve fibres that do not join blood vessels can be found only in the falciform ligament. This is interesting because it shows that noradrenergic nerve fibres enter the liver not only along the portal and hepatic venous channels but also through the peritoneal attachments of the liver (Ungváry and Donáth 1969).

Abundant acetylcholinesterase-positive nerve fibres within the liver could be detected only in the guinea-pig. These fibres are not restricted to the portal channels, where they mainly supply the walls of the bile ducts, but enter between the hepatic cell plates, presumably into the Disse's spaces (Ungváry 1971, Ungváry and Donáth 1975). It seems to be of interest in this respect that the vas deferens, known to possess only sympathetic noradrenergic innervation in other species, in guinea-pigs receives acetylcholinesterase-positive fibres, too (Jacobowitz and Koelle 1965). In the livers of mice, rats, cats and dogs only few acetylcholinesterase-positive nerve fibres are found exclusively in the portal channels where they belong to the walls of bile ducts. We suggest that the fibres originate mainly in the ganglia located in the hilum because there was no considerable change in the number of acetylcholinesterase-positive fibres after extirpation of the celiac or intervertebral ganglia or transection of the vagus nerve.

The musculature of the hepatic vein near the inferior vena cava is particularly well developed. It is located mainly in the adventitia. This strikingly wide musculature may indicate a sphincter function of this vascular segment. The vascular segment was first described by Arey and Simmonds (1920) and Franklin (1937) and had been called "hepatic sphincter" at that time. Later, similar other structures were found in the hepatic venous system with the morphological features indicating a possible sphincter function. They were primarily found at the confluence of the hepatic venous branches of different order of magnitude (Deysach 1941, Gibson 1959). Though the localization and structure of hepatic sphincters may differ in the various mammals, their function seems to be unequivocal and important in influencing hepatic haemodynamics (Andrews et al. 1973). Azarova (1966), using the silver impregnation technique, described that a large number of nerve fibres reach the hepatic venous system. Bánfai et al. (1953) attributed a vasoconstrictor function to the right phrenic nerve in the region of the hepatic sphincters.

Using the degeneration technique, we could follow the fibres from the right phrenic nerve only to the most superficial layer of the adventitia (Fig. 74). This finding alone cannot be taken as a conclusive evidence against the efferent function of these nerve fibres. However, the fact that no ganglion cells can be found in the wall of the hepatic vein rules out the possibility that these fibres would be preganglionic elements. Hence we concluded that the nerve fibres reaching the hepatic vein from the right phrenic nerve are sensory elements but they do not enter into close contact with the muscle layer of the vascular wall (the are not at all sympathetic potsganglionic fibres). On the basis of our histological observations and

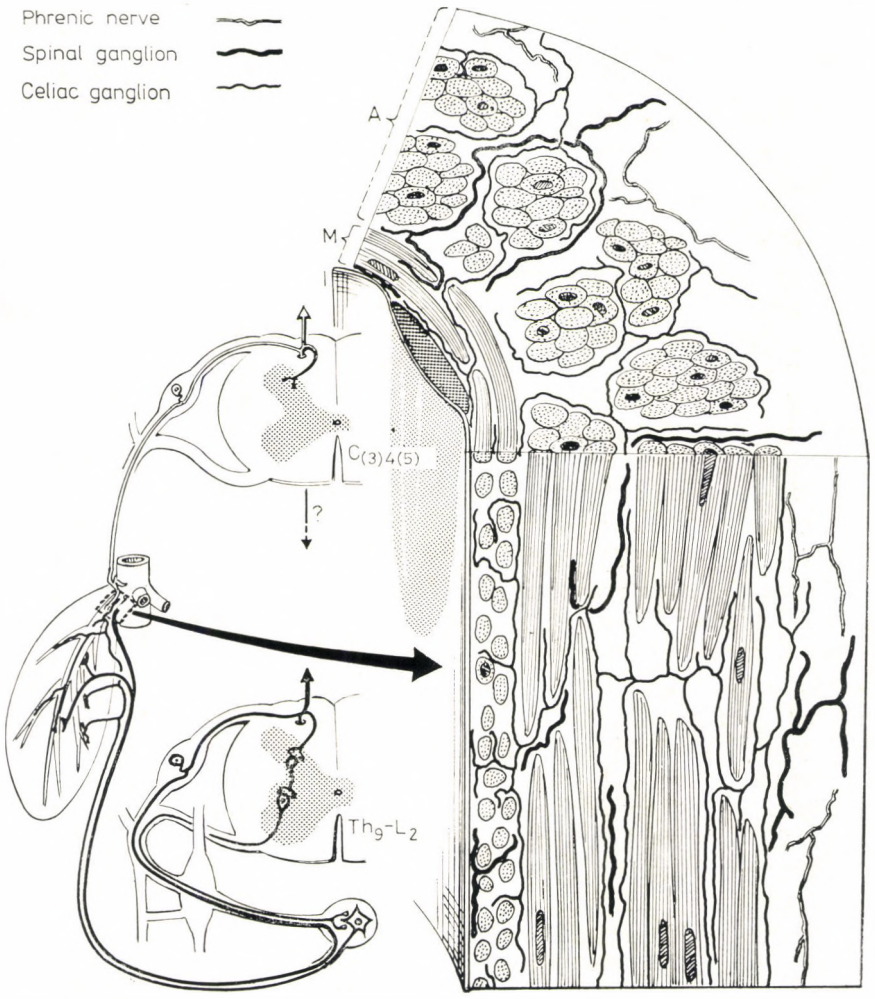


Fig. 74. Scheme summarizing the innervation of the hepatic venous system. For further explanations see Chapter 6

evidence that electrical stimulation of the right phrenic nerve has no direct vasoconstrictor effect on the hepatic vein (cf. p. 141), we concluded that the presumption of Bánfai et al. (1953) suggesting that the fibres from the phrenic nerve were the constrictors of the hepatic sphincters is probably a misconception.

The outer longitudinal (adventitia) and inner circular (media) muscle layers of the hepatic vein, before the hepatocaval junction have an unusually rich innervation (Ungváry and Donáth 1969). Similarly, a large number of nerve fibres reach the smaller, second and third order, hepatic venous branches, too. Both degeneration and catecholamine fluorescence studies indicate that the majority of these nerve fibres are sympathetic postganglionic fibres originating in the celiac

ganglion (Fig. 74). In addition to these fibres, a considerable number of sensory fibres reach the muscle layer and approach even the endothelium. The sensory nerve fibres originate from the right spinal ganglia Th_9–L_2 (Fig. 74). Very unfortunately since the sensory fibres can be identified only by secondary degeneration and it was not possible to recognize structural peculiarities that might distinguish sensory fibre terminals from autonomous endings. The observation that the subendothelial terminal fibres are more often without any visible contact with the Schwann cell processes might indicate however that true naked terminal axons are more likely to be sensory in nature, whereas autonomous terminal fibres at their terminal parts, although they also emerge from the surrounding Schwann cell processes, do not generally loose their contacts with the Schwann cell system.

There are two kinds of local varicose thickenings on the terminal axons in the musculature of the hepatic vein: 1. varicosities containing dense-core vesicles of 450–500 Å in diameter and 2. with empty synaptic vesicles of 400–500 Å in diameter. The two types of terminal axons may correspond to the two types of autonomic nerve fibres. The axons containing the dense-core vesicles are most probably identical with the monoaminergic fibres demonstrated by the fluorescence technique. The fact that there are terminal axons with dense-core vesicles in the vicinity of the endothelium shows that a close association with the endothelium does not unambiguously mean sensory function.

The question whether or not the wall of the hepatic vein is innervated by cholinergic, parasympathetic fibres cannot be answered on the basis of our present findings. As earlier discussed, intense acetylcholinesterase staining of certain preterminal and terminal fibres in the muscle layer cannot be taken as a decisive evidence for the cholinergic nature of the neural elements. Transection of the vagus nerve resulted in no degeneration of terminal axons in the wall of the hepatic vein. Since there are no ganglionic cells in the wall of the hepatic vein which could synapse with possible preganglionic nerve fibres from the vagus, axonal degeneration in the vein after transection of the vagus nerve would indicate sensory fibres. However, no degenerating axons were found after such transection. The question whether or not postganglionic nerve fibres from the vagus participate in the innervation of the hepatic vein cannot be answered at present. Physiological experiments do not support the notion, because following the stimulation of the vagus nerve no effect on hepatic blood flow was observed (Ginsburg and Grayson 1954, Bradley 1963b, Ungváry and Varga 1970). It is possible from a theoretical point of view that the celiac ganglion or some other distal part of the autonomic plexus contains ganglionic cells sending their axons to the hepatic vein which receive their preganglionic fibres from the vagus.

Considering the efferent part of the hepatic circulation, there are three ways by which the hepatic venous system can influence liver haemodynamics: 1. changes in blood pressure in the main hepatic venous trunks, 2. rhythmic changes in venous drainage, and finally 3. local changes in the pressure of the hepatic vein (Brauer 1963). By these ways the hepatic venous system participates in the regulation of hepatic blood flow (reservoir function), in forming the dynamics of intrahepatic pressure, in changes of the fluid composition produced by the cells and in fluid movement within the structure.

Besides the rich vasomotor, primarily monoaminergic innervation, our studies demonstrated the presence of receptor-type nerve fibres running toward the spinal ganglia Th_9–L_2, and the right phrenic nerve. They are located in the hepatic sphincters and in the proximal part of the hepatic venous tree down to the third order divisions. These findings suggest the existence of a reflex arc. This reflex arc receives information concerning the flow and pressure conditions in the hepatic venous system; then, corresponding to intrahepatic requirements, it brings about vasoconstriction in the main hepatic venous trunks (neural control of the reservoir function) or locally, in the smaller hepatic venous branches (neural control of the intrahepatic blood flow redistribution) (Fig. 74; Ungváry and Léránth 1972).

The detection of nerve terminals from the right phrenic nerve only partly supports the conception of Bánfai et al. (1953). As already stated, the right phrenic nerve may have at best a sensory function at the confluence of the hepatic vein and inferior vena cava. The function we attribute here is a possible presumption. It seems to us reasonable to suppose that afferent fibres of a reflex arc run in the right phrenic nerve which participate in the fine regulation of the intermittent changes in hepatic outflow resulting from the rhythmic movements of ventilation.

There is a rather widespread view that the nerve fibres do not penetrate the media of the blood vessels (Rovick and Randall 1967) and that the vascular smooth muscle cells are governed by an outer neural and an inner myogenic activity. Therefore, it is of considerable interest that we have detected nerve fibres between the bundles of smooth muscle and even in the vicinity of the endothelium in both hepatic and portal veins. The minimum distance between axon terminal and smooth muscle cell was found to be 2500 Å in our study. The same distance has been estimated to be 600 Å in arterioles of the rat ear (Appenzeller 1964), 1000 Å in the arterioles of the mesentery of rats (Matthews and Gardner 1966) and 4000 Å in the pulmonary artery of rabbits (Verity and Bevan 1968). Somlyó and Somlyó (1968) thought this minimal distance between nerve terminal and smooth muscle cell to be of great importance regarding the function of blood vessels. The maximal distance between axon and muscle is in general the whole width of the media because nerves do not enter this part of the vascular wall. The fact that terminal axons can be found in the media and even in the intima of the hepatic veins, i.e. the maximal distance is considerably shorter, secures a more intimate connection between the nerves and the smooth muscle cells in spite of the larger minimal distance between them. This may imply that the outer muscle layer under neural regulation dominates the control of the efferent hepatic vessels in this part of the hepatic venous tree. The dominating neural influence enables the faster, more precise and better adaptation of the vascular segment to local changes in hepatic blood flow (Ungváry and Léránth 1972).

On the basis of the data already mentioned earlier, we looked for the terminal processes of Dogiel type II cells in the prevertebrate ganglia. We succeeded in demonstrating that central processes of a group of ganglion cells, presumably those of Dogiel type II cells located in the porta hepatis, gall bladder and bowels, establish synapses with neurones of the prevertebrate ganglia closing thus a reflex arc in a peripheral ganglion. Our results obtained using more advanced morphological methods proved the earlier suggested hypothesis (Ivanov 1937, Kuntz

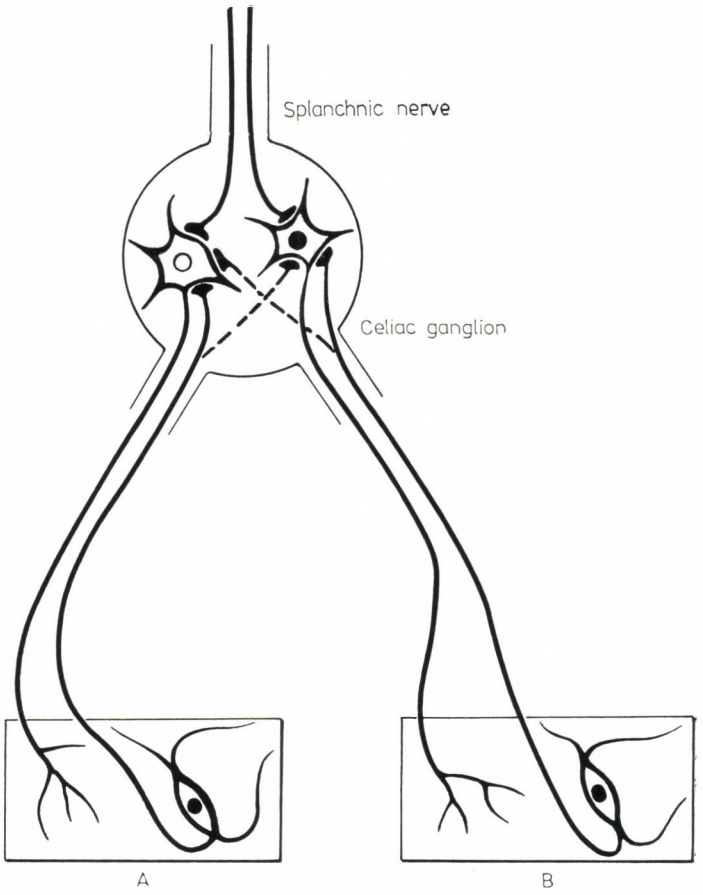


Fig. 75. Scheme showing the suggested peripheral vegetative reflex arc. A or B may correspond to liver, gall bladder or small intestine. For further explanations see Chapter 6

1938, Grigorjeva 1949) on the basis of silver impregnation studies, and which was challenged because of the lack of general acceptance of the method used. The scheme in Fig. 75 indicates that the processes of ganglion cells in the small intestine (A) and porta hepatis or gall bladder (B) project onto the prevertebral ganglia, where at least part of them terminate. Taking into consideration that the neuronal fibres of the prevertebral ganglia reach several organs, the intramural nerve cell processes might close theoretically two different kinds of reflex arcs depending on whether the efferent fibres run to the same or to an other organ. We are of the opinion that this reflex arc might play an important role in establishing the proper functional relationship between the splanchnic and portal vascular beds. Furthermore, through this connection pressure changes in either of the intrahepatic vessel systems might be easily compensated for in the other. Finally, this arc closed in the autonomic ganglia may underlie the solution of a number of physiological problems. Recently, the existence of autonomic periph-

eral reflex arcs has been confirmed (Bulygin and Archakova 1971, Fehér and Vajda 1974, Fehér and Csányi 1974, Rozsos et al. 1974) and accepted (Gabella 1972, Haefely 1972, Szentágothai 1974).

It appears that these reflexes may be the members of a young, undifferentiated reflex group without predetermined function. Szentágothai (1952) wrote that neural centres of determined, fixed physiological and anatomical organization are capable of working out in the biological sense purposeful responses, subserving the animal's existence only under a restricted number of conditions. By no means are they capable of providing orientation under unforeseen changes of environmental conditions, and what is more by no means are they capable of establishing new functional connections between centres which had not been in contact before. Apart from the fact that the Dogiel type II neurons are one of the least differentiated nerve cells there is no supporting evidence that the reflex arc would actually be such an undifferentiated occasional arc with considerable plasticity. It is a fact, however, that the innervation of the visceral blood vessels does not seem to be of too much importance in maintaining the resting state under normal conditions. For example, denervation, i.e. the extirpation of the prevertebral ganglia has no significant influence on any part of the splanchnic or hepatic vascular bed (Bradley 1963a, b). Neural influence may become important, however, during changes in the splanchnic and hepatic system. Because there is a high number of possible changes, one can assume that a less rigid and less differentiated neural structure is more suitable for the detection and correction of the alterations. The above-outlined peripheral autonomic reflex arc may provide a morphological basis for such reflexes. These reflexes may turn out to be important factors in maintaining the vegetative homeostasis under unforeseen conditions.

7. Perihilar (central) "core" and peripheral "shell" of the liver lobe

7.1. Morphological differences between the (central) perihilar "core" and peripheral "shell"

Quantitative analysis of histological sections of the liver have revealed that the sinusoids take up 16% of the total area at the periphery and 18.5% in the central parts of the liver lobe. Taking the value at the periphery for 100%, the central value amounts to 118%. The difference is significant, $p < 0.05$ (Ungváry et al. 1969b, Ungváry and Varga 1971a).

The number of branchings were counted on corroded casts of the portal or hepatic venous system down to the sinusoids in both central part and at the periphery of the lobes. The sinusoids correspond to the 4th–6th, and the 6th–10th branchings in the central part and at the periphery, respectively (Ungváry and Varga 1971a).

By means of the Falck–Hillarp technique we could demonstrate larger number of monoaminergic fibres in the perilobular portal channels only at the periphery of the lobes. These results have been dealt with in details in Chapter 6.

7.2. The effect of vasoactive substances on local blood flow in the central and peripheral regions of the liver lobe

7.2.1. Administration of adrenaline (10 μg/kg b.w.) into the portal vein significantly increased blood pressure in both the femoral artery and portal vein. Local blood flow was found to decrease first and to increase later in both the hilar and peripheral parts of the liver lobe. There was no difference in the response of the two parts at a given period of the experiment. After intravenous administration, the same dose of adrenaline had practically the same effect but there was a significant reduction in heart rate (Fig. 76; Ungváry and Varga 1971 a).

7.2.2. After the administration of noradrenaline (10 μg/kg b. w.) into the portal vein there was a significant increase in blood pressure in both the portal vein and femoral artery, ($p < 0.05$) and a significant decrease in heart rate ($p < 0.05$). The response to noradrenaline in the central area of the lobe was not consistent. Local blood flow decreased in 6 cases and increased in 2. Of the 6

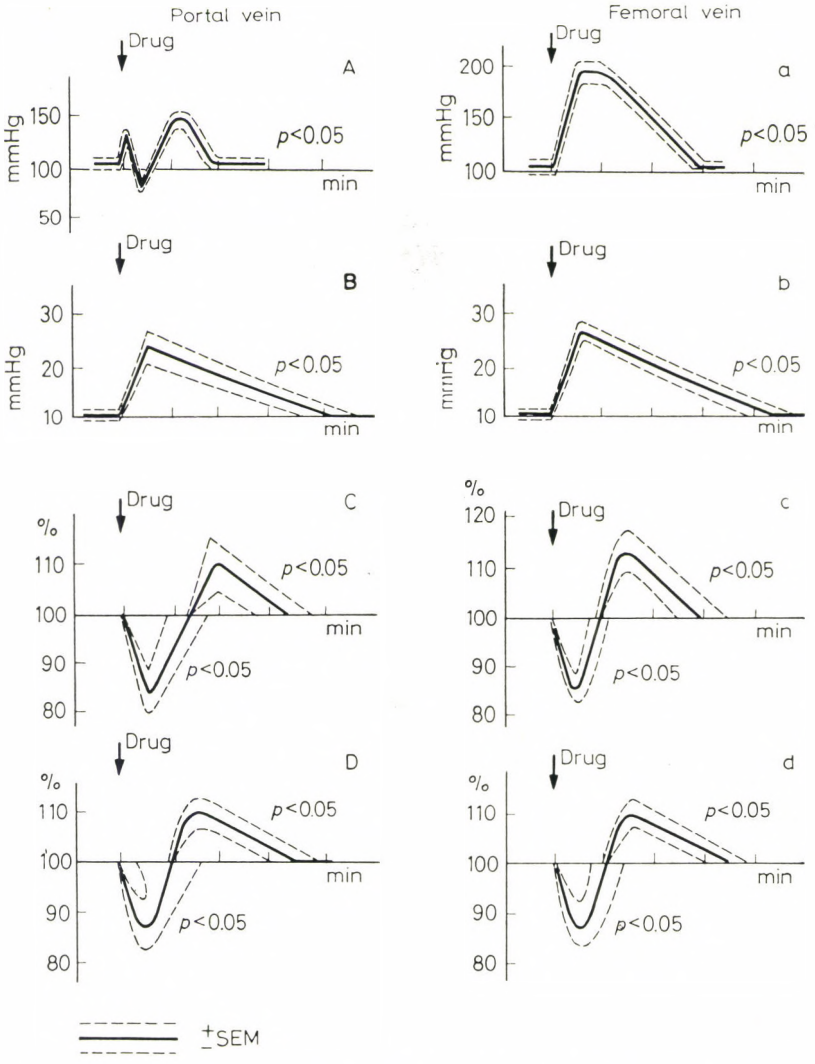


Fig. 76. Effect of adrenaline (10 μg/kg) injected into the portal vein (A, B, C, D) and into the femoral vein (a, b, c, d) on blood pressure (A, a), portal venous pressure (B, b), local blood flow in the peripheral (C, c) and central (D, d) parts of the liver lobe in 8 animals

cases on 2 occasions a short increase preceded the decrease, while in 2 others the initial decrease was followed by a somewhat longer increase. On the periphery of the liver lobe the decrease in response to noradrenaline was more consistent. In 2 cases it was preceded by a short increase and in 2 others it was followed by

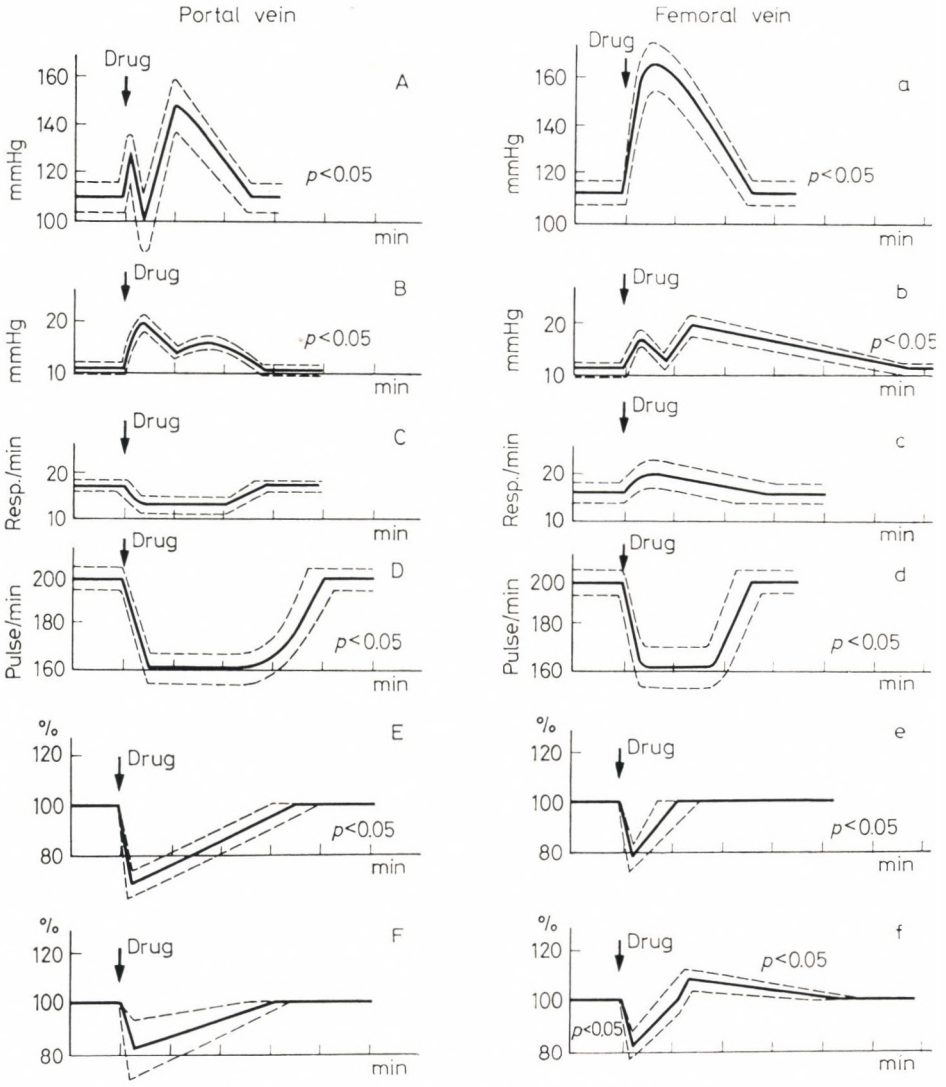


Fig. 77. Effect of noradrenaline (10 μg/kg) injected into the portal vein (A, B, C, D, E, F) or into the femoral vein (a, b, c, d, e, f) of 8 animals on blood pressure (A, a), portal venous pressure (B, b), frequency of respiration (C, c), pulse rate (D, d), local blood flow at the periphery (E, e) and in the central region (F, f) of the liver lobe

a longer increase. There were no significant differences between the local blood flow responses to the drug in the central and peripheral areas. The same dose of noradrenaline intravenously induced similar changes in heart rate, femoral and portal pressures as after portal administration. Local blood flow in the central

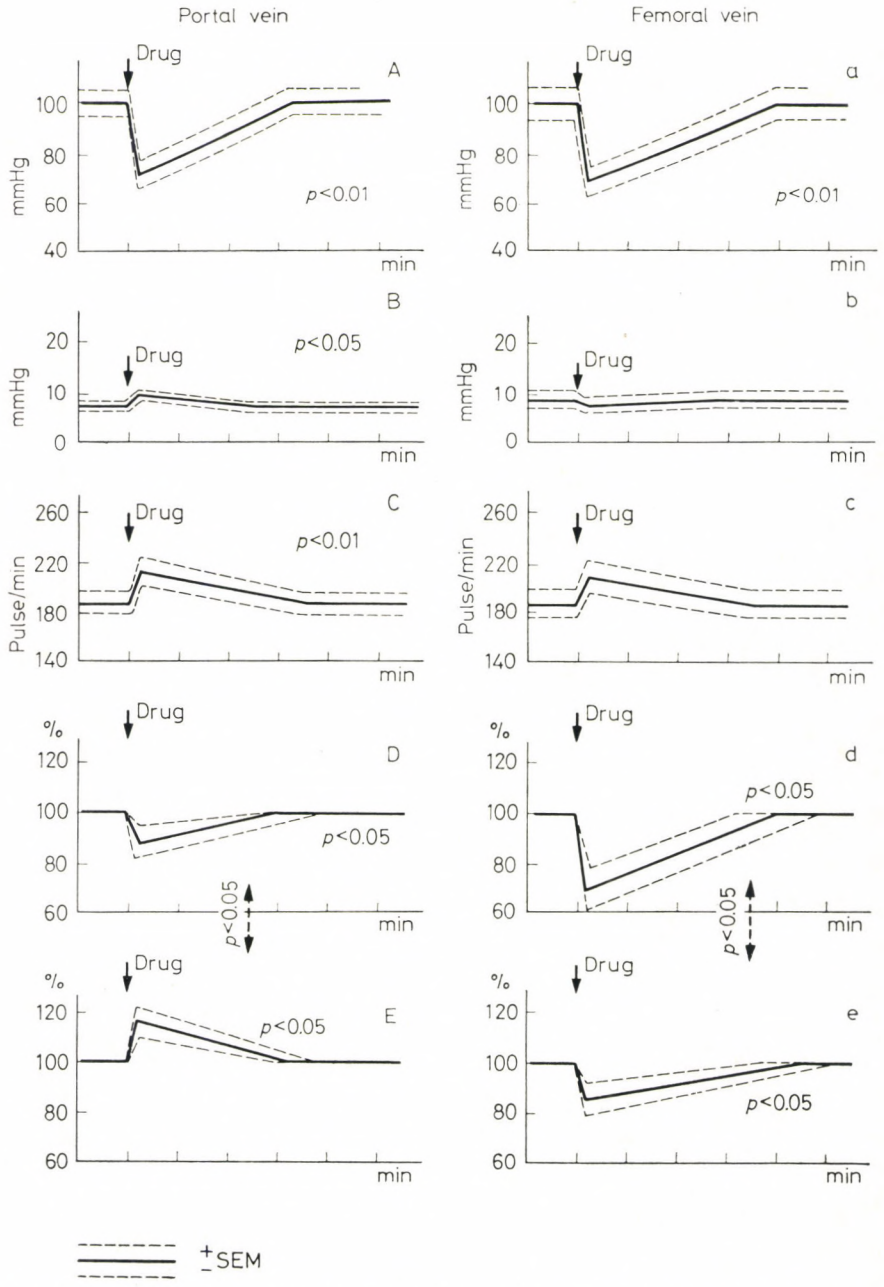


Fig. 78. Effect of isopropyl noradrenaline (2 μg/kg) injected into the portal vein (A, B, C, D, E), or into the femoral vein (a, b, c, d, e) of 7 animals on blood pressure (A, a), portal venous pressure (B, b), pulse rate (C, c), local blood flow at the periphery (D, d), and central region (E, e) of the liver lobe

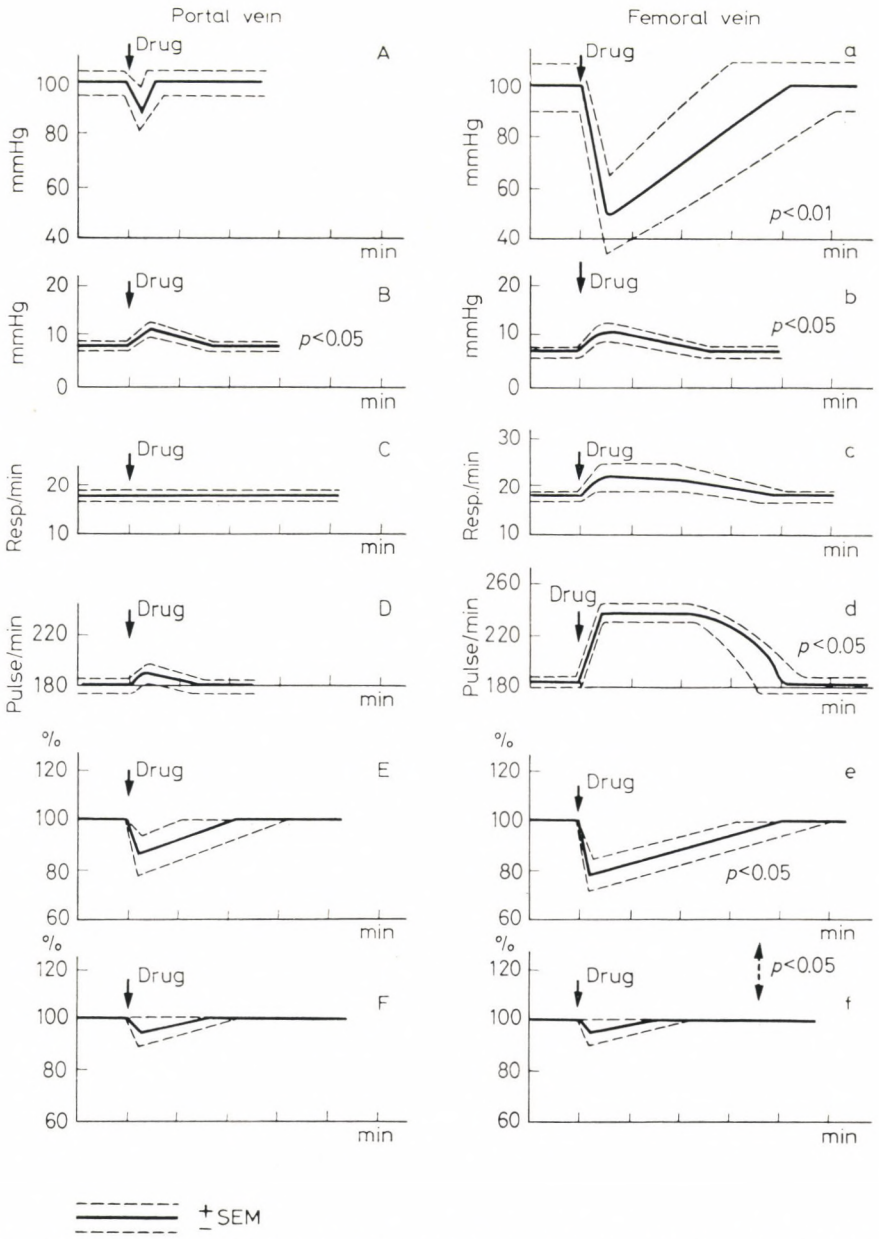


Fig. 79. Effect of acetylcholine (20 μg/kg) injected into the portal vein (A, B, C, D, E, F), or into the femoral vein (a, b, c, d, e, f) of 6 animals on the blood pressure (A, a), portal venous pressure (B, b), frequency of respiration (C, c), pulse rate (D, d) and local blood flow at the periphery (E, e) or in the central region of the liver lobe (F, f)

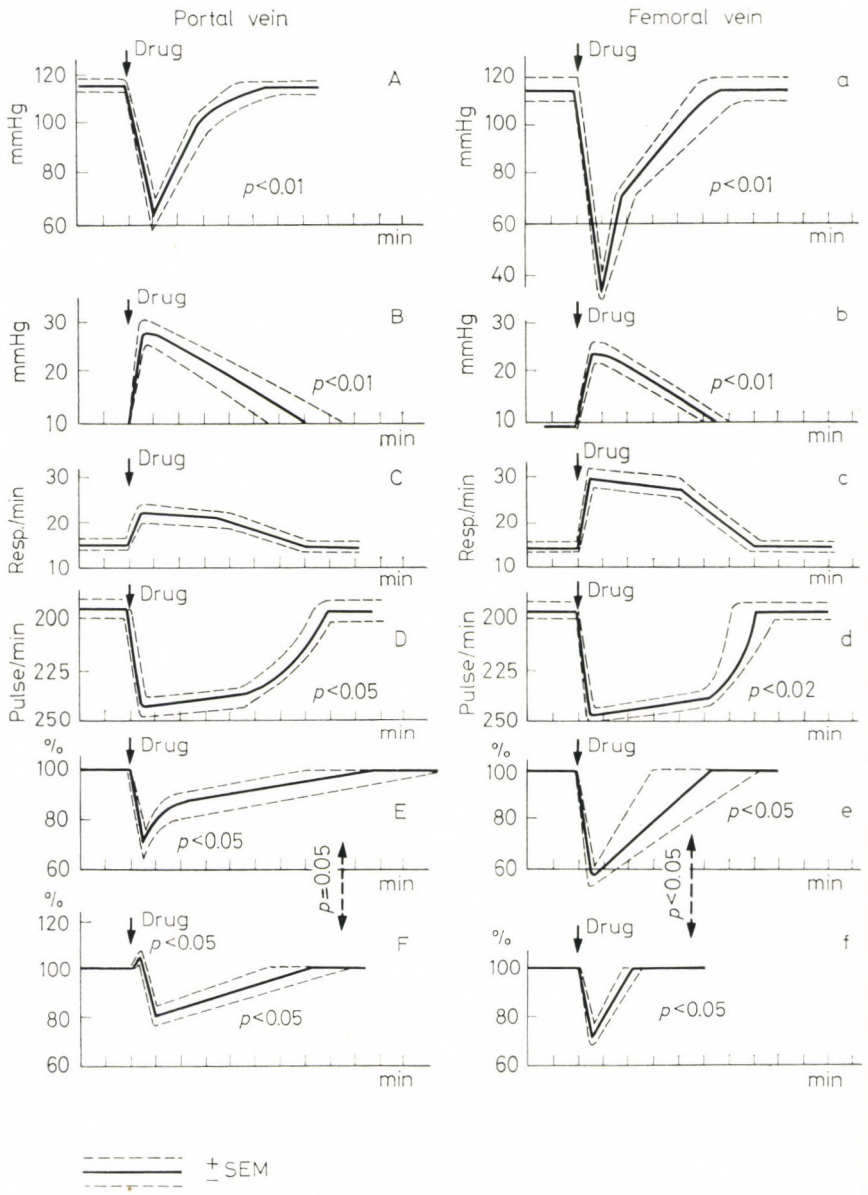


Fig. 80. Effect of histamine (20 μg/kg) injected into the portal vein (A, B, C, D, E, F), or into the femoral vein (a, b, c, d, e, f) of 8 animals on the blood pressure (A, a), portal venous pressure (B, b), frequency of respiration (C, c) pulse rate (D, d) and on the local blood flow at the periphery (E, e) or in the central region (F, f) of the liver lobe

area showed a biphasic change: a decrease was followed by an increase. Both changes were significant ($p < 0.05$). In 3 cases the decrease was preceded by a short initial increase. At the periphery of the liver lobe there was a decrease in local blood flow which was followed in 4 cases by a small increase. No significant difference was found between the identical responses of the two areas (Fig. 77; Ungváry and Varga 1971a).

7.2.3. Administration of 2 μg/kg isopropyl noradrenaline into the portal vein resulted in a significant increase in portal pressure ($p < 0.05$), heart rate ($p < 0.01$) and a significant decrease in blood pressure ($p < 0.01$) in the femoral artery. There was an increase in the local blood flow of the central areas of the lobes. This increase was preceded in 2 cases by a shorter decrease. Local blood flow decreased at the periphery in general except for 2 cases when it increased. There was a significant difference between the responses of the central and peripheral parts ($p < 0.05$). Intravenous administration of isopropyl noradrenaline in a 2 μg/kg dose resulted in a decrease in mean arterial blood pressure ($p < 0.01$). Pressure in the portal vein rose moderately in 4 cases and dropped slightly in 3 cases. The local blood flow response to the drug was uniform, there was a decrease in the central area as well as at the periphery of the lobe. In 2 cases an initial increase preceded the decrease in the central area. The change in blood flow in the central and peripheral regions was significantly ($p < 0.05$) different (Fig. 78; Ungváry and Varga 1971a).

7.2.4. Injection of 20 μg/kg acetylcholine into the portal vein was followed by a significant increase in portal pressure ($p < 0.05$). Local blood flow in the central area increased in 2 and decreased in 4 cases. In 2 of the 4 cases the decrease was preceded by an increase. Local blood flow at the periphery showed similar changes. Intravenous administration of 20 μg/kg acetylcholine resulted in a significant drop of blood pressure ($p < 0.01$) and a significant rise in portal pressure ($p < 0.05$) and heart rate ($p < 0.05$). In the central part of the lobe local blood flow decreased in 4 cases slightly and increased in 2 cases after a short initial decline. At the periphery of the lobe local blood flow decreased in response to acetylcholine in all the 6 cases. The difference between the responses of the central area and periphery was significant ($p < 0.05$, Fig. 79; Ungváry and Varga 1971a).

7.2.5. Injection of 20 μg/kg histamine into the portal vein was followed by a significant decrease in blood pressure ($p < 0.01$), and by a significant increase in portal pressure ($p < 0.01$). In 6 out of 8 animals a short initial increase in blood flow of the central area was followed by a longer, marked decrease. At the periphery a similar biphasic response was observed in 2 cases only, the other animals responded to the injection of histamine with a decrease in local blood flow. The difference between the responses of the central part and periphery was at the limit of significance. The intravenous administration of histamine in a 20 μg/kg dose had the same effect on blood pressure, heart rate and portal pressure as injection via the portal route. Local blood flow decreased in both the central and peripheral parts of the lobe. The decrease was more pronounced at the periphery than in the central area ($p < 0.05$, Fig. 80; Ungváry et al. 1969b, Ungváry and Varga 1971a).

7.3. Effect of haemorrhage on local blood flow in the central and peripheral regions of the liver lobe

In experimental hypotension of dogs with a blood pressure stabilized at 45 mm Hg there was a significant increase in heart rate ($p < 0.05$). A reduction in local blood flow was observed in both the central area and at the periphery of the lobe, the extent of decrease was more marked, however, at the periphery ($p < 0.001$). Within 2 min after the stabilization of blood pressure at 40–45 mm Hg local blood flow stabilized at a low level and did not change further within the next 30–60 min period of observation (Fig. 81; Ungváry et al. 1969b, Ungváry and Varga 1971a).

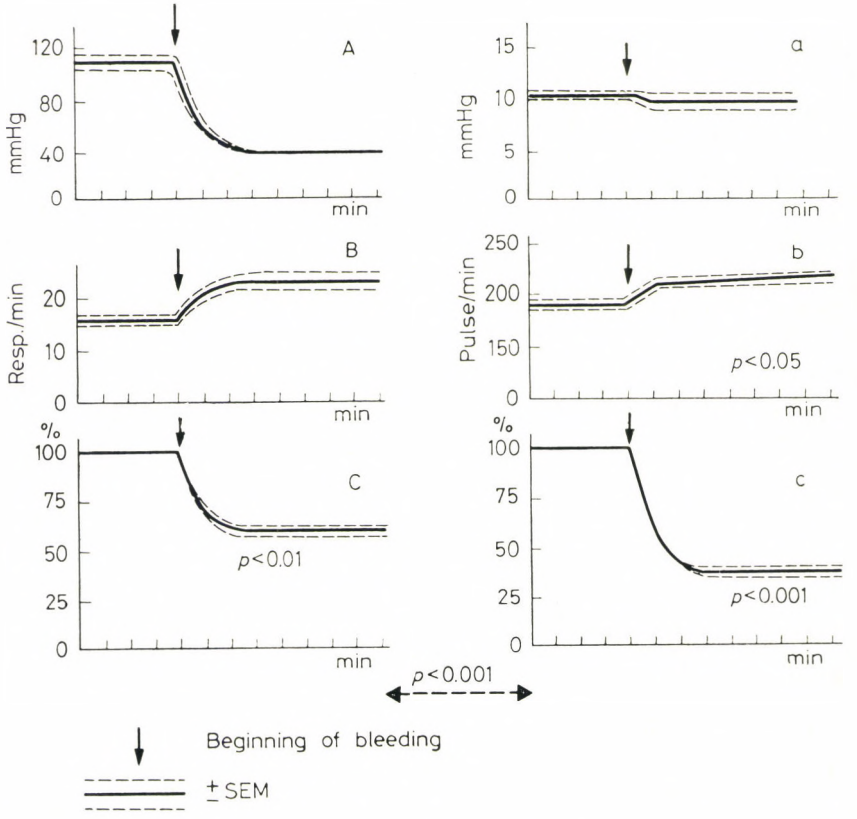


Fig. 81. The effect of bleeding on blood pressure (A), portal venous pressure (a), frequency of respiration (B), pulse rate (b) and on local blood flow in the central (C) or peripheral region (c) of the liver lobe in 15 animals

7.4. Effect of electrical stimulation of nerves on the blood flow in the central and peripheral regions of the liver lobe

7.4.1. Electrical stimulation of the hepatic plexus resulted in the significant elevation of portal pressure ($p < 0.05$) and in temporary apnoea. Local blood flow in the central area differed from that at the periphery during and even shortly after stimulation. Both responded with a decrease which was significantly more pronounced at the periphery ($p < 0.05$, Fig. 82; Ungváry and Varga 1970b, c).

7.4.2. Electrical stimulation of the splanchnic nerve brought about an increase in blood pressure ($p < 0.001$). Portal pressure was first elevated ($p < 0.01$), then it declined ($p < 0.05$). When the stimulation was interrupted a moderate increase occurred again ($p < 0.05$). Heart rate decreased ($p < 0.01$) accompanied by a transitory apnoea. After a temporary increase, a decrease in local blood flow was registered at the central and peripheral areas of the lobe ($p < 0.05$ and $p < 0.02$, respectively). The response at the periphery was more marked and longer and differed significantly from the response of the central area ($p < 0.05$, Fig. 83; Ungváry and Varga 1970b, c).

7.4.3. Electrical stimulation of the left vagus nerve on the neck elicited a significant drop in blood pressure ($p < 0.01$) and a rise in portal pressure ($p < 0.01$). Heart rate fell nearly to zero ($p < 0.001$) and apnoea, almost 30 sec in duration, was recorded. Local blood flow decreased both near the hilum and at the periphery with a deeper and more prolonged response in the latter region. There was a significant difference between the responses of the two areas ($p < 0.02$, Fig. 84; Ungváry and Varga 1971b).

Electrical stimulation of the vagus nerve at the cardia failed to produce measurable changes in the recorded parameters (Ungváry and Varga 1971 b).

7.4.4. Apart from a transitory apnoea no detectable alterations were brought about by the electrical stimulation of the left phrenic nerve on the neck (Ungváry and Varga 1970b, c).

7.4.4. Electrical stimulation of the right phrenic nerve on the neck resulted in an increase in portal pressure ($p < 0.001$) and a transitory apnoea in cases when the diaphragm was not transected and the pleural cavity was left intact. Regional blood flow in the central area showed a moderate increase ($p < 0.05$) at the beginning and then it fell back to the original value at the end of the stimulation. There was a pronounced decrease in local blood flow at the periphery throughout stimulation ($p < 0.02$). The difference between the responses of the two areas was significant ($p < 0.01$, Fig. 85; Ungváry and Varga 1971 b, c).

After transection of the diaphragm around the inferior vena cava, mediastinal stimulation of the right phrenic nerve did not give rise to changes in the parameters studied (Fig 85; Ungváry and Varga 1970b, c).

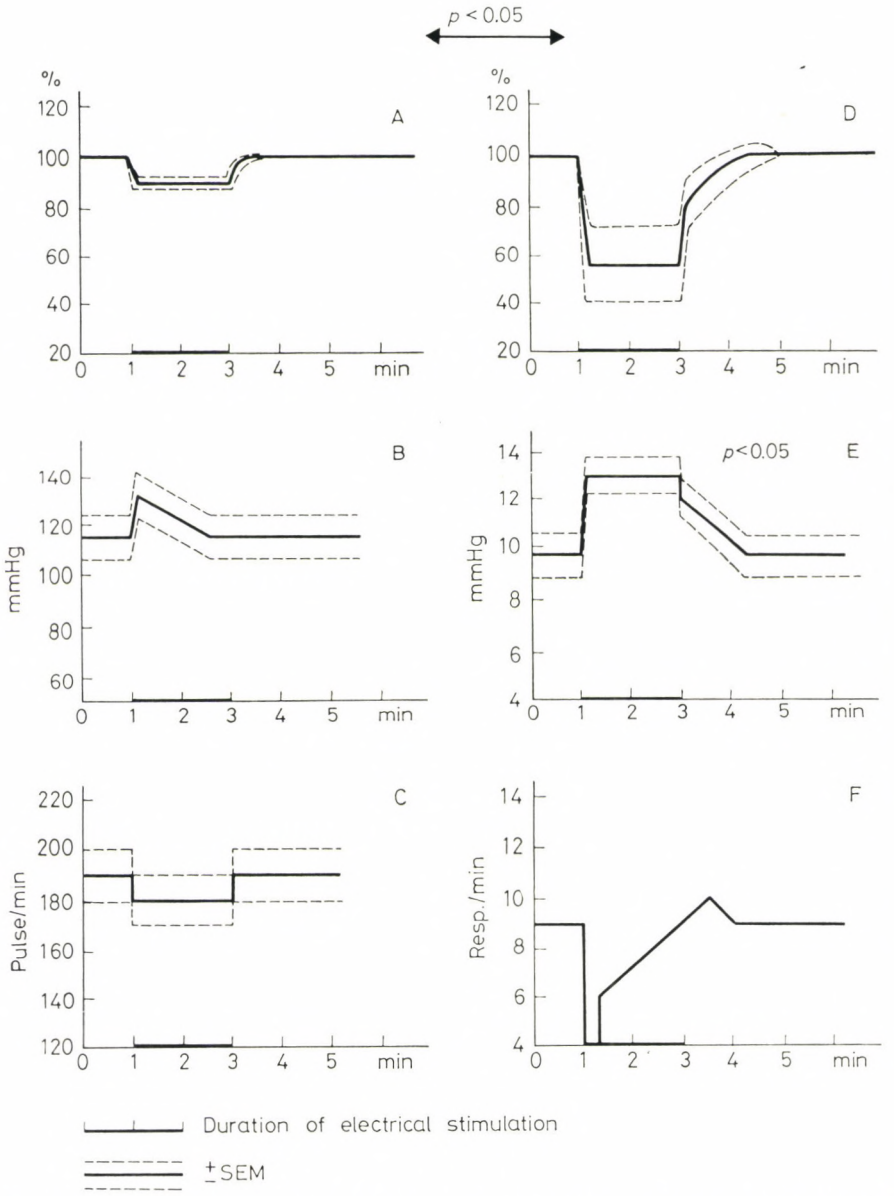


Fig. 82. Effect of electrical stimulation (5 V, 20 c/s, 1 msec, 2 min) of the hepatic plexus on the local blood flow in the central (A) or in the peripheral (D) region of the liver lobe on blood pressure (B), portal venous pressure (E), pulse rate (C) and frequency of respiration (F) in 8 animals

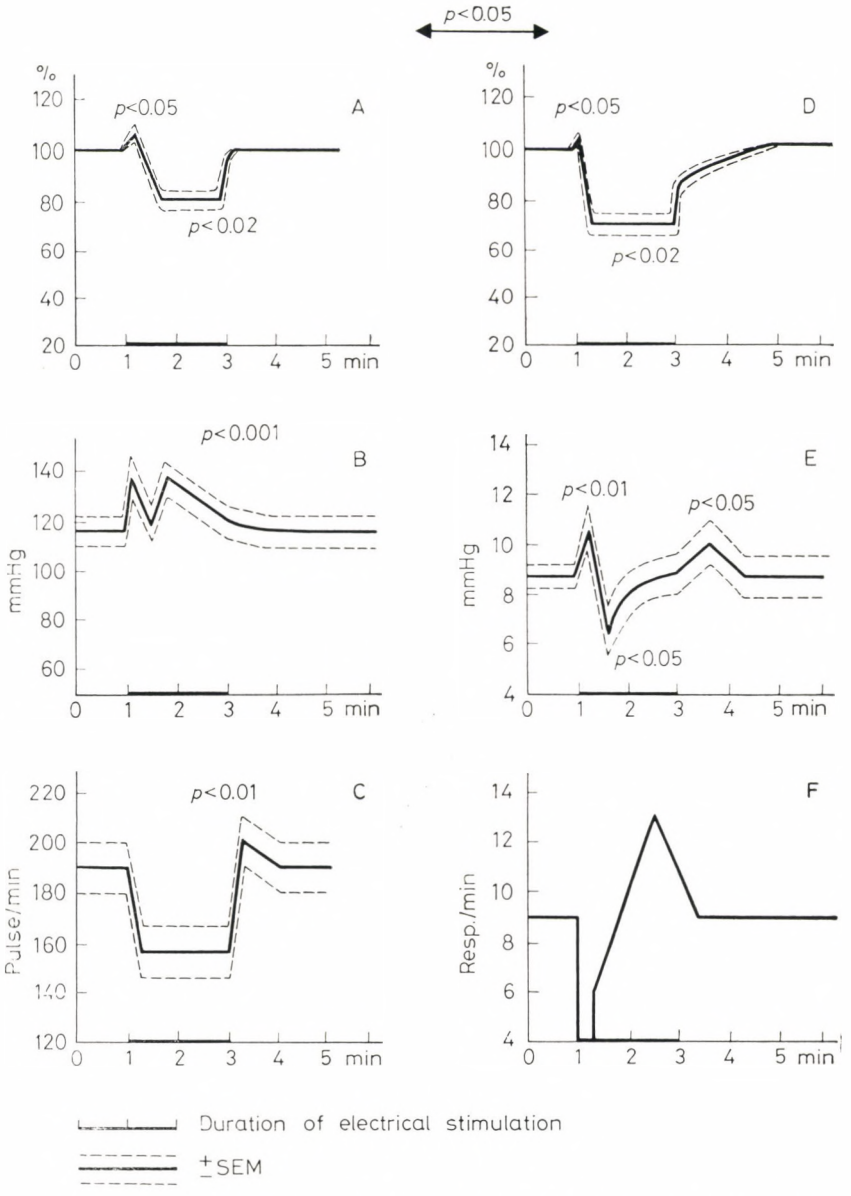


Fig. 83. Effect of electrical stimulation (5 V, 20 c/s, 1 msec, 2 min) of the splanchnic nerve on local blood flow in the central (A) or peripheral (D) region of the liver lobe, on blood pressure (B), portal venous pressure (E), pulse rate (C) and frequency of respiration (F) in 8 animals

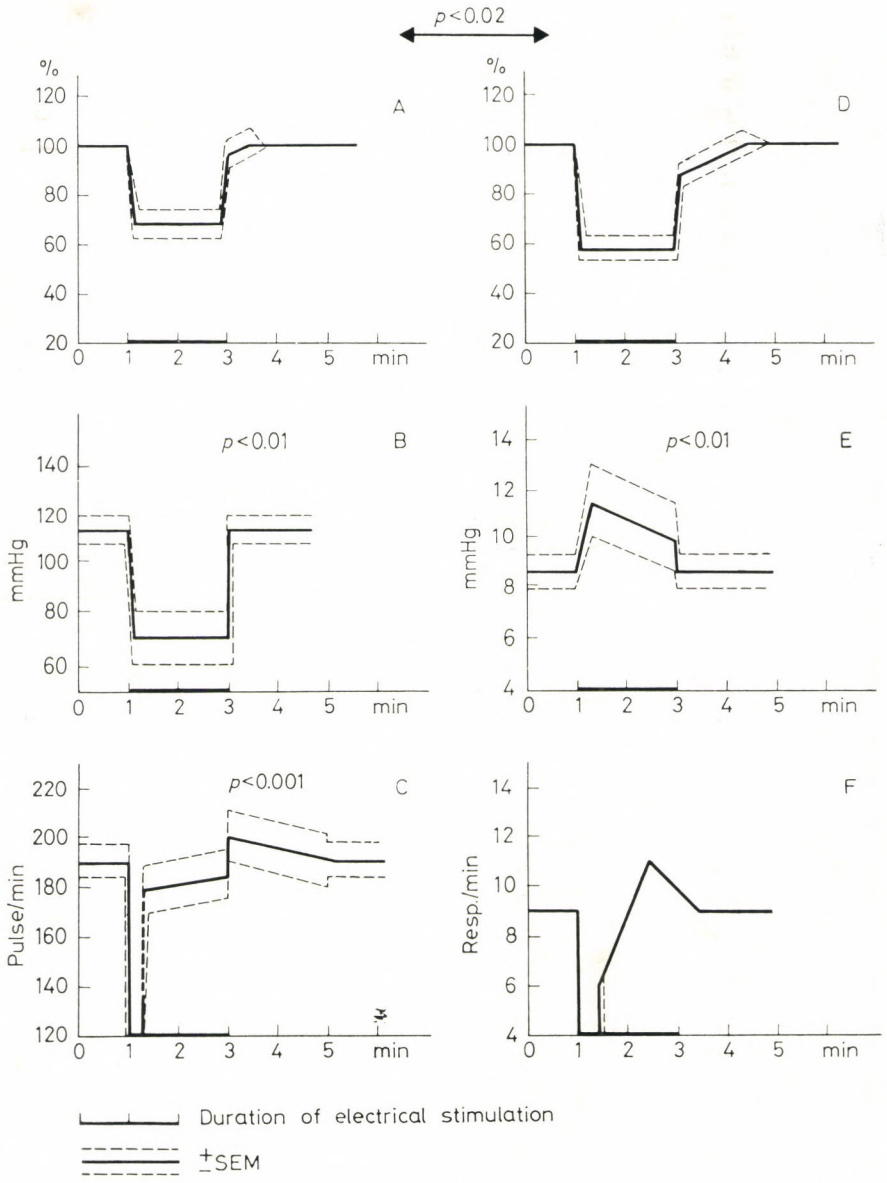


Fig. 84. Effect of electric stimulation (5 V, 20 c/s, 1 msec, 2 min) of the cervical portion of the left vagus nerve on local blood flow in the central (A) or peripheral region (D) of the liver lobe, on blood pressure (B), portal venous pressure (E), pulse rate (C) and frequency of respiration (F) in 6 animals

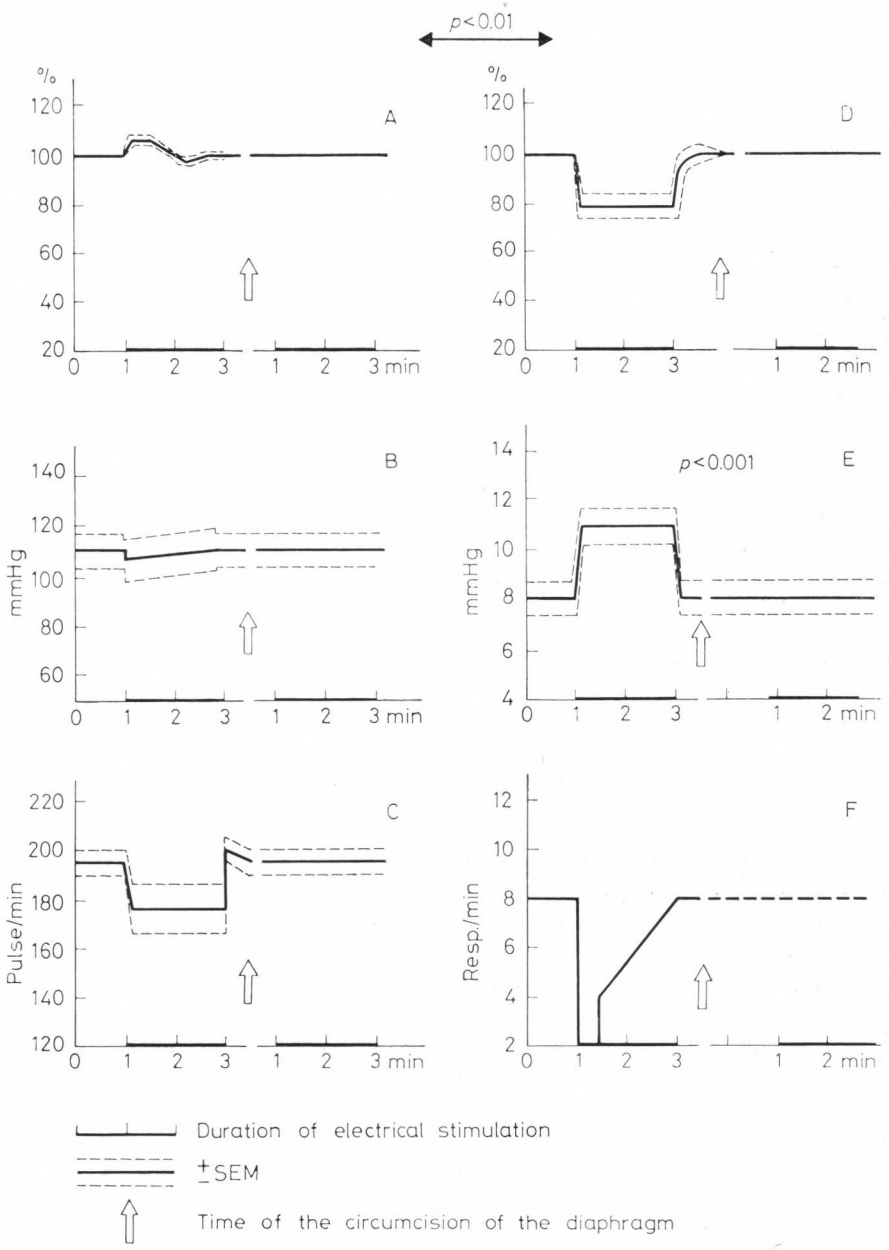


Fig. 85. Effect of electrical stimulation (5 V, 20 c/s, 1 msec, 2 min) of the right phrenic nerve on local blood flow in the central (A) or peripheral (D) region of the liver lobe, on blood pressure (B), portal venous pressure (E), pulse rate (C) and frequency of respiration (F) in 6 animals

7.5. Morphological autonomy of the (central) perihilar "core" and peripheral "shell" of the liver lobe

We succeeded in showing that the course of the blood stream within a lobe of a dog liver may be shorter in a region near the hilum (central area or core) than in the peripheral part (shell) of the same lobe. Daniel and Prichard (1951a, b) made similar observations on rats. Sinusoids in the resting state cover a larger portion per unit area of the liver tissue in the central region than they do in the peripheral part (Ungváry et al. 1969b, Ungváry and Varga 1971). We have shown earlier that considerable monoaminergic innervation of intrahepatic blood vessels in the perilobular area could be observed mainly in the peripheral parts of the lobe, whereas innervation of the smaller vessels in the central region seemed to be poor. Hence, it may be assumed that at the periphery of a liver lobe the smaller blood vessels can respond more efficiently and quickly to stimuli affecting circulation than in the central perihilar area. A part of the vascular tree of the hepatic artery and portal vein near the hilum and the trunks of the hepatic vein near the inferior vena cava receive a richer innervation than their peripheral branches. However, vasoconstriction in the proximal region will also primarily affect blood flow in the peripheral region (Ungváry and Donáth 1969, Ungváry and Varga 1971b).

7.6. Restriction. Intralobar redistribution of hepatic blood flow due to hypotension

Daniel and Prichard (1951c) often induced restriction of intralobar blood flow by injecting adrenaline into the superior mesenteric vein or by stimulating the hepatic plexus. As the hepatic vessels have virtually no other but monoaminergic innervation (Ungváry and Donáth 1969) we studied the effect of catecholamines after intravenous or intraportal injection. It was generally assumed that only alpha receptors are present in the vascular system of the liver (Green and Kepchar 1959) and that adrenaline, noradrenaline and isopropyl noradrenaline, in decreasing efficiency (Ahlquist 1948), bring about only vasoconstriction in the organ. Later Fischer and Takács (1964), Fischer et al. (1970), Krarup (1973) showed that intraarterial injection of a small dose of adrenaline evokes dilatation of the hepatic arteries and increases total hepatic blood flow indicating that there are also beta receptors in the system of the hepatic artery. Therefore we have tested the effect of isopropyl noradrenaline, the most potent beta receptor-stimulating agent

Portal and intravenous administration of adrenaline produced a biphasic change in local hepatic blood flow of both the central and peripheral region of the lobe, i.e. an initial decrease was followed by an increase. There was a significant increase in blood pressure and portal pressure during the response.

The effect of noradrenaline was only roughly similar to that of adrenaline because the second phase of the response developed only in some of the cases. Our

results may agree with the observations of Garbulinsky et al. (1959). In dogs they recorded after the intravenous administration of adrenaline (5 μg/kg) an initial drop in blood flow in the hepatic artery and portal vein, followed 40 sec later by a 40% increase in the blood flow of the portal vein. Complexity of the mechanism was demonstrated by Green and Kepchar (1959) who assumed in their review that at least 5 different mechanisms are involved in the effect of adrenaline injected intravenously: direct stimulation of alpha receptors, stimulation of beta receptors, reflex inhibition of the sympathetic vasoconstrictor tone, the release of vasodilator substances and the activation of central gamma receptors. To these factors one should add the direct vasoconstrictor effect of adrenaline which affects the sinusoids and mainly the outlet sphincters (Wakim 1944, Seneviratne 1949/50). No conclusion as to the restriction of intralobar blood flow could be drawn from the complex and partly ambiguous changes we have observed in response to adrenaline and noradrenaline (Ungváry and Varga 1971a). Recently, Krarup (1973) has also pointed out in cats that the infusion of noradrenaline and adrenaline (in doses of 0.5, 1.0, 2.0 and 5.0 μg/kg/min infused continuously for about 1 hr into the femoral vein) although it is accompanied by marked changes in hepatosplanchnic haemodynamics and liver metabolism, the intrahepatic distribution of blood flow is not subject to gross alterations.

In contrast to the two catecholamines tested, injection of isopropyl noradrenaline directly into the portal vein or intravenously revealed a significant difference between the responses of the two central and peripheral regions to the drug. On portal administration there was a rise in portal pressure, a decline in blood pressure and an increase in local blood flow to the central region, with a concomitant decrease in local blood flow at the periphery of the lobe. On intravenous administration blood flow decreased in both parts of the lobe, the change being more pronounced at the periphery. Portal pressure did not change, blood pressure decreased. The latter changes can be regarded with some reservation as restriction of intralobar blood flow. We assumed that from the effects of isopropyl noradrenaline the decrease of blood pressure was responsible for the phenomenon (Ungváry and Varga 1971a).

Injection of acetylcholine (20 μg/kg) into the portal vein brought about a significant elevation of portal pressure, but no changes in the other parameters were recorded. This finding was not surprising if we consider the variability of data published on the effect of acetylcholine on hepatic circulation. Wakim (1944) found no effect of acetylcholine on the blood flow of the sinusoids in his studies by transillumination microscopy. Bauer et al. (1932) could not decide whether acetylcholine affected circulation in the isolated, perfused liver of the dog, cat and the goat. Andrews et al. (1955) injected acetylcholine into the hepatic artery of the perfused dog liver. Flow rate in the hepatic artery did not change, in the portal and hepatic veins it diminished; the volume of the liver increased. On portal administration, 10–15 times higher doses of the drug were needed to evoke the same effects, they attributed this to the rapid portal degradation of acetylcholine. When injecting acetylcholine directly into the hepatic artery, Green et al. (1959) and later Fischer (1964) observed, however, a marked increase in blood flow and a decrease in resistance in the

hepatic artery. In the experiments of Fischer (1964) total hepatic blood flow was not affected by the drug.

In our experiments the intravenous injection of acetylcholine (20 μg/kg) produced marked effects presumably because it was not directly exposed to the large quantity of esterase and cholinesterase in the liver. There was a significant drop in blood pressure and a rise in portal pressure. This result can be well explained by the intrahepatic vasoconstriction in hypotension, a phenomenon described by Ginsburg and Grayson (1954). In addition, the response to acetylcholine of the central area was smaller than that of the periphery of the lobe (Ungváry and Varga 1971a).

Histamine, in a dose of 20 μg/kg, injected intravenously or into the portal vein induced a fall in blood pressure and a considerable elevation in portal pressure. The former change was particularly marked on intravenous administration. After histamine injection into the portal vein local blood flow diminished only after an initial increase in the central area, but it dropped immediately at the periphery of the lobe. Greenway and Oshiro (1972a) infused histamine (4 μg/min/kg) into the portal vein of 4 dogs, then ^{141}Cr-microspheres were injected into the portal vein before, and ^{51}Cr-spheres were injected 5 min after the infusion of histamine was started for the measurement of blood flow. Comparing the mean relative portal flow in each area and lobe for the 4 experiments before and during histamine infusion they have stated that the relative portal flow in the free ends (peripheral parts) of the liver lobes showed a significant decrease except in the caudate lobe, while the flow in the hilar ends and papillary process showed a relative increase and these increases were significant in 5 of the 7 lobes. In other words, they have pointed out the same effect of histamine as it was demonstrated in the first stage of our experiments when the histamine was given intraportally. The intravenous administration of histamine produced a decrease in blood flow of both parts of the lobe, with a more pronounced response at the periphery (Ungváry and Varga 1971a). Concerning the mechanism of action of histamine an abundance of often contradictory literary data are available. Bradley (1963b) reviewed the relevant reports and concluded that histamine acts as a vasoconstrictor agent on the hepatic and splanchnic veins, whereas in other parts of the organism it produces a dilatation of the arterioles and arteries. Haddy's experiments (1960) on the foreleg of dogs have revealed that histamine has a pronounced dilating effect on the arterioles and a secondary constrictor effect on the veins, due probably to the release of catecholamines from the adrenal medulla. The constrictor ("throttle") mechanism in the hepatic veins has been observed already long ago in anaphylaxis and after the injection of histamine into the portal vein when the musculature of the hepatic veins shows a sphincter-like contraction at the confluence with the caudal vena cava. In our experiments we attributed the extreme elevation of portal pressure in response to histamine to the constriction of hepatic veins. Although portal vasoconstriction has to be considered as a possible factor, too, alone it can hardly account for the extreme portal hypertension. The in vivo transillumination microscopic studies of Seneviratne (1949/50) showed that circulation in the sinusoids decelerates on local or intraperitoneal administration of histamine, which may again indicate the constriction of the hepatic veins. Under these circumstances

blood flow would be maintained through the central core of the liver. Greenway and Oshiro (1972a) could not demonstrate the intrahepatic portal or arterial blood flow redistribution simultaneously with an increase of the hepatic venous pressure. However, Greenway and Oshiro (1972a) increased the hepatic venous pressure by the partial occlusion of the thoracic inferior vena cava through ligature, or by raising the outlet of hepatic venous cannula inserted into the thoracic inferior vena cava. In this experimental condition there is a pressure increase in the hepatic veins (mainly in the proximal part) that involves the entire hepatic venous system. At this pressure the hepatic sphincters (hepatic venous vessels) cannot exert a finer control on the hepatic outflow anymore.

The vasoconstrictor effect of histamine upon the hepatic venous system (sphincters), and also the mechanism of the pressure increase caused by the vasoconstriction are different from the above-mentioned mechanism of experimental pressure increase in the hepatic veins. For this reason, the effect of these two interventions upon intraphepatic blood flow is also different.

Changes in local blood flow of the central and peripheral parts of the lobe were studied (*see* section 7.3.) in hypotension due to bleeding. With a blood pressure stabilized at 40–45 mm Hg, the pressure in the portal vein hardly changed. Local blood flow in the central part responded to bleeding with a smaller decrease than at the periphery of the lobe (Ungváry and Varga 1971a). Fischer et al. (1960) observed in dogs that in arterial hypoxaemia there was no parallelism between the changes of hepatic blood flow and cardiac output. In rats bleeding resulted in an increased hepatic resistance and in a decreased total splanchnic fraction of the cardiac output which was at the margin of statistical significance (Takács 1963). Seneviratne (1949/50) observed by transillumination microscopy the narrowings of the sinusoids and smaller vessels, the spindle-like narrowing of the larger vessels and the deceleration of circulation in the rat liver after draining 4 ml of blood from the jugular vein. The method of transillumination can be used only to study the periphery of the liver lobe. Frank et al. (1962) reported that in non-anaesthetized dogs, with a blood pressure stabilized at 35 mm Hg after bleeding, the total hepatic blood flow determined by measuring hepatic venous outflow, hardly reached 10% of the control value. Similarly, Grayson (1954) found a considerable decrease in hepatic blood flow at blood pressures below 60 mm Hg. Fischer (1964) concluded that in hypotension the hepatic artery supplied the larger part of total hepatic blood flow. When comparing the above data with our results one can conclude that a restriction, the intralobar shift toward the central part of blood flow, develops when the total hepatic blood flow is decreasing. Restriction most probably does not affect only the portal system but also the hepatic artery (Ungváry and Varga 1971a, 1975).

Griffen et al. (1970) and Lifson et al. (1970) perfused the dog liver in situ via the portal vein, hepatic artery or via both blood containing tracer amounts of heavy water. Radioactivity varied in the different parts of the liver. To explain their findings they suggested the possibility of the restricted circulations, described by Daniel and Prichard (1951a, b), but they could not prove this hypothesis. This is not surprising since the authors used physiological perfusion pressures under which condition, as we have shown, restriction could not devel-

op. Recently, Larsen (1971) demonstrated that a 1–2°C reduction in the body temperature, or cooling of the portal vein reduced the elimination rate of glycerol and ethanol, as well as the hepatic uptake of Indocyanine green, by about 40 %. According to Larsen (1971), the experimental findings may be explained by restricted distribution of blood flow in the liver and a corresponding reduction of the functional capacity. Krarup and Larsen (1972) have stated that cooling causes changes in the intrahepatic vascular system: in this condition the number of perfused sinusoids decreases and leads to a reduction in the functional capacity of the liver. Greenway and Oshiro (1972a) have also demonstrated the restriction in intrahepatic redistribution of portal blood flow due to histamine infusion in dogs.

Earlier, Brauer (1963) reviewed the mechanism of restriction and concluded that restriction most often results from vasoconstriction within the portal venous system. Portal constriction could account for the decrease in blood flow at the periphery of the lobe. This decrease can be compensated by the hepatic artery and thus no real ischaemia develops even at the periphery of the lobes. In the present experiment we could not elicit restriction consistently either with adrenaline or with noradrenaline. Both raise blood pressure and portal venous pressure, and both have been shown by others with serial portograms often to induce restriction. Bleeding or the administration of vasoactive substances in addition to causing a significant fall in systemic blood pressure (acetylcholine, histamine, isopropyl noradrenaline) evoked significantly different local blood flow responses in the central and peripheral parts of the liver lobe. As a result of either intervention blood flow to the central part was higher (either increased, did not change, or decreased less) than that of the peripheral part. This relation might correspond to the phenomenon of restriction or to a similar event. Presumably, redistribution of blood flow within the lobe seems to develop invariably under the simultaneous effect of the fall in systemic blood pressure and the consequent portal vasoconstriction. The peripheral parts of the liver lobe are much more seriously affected by the vasoconstriction than the central core. The opposite changes in the different parts of the lobe may account for the fact that increase in portal venous pressure cannot always be observed in restriction when measured in the portal vein. (Opposite changes may occur in the core of the organ.)

7.7. Restriction affecting the hepatic artery

When there is a severe blood pressure reduction, the liver is mostly supplied only by the hepatic artery. As also in this case, there is an uneven distribution of blood flow between the central and peripheral parts of the lobe. It can be assumed that redistribution may develop due to a selective reflex vasoconstriction within the hepatic artery. The involvement of the hepatic artery is probable because the nerve fibres to the portal vein originate in the same monoaminergic nerve bundles that follow the course of the hepatic artery in the portal channels. In addition, the nerve fibres to the two vessels have a common origin in the celiac ganglion (Ungváry 1971). In contrast to our presumption, Greenway and Oshiro (1972b) have dem-

onstrated, using microspheres labelled with ^{141}Ce and ^{51}Cr for measuring intrahepatic distribution of arterial flow, that stimulation of the hepatic nerves did not cause a redistribution of arterial flow within the feline and canine livers. However, recently we demonstrated the intrahepatic redistribution of arterial flow. (Ungváry and Varga 1975). In cats we made a portal-jugular bypass, then one thermocouple was inserted into the central and another into the peripheral part of the left medial liver lobe for the measurement of local (arterial) blood flow. With the electrical stimulation of the left celiac ganglion local blood flow differed significantly between the central (perihilar) and peripheral areas of the left medial liver lobe; in the peripheral part local blood flow was less than it was in the central area. We assumed on the basis of our experiment that redistribution could be elicited in the hepatic arterial system, although this is characteristic mainly of the portal and only secondarily of the arterial system.

7.8. Efferents of the reflex arc causing restriction

If the restriction were a reflex response, the efferents of the reflex arc, i.e. at least the processes of the postganglionic neurons, could obviously be found in the hepatic plexus. If our hypothesis were correct then suitable stimulation of the hepatic plexus should evoke restriction consistently.

As it has already been mentioned, Greenway and Oshiro (1972b) could not elicit the redistribution of either the arterial or portal flow within the liver by the electric stimulation of the hepatic nerves. Their results are in contradiction with our relevant data (Ungváry and Varga 1971b, 1975). At present we do not know the reason for this contradiction. However, we have to bear three facts in mind:

1. The parameters employed for electric stimulation differed in Greenway and Oshiro's (1972b) experiments from ours (Ungváry and Varga 1971b).

2. The radio-microsphere method of Greenway and Oshiro (1972b), used in the registration of the redistribution within the liver, can register only one definite moment of the blood flow conditions, the thermocouple method of Hensel (1953/54), used in our experiments for the registration of the redistribution of the local blood flow within the liver, can measure the changes of local blood flow continuously for minutes or hours. Applying two thermocouples at the same time in the peripheral and central parts of the same liver lobe we could record the changes in local blood flow in them continuously and parallelly (Ungváry and Varga 1971b). It is worth noting that Greenway and Oshiro (1972a) have demonstrated the same effect of the intraportally administered histamine on the redistribution as we found it in the first stage of the effect exerted by the intraportally administered histamine upon redistribution (Ungváry and Varga 1971a).

3. Before Greenway and Oshiro (1972b) stimulated the hepatic nerves they had ligated all the branches of the celiac artery (gastric, gastroduodenal, splenic branches) except for the hepatic one; so they had ligated or cut numerous sympathetic nerves belonging to the prevertebral autonomic ganglia. In other words, they had to get information about a fine neural control mechanism under insufficient, undesirable experimental conditions.

In our experiments following the stimulation of the hepatic plexus a significant difference between the blood flow of the central and peripheral territories of the liver was observed (Ungváry and Varga 1971b, c). Redistribution of intralobar blood flow ensued in every case of electric stimulation of the hepatic plexus in contrast to the report of Daniel and Prichard (1951c) who consistently failed to observe restriction in rats. It should be noted, however, that with a stimulating current of less than 5 V, or with a stimulation not affecting the whole hepatic plexus due to its segmental innervation, we also failed to induce restriction in every case. Stimulation of the hepatic plexus provided experimental evidence that the efferents of the hypothetical reflex are in the hepatic plexus (Ungváry and Varga 1971b, c). As to the intrahepatic distribution of the hepatic plexus, it has been shown that the plexus sends primarily monoaminergic fibres to the hepatic artery, portal and hepatic veins, and an especially abundant plexus is formed in the wall of the hepatic vein just before its confluence with the inferior vena cava (Ungváry and Donáth 1969). Although one can assume that the hepatic vessels, at least in most of the animal species, are innervated by monoaminergic fibres only, adrenaline and noradrenaline failed to induce consistently restriction in our experiments (Ungváry and Varga 1971a) Recently, Krarup (1973) was likewise unable to elicit the intrahepatic distribution of blood flow with either noradrenaline or adrenaline. A probable explanation for the failure can be offered by assuming differences either in the administration of the two catecholamines or between the effect of endogenous and exogenous catecholamines. Recent pharmacological experiments neither support nor deny the hypothesis stating that the distribution of sympathin, the transmitter substance released from the nerve terminals, is similar to that of infused noradrenaline (Brown and Gillespie 1957, Ferry 1967). The overwhelming majority of the monoaminergic fibres originate in the celiac ganglion (Ungváry and Léránth 1970a, 1972), and therefore similar responses were anticipated after the stimulation of the splanchnic nerve or hepatic plexus. In fact, a close resemblance of the responses was found after stimulation. The only difference was that in case of splanchnic stimulation the pronounced and prolonged reduction in blood flow was preceded by a brief moderate increase (Ungváry and Varga 1971b, c). The reason for this difference may lie in the fact that splanchnic stimulation causes vasoconstriction in the whole splanchnic area and not only in the liver (an increase, a decrease and another increase in portal pressure.) Fibres of the vagus nerve can be excluded as possible efferents of the reflex arc, as no change in local hepatic blood flow was observed after the electric stimulation of the vagus nerve at the cardia (Ungváry and Varga 1971 b). Our results are in agreement with those of Ginsburg and Grayson (1954) who failed to find any change in hepatic circulation after the electric stimulation of the peripheral stump of the transected vagus nerve.

Surgical circumsection of the diaphragm around the caudal vena cava abolished the response of the hepatic blood flow to stimulation of the right phrenic nerve, therefore the nerve cannot be regarded as efferent to a reflex arc along which restriction can develop (Ungváry and Varga 1971b, c).

Stimulation of the vagus nerve on the neck already with 5 V resulted in a drop of blood pressure. The consequent increase in portal venous pressure may have

developed partly due to a congestion in the venous system in general. Local blood flow to the central and peripheral parts of the lobe significantly differs due to a much smaller reduction in the central than in the peripheral region. It has already been discussed that a pronounced fall in blood pressure is always followed by intralobar redistribution similar to restriction. Hypotension due to vagus stimulation can be considered to be the underlying cause which can activate a reflex, described by Ginsburg and Grayson (1954), leading to restriction via portal vasoconstriction. This, too, may partly be responsible for portal hypertension.

Bánfai et al. (1953) reported the decrease of the pressure in the inferior vena cava and the simultaneous enlargement of the liver after right phrenic nerve stimulation. They suggested that the phenomenon may be due to the fact that the motor innervation of the hepatic sphincters is supplied by the right phrenic nerve. Degenerating nerve fibres from the right phrenic nerve to the hepatic veins were demonstrated by electron microscopy (Ungváry and Léránth 1970a, 1972). The number of these fibres, however, cannot be large as only a few degenerating axons were found in the adventitia. It is undecided whether vasomotor innervation of the sphincters can be attributed to the right phrenic nerve. In the description of the innervation of the hepatic sphincter we have already presented our indirect morphological evidences on the sensory nature of these fibres (Ungváry and Léránth 1972). Our present physiological results provide further supporting evidences (Ungváry and Varga 1971b, c). Cervical stimulation of the left phrenic nerve, as can be expected, failed to change hepatic blood flow (Ungváry and Varga 1971b, c). Cervical stimulation of the right phrenic nerve, however, produced a significant increase in local blood flow in the central area and a significant decrease at the periphery of the lobe (Ungváry and Varga 1971b, c). However, repeated stimulation of the right phrenic nerve after the surgical circumsection of the diaphragm around the inferior vena cava and hepatic veins, carefully sparing the branches that enter the wall of the vein, elicited no response indicating that the phrenic nerve does not supply the hepatic veins with vasoconstrictor innervation (Ungváry and Varga 1971b, c). Different explanations may be offered for the effect of phrenic nerve stimulation on local hepatic blood flow with the diaphragm intact. One can assume that contraction of the diaphragm may result in a reflex restriction of the blood flow to the central area via an increase in abdominal pressure. Olerud (1953) observed the restriction of hepatic blood flow on serial portograms when he raised intraabdominal pressure by air insufflation into the peritoneal cavity in rabbits. Perhaps it is not the best explanation because an elevation of intraperitoneal pressure may be produced by the stimulation of the left phrenic nerve which was not followed by the redistribution of hepatic blood flow. Another explanation should be probably sought for. The movements of the diaphragm may exert a direct mechanical effect on hepatic circulation. They may divert the blood from the thinner peripheral part of the lobes to the central area either by locally increasing the sinusoid resistance at the periphery or by functioning around the inferior vena cava as a suprahepatic sphincter of the hepatic circulation. Only further investigations could settle the question (Ungváry and Varga 1971b).

On the basis of the above investigations one may conclude that the functional changes do not respect segmental division but affect primarily the periphery of the lobe. This part becomes first excluded more or less from the circulation, consequently from the function of the liver (Ungváry and Varga 1971a, b, c, 1975). In a trivial analogy the liver can be regarded as a fruit with a stone. Blood flow to the core is always ensured thus it provides rapid drainage of the splanchnic area under all circumstances, while the whole liver is involved in the circulation only when the need for specific functions arises in accordance with the requirements of the organism. A schematic representation of two circuits in the liver, the inner one in the core and the outer one in the shell, including also the concept of Daniel and Prichard is shown in Fig. 126 (p. 203). The simplified figure is meant to call attention to the possible tendency of hepatic circulation to polarize into two circuits. Mechanical separation of the liver function or blood flow are by no means suggested. Besides the above type of control affecting the whole organ, there is the regulation of the microcirculation of the sinusoids, simple or complex acini, in which neural regulation may be of secondary importance to a humoral regulation by vasoactive substances and local metabolites.

8. Hepatic vasculature in liver atrophy and in experimental liver injury

8.1. Liver atrophy due to fulminant virus hepatitis

The liver of patients who died of liver atrophy after fatal virus hepatitis weighs less than two-thirds of the weight of the control livers. The portal venous casts of the atrophied livers weigh $^1/_5$–$^1/_2$ of that of the controls. The weight of the vascular cast per unit mass of liver tissue was found to be 2–4 times more in the controls than in the atrophied livers. The data show beyond doubt that besides the expected absolute decrease there is also a relative decrease in the vascular capacity of atrophied livers (Ungváry and Somogyi 1969, Ungváry et al. 1974c).

Qualitative analysis of the vascular casts yielded the following results: besides the striking difference in size (Figs 86, 87) the atrophic livers differ in shape from the controls. The shape of the vascular cast of an atrophic liver hardly resembles that of a control (Ungváry and Somogyi 1969, Ungváry et al. 1974c).

The portal venous cast of a control liver has a dense surface, the filling is even; the majority of sinusoids are filled. The portal cast of an atrophic liver has a much looser appearance, considerably less sinusoids are filled. Further investigations using stereomicroscope revealed that instead of the portal lobules only the bare circumlobular veins, deprived of the sinusoids, were most often seen (Figs 88 a, b, c, d). Occasionally, a few dilated sinusoids connect the portal twigs that run as portaportal anastomoses at a considerable distance (Figs 89a, b, Ungváry and Somogyi 1969, Ungváry et al. 1974c).

On corroded casts of the hepatic venous system long, bulky vessels, isolated from the surroundings, can be observed below the capsule. They are not seen in the control livers, where they are covered by a large number of vessels running at right angles to the surface. Thus, in the atrophied liver the long, bulky vessels run parallel with and one layer closer to the surface (Fig. 90). Stereomicroscopic investigations of the hepatic venous casts occasionally showed dilated central veinlets joined by small stumps of sinusoids at some sites, while in other places the veinlets were entirely missing (Fig. 91 a). With the injection of gelatin and India ink we could hardly achieve the complete filling of larger congruent marginal areas. In other regions the vascular pattern of the liver was hardly recognizable because of the abundant extravasates replacing the completely destructed parenchyma cell plates and sinusoids. Between the branches of the hepatic venous system a considerable number of anastomoses develop (venovenous anastomoses, Fig. 91 b). These anastomoses presumably develop from connected, dilated sinusoids conveying blood in one direction (Fig. 92; Ungváry and Somogyi 1969, Ungváry et al. 1974c).

Fig. 86. Corroded vascular PVC cast of the portal venous system of a man died at 61 years without any obvious liver disease in the anamnesis. The cast can be regarded as the normal portal venous system

Fig. 87. Corroded vascular PVC cast of the portal venous system of a man died at 57 years on account of acute liver atrophy (fulminant virus hepatitis). The shape of the cast is flattened, extremely oval, its size is much smaller than usual. The magnification is the same as in Fig. 86

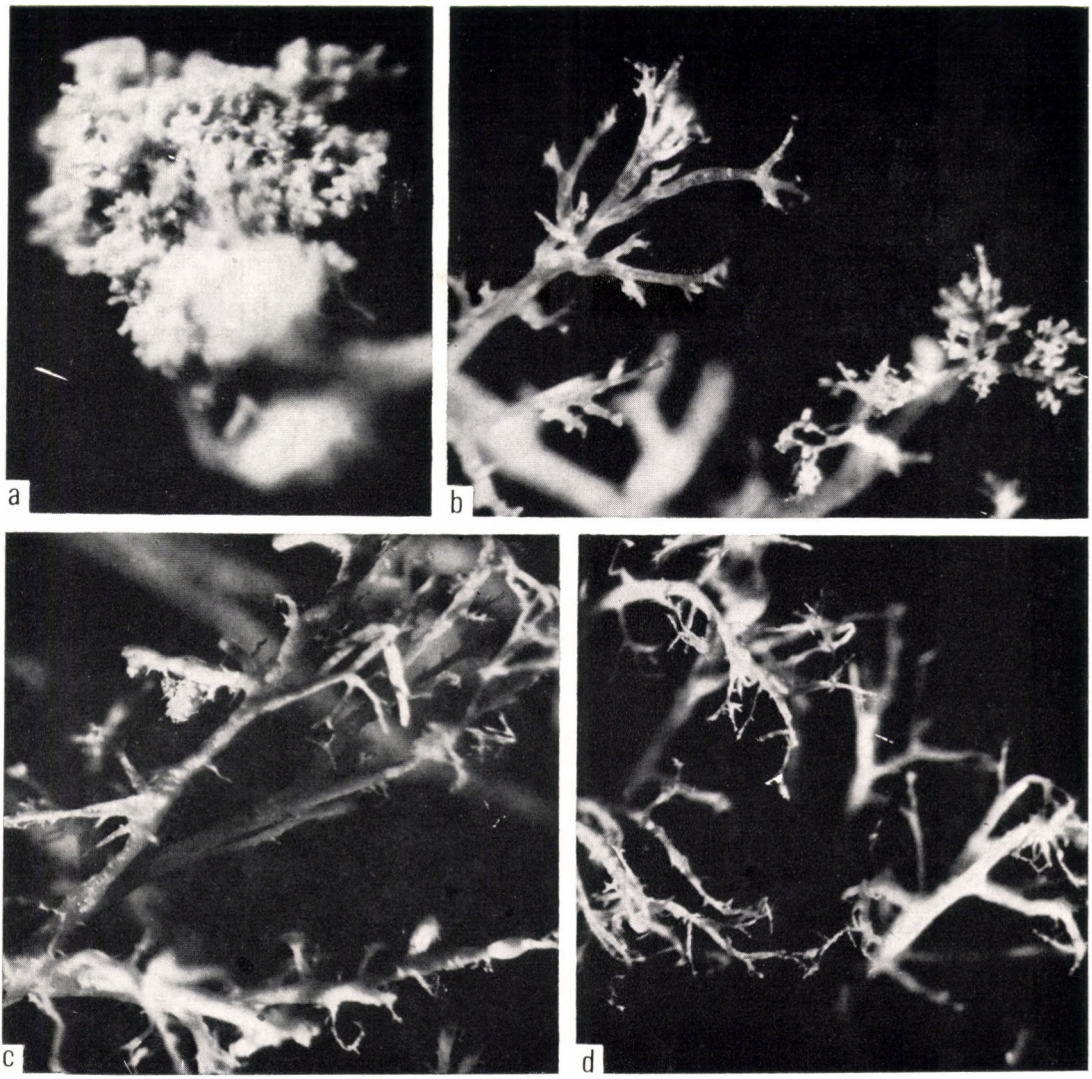


Fig. 88. Corroded vascular cast of the portal venous system in fulminant virus hepatitis (acute liver atrophy). (a) Intact portal lobule (an unusual finding in these cases). × 55.(b) Incomplete filling of the sinusoid system. × 55. (c) The cast of the vessels is extensively destructed. Occasionally spindle- or pearl-shaped dilatations can be seen on the casts; the sinusoids are hardly filled. × 35. (d) Destructed vasculature. × 35

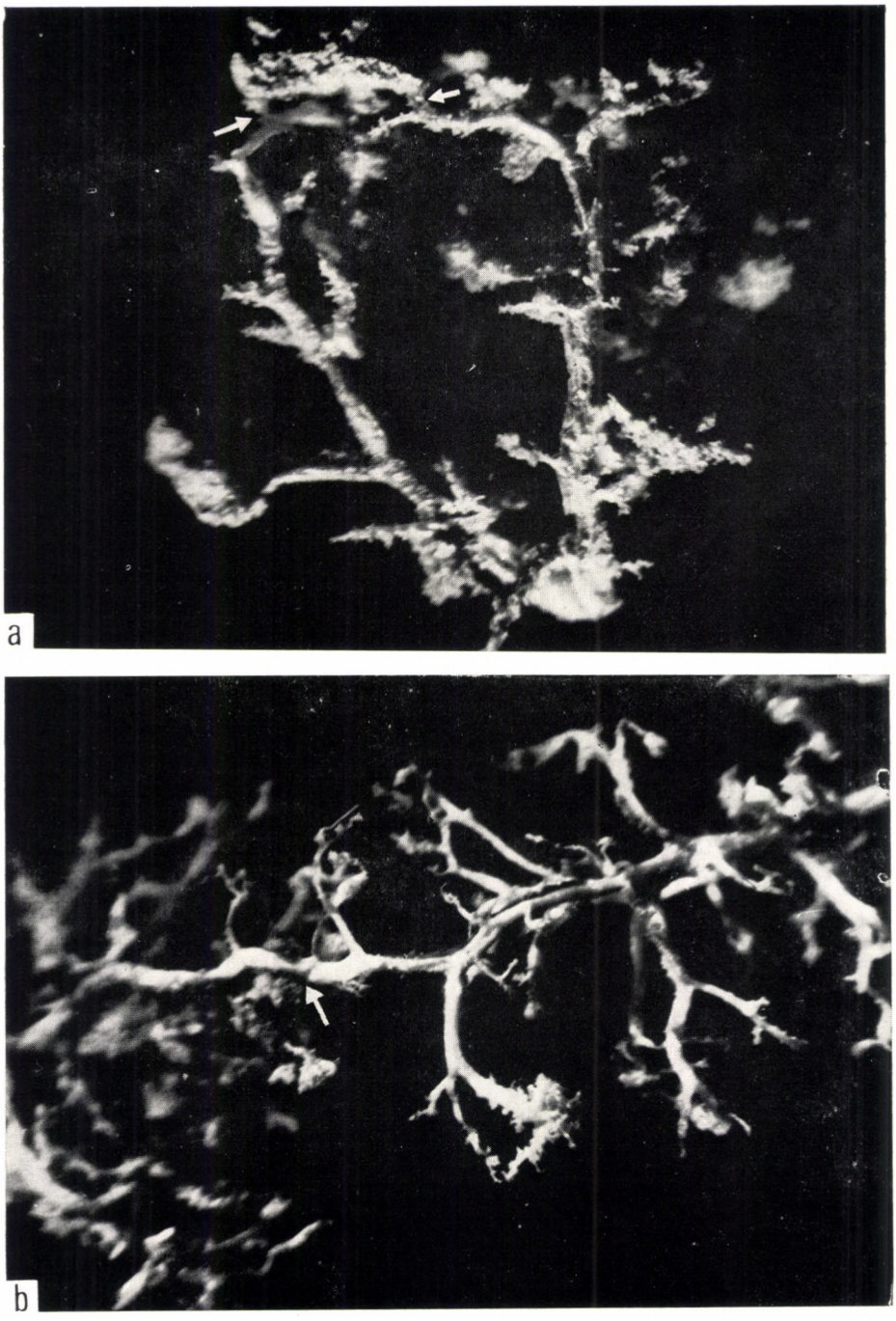


Fig. 89. Corroded vascular cast of the portal venous system in fulminant virus hepatitis (acute liver atrophy). (a) Portaportal anastomosis (→). (b) Portaportal anastomosis between two larger twigs (→). ×22

Fig. 90. Corroded vascular cast of the hepatic venous system in fulminant virus hepatitis (acute liver atrophy). Arrows indicate the veins below the Glisson's capsule; in control livers the corresponding veins are located in a deeper layer

The three portobiliary lobes of the atrophied livers can in general be distinguished although it often occurred that the 5% PVC injected into the portal vein immediately reappeared in one of the hepatic venous trunks. This hardly occurs when filling control livers. The finding can be explained by the presence of intralobar or translobar portovenous anastomoses between larger branches of the hepatic and portal veins (Fig. 93). These anastomoses may drain portal blood, without satisfying nutrient tasks, from the peripheral region of a lobe toward the hepatic trunks (Ungváry and Somogyi 1969, Ungváry et al. 1974c).

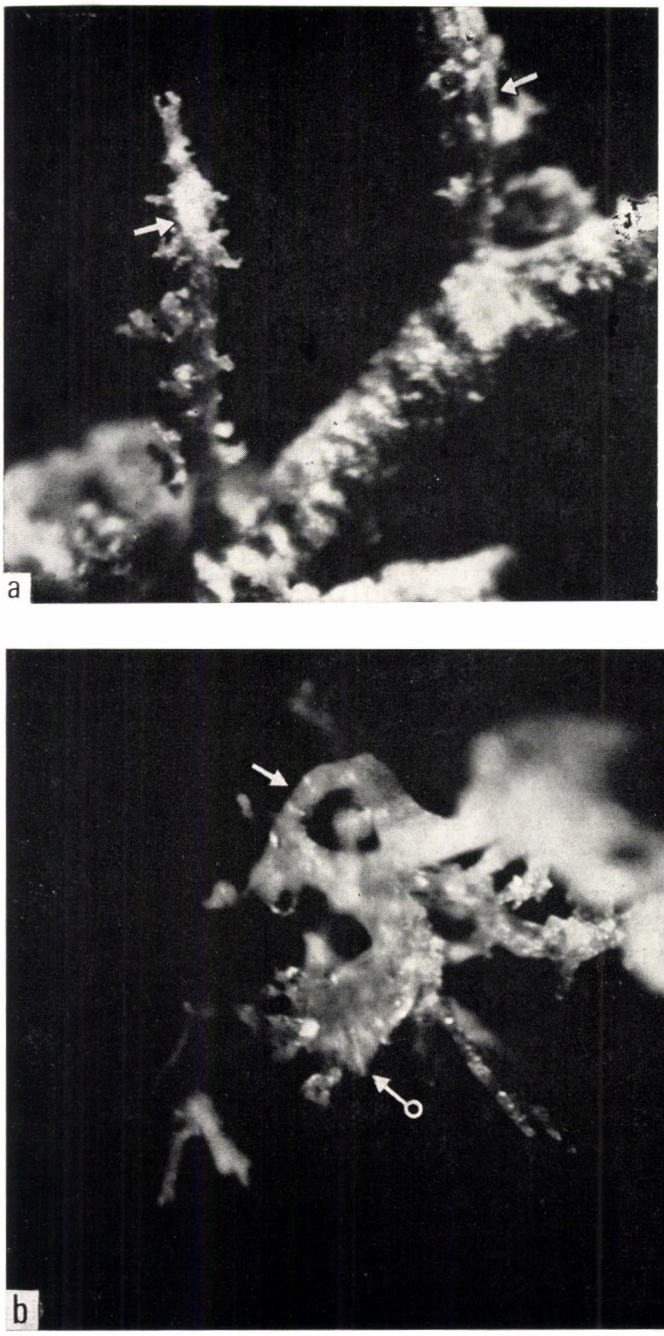


Fig. 91. Corroded vascular cast of the hepatic venous system; in fulminant virus hepatitis (acute liver atrophy). (a) The arrow points to the dilated central vein connected with the stumps of the sinusoids. ×90. (b) Widely dilated sinusoid system forming a venovenous anastomosis (→), extravasation (o→). ×200

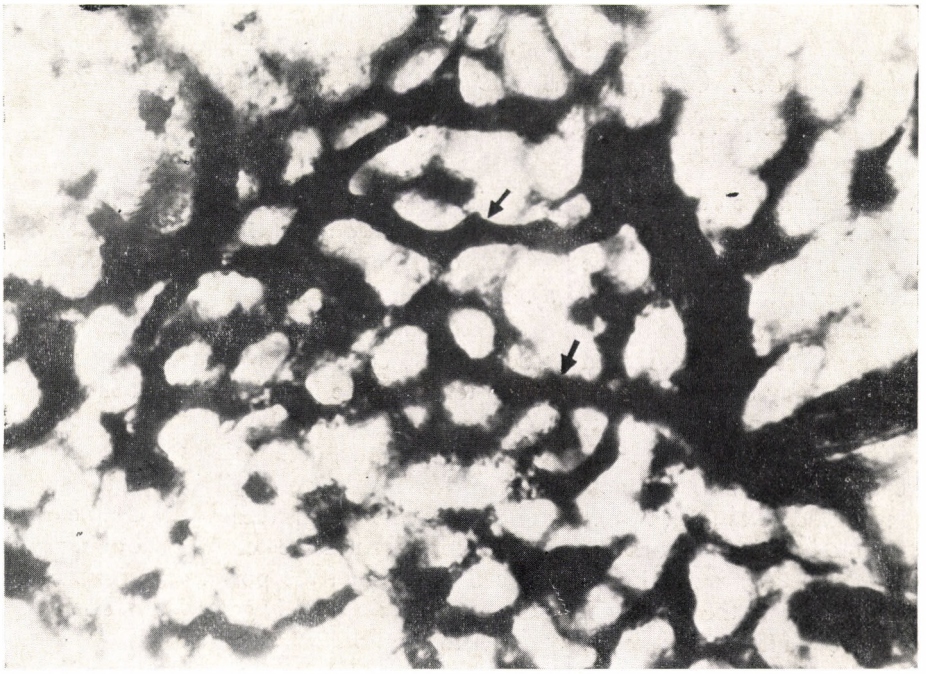


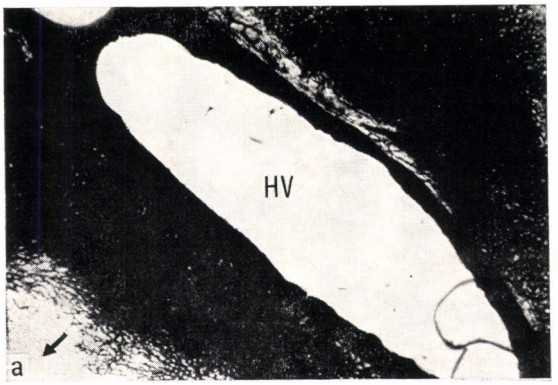
Fig. 92. Spalteholz's thick preparation. The portal venous system was injected with 8% gelatin in India ink. Fulminant virus hepatitis (acute liver atrophy). Dilated sinusoids capable of forming shunts (→) are randomly found. ×880

Fig. 93. Extremely large portovenous anastomosis (→) between the middle trunk of the portal and the left hepatic vein in fulminant virus hepatitis (acute liver atrophy). 5% PVC solution was injected through the portal vein. Portal venous branch (⟹); hepatic venous branch (o→)

8.2. Changes in the hepatic vasculature of rats in experimental carbon tetrachloride intoxication

When a mixture of gelatin and India ink was injected retrogradely via the hepatic vein into the liver of rats 2–24 hrs after carbon tetrachloride administration, a continuous filling could be achieved only in the vicinity of the larger vessels near the porta hepatis (Fig. 94 a). The centre of the lobules underwent necrosis, the sinusoids were destroyed and centrolobular spots could be seen because of the filling defect of the damaged tissue (Fig. 94 b). Similar damages were seen on the third day of experimental carbon tetrachloride intoxication, but in addition to this, the periphery of the liver lobes could not be filled more satisfactorily through the portal vein (Fig. 94 c). Shunts, conducting toward the large hepatic venous branches could be seen bridging the "empty" gaps in the central area of the lobes (Fig. 94 e). Impairment of the venous drainage is characteristic of acute intoxication that could be well seen even in the central area of the lobes on preparations made by filling the liver through the portal vein (Fig. 94 d). When injecting the solution into the hepatic vein a fairly good filling of the vasculature could be achieved, way down to the portal channels. Filling was more complete in the central area of the lobes (Fig. 94 h). With the progress of intoxication also larger vessels underwent damage. On the rami and ramuli of the portal vein constrictions appeared, the width of the vessels became subject to fluctuations (Fig. 94 f), and finally the odd vascular patterns, characteristic of the cirrhotic liver, developed (Fig. 94 g). These changes, however, can be already observed in both the central and the peripheral areas of the lobes (Nagy and Ungváry 1970).

Fig. 94. (a) 8% gelatin in India ink was injected into the hepatic vein of rats 24 hrs after carbon tetrachloride administration. The gelatin in India ink are seen only in the vicinity of larger vessels, there is no filling more distantly (→). HV — hepatic vein. ×55. (b) 8% gelatin in India ink was injected into the portal vein of rats 24 hrs after carbon tetrachloride administration. Destructed sinusoids and extravasation are seen around the central vein (CV). ×140. (c) 8% gelatin in India ink was injected into the portal vein of rats on the 3rd day of carbon tetrachloride intoxication. The sinusoids are hardly filled at the periphery of the liver lobe. PV — portal vein. ×55. (d) 24 hrs after carbon tetrachloride administration, rat. 6% gelatin in India ink was injected into the portal vein. The venous drainage is hindered (→); PV — portal venous branches; ×55. (e) 24 hrs after carbon tetrachloride administration, rat. 8% gelatin in India ink was injected through the portal vein. Shunt-forming vessels (→) in the central area of the liver lobe. ×55. (f) 6 weeks of carbon tetrachloride intoxication, rat. 8% gelatin in India ink was injected through the portal vein. Narrowing (→) of the lumen of a larger portal vein. ×140. (g) 16 weeks of carbon tetrachloride intoxication, rat. 8% gelatin in India ink was injected through the portal vein. Odd vascular pattern — peculiar to cirrhosis — which cannot be seen in normal liver. ×140. (h) 24 hrs after carbon tetrachloride administration, rat. 6% gelatin in India ink was injected through the hepatic vein. PV — portal vein. ×55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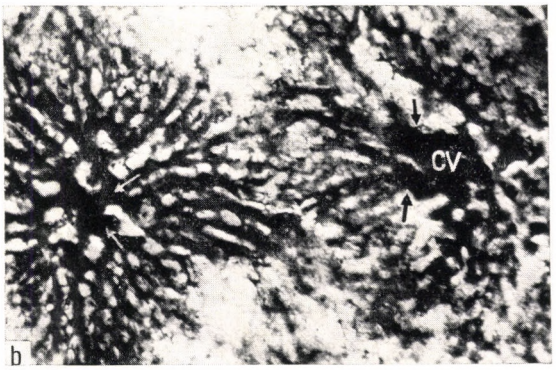
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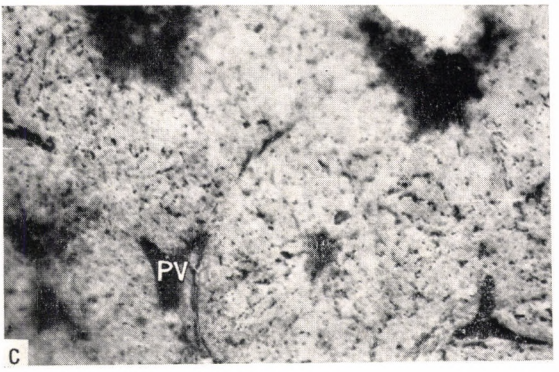
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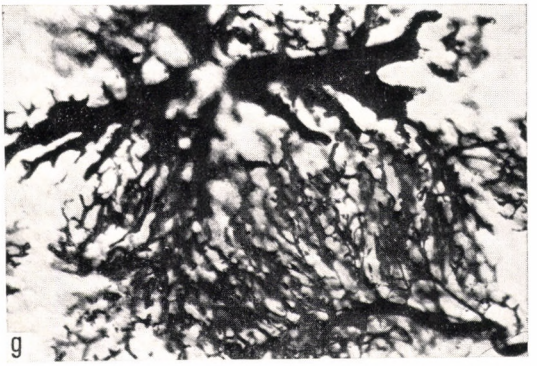
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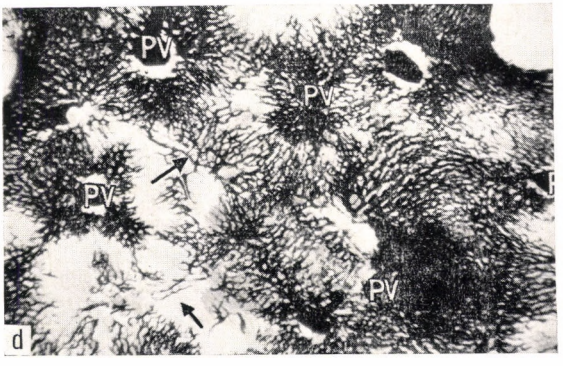
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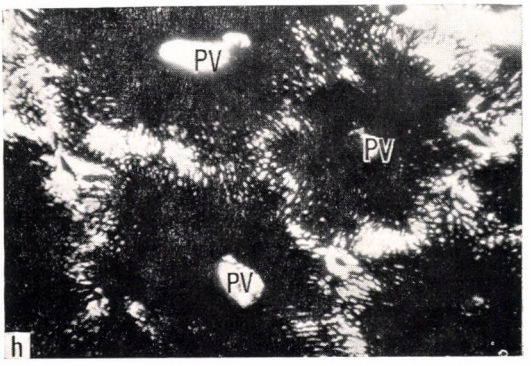
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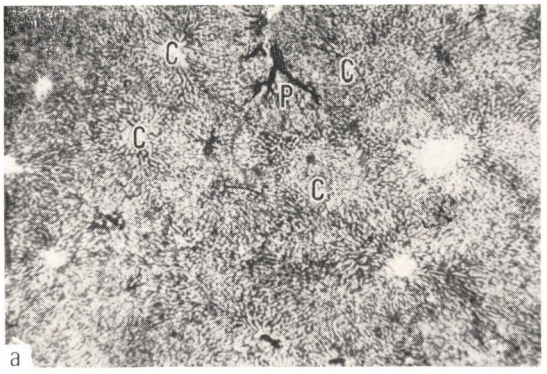
8.3. Effect of the ligation of the common bile duct on the hepatic vasculature of rats

There is a less pronounced difference between the vascular patterns of the periphery and central area of the lobes after the ligation of the common bile duct when studied after India ink injection or with the benzidine reaction. Both methods indicated the inversion of the lobules 1 to 3 days after the ligation of the common bile duct. Bulky benzidine-positive, or India ink-filled bridges could be observed between the portal spaces and the sinusoids which were directed rather toward the portal channels than toward the central veinlets (Figs 95 a, b, e, f). A few weeks after operation (in guinea-pigs one week only) the vasculature became similar to that seen in cirrhosis, with the conspicuous impairment of venous drainage as seen after filling via portal and hepatic venous routes alike (Figs 95 c, d). Powerful arterialization (Fig. 95 g) was a characteristic finding. This was, however, different from the arterialization seen after constriction of the portal vein described in section 5.3. No new arterial branches developed, only the existing ones became dilated after the constriction of the portal vein, while en tirely new arteries arose and developed after the ligation of the common bile duc

Fig. 95. (a) Benzidine reaction in the liver of a control rat. The reaction shows the outlines of regular lobules. P — portal area; C — central vein. ×55. (b) Benzidine reaction 3 days after the ligature of the common bile duct, rearrangement of the sinusoids is characteristic, a group of sinusoids "radiate" toward the portal spaces, benzidine-positive straight lines connect the portal spaces. P — portal space; C — central vein; SV — sublobular vein. ×55. (c and d) 6% gelatin in India ink was injected through the portal vein (c), or hepatic veins (d) of rats two weeks after the ligature of the common bile duct. The hepatic veins rarely filled after portal injection, while the portal venous system could be filled through the narrow, irregular hepatic venous branches (→). P — branch of the portal vein; * — area drained by the hepatic vein. ×55. (e) Liver of a control rat injected through the portal vein with 8% gelatin in India ink — Spalteholz's thick preparation. C — central vein. ×140. (f) "bridges" connecting the portal vein as demonstrated by filling through the portal vein with 8% gelatin in India ink 3 days after the ligature of the common bile duct. The picture corresponds to the inversion of the lobule as described by Elias. P — portal vein. ×140. (g) There is a rich periductal (Pd) arterial plexus around the biliary ducts two weeks after the ligature of the common bile duct in rat. 6% gelatin in India ink was injected through the hepatic artery. ×140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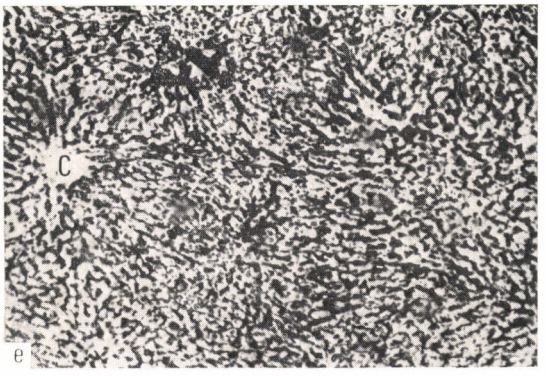
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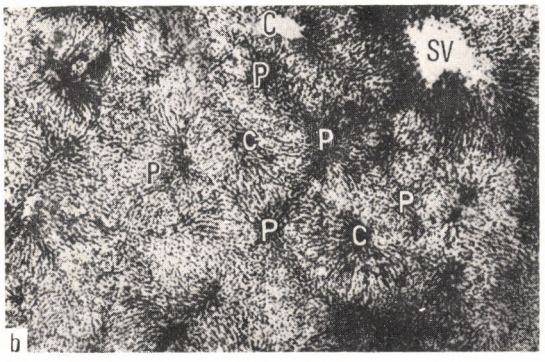
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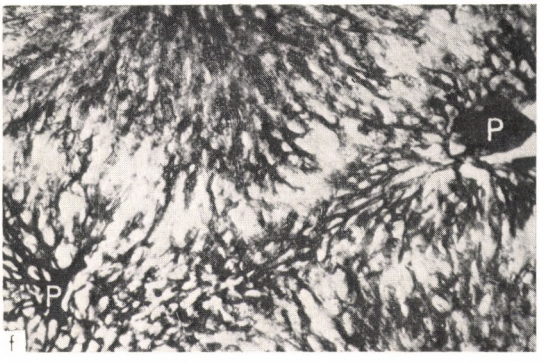
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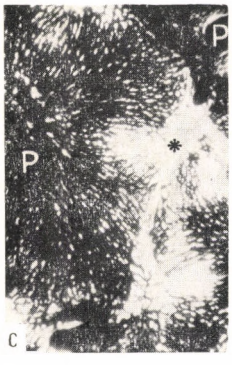
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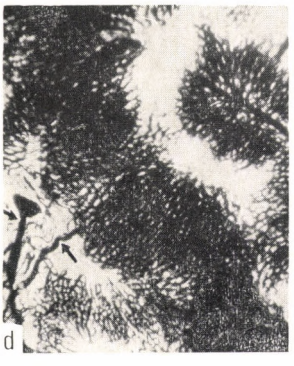
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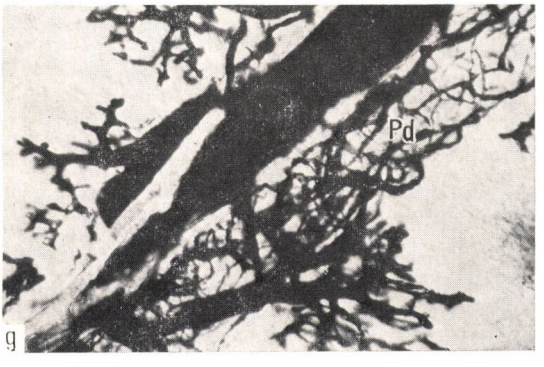
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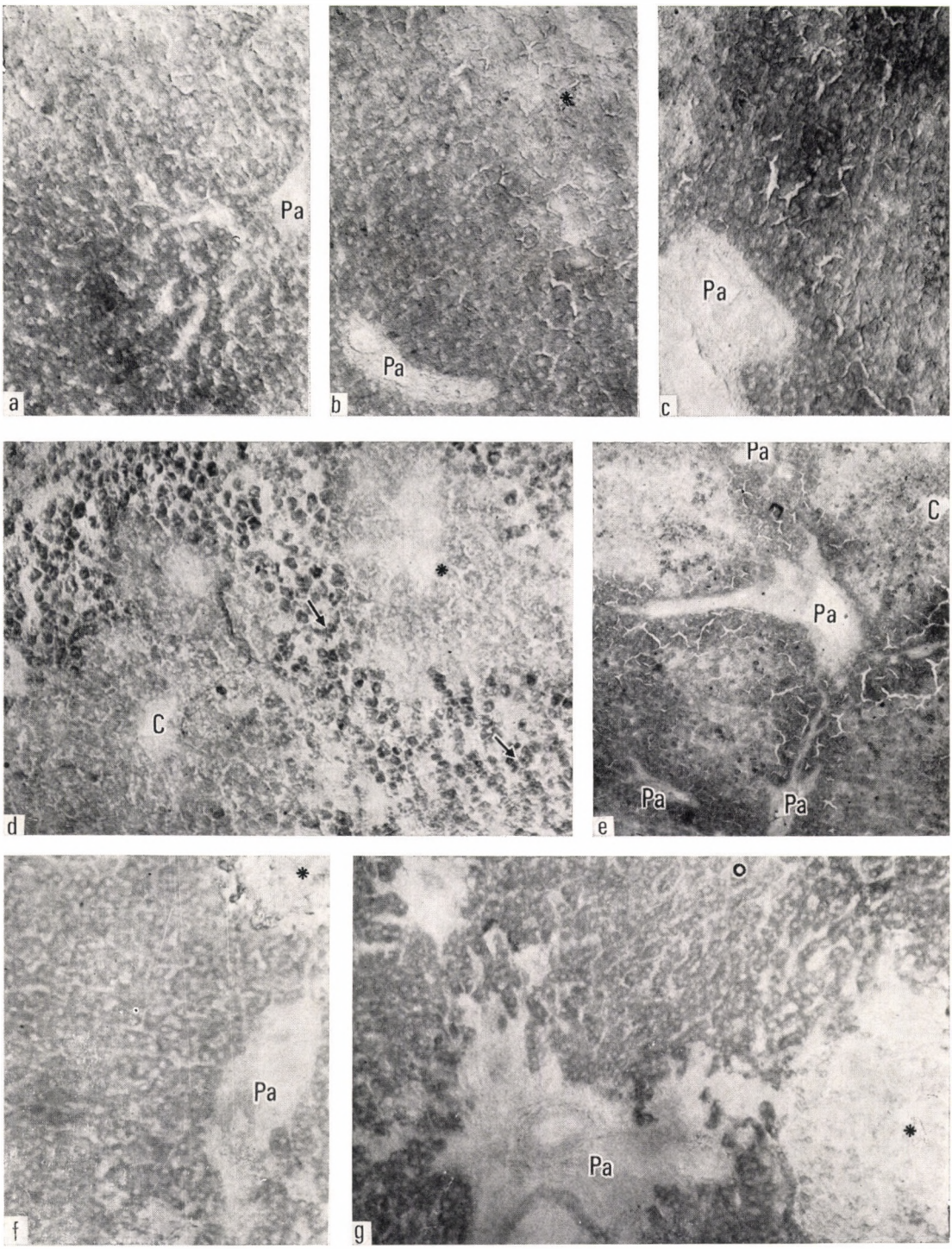
8.4. Effects of carbon tetrachloride intoxication and of the ligation of the common bile duct on the histochemical characteristics of the hepatic enzyme system

Under physiological conditions the succinic dehydrogenase reaction is more intense in the outer periportal area of the liver lobule than in the inner centre (Fig. 96 a). A few hours after carbon tetrachloride intoxication the originally weaker reaction of the centrolobular area lost further intensity (Fig. 96 b). At the periphery one day after carbon tetrachloride administration succinic dehydrogenase could be detected only in the periportal region, although here the parenchyma cells suffered severe damage, too (Figs. 96 d, e). Similarly, in the core of the lobe the succinic dehydrogenase-positive reaction was localized to the periportal area of the liver lobule where the parenchyma cells remained entirely intact (Fig. 96 c). One day after the ligation of the common bile duct, the decrease in succinic dehydrogenase activity of the guinea-pig liver had an irregular pattern and showed a random distribution in the outer and inner parts of the lobule (Fig. 96 f). Four days after ligation the succinic dehydrogenase-positive cells were localized groupwise in small islets, the impairment of the parenchyma was more pronounced at the periphery of the lobe (Fig. 96 g, Ungváry 1971, Ungváry et al. 1971a).

In normal livers the monoamine oxidase reaction does not have quite a regular localization, being more intense in the inner central, than in the outer part of the lobule. A few hours after the intraperitoneal administration of carbon tetrachloride an increase in periportal monoamine oxidase reaction occurred and as a result the difference in reaction intensity between the zones of the lobules levelled off. One day after carbon tetrachloride administration the monoamine oxidase reaction of the liver was localized primarily in the perilobular area. This change was characteristic mainly at the periphery of the liver lobes. In carbon tetrachloride intox-

Fig. 96. (a) Succinic dehydrogenase reaction in the liver of a control rat. The reaction is more intensive around the portal triad than in the centrolobular area. ×130. (b) Shortly after carbon tetrachloride administration to a rat. Intensity of the reaction in the periportal areas is not affected, while no reaction is seen in the region indicated by the star. ×140. (c) 24 hrs after carbon tetrachloride administration to rats; the central area of the liver lobe. The reaction is present only in the periportal area, here the cells are intact, no succinic dehydrogenase activity can be detected in the nuclei. ×140. (d) 24 hrs after carbon tetrachloride administration to rats; peripheral part of the liver lobe. Bridge-like succinic dehydrogenase-positive areas connect the portal spaces (→); the cells here are strongly damaged, too; C — central vein; no reaction can be seen in the areas indicated by the star. ×140. (e) 24 hrs after carbon tetrachloride administration to a rat; peripheral part of a liver lobe; positive reaction only in the periportal area. C — central vein. × 55. (f) In the liver of a guinea-pig one day after the ligature of the common bile duct; there is no reaction in the areas indicated by the star, following bile imbibition and cell necrosis. ×140 (g) Periportal region of a guinea-pig liver lobe 4 days after the ligature of the common bile duct; there is even a slight increase in reaction intensity in some islets, while there is no reaction in others indicated by the star (bile imbibition, necrosis). The succinic dehydrogenase-positivse area indicated by the circle toward the sublobular vein. ×140. Pa — portal area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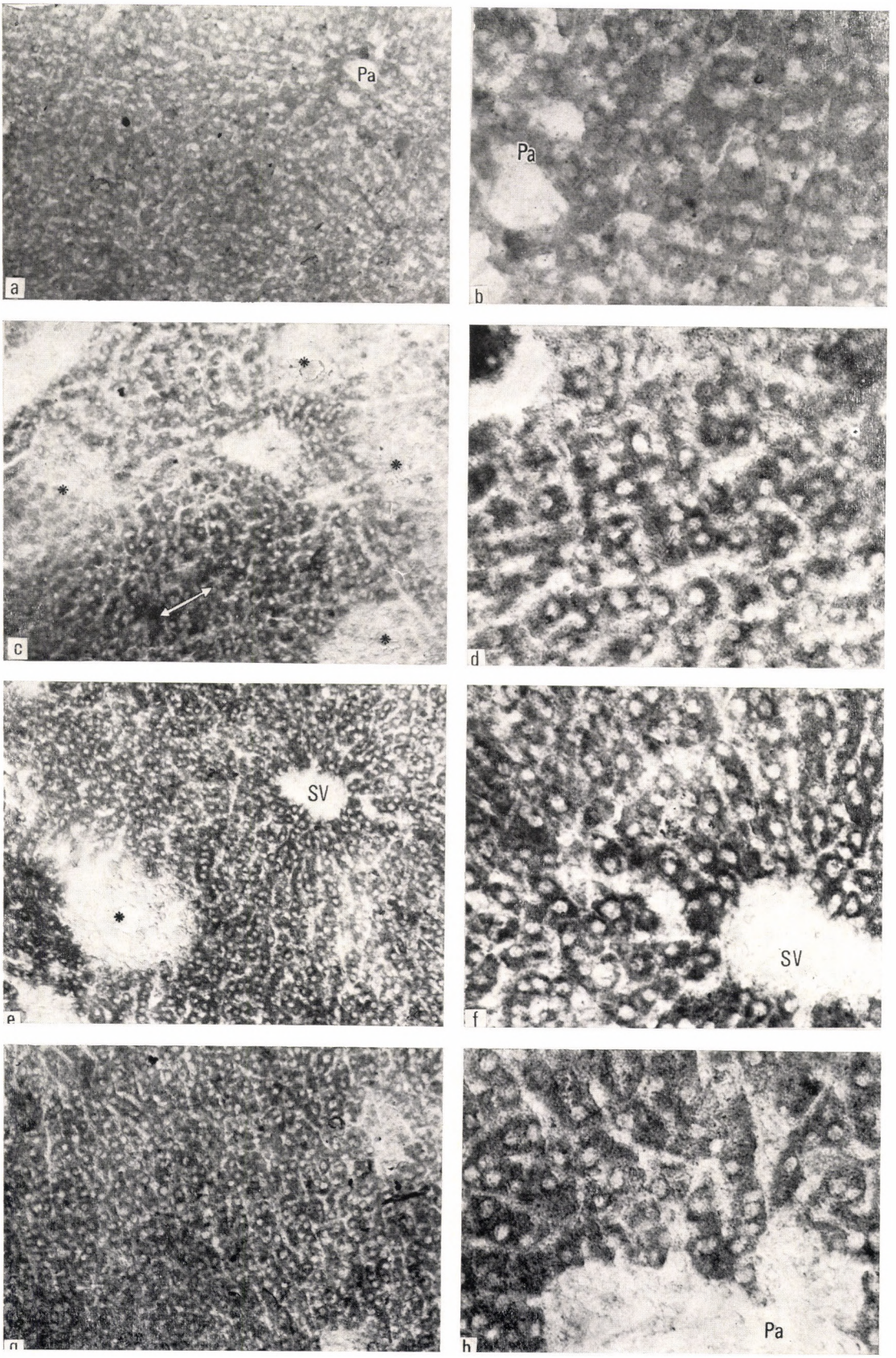
ication, at the same site pale, ischaemic spots could often be observed even on macroscopic inspection (Ungváry 1971, Ungváry et al. 1971a).

One day after the ligation of the common bile duct numerous small yellow, pinheads or lentil-seed sized spots with bile imbibitions appeared on the surface of the guinea-pig liver. There was hardly any continuous monoamine oxidase-positive area at the periphery of the liver (Figs 97, c, d). The enzyme could not be detected in the yellow spots. The succinic dehydrogenase, nonspecific esterase, nonspecific cholinesterase reactions were negative, while a positive alkaline phosphatase reaction and autofluorescence were found in the spots. One, but especially two days after the ligation of the common bile duct, the intensity of the monoamine oxidase reaction increased in the undamaged parenchyma cells, which were localized in continuous areas only in the central region of the lobes (Figs 97 e, f). Three days after operation it was still more intense there than in the controls (Figs 97 a, b, g, h; Ungváry 1971, Ungváry et al. 1971a).

Intensity of the cytochemical reaction for nonspecific esterases was stronger in the inner centre than at the margin of the lobule under physiological conditions (Fig. 98 a). A few hours after carbon tetrachloride injection the staining intensity in the centrolobular area increased (Figs 98 b, e) presumably as a consequence of parenchyma cell damage. One day after its administration the histochemical nonspecific esterase reaction became weaker or was absent at a number of sites (Figs 98 c, f), and changed its localization. The perilobular activity increased and in several lobules nonspecific esterase-positive parenchyma cell bridges were observed to connect adjacent portal spaces (Fig. 98 d). The intensity of the histochemical reaction was much weaker at the periphery than in the central area of the liver lobe due to the fact that at the periphery larger continuous areas failed to give the nonspecific esterase reaction, while in the centre of the lobe the continuous masses of damaged parenchyma yielded a weak reaction (Ungváry 1971, Ungváry et al. 1971a).

The nonspecific esterase reaction is significantly affected by the ligation of the common bile duct. One day after operation only a few cells containing nonspecific esterase could be found at the periphery of the liver lobes, located mainly around the portal spaces. These groups of cells were in contact with each other only at a few sites. Some of the cells, presumably those just before necrosis, gave

Fig. 97. (a and b) Monoamine oxidase reaction in the liver of a control guinea-pig. The reaction is weaker in the periportal area than in the centre of the lobules. No monoamine oxidase activity can be detected in the nuclei. (a) × 140; (b) × 350. In the peripheral part of a liver lobe of a guinea-pig one day after the ligature of the common bile duct. There is no or hardly any monoamine oxidase activity in continuous areas indicated by the stars. Bridge-like area showing increased monoamine oxidase activity is indicated by the arrow; the more intensive staining can also be observed under higher power. (c) × 140; (d) × 350. In guinea-pig liver 2 days after the ligature of the common bile duct. The intensity of the reaction is increased; no reaction was seen in the area indicated by the star (bile imbibition, necrosis). (e) × 140; (f) × 350. In the central area of a liver lobe of a guinea-pig 3 days after the ligature of the common bile duct. The reaction is similar to that of controls but a little more intensive. (g) × 140; (h) × 350. The method of Glenner et al. was used for the detection of the monoamine oxidase Pa — portal area; SV — sublobular vein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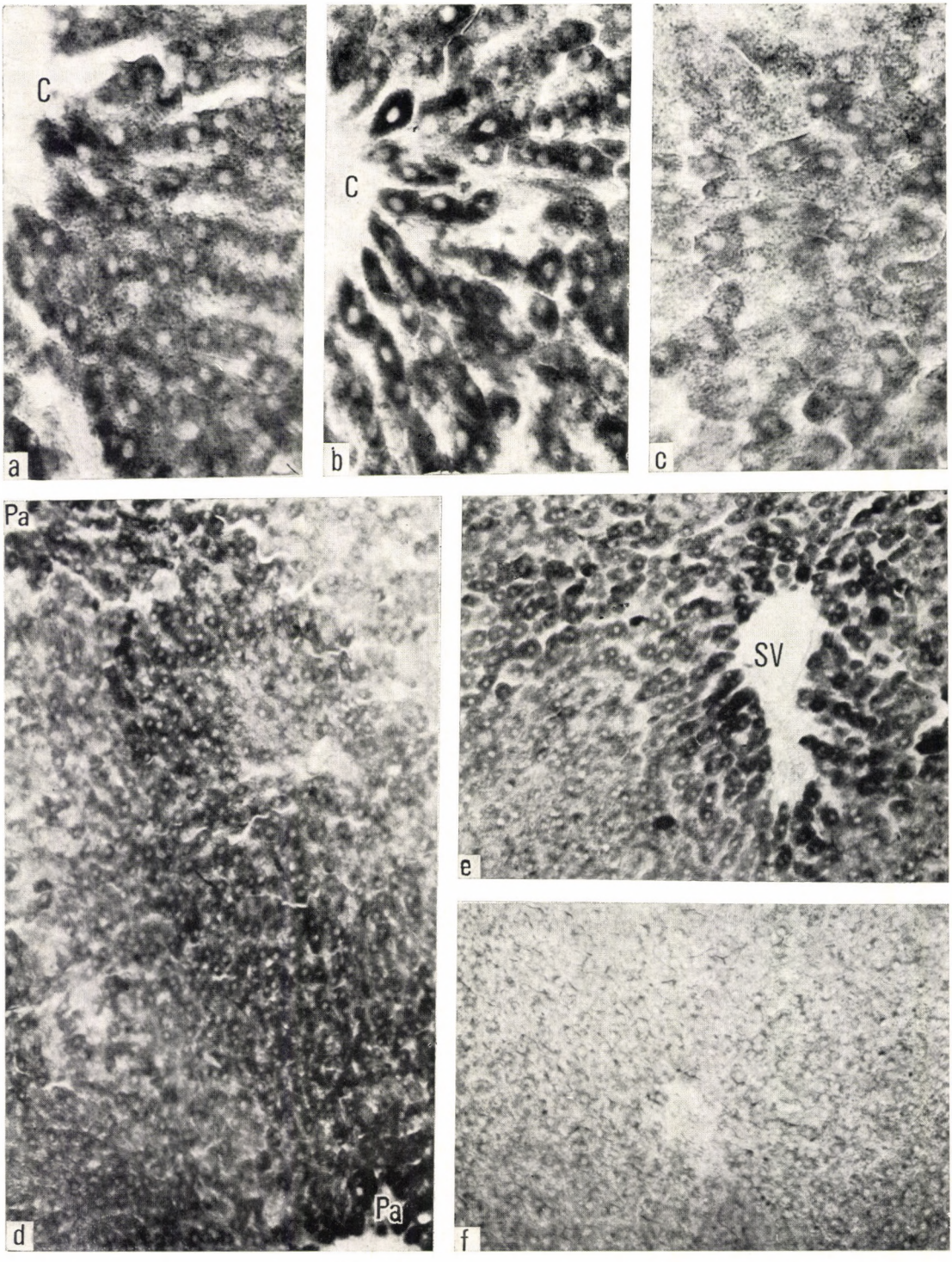


Fig. 98. Nonspecific esterase reaction (a) in the liver of a control rat. Staining is more pronounced in the central area of the lobule. × 350. (b) In rat liver shortly after carbon tetrachloride administration. The intensity of the reaction is increased in the centrolobular area. C — central vein. × 350. (c) In rat liver one day after carbon tetrachloride administration. The intensity of the reaction is decreased. × 350. (d) In rat liver one day after carbon tetrachloride administration. Two distant portal areas (Pa) are connected with a bridge of liver parenchyma showing positive reaction. × 140. (e) In rat liver shortly after carbon tetrachloride administration. The cells around the sublobular vein (SV) that undergo necrosis later, yield a more intensive reaction. × 140. (f) One day after carbon tetrachloride administration; peripheral part of the rat liver lobe. The intensity of staining is extremely low in general or lacks completely at some sites. × 140

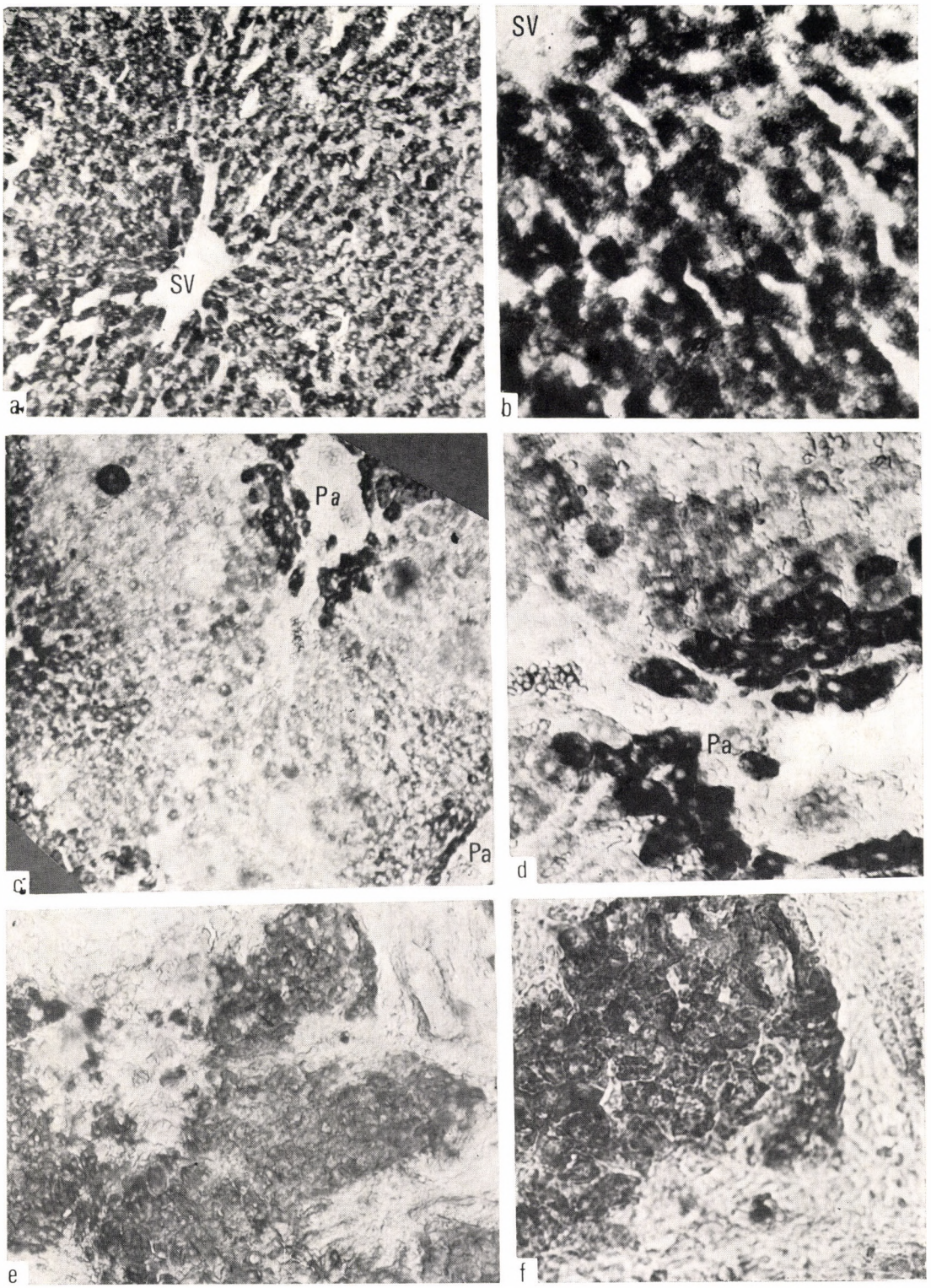


Fig. 99. Nonspecific esterase reaction in the liver of a control guinea-pig. The reaction is more intensive in the centrolobular than in the perilobular area. (a) ×140; (b) ×350. In the peripheral part of a liver lobe of a guinea-pig one day after ligature of the common bile duct. Only parenchyma cells in the periportal area of a few lobules yield reaction. A few cells display increased intensity; no enzyme activity can be detected in large continuous areas. (c) ×140; (d) ×350. In the guinea-pig liver 4 days after the ligature of the common bile duct. Positive reaction is seen only in a few islets of the parenchyma. (e) ×140; (f) ×350. Pa — portal area; SV — sublobular vein

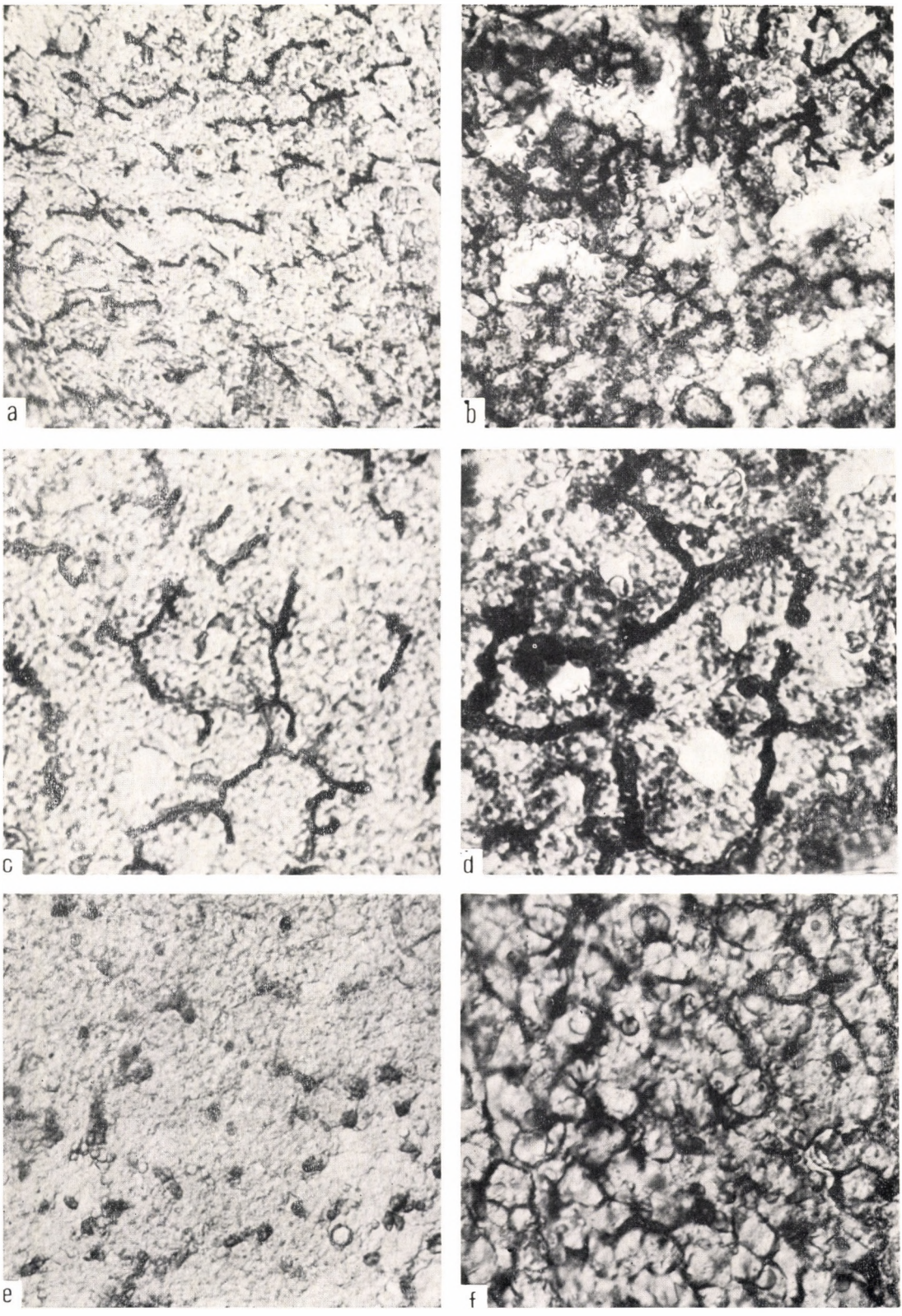
a very strong reaction (Fig. 99 a, b, c, d). Four days after the ligation of the duct, cells containing nonspecific esterase could be detected only in islets. At this time no difference could be observed between the shell and the core of the lobe on the basis of the histochemical reaction (Fig. 99 e, f; Ungváry et al. 1971a).

In the rat liver the histochemical localization of alkaline phosphatases is confined to the biliary system under physiological conditions (Fig. 100 a, c). In the guinea-pig liver alkaline phosphatases did not outline the bile canaliculi, tiny positive spots were only seen (Fig. 100 e). The intensity of the alkaline phosphatase reaction increased after carbon tetrachloride administration or after the ligation of the common bile duct (Fig. 100 b, d, f; Ungváry et al. 1971).

In control livers acid phosphatase reaction may be moderately more intensive in the perilobular area (Fig. 101 a, b). This difference became more pronounced a few hours after carbon tetrachloride injection, due to an increase of the perilobular and a concomitant decrease of the centrolobular staining (Fig. 101 c, d). One day after carbon tetrachloride administration acid phosphatases could be detected almost exclusively in the perilobular area. There is no reaction centrolobularly in the peripheral lobar area. The increased acid phosphatase reaction of the Kupffer's cells was conspicuous (Fig. 101 e, f; Ungváry et al. 1971a).

In the quantitative analysis of the histochemical reactions in livers from animals one day after carbon tetrachloride administration the positive histochemical reaction in the sections was covered by the intersections of the projected square grid in $85 \pm 5\%$ and $72 \pm 4\%$ ($\bar{x} \pm$ SEM) of the cases in the central and peripheral region of the liver lobe, respectively. In control livers the corresponding values were $93 \pm 3\%$ in the centre and $95 \pm 4\%$ at the periphery. In a similar investigation histochemical enzyme activity was detected in $74 \pm 6\%$ in the core and $65 \pm 5\%$ in the shell of the liver lobe of guinea-pigs one day after the ligation of the common bile duct. The corresponding control values were $94 \pm 3\%$ and $95 \pm 4\%$ in the core or shell of the lobe, respectively. Comparison of the enzyme activities in the core and the shell revealed that there was a significant difference ($p < 0.05$) in carbon tetrachloride intoxication and that the effect of ligation of the common bile duct was only at the margin of significance (Ungváry 1971).

Fig. 100. Alkaline phosphatase reaction in the liver of a control rat (a and c); the positive reaction is localized mainly to the wall-less bile canaliculi; (a) ×140; (c) ×350. (e) Alkaline phosphatase reaction in the liver of a control guinea-pig; the positive reaction is localized in spots and does not reveal longer sections the biliary vessels. ×350. Alkaline phosphatase reaction in rat liver after ligation of the common bile duct (b and d). Extensive positive areas are seen, occasionally the endothelium of the sinusoids and Kupffer cells give the reaction also. (b) ×140; (d) ×350. (f) Alkaline phosphatase reaction in the guinea-pig liver following ligation of the common bile duct. Sinusoid endothelium and Kupffer cells stain also. ×350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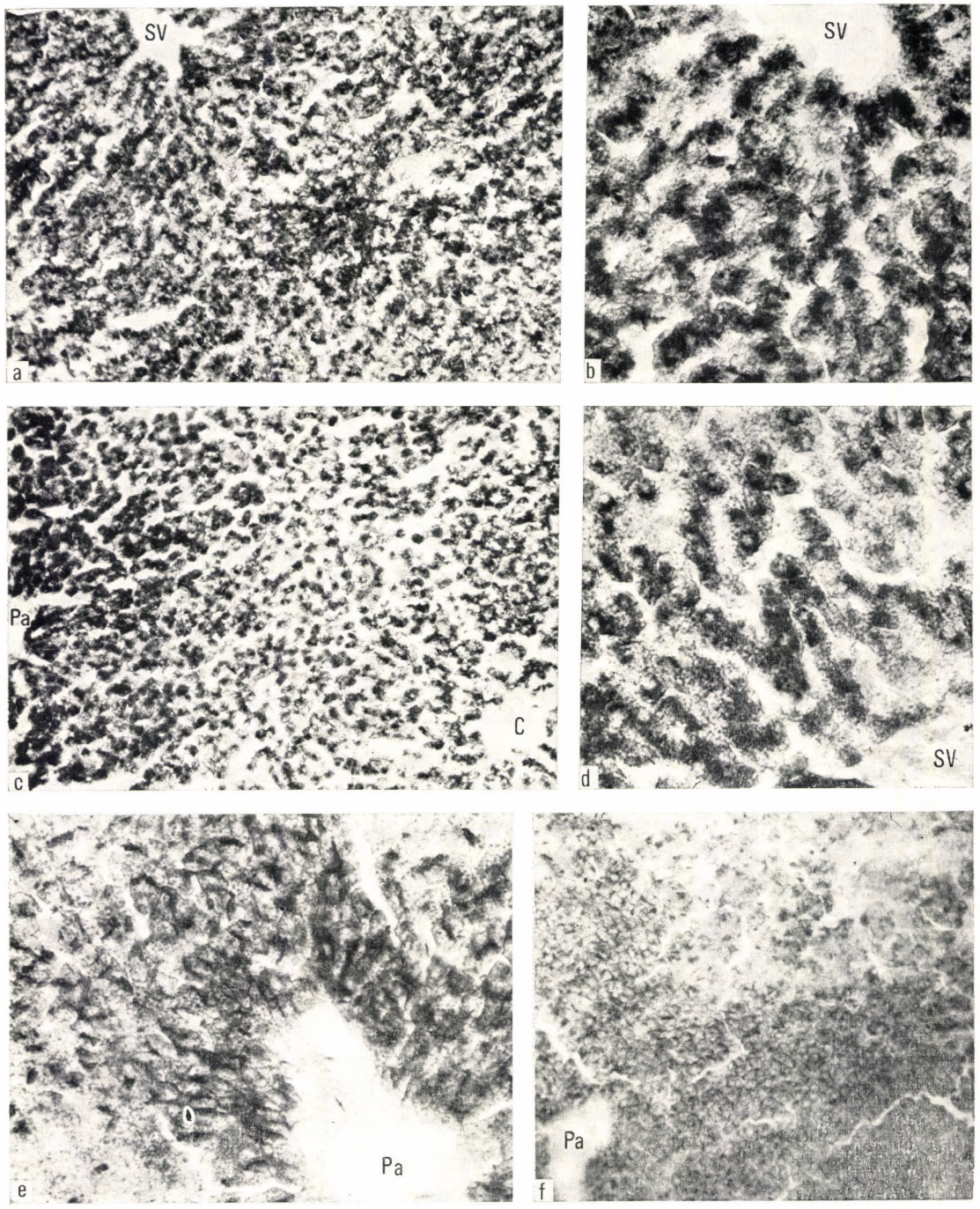
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8.5. Changes in the perihilar core and peripheral shell of the lobe in diffuse hepatic injury

In fatal cases of acute virus hepatitis (acute liver atrophy in fulminant virus hepatitis) we tried to estimate the viability of liver tissue or the amount of viable liver parenchyma by studying the vasculature with injection methods. It is known that in atrophic livers detached, degenerated parenchyma cells and other tissue debris may focally obstruct the vessels resulting in the ischaemic necrosis of further masses of liver tissue. Our results revealed that the blood vessels became obstructed primarily in the peripheral shell of the organ. In the vascular casts of the hepatic venous system of atrophic livers the small hepatic venous branches that run perpendicularly to the surface and form there a star-shaped confluence, were absent. They were replaced by longer veins running from the edge of the liver toward the inferior vena cava or to one of the trunks of the hepatic vein. As a result, the "surface" of the hepatic venous casts of the atrophic liver is formed by a layer which lies usually deeper in the healthy liver. This change in the vasoarchitecture offers an explanation for the well-known wrinkled surface of the atrophic liver. Portaportal and portohepatic anastomoses are frequent findings. They are capable of functioning as shunts through which blood from the peripheral shell of the organ can be drained to the hepatic venous system without accomplishing nutritive function. All these data indicate that the peripheral shell of the liver is more vulnerable than the central area (Ungváry and Somogyi 1969, Ungváry et al. 1971c). Postmortem investigation of atrophic livers alone, however, cannot decide the question. The pathological changes in the core and shell may tend to level on progression because severe, fatal hepatic failure develops only when large masses of the central liver parenchyma become also impaired. Irrespective of whether there are differences in the pathogenesis of liver atrophy in the inner core and outer shell of the liver the significant decrease in the vascular capacity, both the absolute weight and that calculated per unit of liver tissue, may deserve attention. The decrease in vascular capacity indicates again the impairment of local blood flow due to the pathological process. It seems to be important to emphasize that primarily the presinusoidal blood vessels and sinusoids were found to be affected by the damage and obstruction (Ungváry and Somogyi 1969, Ungváry et al. 1974c).

For the above reasons, X-ray pictures taken of an atrophic liver show mostly dilated blood vessels, while ischaemic necrosis is regularly found at autopsy.

Fig. 101. Acid phosphatase reaction in the liver of a control rat (a and b). The staining is more intensive in the perilobular area. (a) × 140; (b) × 350. (c and d) shortly after carbon tetrachloride administration to a rat. There is a more intensive reaction in the perilobular than in the centrolobular area. (c) × 140; (d) × 350. (e and f) the peripheral part of a liver lobe of a rat one day after carbon tetrachloride administration. There is a change in the localization of the staining; the Kupffer cells show pronounced staining. (e) × 350; (f) × 140. SV — sublobular vein; Pa — portal space, C — central vein

Further information may be expected from liver biopsy during fulminant hepatitis (Dible et al. 1943, 1947). However, neither liver biopsy nor the great number of postmortem histological investigations (Lucke and Mallory 1946, Wood 1946, Popper and Franklin 1948, Popper and Schaffner 1957, 1969) can reveal the difference between the processes that take place in the central and peripheral area.

Szabó and Magyar (1963) emphasize that vascular lesions may play a role in obstructive jaundice and think it possible that focal necrosis might result from impaired local blood flow, congestion and thrombosis. Early changes in the hepatic microcirculation after the ligature of the common bile duct, as an experimental model of obstructive jaundice, have not been much studied so far. The majority of investigators studied hepatic vasculature only late, after the ligation of the common bile duct near the time when cirrhosis started to develop or in human biliary obstruction. Most authors described the formation of arterioportal (Herrick 1907, Bradley et al. 1952, Popper et al. 1952) and portohepatic (Moschowitz 1948, Bradley et al. 1952, Popper et al. 1952) anastomoses or deformities and constrictions of the hepatic (Kelty et al. 1950, Madden et al. 1954) and portal (Lozano and Andrews 1965) venous systems. In our earlier study (Füsy et al. 1968) a significant decrease in the vascular capacity of the hepatic and portal venous systems of rats 7–10 days after the ligature of the common bile duct and the development of portohepatic anastomoses were demonstrated. Although these studies were aimed at the investigation of early changes, retrospectively one can see that the 7–10 days' interval after the operation means an advanced stage in the deterioration of the hepatic circulation. Diffuse rearrangement of the liver structure, indicating changes in hepatic circulation, was found. The finding agreed with the changes described by Elias and Sokol (1953) as the inversion of the lobule. In the present study a systemic investigation of the differences between the morphological changes of the periphery and the central area of the liver lobe was undertaken following the ligation of the common bile duct. The India ink–gelatin injection and the benzidine reaction studies indicated that the development of circulatory impairment at the periphery preceded that in the central area only in a part of the cases. On the other hand, the histochemical reactions for succinic dehydrogenase, monoamine oxidase and nonspecific esterase reactions, except for a few intensively stained damaged cells, were generally weaker at the periphery of the liver lobe, especially in guinea-pigs 1 day after the ligation of the common bile duct. The above findings show that the histochemical changes after the ligation of the common bile duct develop at least in part parallel to the impairment of blood flow and that the damage first inflicts the shell of the organ (Ungváry 1971, Ungváry et al. 1971a).

A close parallelism was found between the changes in vascular pattern and intrahepatic topography of enzyme histochemical alterations of the rat liver in carbon tetrachloride intoxication (Fig. 102). This correlation supports the idea that profound changes in local blood flow of considerable duration may be detected by the enzyme histochemical investigations of the parenchyma cells. The pathogenesis of carbon tetrachloride intoxication is a still debated and unsettled question. Glynn and Himsworth (1948) and Andrews and Maegraith (1948) explained the development of centrolobular necrosis in carbon tetrachloride intox-

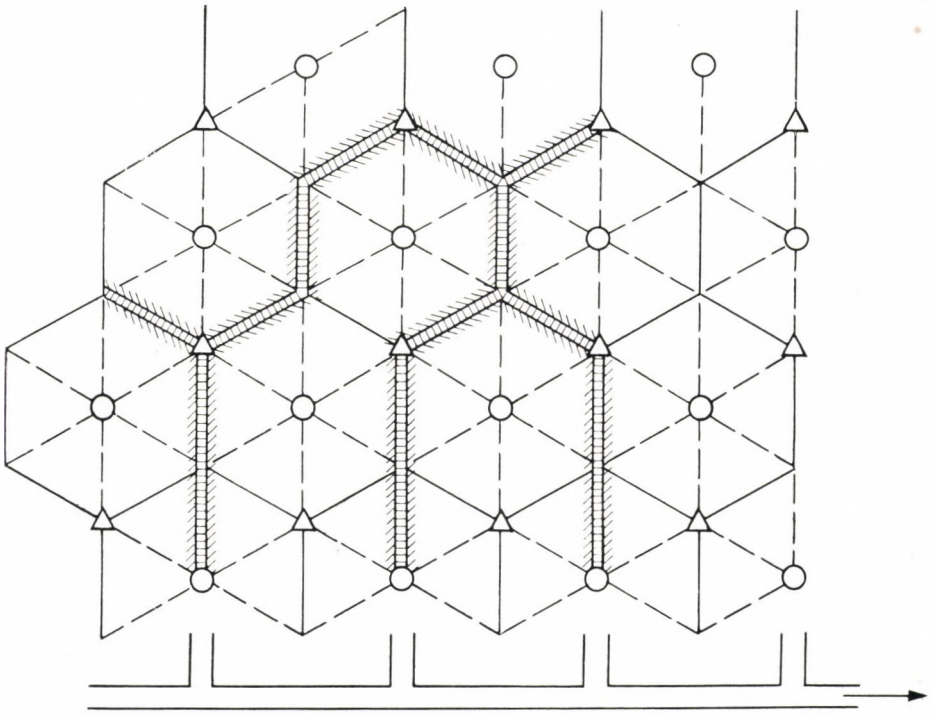


Fig. 102. Schematic representation of the relationship between the vascular rearrangement and rearrangement of the histochemical reactions of the lobules. Circles indicate central vein, triangles the portal vein and the hepatic artery, broken lines the usual arrangement of the sinusoids, continuous lines the interlobular border; shaded double lines the portoportal connections (inversion of the lobule); oblique short lines on both sides of the shaded double ones indicate the change in the localization of the histochemical enzyme reaction. A hepatic venous branch drains in the direction shown by the arrow. The scheme is characteristic mainly of the peripheral part of the liver lobe. For further explanation see discussion of Chapter 8

ication with ischaemia due to the swelling of the parenchyma cells in the centrolobular area, where they are affected earlier than in the periportal area, though the agent reaches the latter earlier. Christie and Judah (1954), Dianzani (1954, 1955) claimed that the damage to the mitochondria and severe impairment of energy production are the primary factors in carbon tetrachloride intoxication. Reynolds (1963) thought on the basis of histochemical and electron microscopic studies that degeneration of the endoplasmic reticulum preceded the involvement of the mitochondria. Leduc and Wilson (1958), using histochemical, biochemical and electron microscopic methods for investigation, suggested the following course of pathogenesis: carbon tetrachloride which is a lipid soluble agent enters the cells, damages membrane structures, first the endoplasmic reticulum. This results in an increase in permeability and a consequent swelling of the cells, to be followed by damage to the mitochondria and the desintegration of the mitochondrial enzyme system. Bartók (1964) thought that recent results were not compatible

with this hypothesis. It is more probable that more cell organelles suffer damage at the same time when carbon tetrachloride enters the cells. On the basis of newer investigations, the cytotoxic effect of carbon tetrachloride is due to its toxic metabolites (Reid and Krishna 1973).

Our studies do not allow us to draw any conclusion as to the pathomechanism of carbon tetrachloride intoxication. We observed, however, the inversion of the hepatic lobule, described originally by Elias and Sokol (1953) and accepted it in general as the sign of decreased portacaval pressure gradient. During the first stage of carbon tetrachloride intoxication there is no rise in hepatic venous pressure. Actually Daniel et al. (1952) found physiological portal venous pressure values even in longer intoxication. Recently, Lautt and Plaa (1974) have stated that there are no significant changes in the feline liver 4 hrs after the intraduodenal injection of CCl_4. The inversion of the lobule may develop perhaps not because of the decrease in portal pressure but as a consequence of the direct cytotoxic effects of the agent on the parenchyma cells in the central region resulting in the swelling of the cells and compression of the sinusoids that drain the blood toward the central veinlet. The central region in a number of lobules is bypassed and the parenchyma cells here are not supplied with blood, thus the direct cytotoxic effect and the ischaemia add to the damage of the central region of the lobule. This phenomenon may be expected to occur throughout the entire liver substance because it is grounded on the inhomogeneity of the liver structure within the acini or lobules. Hence, what can be the reason for the changes that appear significantly earlier in the peripheral shell than in the central core of the organ?

Brody (1959, 1963), Brody and Calvert (1960) and Brody et al. (1961) assumed that hypoxaemia in the liver in carbon tetrachloride intoxication would be due to the activation of the adrenergic system resulting in vasoconstriction and a consequent centrolobular hypoxaemia. Szlamka (1971) observed significant circulatory changes in dogs following the injection of carbon tetrachloride into the blood stream. There was a pronounced decrease in blood pressure and in hepatic blood flow. He concluded that the development of experimental liver injury depends on the function of the nerve centres in the spinal cord. The lack of the hepatotoxic effect of carbon tetrachloride after spinal cord lesion might be explained either by the absence of direct neural influence or by some indirect mechanism. The catecholamine release in carbon tetrachloride intoxication, suggested by Brody (1959, 1963), Brody and Calvert (1960), may account for the relative protection of the central core of the liver. The observations of Szlamka (1971) make the pathomechanism even more understandable. We think that the hypotension after carbon tetrachloride administration activates a reflex (Ginsburg and Grayson 1954) causing vasoconstriction in the portal venous system. The intactness of the reflex is obviously necessary for the rapid development of the toxic effects. Portal vasoconstriction, as we have shown, impairs local blood flow primarily in the peripheral shell of the organ. It is thought to be a relevant phenomenon that the damaged liver tissue gives a more intensive monoamine oxidase histochemical reaction 1 to 3 days after application of the noxious stimulus. The intensive staining was more pronounced after the ligation of the hepatic duct than in carbon tetrachloride intoxication. One may perhaps conclude that there are changes in catechol-

amine metabolism of the liver (Ungváry et al. 1971a). Our hypothesis on the pathogenesis of this toxic liver injury is compatible with that of Brody (1959, 1963), Brody and Calvert (1960), who stress that in carbon tetrachloride intoxication, but on the basis of our studies, perhaps also after the ligation of the common bile duct also, one has to consider the catecholamine-induced ischaemia.

In this chapter we used a model from human pathology, viz. acute liver atrophy obtained from fatal virus hepatitis cases, and two kinds of experimental liver injuries, carbon tetrachloride intoxication and that developing after the ligation of the common bile duct. We studied the possibility whether the central core of the liver adjacent to the hilum, because it has a more favourable blood supply and circulation, as already pointed out, might behave in a way different from the peripheral shell in the pathogenesis and progression of certain diseases.

The studies provided some pertinent data but they cannot settle the question yet.

On the basis of the above data, one may assume a long-lasting intrahepatic redistribution of blood flow in the pathological processes, and a restricted circulation toward the core of the liver predominates that leads to a shift in time of the pathogenetic events between the peripheral and central parts of the organ.

9. Summary

9.1. *The portobiliary system.* The tributaries of the vessels, localized in the three Glisson's peduncles that are formed in the porta hepatis, build up a portobiliary lobe each: the right, the middle and the left liver lobe. They are separated by portobiliary fissures I and II. The distribution of the portal venous system (followed by the hepatic artery and bile ducts) varies widely within the portobiliary lobes, therefore further subdivision into smaller units, the so-called segments, seems to be of no use. The left part of the left portobiliary lobe (the "classic" left lobe) is an exception of great surgical significance.

9.2. *The hepatic venous system.* The right, middle and left hepatic veins can be regarded as the lobar trunks of one vascular lobe each. Thus they form with their tributaries the right, middle and left hepatic venous lobes. The latter essentially corresponds to the left lobe (the "classic" left lobe) of the liver. These lobes are separated by the hepatic venous fissures I' and II'. The number and course of the branches and the angle of confluence and, as a consequence, the size of the lobes show great variations. Nevertheless, it is generally valid, that the hepatic venous fissure I' is located to the left of portobiliary fissure I and the hepatic venous fissure II' to the left of portobiliary fissure II.

9.3. *Structures in the portobiliary and hepatic fissures, the types of liver shape.* Portobiliary fissure I contains the right, portobiliary fissure II either the middle or one branch of the middle hepatic vein. Between the hepatic venous lobes the middle Glisson's peduncle is situated in fissure I', and the left Glisson's peduncle lies in fissure II'.

According to shape, the livers can be divided into oval, triangle and intermediary types. The size and shape of the lobes vary with the shape of the liver and with the type of distribution of the hepatic vasculature. The number of lobes does not change and the interlobar fissures contain the above-described tracts. The position of the fissures and thus the size and shape of the lobes can be determined by either cholangiography or portovenography, supplemented with the roentgenographic delineation of the hepatic venous system that can be performed through a catheter introduced into the hepatic vein.

9.4. *Data on the ontogenesis of the liver.* In human fetuses the proportion of the liver substance situated to the right of the Rex–Cantlie's line is smaller than that to the left of the line. The proportion of the two main parts in the fetus is about the reciprocal of the proportion found in adults. Terminal afferent vessels, the so-called fetal sinusoids, do not enter only the smallest roots of the fetal hepatic system but even larger hepatic venous branches. The parenchyma is built up in

general of two-cell-thick plates. The sinusoids vary in shape and width. The liver lobes are built up of irregularly arranged fetal acini. The histo-functional units of the fetal liver resemble much the terminal and complex acini of the adult lobe but they are not arranged regularly. The organization of acini into Kiernan's lobules, characteristic of the adult, appears by 3 years of age in humans and by 3 weeks of age in rats. A prerequisite of the development of the Kiernan's lobules is the general appearance of the more plastic one-cell-thick hepatic plates that replace the two-cell-thick ones (Fig. 127, p. 204).

9.5. *Obsevartions made on the regenerating rat liver.* After partial hepatectomy the hepatic cell plates, two or more cells in thickness, can be found only in a few places, clusters of cells, nodules are more frequent. Kiernan's lobules are more often found in the regenerate than in the fetus; the acini are similar to those in adult or fetal liver.

The rate of vascular regeneration as well as the increase in vascular capacity of the portal and hepatic venous systems were found to be less than the rate of increase in wet liver weight 1 to 7 days after partial hepatectomy. The changes in portal and hepatic venous vascular capacity showed no close parallelism.

The number as well as the size of both portal and hepatic venous lobules were seen to increase during liver regeneration. The distance of the peripheral zone of the acinus from its centre increases on account of the longer sinusoids, therefore a larger area of the acinus falls under zone Z_3, the circulatory periphery of the liver acinus having a less favourable blood supply. The increase in size and the change in shape of the liver lobes result in an increase in the angle of vascular divisions.

9.6. *The hepatic artery.* The hepatic artery with its most abundant tributary supplies the liver tissue with blood via arterioportal anastomoses and arterio-sinusoidal (precapillary) sphincters which open according to requirements. Filling of the hepatic artery system is more "complete" following the constriction of the portal vein. In this way the terminal connections of the hepatic artery with the portal venous system can be studied better. Both on the surface and in the deeper part of the liver lobe the acini can be filled either through the hepatic artery or through the portal venous system (Fig. 127, p. 204).

There is an increase in the capacity of the portal venous system and more inlet sphincters are open 1–2 hrs after the ligation of the hepatic artery, while 1 week after ligation there is a decrease in portal venous vascular capacity, and a smaller number of inlet sphincters are open than in the control livers.

9.7. *Innervation of the portal vein.* Forty-eight hours after the bilateral removal of the celiac ganglion the nerve fibres of the vessel wall, yielding the catecholamine fluorescence, disappear and autophagous cytolysomes can be demonstrated in the degenerating axons under the electron microscope.

Within 24–48 hrs after the extirpation of the right spinal ganglia (Th_6–L_2) degenerating axon terminals can be demonstrated in the intima of the portal vein.

Transection of the vagus nerve either on the neck or at the cardia was not followed by nerve degeneration in the wall of the portal vein.

Acetylcholinesterase-positive preterminal nerve fibre bundles could be demonstrated only in the connective tissue layer of the adventitia. At the border between

the media and adventitia there is a dense "two-dimensional" network of monoaminergic nerve fibres. Nonspecific cholinesterases are equally present in the inner circular and outer longitudinal smooth muscle layers, monoamine oxidase is localized preferentially in the longitudinal muscle layer. Zinc-iodide-osmium-positive nerve fibres are present in all layers of the vessel.

There is a fairly good overlap between the localization of monoaminergic nerve fibres and axons containing dense-core vesicles in the wall of the portal vein. Axon profiles containing neurotubules or small clear vesicles, that are partially or completely engulfed by Schwann cell processes, are present in the adventitia and media at a distance of 2–4000 Å from the muscle cells. Axon profiles are located in the intima of the vessel wall too.

9.8. *Innervation of the common hepatic artery.* The innervation of the wall of the artery is similar to that present elsewhere in the organism. The majority of catecholaminergic fibres disappear after the extirpation of the celiac ganglia and autophagous cytolysomes can be demonstrated in the axons at the border between the media and adventitia. No axon degeneration could be observed after the surgical ablation of the right spinal ganglia Th_5–L_3 or transection of the left vagus nerve.

9.9. *Innervation in the intrahepatic structures.* The larger intrahepatic portal branches are supplied by a rich noradrenergic innervation in every species studied (Fig. 127, p. 204). Catecholamine fluorescence in the cross-section is preferentially localized at the border between the media and adventitia. Along the vessels the most intensive fluorescence was seen at the site of the branchings. In the intrahepatic branches of the hepatic artery, too, an abundance of monoaminergic nerve fibres could be observed at the border between the media and adventitia in every species studied (Fig. 127, p. 204). There are only very few fibres with noradrenergic fluorescence along the intrahepatic bile ducts in contrast to the rich noradrenergic nerve supply of the gall-bladder and extrahepatic bile ducts. The nerve fibres with catecholamine fluorescence follow the blood vessels in the wall of the biliary system as well as in the Glisson's capsule. Except for the guinea-pig, only a few acetylcholinesterase-positive nerve fibres, that follow mainly the bile ducts, can be found in the portal channels.

A considerable number of nerve fibres with monoamine fluorescence can be observed in the inter- and circumlobar areas especially at the periphery of the liver lobe. At the periphery of the Kiernan's lobule the nerve fibres with monoamine fluorescence reach approximately a point where the terminal branches of the hepatic artery join the portal sinusoids. The same regularity can be seen with the acetylcholinesterase-positive fibres in the guinea-pig. Innervation of the parenchyma cells, at least in most part of the liver, can be excluded almost with complete certainty.

9.10. *Innervation of the "hepatic sphincter".* In a narrower sense the junction of the hepatic venous system with the inferior vena cava is called the hepatic sphincter. In a broader sense and with regard to function, however, the branches of the second, third, and even of higher order of the hepatic vein are also included. The nerve fibres among the smooth muscle cells of the hepatic sphincter come from the celiac ganglia. Axon terminals containing dense-core vesicles can be seen in the intima, too. Axon terminals of the nerve fibres from the right Th_9–L_2

spinal ganglia enter also the intima of the vessel wall. Presumably sensory fibres of the right phrenic nerve reach the adventitia (Fig. 127, p. 204). No secondary degeneration was seen in the vessel wall 24–48 hrs after transection of the vagus nerve.

The hepatic sphincter is supplied by a dense network of nerve fibres yielding characteristic monoamine fluorescence that extends partly into the media, too. The nerve fibres of the sphincter could be traced down to the intima by means of the zinc-iodide-osmium method. A strong nonspecific cholinesterase reaction was found in the smooth muscle layers, while only a very few acetylcholinesterase-positive nerve fibres were seen.

Axons with dense-core vesicles, empty vesicles, neurotubules engulfed by Schwann cell processes and myelinated nerve fibres are present in the adventitia. The axon terminals are present in the media and intima. The surface of the axon terminals opposite the smooth muscle cells is covered while the surface facing the endothelial cells in the intima is free of the Schwann cells envelope in general. Varicose monoaminergic axons from the celiac ganglion containing dense-core vesicles and sensory fibres from the spinal ganglia were observed in the wall of the smaller branches of the hepatic vein also.

9.11. *Reflex arcs closing in the spinal cord.* Receptor endings of the portal and hepatic venous systems belong to neurons in the right Th_{6-9}–L_2 spinal ganglia. The central processes of neurons in this region may synapse with the preganglionic neurons of the prevertebral ganglia. Postganglionic fibres of the prevertebral ganglia supply the portal and hepatic venous and hepatic arterial systems (Fig. 127, p. 204).

Another reflex arc whose afferents use the phrenic nerve as pathway, takes its origin in the hepatic sphincter, too (Fig. 127, p. 204).

9.12. *Reflex arcs closing at the periphery.* Degenerating axon terminals synapsing in the celiac and superior mesenteric ganglia were found 24–48 hrs after cholecystectomy or resection of the liver or jejunum. Two weeks after extirpation of the prevertebral ganglia a small number of thin, intact axons can be found in the postganglionic bundle of nerve fibres running to the viscera (liver, small intestines). Peripheral reflex arcs, built up of two neurons that do not enter the central nervous system, close in the prevertebral ganglia of the splanchnic area. These reflex arcs might be important factors in the regulation of blood flow within and among the organs.

9.13. *Morphological features of the "core" and the "shell" of the liver lobe.* The sinusoids emerge at the 4th to 6th division, or at the 6th to 10th division of both the portal and hepatic veins in the central or peripheral region of the liver lobe, respectively. Therefore, the course of the blood stream is shorter near the hilum, in the core of the lobe than on its peripheral shell.

The total volume of sinusoids per unit weight of liver in the central core exceeds that at the periphery of the lobe in the dog liver.

9.14. *Different blood flow responses of the core and shell of the liver lobe.* Adrenaline and noradrenaline evoke an increase in portal venous pressure and a decrease in local blood flow in the core and shell of the liver lobe alike. Isopropyl noradrenaline causes an increase in the central and a decrease in peripheral local

blood flow of the lobe. Acetylcholine administration into the portal vein leaves hepatic flow unaffected. Portal pressure increases and local blood flow decreases mainly in the peripheral part of the lobe in response to the intravenous injection of acetylcholine. Histamine administration into both the portal and femoral vein increases portal pressure and decreases local blood flow in both parts of the lobe. The decrease in local blood flow is slighter in the central area than at the periphery of the lobe.

In experimental hypotension due to bleeding there is a decrease in local blood flow in both the central area and at the periphery. The response in the latter is significantly more pronounced.

Every treatment that results in a considerable drop in blood pressure in normovolaemia or in hypotension due to bleeding, induces restriction, i.e. the intralobar redistribution of hepatic blood flow in dogs (Fig. 127, p. 204).

Electric stimulation of the hepatic plexus, the splanchnic, the left vagus and the right phrenic nerves resulted in a significant decrease in local blood flow in the central region and at the periphery of the lobe. The decrease is more pronounced at the periphery. Electrical stimulation of the right phrenic nerve caused an increase in the central and a decrease in the local blood flow at the periphery of the lobe (Fig. 127, p. 204).

The efferent of the reflex arc through which restrictive redistribution of hepatic blood flow is elicited runs in the splanchnic nerve–hepatic plexus system.

Stimulation of the vagus nerve on the neck evokes restriction of hepatic blood flow via systemic arterial hypotension because stimulation of the nerve at the cardia does not interfere with hepatic blood flow.

Stimulation of the right phrenic nerve after the transection of the diaphragm around the inferior vena cava has no vasoconstrictor effect in the hepatic venous system. Thus, on stimulation of the nerve with the diaphragm intact, restriction is probably evoked by the mechanical effect of the diaphragmatic movements.

The part of the liver around the hilum can be considered an area with lower resistance through which blood can pass faster toward the hepatic veins and the inferior vena cava. Restriction of the hepatic blood flow to the core of the lobe may be the consequence of a reflex vasoconstriction affecting the portal venous and hepatic arterial systems (Fig. 127, p. 204).

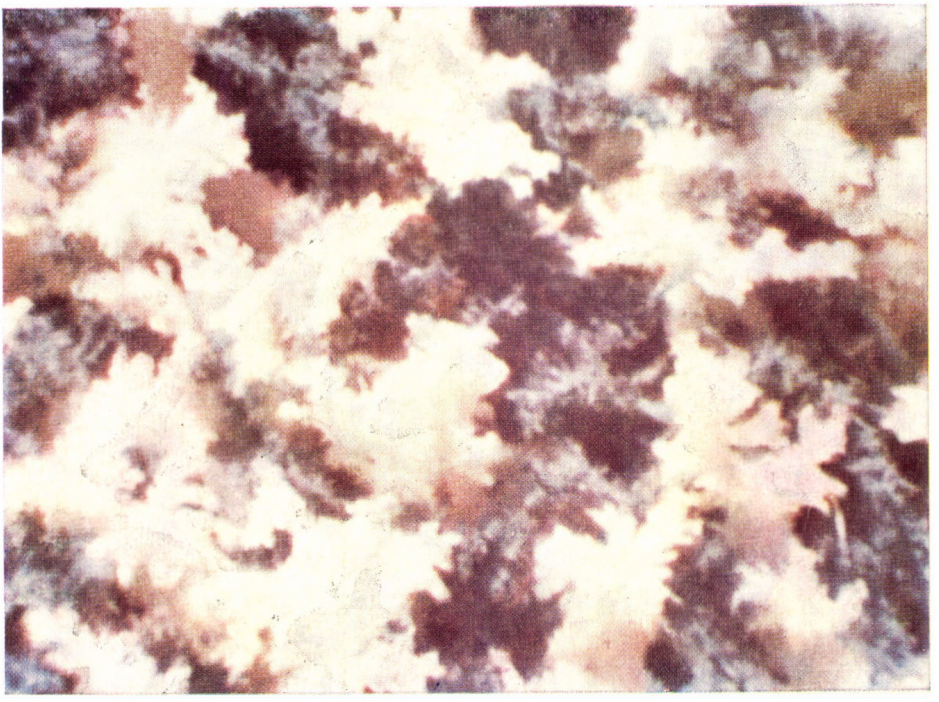
9.15. *Independence of the core and the shell of the liver lobe under pathological conditions.* In cases of liver atrophy due to acute virus hepatitis the weight of vascular cast per unit weight of liver (vascular capacity) is significantly lower than in the control. Both the portal and hepatic veins are affected. The most conspicuous feature is the insufficient filling of the sinusoids. Vessels covered by others and thus not seen in the control livers become "superficial" and appear beneath the capsule. The great number of intra- and translobar portohepatic anastomoses is conspicuous. Via these shunts the blood may bypass the shell of the lobe and flow toward the core and inferior vena cava without fulfilling a nutritive function.

One day after the ligation of the common bile duct the vasculature of the rat and guinea-pig liver is like the pattern described as inversion of the lobule. Succinic dehydrogenase, monoamine oxidase and nonspecific esterase-positive areas are smaller at the periphery than in the central part of the liver lobe.

A few hours after carbon tetrachloride administration to rats the vascular pattern of the liver shows inversion of the lobule, which becomes more pronounced one day later. Larger continuous areas are cut of from the circulation at the periphery of the liver lobe. Changes in the localization of the enzyme histochemical reaction parallel the changes in liver circulation. The succinic dehydrogenase, monoamine oxidase and nonspecific esterase-positive area per unit area is significantly less at the periphery than in the central area of the liver lobe.

Liver atrophy in acute virus hepatitis, carbon tetrachloride intoxication and the ligation of the common bile duct all result in the intralobar redistribution of hepatic blood flow. Local blood flow of the shell diminishes and the core of the lobe works as a shunt. Persistence of the redistribution results in a shift in time of the development of lesions between the central and peripheral parts of the liver lobe (Fig. 127, p. 204).

Coloured plates



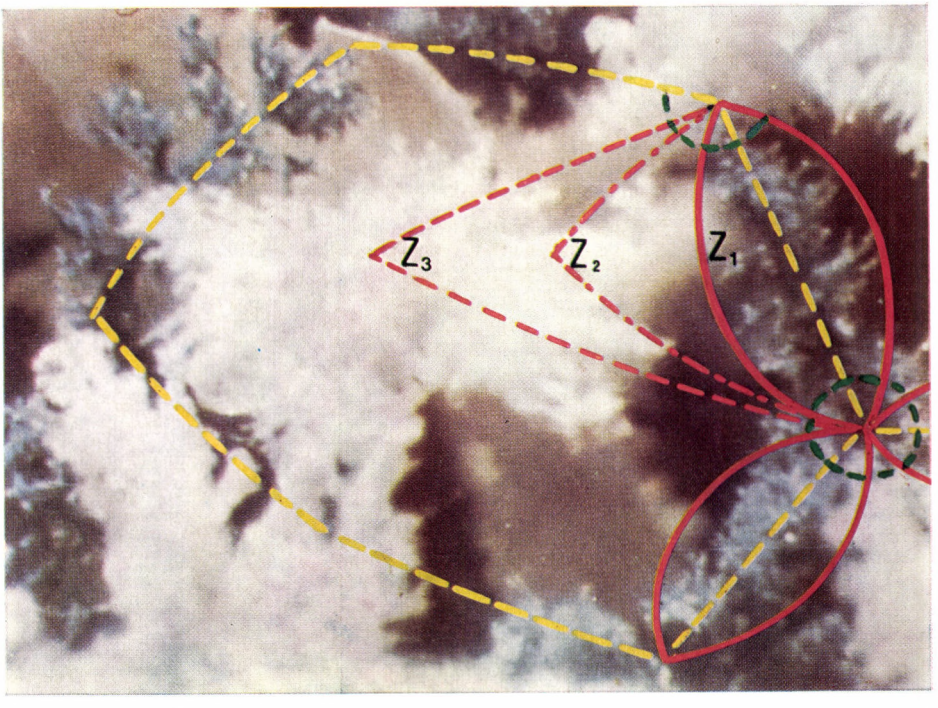

Z_3
Z_2
Z_1

Fig. 103. The vasculature providing a supporting framework of the liver lobule. Light and dark PVC were injected into the hepatic venous and portal venous systems, respectively. Rat. Ijnection–corrosion preparation. ×35

Fig. 104. Enlarged portion from Fig. 103 showing the relationship between the Kiernan's lobule (enclosed by a broken yellow line) and the circulatory zones of the Rappaport's simple liver acinus (Z_1, Z_2, Z_3 areas enclosed by a red line). The area indicated by the green lines may belong to Z_1, Z_2, or Z_3 zones alike. With a portocaval pressure gradient in the physiological range it belongs to Z_3, however, its blood flow becomes equal to that of Z_1 in case of inversion of the lobule. The last threefold division of a terminal portal branch is seen on the right side, the twigs forme an angle of 120°. ×88

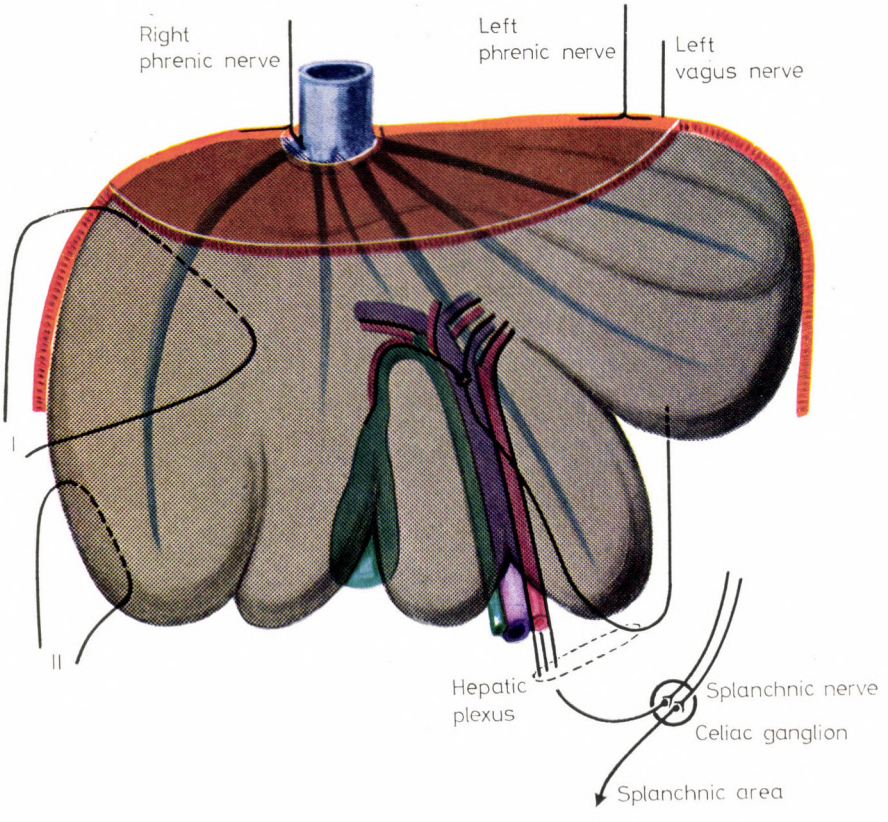


Fig. 105. Schematic representation of a dog liver showing the nerves stimulated and the sites of thermoprobes: I. flexible thermoprobe in the central part of the lobe; II. flexible thermoprobe in the peripheral part of the lobe. A circular incision was made through the diaphragm, all around the inferior vena cava

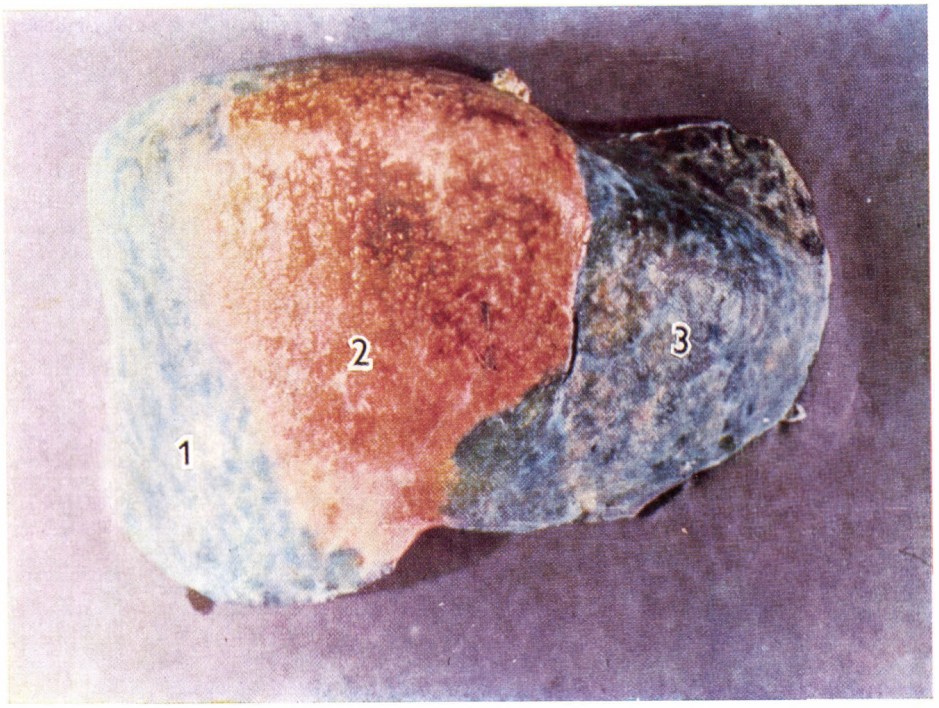
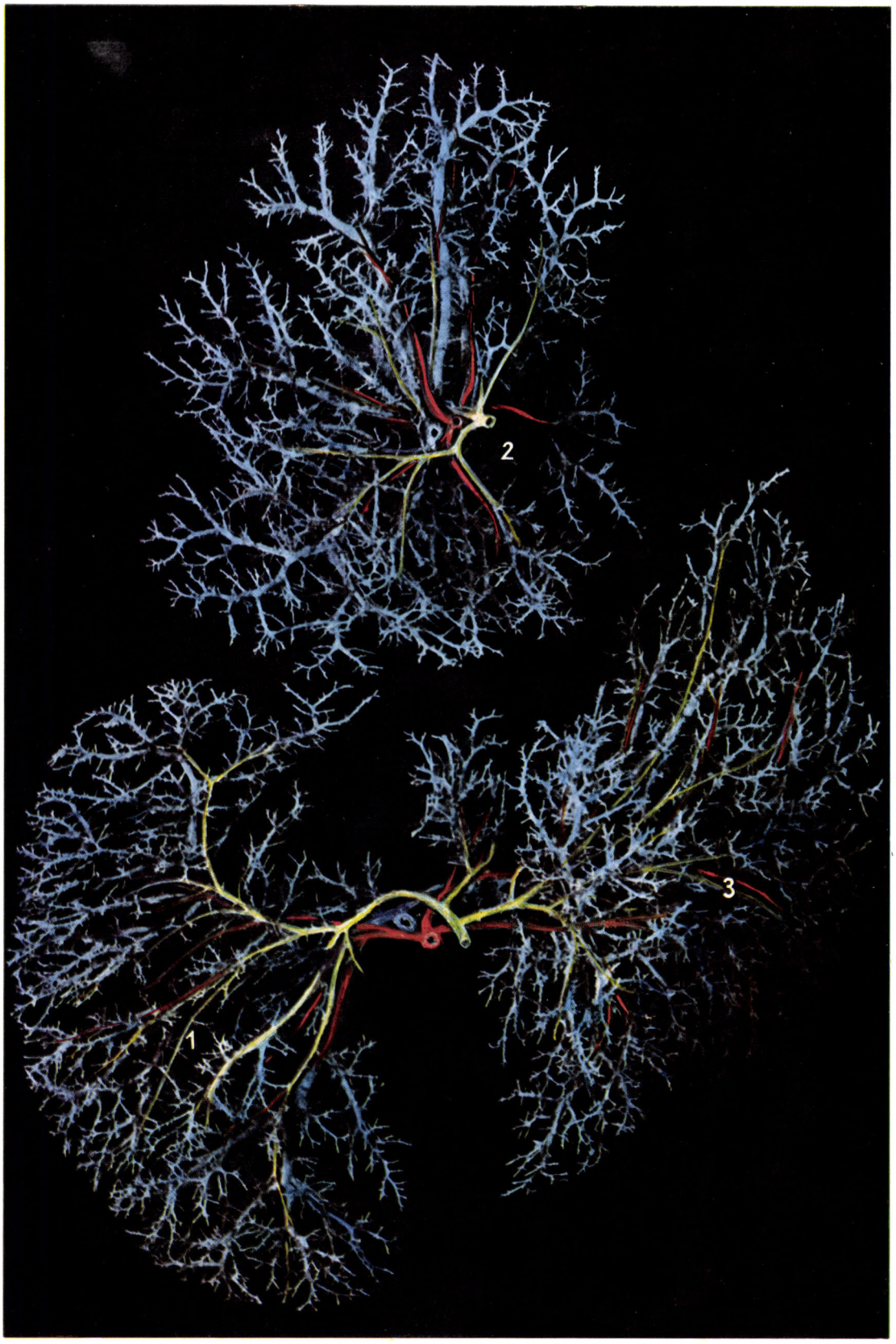


Fig. 106. Portobiliary lobes of the human liver. Methylene blue solution (1%) was injected into the right and left trunks of the portal vein. 1 — right lobe; 2 — middle lobe; 3 — left lobe

Fig. 107. PVC cast of all three vascular trees of the portobiliary vessel systems. The wedge-shaped middle portobiliary lobe (2) was separated from the right (1) and left (3) portobiliary lobes. The portal vein is blue, the hepatic artery is red, the biliary duct is yellow


2
3
1

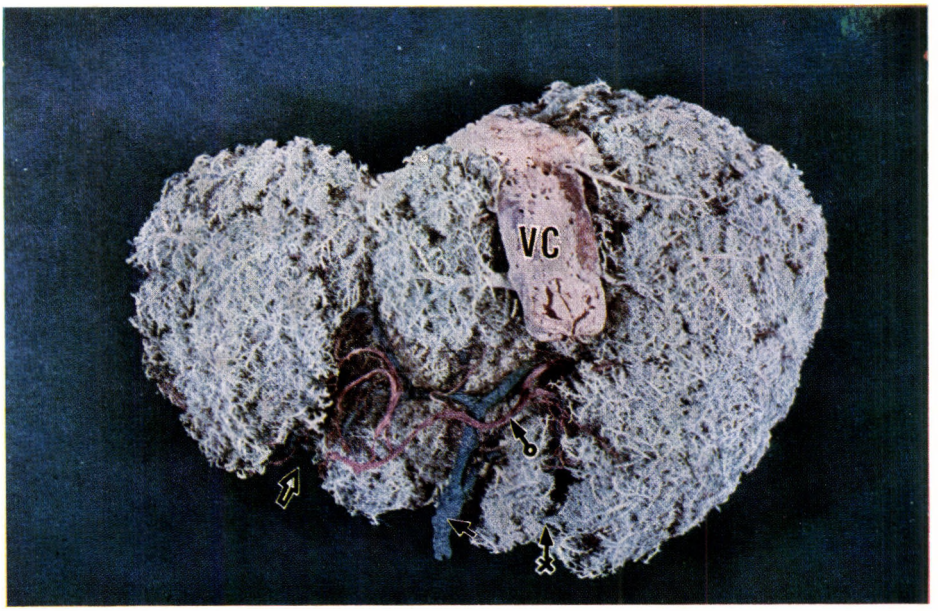


Fig. 108. Injection-corrosion preparation of a human liver. VC — inferior vena cava; common hepatic duct (→); hepatic artery (o→); fissure I' (x→); fissure II' (⟹)

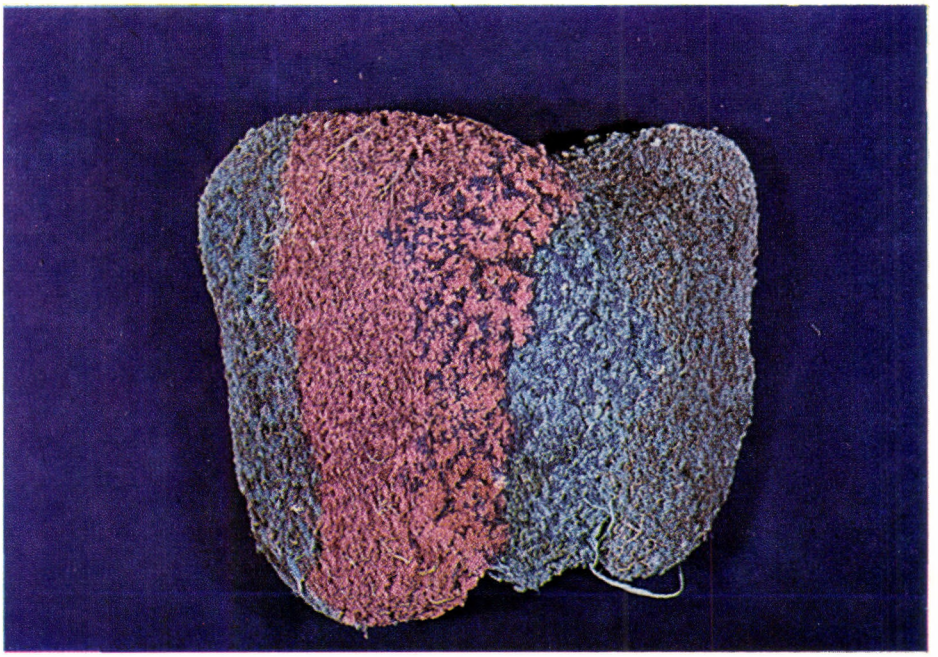


Fig. 109. Convex surface of a human liver; corroded cast. Plastics of red, blue, black and yellowish-brown colour were injected into the middle trunk of the portal vein, right and left trunks of the portal vein, middle hepatic vein and right and left hepatic veins, respectively. The lobes and the fissures separating them are distinct on the surface

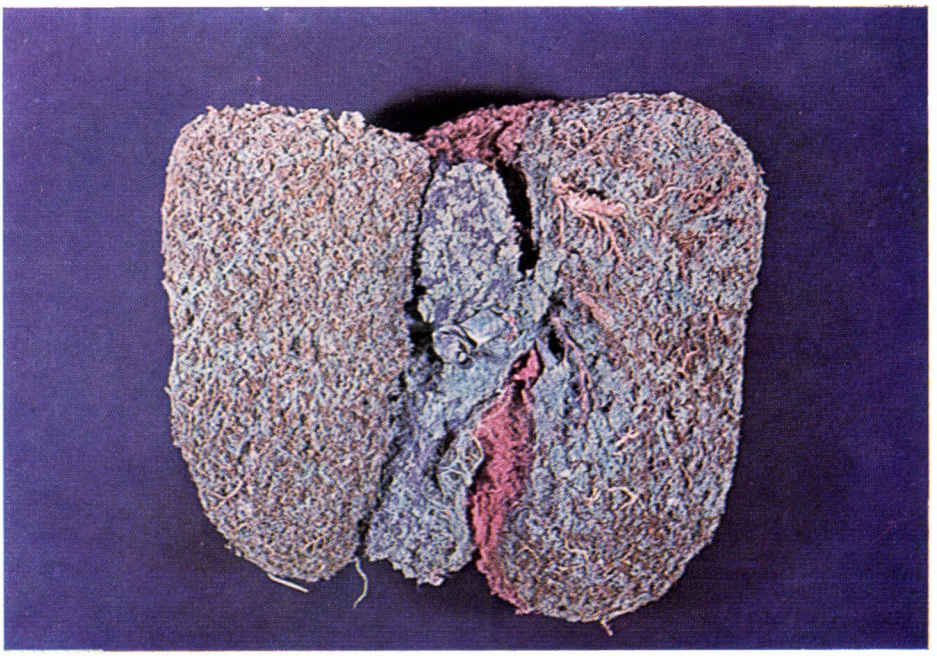


Fig. 110. Visceral surface of a human liver; corroded cast. The middle, the right and left trunks of the portal vein, the right and left and the middle hepatic veins were injected with red, blue, yellowish-brown and black plastics (violet-grey in the photo)

Fig. 111. Vascular cast of the human liver. The portal vein and the hepatic vein were injected with light and dark plastics. The borders of the lobes do not appear

Fig. 112. Vascular cast of a human liver. The cast of the portal vein is violet, the cast of the hepatic venous system is yellowish-brown. The arrows indicate the crossings at right angles of hepatic and portal branches

Fig. 113. Vascular cast of the dog liver. The hepatic and portal venous systems were injected with white and blue plastics, respectively. The arrows point at the parallelly running portal and hepatic venous branches

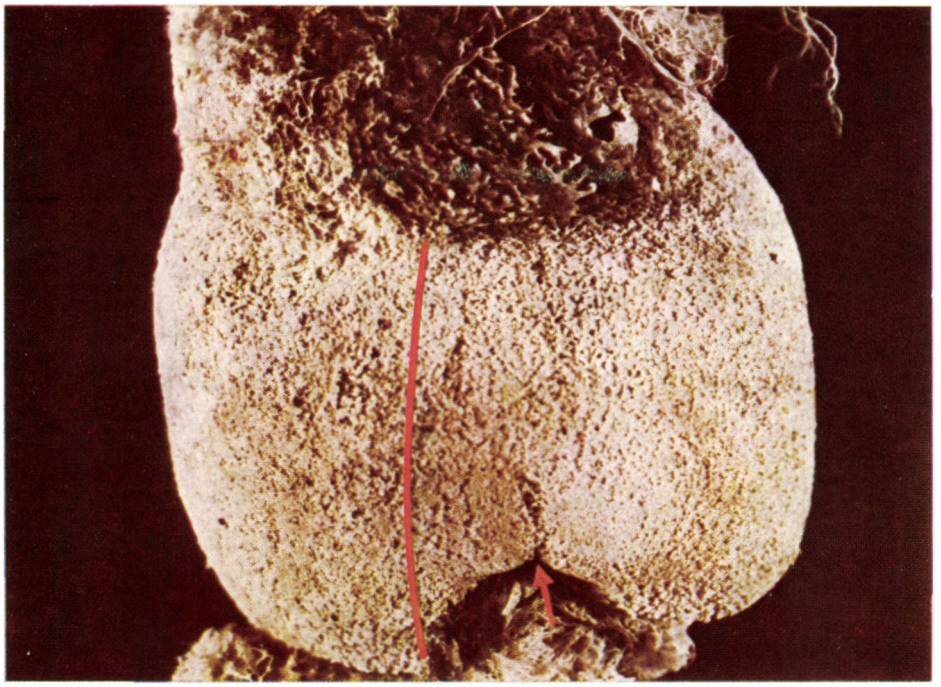


Fig. 114. PVC cast of the liver vasculature of a human fetus in the 8th month of gestation. The left hypochondrium is occupied by the liver; thick line corresponds to the Rex–Cantlie's line; the left main part of the liver is larger than the right one. Arrow indicates the umbilical vein and the umbilical incisure

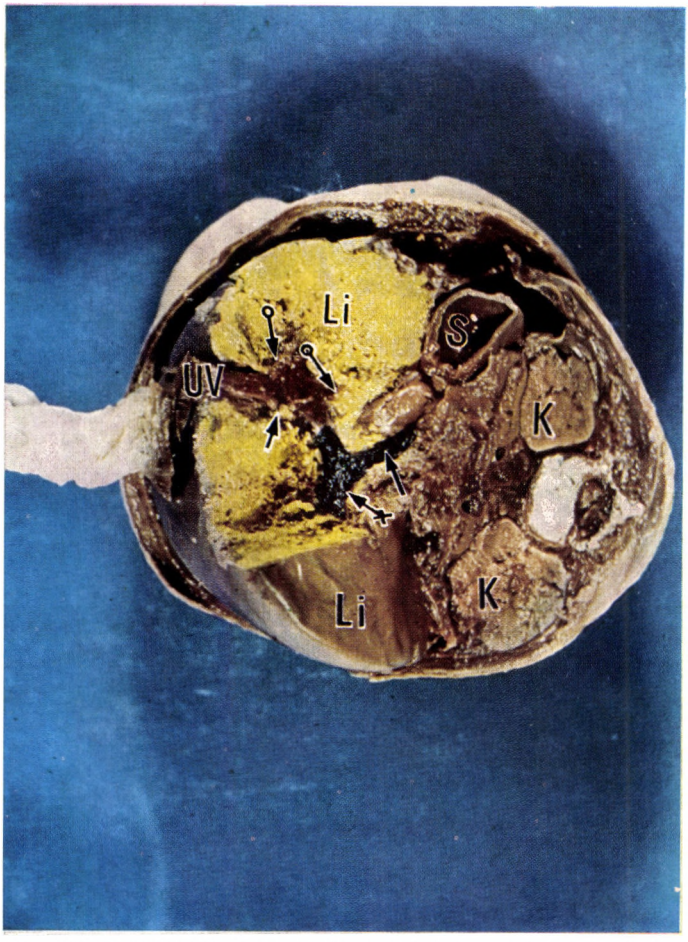


Fig. 115. Relationship between the portal and umbilical veins in the human fetus. Liver (Li); stomach (S); kidney (K); umbilical vein (UV); portal vein (⟶); arc of the umbilical vein (→) joining the left trunk of the portal vein; umbilical vein and the branches of the left trunk of the portal vein (o→); right trunk of the portal vein (x→)

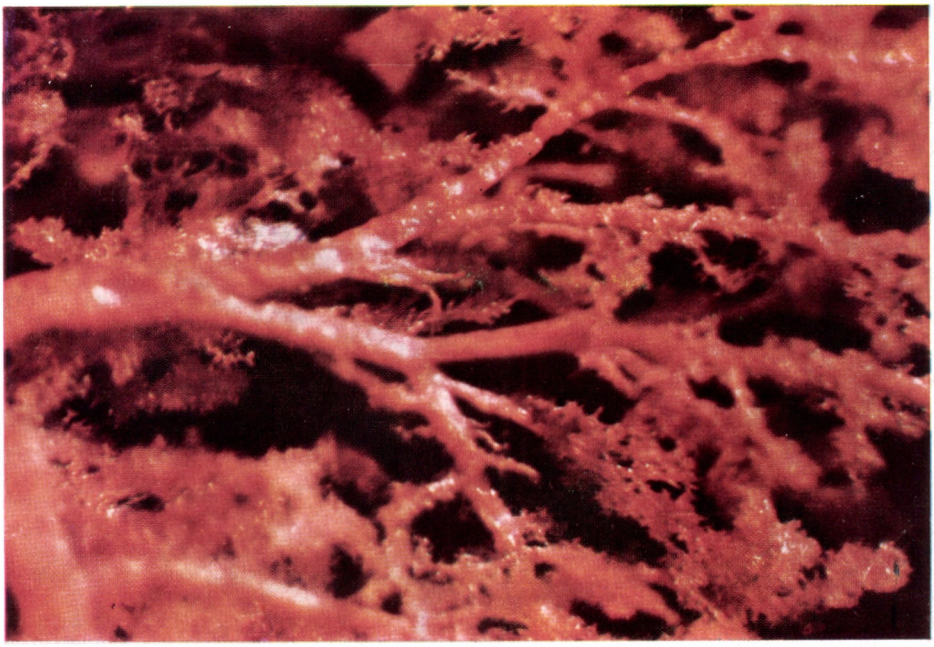


Fig. 116. Corroded vascular cast. Vasculature of the lobules in fish liver. ×50

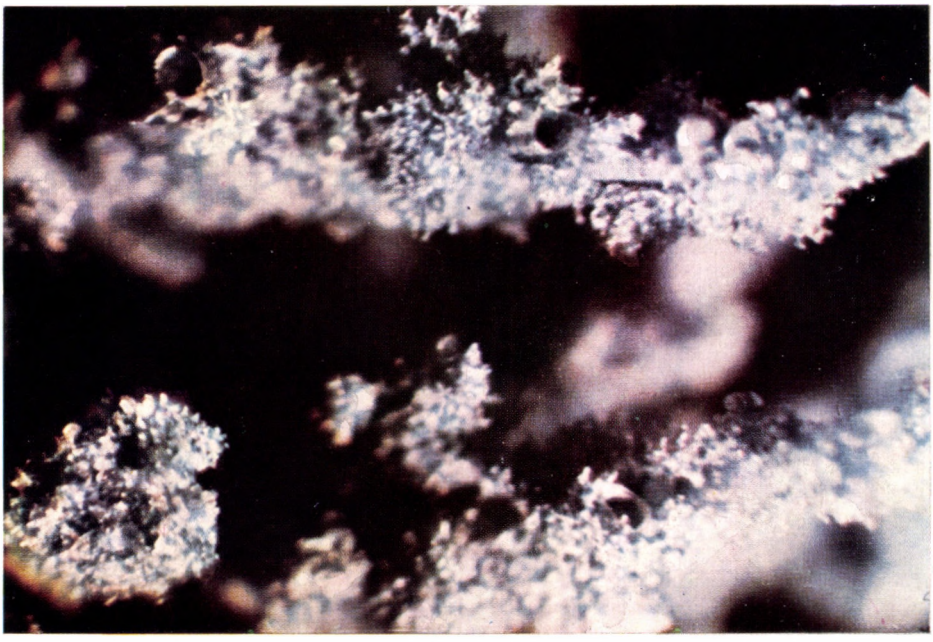


Fig. 117. Corroded vascular cast. Vasculature of the lobules in frog liver. ×88

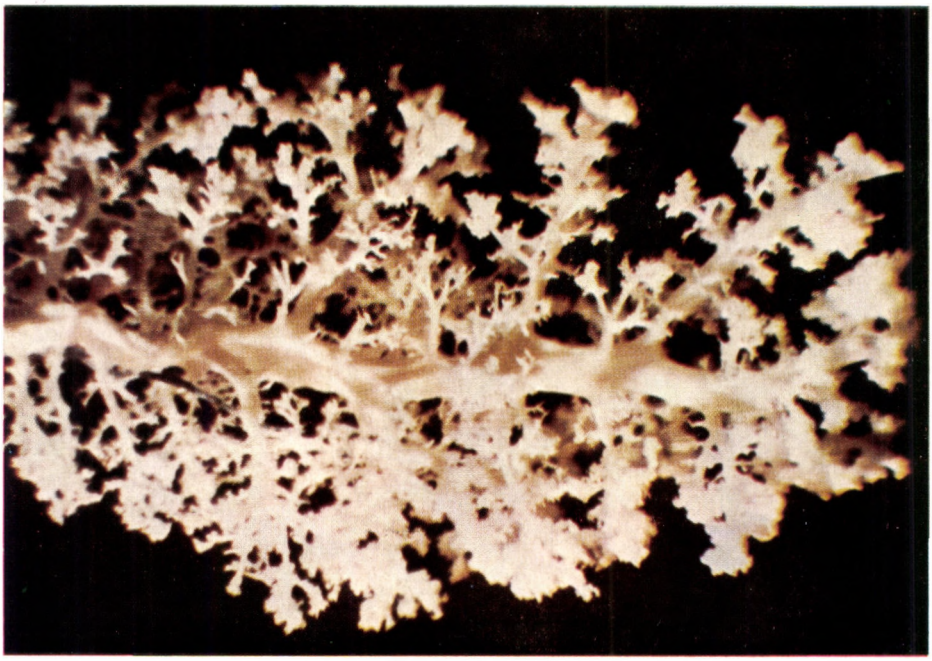


Fig. 118. Corroded vascular cast. Vasculature of the lobules in a chicken liver. ×16

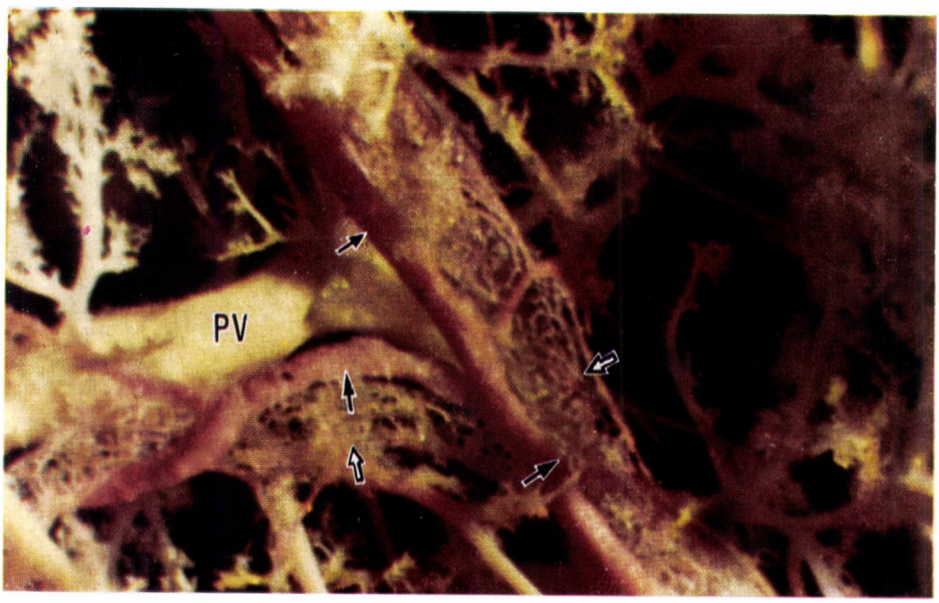


Fig. 119. Corroded vascular cast. An abundant dense network of arterioles and capillaries formed by the branches of the hepatic artery along the biliary system is shown. 3% red PVC and 5% white PVC solutions were injected into the hepatic artery and the portal vein, respectively. Portal vein (PV); branches of the hepatic artery (→); peribiliary network (⟹). Guinea-pig. ×35

Fig. 120. Corroded vascular cast. Red, yellowish-grey and green PVC solutions were injected into the hepatic artery, portal vein (o→) and common hepatic duct, respectively. Arterial twigs running to the surface of the liver (→); arterial twigs dividing into sinusoids (x→). Dog. ×3.5

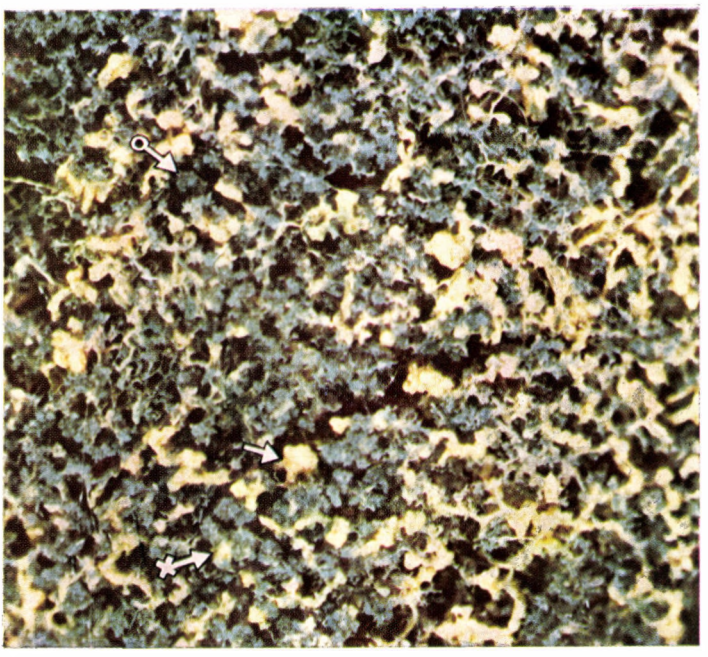


Fig. 121. Corroded vascular cast. The portal vein and hepatic artery were injected with blue PVC or yellowish-white latex solutions, respectively. The photograph shows the acini filled through the hepatic artery (→), portal vein (o→) and through both portal vein and hepatic artery (x→). Cat. ×5

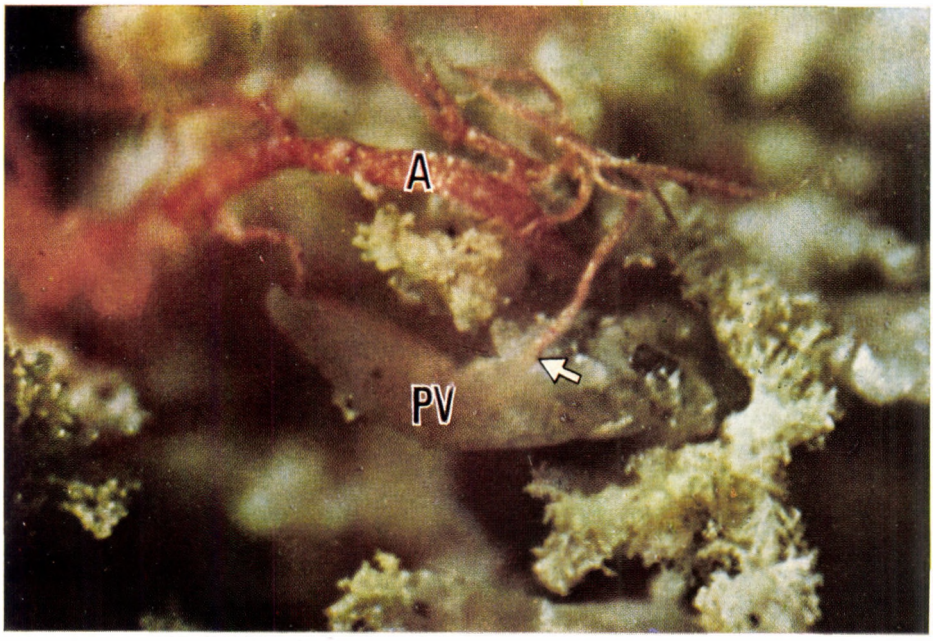


Fig. 122. Corroded vascular cast of the portal venous (PV) and hepatic arterial (A) systems shown by green-white and red colour, respectively. The arrow indicates an arterioportal anastomosis. Human liver. ×55

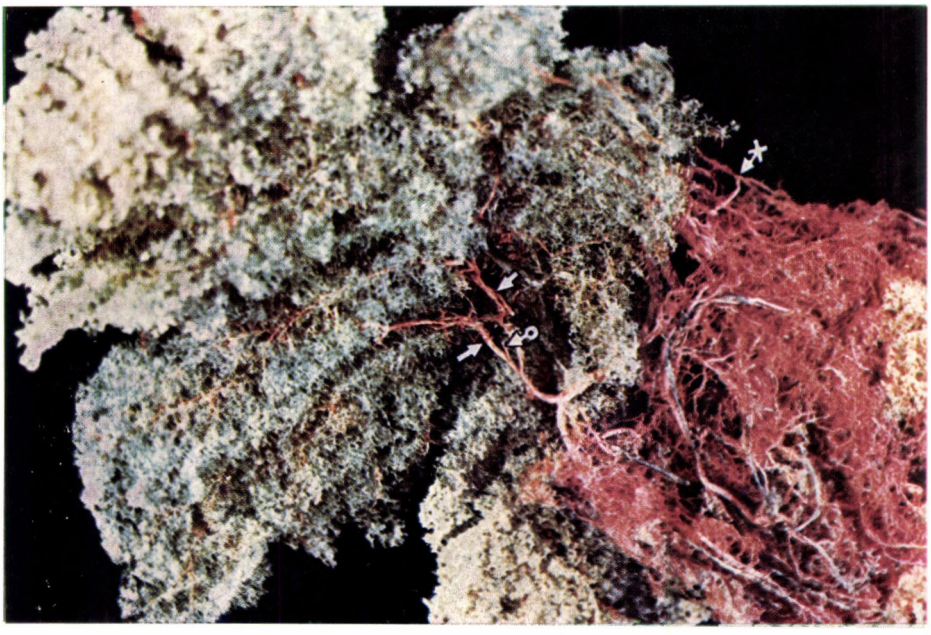
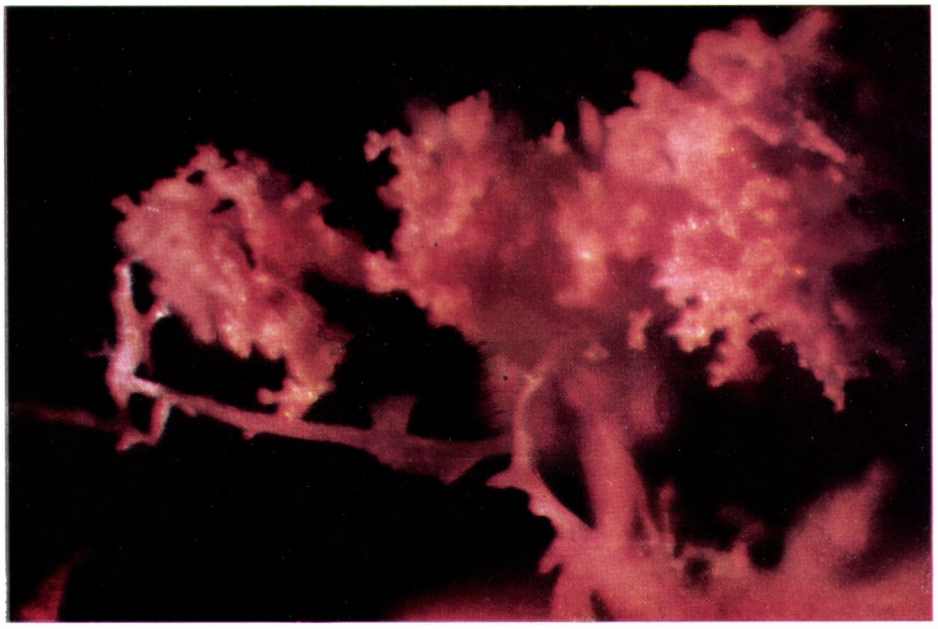


Fig. 123. Corroded vascular cast. Blue and red PVC were injected through the portal vein and in the aorta, respectively. Cat liver, 3 weeks after ligation of the hepatic artery; stump of the hepatic artery (o→); two dilated collateral arteries (→); collateral arteries reach the liver through the adhesions (x→)

a



b

Fig. 124. (*a*) Corroded vascular casts. Blue PVC was injected through the previously constricted portal vein, while red PVC through the hepatic artery. The cast is characterized by dilated arterial system in a number of regions. Cat. *(b)* A number of liver acini are filled up through the dilated arteries. Cat, after constriction of the portal vein. ×88.

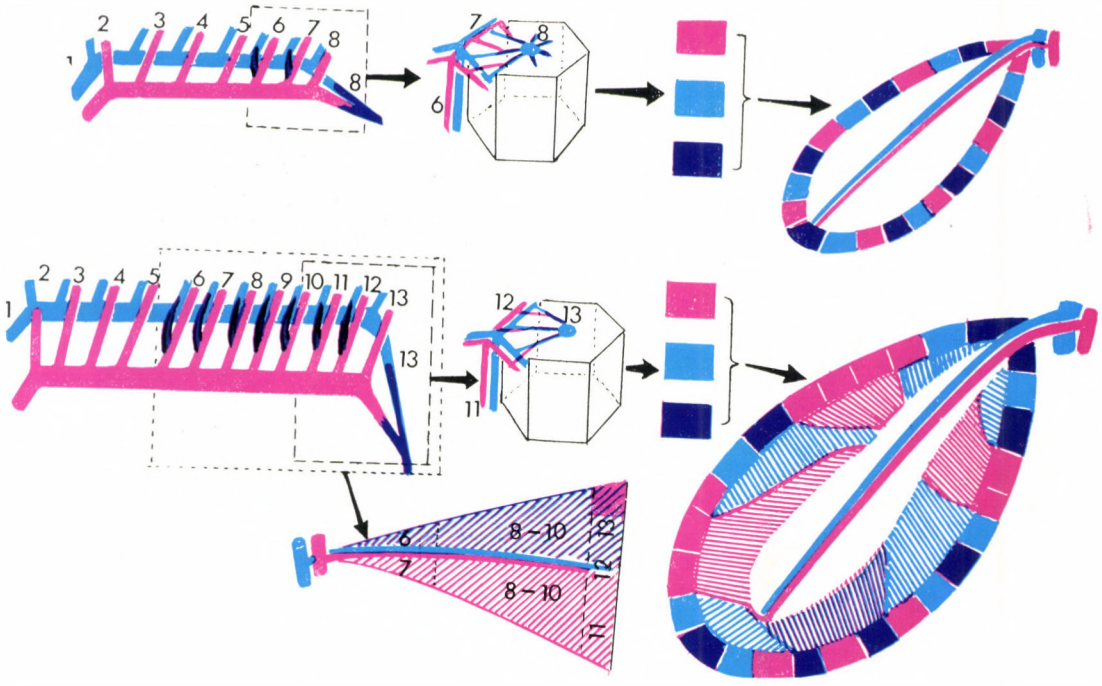
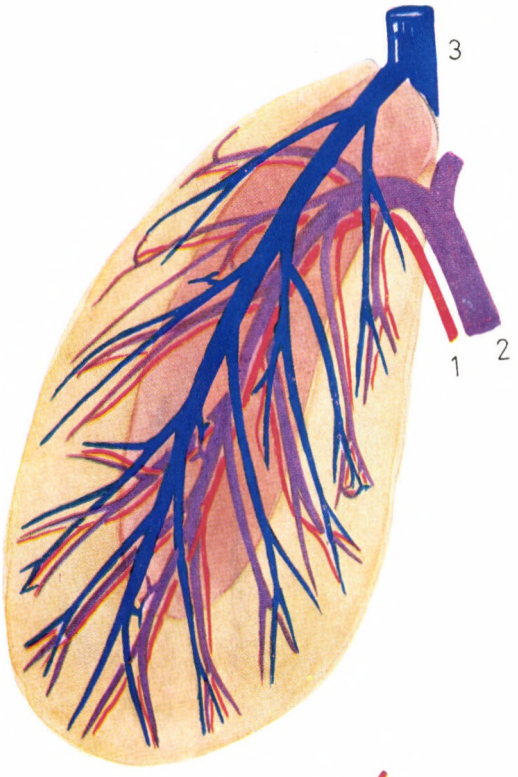
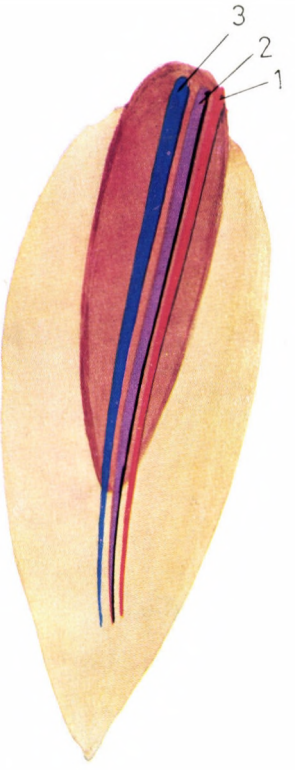
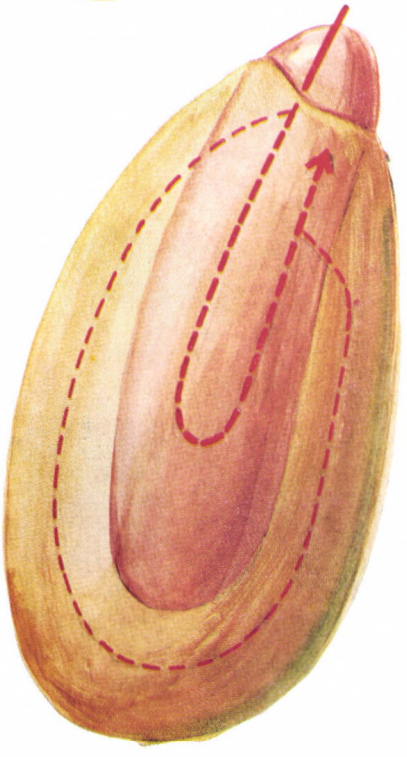


Fig. 125. The distribution pattern of the portal venous and hepatic arterial systems and their communications are outlined in control (above) and in regenerating (below) liver. In the control the sinusoids are of the 8th order of distribution along the axis of the lobe, while the portal venous and hepatic arterial systems anastomose at the 6th–8th order distributions. In the regenerated liver the sinusoids are of the 13th order distributions along the longest axis of the lobe, while the portal venous and hepatic arterial systems anastomose between the 6th—12th order distributions. The arterioportal connections functioning at the 6th–8th level of distribution as widely open arterioportal anastomoses provide a segmental control of hepatic blood flow (shaded areas). Coloured rectangles — liver acini, red — arterial blood, blue — portal blood, violet — mixed blood; the acini functioning in intermittent form are not outlined in the entire schematic liver lobe. Rectangle outlined with broken line — the area of the acinus in control (above) and in regenerated (below) liver; rectangle outlined with dotted line — area of the segment controlled by arterioportal anastomoses.

Fig. 126. The relationship between the central "core" (perihilar, or central region) and outer "shell" (peripheral region) of the liver lobe in dogs. Hepatic circulation may polarize into two intrahepatic circuits according to the two regions. In general, during redistribution blood entering the liver is thought to pass preferentially through the inner circuit of the core. Our modified version of Daniel and Prichard's concept (1951)



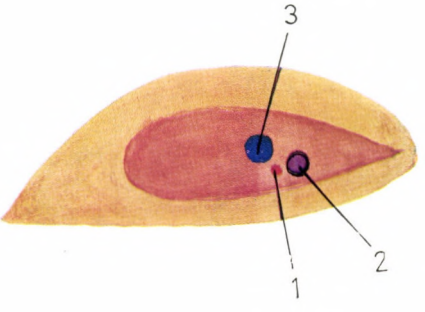




1 - Hepatic artery

2 - Portal vein

3 - Hepatic vein



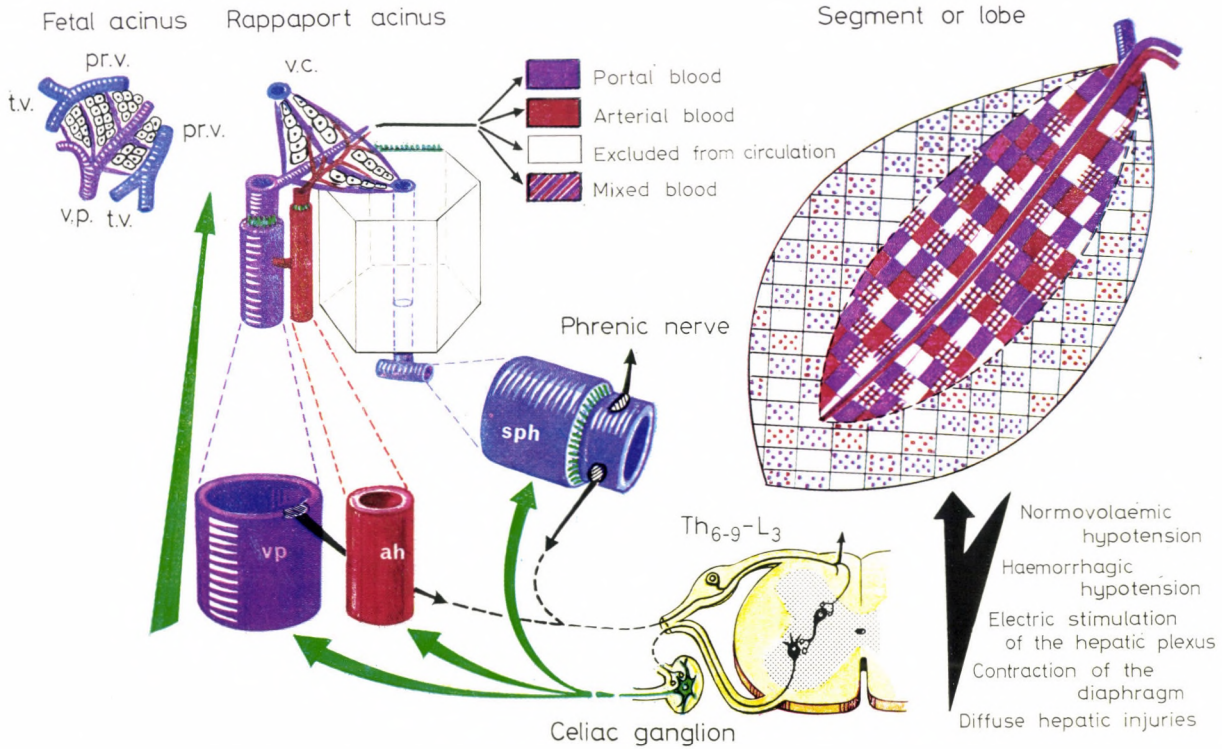


Fig. 127. The fetal acini develop into Rappaport's acini or Kiernan's lobules after the disappearance of the two-, or more cell-thick hepatic plates. The blood flow through these lobules, characterized by intermittent cessations, is dependent among others upon the function of the terminal branches of the hepatic artery. They may be supplied by portal, arterial, or mixed blood, or bypassed as shown by the violet, red, striped and empty rectangles, respectively. The terminal branches of the artery and the portal vein along the axis of the acinus as well as the larger branches of the hepatic vein are abundantly innervated by catecholaminergic fibres (green). Both the core and the shell of the lobes are built up of Rappaport's acini. The entering and leaving portions of the lobar (segmental) vessels are regulated by direct reflex control. Blood supply within a lobe shows a random distribution among the acini bypassing one acinus and passing through the other. Under the influence of both normovolaemic and haemorrhagic hypotension, electrical stimulation of the hepatic plexus, contraction of the diaphragm or diffuse hepatic injuries, intralobar redistribution of blood flow occurs with an increase of blood flow to the acini in the core of the lobe

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