The Liver and Anaesthesia

LEO STRUNIN, MD, FFARCS

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Foreword

The liver is probably the most complex organ in the body, involved as it is in a multitude of metabolic, hormonal and enzymatic processes. It would, therefore, be natural to suppose that a study of, and knowledge about, anaesthesia and the liver would be central to good anaesthetic practice. Yet this is not so. Studies by anaesthetists of the effects of anaesthesia on the liver have been sparse, and information from other fields is scattered and difficult to gather. Sadly, so far as anaesthetists are concerned, neither clinicians nor investigators have shown a conspicuous interest in the liver except where sporadic and isolated problems have occurred concerning particular anaesthetics.

Professor Strunin's book breaks new ground. In addition to his considerable and original contributions, he has woven together widely separated strands concerning anaesthesia and the liver, to form an intelligible and extremely useful fabric. Clinicians and researchers alike will be grateful to him, for here, in readily accessible form, are the answers to a host of questions, and the stimulus to many more, for future investigation.

Cardiff
June 1977

William W. Mushin

Preface

Some of my anaesthetist colleagues, on hearing that I was contemplating writing a book on the liver and anaesthesia, commented that there are no real problems—all one has to do for the patient with liver disease is give an anaesthetic. These colleagues all have considerable practical experience of dealing with liver problems and have long forgotten their initial difficulties. It is my intention to relate this experience, hopefully in a readable form, so that those less familiar with the interactions between the liver and anaesthesia may find the information helpful and of practical use. What I have attempted to do is to gather together in one place those aspects of the liver which are relevant for the anaesthetist. Particular emphasis will be placed on the information needed about patients with liver problems in the preoperative phase, as well as the current concepts on dealing with difficulties that may arise peroperatively and in the immediate postoperative period. Since many anaesthetists are engaged in intensive therapy, there are sections dealing with viral hepatitis and acute liver failure.

It seems only fair to present some credentials before embarking on a publication in a very specialized field. My own interest in the liver was kindled some ten years ago by Professor Roy Simpson at The London Hospital. Under his direction I set up an isolated canine liver perfusion preparation in order to study the effects of volatile anaesthetic agents and other drugs on the liver. Out of this work and in co-operation with Dr Brian Walton, also at The London Hospital, a nationwide survey of postoperative jaundice was undertaken which increased my understanding of the many problems associated with the investigation of liver dysfunction after general anaesthesia. Also at The London Hospital, Professor David Ritchie, Professor of Surgery, and Professor Robert Cohen, Professor of Metabolic Medicine, influenced my thinking on surgical and medical aspects of liver disease. On moving to King's College Hospital some five years ago, I was fortunate enough to be involved in the first ever Intensive Care Unit in the United Kingdom devoted entirely to acute liver failure. This is under the direction of Dr Roger Williams, Director of the Liver Unit, King's College Hospital and Medical School, and, in addition to his interests in acute liver failure, his Unit covers the span of liver disease and presents many problems for the anaesthetist. Mr John Dawson, Consultant Surgeon to King's College Hospital, has taken a particular interest in

the surgical aspects of patients with liver disease, and an association with him has been extremely informative. Finally, King's College Hospital is one of the two hospitals in the United Kingdom engaged in liver transplantation, and Professor Roy Calne, Professor of Surgery, University of Cambridge, has undertaken several hepatic transplantation operations at King's College Hospital which have involved the anaesthetic services of the Anaesthetic Department, King's College Hospital. In this respect I am grateful to Dr Stanley Mason, Chairman, Department of Anaesthetics, for helpful discussions. I am indebted to Dr Brian Walton for up-to-date information on aspects of immunology relevant to the liver.

I would particularly like to acknowledge my indebtedness to Roy Simpson for having guided me to the liver in the first instance and to many other areas thereafter. Many of the discussions that I have had with him are incorporated into this book, as well as the views of those named above and others, both at the London Hospital and King's College Hospital, with whom I have had the privilege of working. Naturally, much as one would like to spread the blame to others, any omissions or errors in the text must rest with me.

Miss Amanda Shaw, my Secretary, has typed and retyped the manuscript with unfailing patience, and it is doubtful whether without her help it would ever have been completed. My wife Jane has undertaken the arduous task of proof reading and verification of the references.

Finally, last but by no means least, the publishers of this volume, W. B. Saunders Company, in the shape of Mr Bill Schmitt, have shown unfailing patience and courtesy. It would be embarrassing for me to record how long ago the initial concept for this book arose and the many reasons and excuses that I have been able to put forward in order to delay delivery of the manuscript. I am grateful both to Bill Schmitt and to the Consultant Editor for this series, Professor W. W. Mushin, CBE, for their helpful comments and constructive criticism.

April 1977 Leo Strunin

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ANATOMY

The liver is the largest organ in the body, weighing in adult man some 1500 g. It is situated in the right upper quadrant of the abdomen, sheltered by the ribs and diaphragm. The liver extends past the mid-line, with its upper border at approximately the level of the fifth and sixth ribs. Anatomically, there are two lobes, the right being about six times the size of the left in adult life. The right lobe consists of two segments, the quadrate lobe on its inferior surface, and the caudate lobe on the posterior surface. The falciform ligament, a fold of peritoneum, separates the right and left lobes anteriorly. The fissure for the ligamenta teres lies inferiorly and that for the ligamenta venosum is posterior. Morphologically, five types of hepatic resection may be carried out:

1. Right hepatic lobectomy: the liver to the right of the main lobar fissure, namely the anterior and posterior segments of the right lobe, is removed.
2. Extended right hepatic lobectomy: all of the liver tissue to the right of the falciform ligament, that is, the right lobe and median segment of the left lobe, is resected.
3. Middle hepatic lobectomy or median segmentectomy: the median segment or the liver tissue between the main lobar fissure and the left segmental fissure is removed.
4. Left lateral segmentectomy: the liver tissue to the left of the falciform ligament is resected anteriorly.
5. Left hepatic lobectomy: all of the liver tissue to the left of the main lobar fissure, namely the median and lateral segments of the left lobe, is removed (Lin, 1976).

Finally, during the operation of hepatic transplantation the liver is removed entirely and replaced by a donor liver.

The liver is unique among the organs in the body in having a double blood supply. Seventy per cent of its blood supply comes via the portal vein, with the

remaining 30 per cent from the hepatic artery. These vessels enter the liver through a fissure, the porta hepatis, which lies on the inferior surface of the right lobe. Inside the porta, the portal vein and hepatic artery divide into branches to the right and left lobes of the liver, and the right and left hepatic bile ducts join to form the common hepatic duct draining eventually into the duodenum. The venous drainage of the liver is via the right and left hepatic veins which issue from the back of the liver and enter the inferior vena cava just below the diaphragm.

The liver is completely covered with peritoneum except where it comes into direct contact with the diaphragm, the interior vena cava and the gallbladder. This peritoneum attachment, together with the intra-abdominal pressure generated by the tone of the muscles of the abdominal wall, helps to keep the liver in position.

The Intrahepatic Portal System (Figure 1.1)

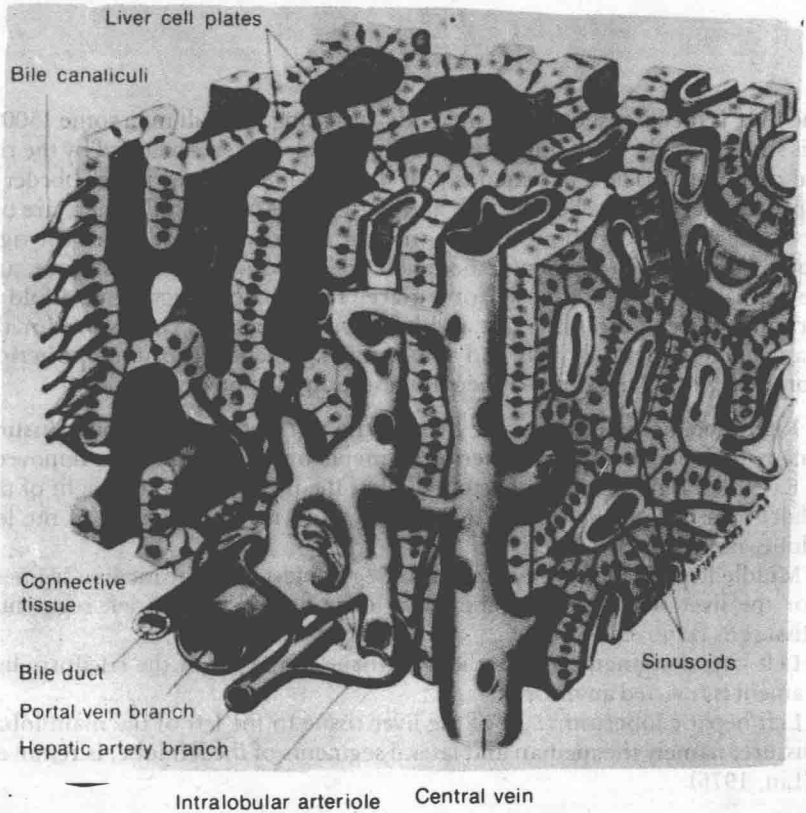

Figure 1.1. The intrahepatic portal system. The portal tract contains a branch of the portal vein, hepatic artery and bile duct. At the centre of the lobule is a branch of the central or hepatic vein. The sinusoids lie between adjacent rows of hepatocytes and are lined by Kupffer cells. The bile canaliculi are formed between the hepatocytes. From Tietz (1976) with kind permission of the editor and W. B. Saunders Company, Philadelphia.

Within the liver the bile duct, portal vein and hepatic artery have the same pattern of branching. At each level they are bound together in a fibre sheath to form the portal tract. These end in a network of sinusoids which connect the terminal branches of the hepatic venous and portal systems together and are usually described in terms of lobules. However, these are difficult to distinguish in human liver sections, although they are easily seen in pig and other animal livers. An alternative functional unit called the acinus has been defined by studies of the distribution of Indian ink after injection into the portal vein. The acinus consists of the group of sinusoids running between the terminal portal tract and two or more hepatic venules. These intersect approximately at right angles, and each half acinus is therefore basically a tetrahedral structure. In section the acinus appears rhomboidal (Figure 1.2).

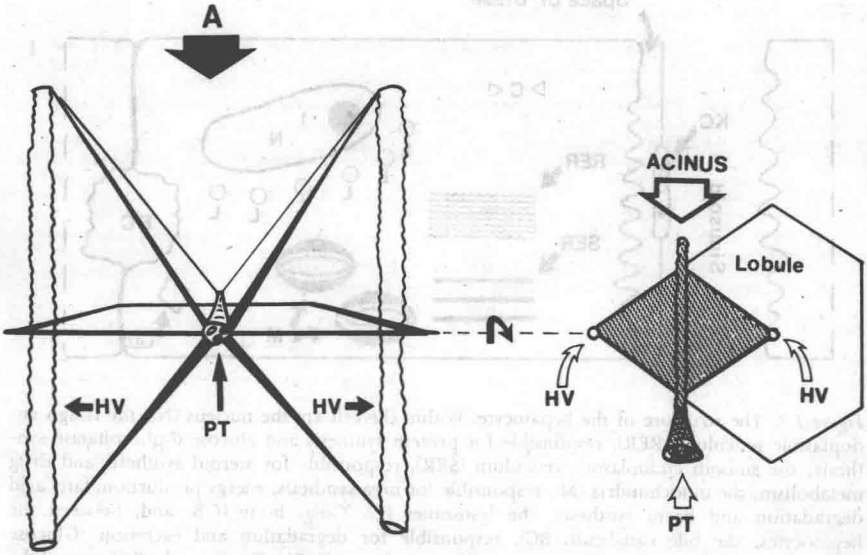

Figure 1.2. The structure of the acinus. The acinus consists of groups of sinusoids running between a terminal portal tract (PT) and two or more hepatic venules (HV). Viewed from A, each half acinus is tetrahedral in structure and on section the acinus is rhomboidal.

The branching pattern of the hepatic veins is distinct from that of the portal system. The terminal hepatic venules intersect the terminal portal branches approximately at right angles and the sinusoidal network is formed between them. The main right and left hepatic veins drain most of their respective functional liver lobes, but the caudate lobe is drained by independent veins. In the Budd–Chiari syndrome when the main hepatic veins are occluded by thrombus the drainage of the caudate lobe is usually unaffected.

Occlusion of the hepatic artery in man does not normally lead to infarction since most of the blood supply of the liver comes from the portal vein. Primary and metastatic tumours, however, receive almost all their blood supply from the hepatic artery, the portal vein usually supplying only the peripheral rim of a tumour. Therefore ligation of the hepatic artery with infusion of cytotoxic drugs is used in the treatment of inoperable hepatic tumours.

Histology

The hepatocyte

Histological examination of a section of the liver in man reveals a lobular structure with central veins, and two distinct types of cells—the liver cell or hepatocyte and the Kupffer cell. Liver cells nearest the centre of the lobule are most prone to damage as a result of lack of oxygen, due either to hypoxia or hypotension (centrilobular necrosis). Electron microscopic examination of an hepatocyte reveals a number of structures within the cell, some of which have been linked to its functions (Figure 1.3).

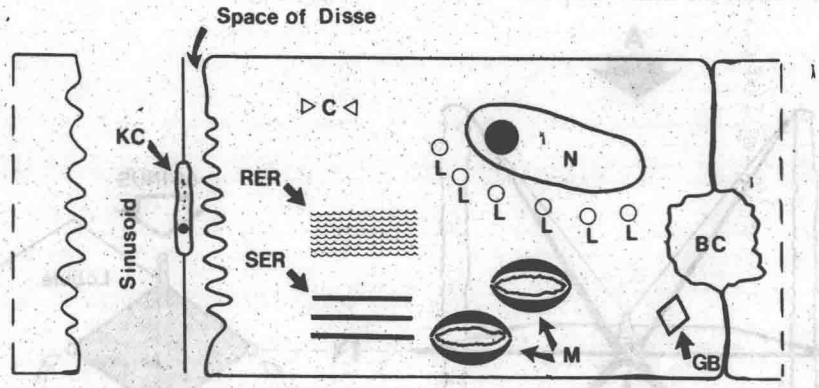

Figure 1.3. The structure of the hepatocyte. Within the cell are the nucleus (N); the rough endoplasmic reticulum (RER), responsible for protein synthesis and glucose-6-phosphatase synthesis; the smooth endoplasmic reticulum (SER), responsible for steroid synthesis and drug metabolism; the mitochondria (M), responsible for urea synthesis, energy production, fatty acid degradation and haem synthesis; the lysosomes (L), Golgi body (GB) and, between the hepatocytes, the bile canaliculi (BC), responsible for degradation and excretion. Glucose metabolism and fatty acid synthesis occur in the cytoplasm (C). The Kupffer cells (KC), part of the reticuloendothelial system, line the sinusoids.

The cell membrane of the hepatocyte has microvilli projecting from its surface where the cell comes into contact with the sinusoids or bile canaliculi. Microvilli on cell surfaces usually indicate that the cell is involved in active secretion of substances, or absorption of fluid.

The mitochondria have a characteristic double membrane, the inner being invaginated to form grooves or cristae. Mitochondria are concerned with energy production, particularly that involving oxidative phosphorylation. They have a high phospholipid content and contain many enzymes capable of oxidizing many substrates including fatty acids and intermediates of the Krebs citric acid cycle. The energy so released is transformed into high energy phosphate bonds of adenosine triphosphate (ATP)—a compound made up of a nitrogenous base (adenine), the pentose sugar ribose, and three phosphate radicals. The last two phosphate radicals are the site of the energy phosphate bonds (Figure 1.4).

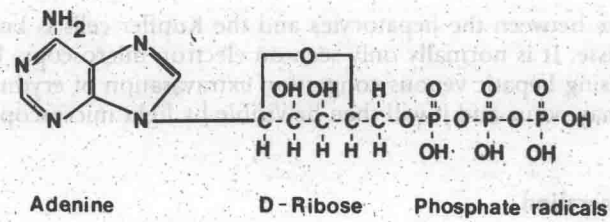

Figure 1.4. Formula for adenosine triphosphate (ATP).

The endoplasmic reticulum is seen as a series of vesicles and tubules within the cytoplasm of the cell. It corresponds to the microsomes produced by ultracentrifugation of liver cells. Two distinct parts of the endoplasmic reticulum are seen. The rough endoplasmic reticulum (RER) is characterized by the presence on the tubular membranes of small particles of ribonucleic acid (RNA). The RER is responsible for protein metabolism.

The smooth endoplasmic reticulum (SER) does not contain granules and is the site of metabolism of drugs, conjugation of bilirubin and the synthesis of steroids and some enzymes. Most of the specific functions of the liver cell take place within the endoplasmic reticulum. The SER may be increased in capacity by enzyme-inducing agents or may be inhibited by enzyme inhibitors.

Lysosomes are vesicles which are found within the cytoplasm and contain hydrolytic enzymes. Their primary functions seem to be to act as scavengers within the liver cell and to act as sites of pigment depostion, such as ferritin, lipofuscin, bile pigment and copper. It may also be that they are involved in disorders affecting lipid metabolism and thus be relevant in lipid storage diseases.

The biliary canaliculus is the beginning of the route of excretion of compounds into the bile. These usually arise following metabolism by the SER. Adjacent to the biliary canaliculus within the hepatocyte is a system of particles know as the Golgi apparatus. It seems likely that this represents some sort of gathering, or preparation area, prior to the excretion of substances into the bile.

The Kupffer Cell

The flattened Kupffer cells (named after Karl Wilhelm Kupffer, 1829–1902, a German anatomist) line the sinusoids and are phagocytic in nature. They actively take up foreign particulate matter from the blood. This applies particularly to bacteria which enter portal blood from the gastrointestinal tract. The Kupffer cells are part of the reticuloendothelial system and, in addition to taking up bacteria, will also take up endotoxin and other toxins.

In the fetus the Kupffer cells are related to haemopoiesis. This function usually disappears within a few weeks of birth but the potential for producing red cells is retained throughout life. In disease conditions which destroy the bone marrow, particularly myelofibrosis, some red cell production occurs in the Kupffer cells of the liver.

The space between the hepatocytes and the Kupffer cells is known as the space of Disse. It is normally only seen on electron microscopy, but in conditions causing hepatic venous congestion extravasation of erythrocytes into the space may occur and it will then be visible by light microscopy.

Liver Regeneration

There is a slow but constant turnover of liver cells and occasional mitosis will be found in the normal tissues. After liver injury or partial hepatectomy the surviving liver tissue will regenerate until the normal liver mass is restored. After hemi-hepatectomy human liver size returns to normal within two weeks (Blumgart and Vajrabukka, 1972). This implies a growth rate of some 50 to 100 g of liver tissue daily. Man has sustained up to 80 per cent loss of liver mass and has made a successful recovery. The factors which stimulate and control hepatic regeneration are unknown. Changes in blood or bile flow do not seem important, nor is the process dependent on an intact hepatic nerve supply. Humoral factors have been postulated, and certainly splenic and lymph node endothelial cells proliferate during liver regeneration. The increased metabolic load after loss of liver tissue may itself be the stimulus to regeneration. In addition, local factors such as resistance to blood flow and oxygen tension may play some part in determining the exact pattern of liver growth.

Although after liver injury, or sugery, liver regeneration proceeds in an orderly fashion this may not be the case following hepatitis. Here the condition causing liver injury may continue at the same time as regeneration is taking place. In this instance regeneration is characterized by excessive proliferation of fibrous tissue and nodular growth of surviving hepatocytes. This accounts for the characteristic 'knobbly liver' seen in cirrhosis.

APPLIED PHYSIOLOGY

The central role of the liver in metabolism is well recognized. Thus, for example, the hepatectomized animal dies rapidly of hypoglycaemia. Albumin synthesis, moreover, is determined by the liver, and free fatty acids (FFA) generated by the liver provide 80 to 90 per cent of the energy consumption of the body. In addition to the part played by the liver in carbohydrate, protein and fat metabolism the liver is responsible for production of bile, bile salts and the excretion of bilirubin. Drug, cholesterol and steroid metabolism is carried out within the hepatocytes, and water-soluble metabolites are excreted both into the bile and into the plasma. The liver also represents a major storeplace for a variety of substances. These include vitamin B_{12}, iron, copper and glycogen. The reader is referred to standard physiology texts for a more detailed description of the mechanisms involved in normal metabolism. The intention here is to draw attention to those physiological functions of the liver which may be particularly disturbed in liver disease.

Carbohydrate Metabolism

Dietary carbohydrates are, for the most part, polymers of hexoses, of which galactose, fructose and glucose are the most important. Fructose and galactose are normally converted to glucose by enzymatic action. The hepatocyte membrane is unusually permeable to glucose and once within the cell glucose is normally phosphorylated to form glucose-6-phophate, a reaction catalysed by hexokinase and glucokinase. Glucose-6-phosphate is either polymerized into glycogen or catabolized.

The process of glycogen formation is called glycogenesis, and glycogen breakdown is glycogenolysis. Glycogen, the storage form of glucose, is present in most body tissues but is found mainly in the liver and skeletal muscle. Glycogen formation from glucose-6-phosphate proceeds via glucose-1-phosphate and UDP glucose (uridine diphosphate glucose). UDP glucose is important in the conversion of galactose to glucose and is also a precursor for UDP glucuronic acid, a substance highly relevant to the fundamental process of glucuronide conjugation. Glycogen storage diseases arise when there are deficiencies in the enzymes catalysing the various steps in the formation of glycogen. The major features of these disorders are growth retardation and hypoglycaemia. Portacaval bypass may produce a substantial improvement in these symptoms. The anaesthetic management of such cases has been described by Casson (1975). The major anaesthetic problem is maintenance of an adequate blood glucose during surgery. Casson (1975) also describes the use of portacaval bypass with familial hyperlipidaemia type II, which is characterized by overproduction of cholesterol and lipoproteins.

The breakdown of glucose to carbon dioxide and water with the production of energy is called glycolysis. Such glucose catabolism may proceed by two pathways, either via cleavage to trioses or via oxidation and decarboxylation to pentoses. The pathway via trioses ends in pyruvic acid and is known as the Embden–Meyerhof–Parnas pathway (Figure 1.5). The pathway through gluconic acid and pentoses is the direct oxidative pathway or hexose monophosphate shunt. Pyruvic acid is converted to acetyl-coenzyme A (acetyl-CoA) and enters the Krebs cycle (citric acid cycle). Although glucose can be converted to fats through acetyl-CoA, the reaction from pyruvic acid to acetyl-CoA is irreversible and therefore fats are not converted to glucose via this pathway. However, some conversion of fats to carbohydrates may take place via glycerol which can enter the glycolysis pathway. Amino acids with carbon skeletons, after deamination, can also enter the glycolysis pathway. In this way non-glucose molecules can be converted to glucose, i.e. gluconeogenesis.

The regulation of carbohydrate metabolism is mediated by a number of hormones. Adrenaline increases the rate of glucose production in the liver by stimulating both glycogenesis and gluconeogenesis. In addition, potassium is released from the liver. It is likely that some of the effects of adrenaline are mediated by the so-called 'second messenger', cyclic adenosine-3′5′-monophosphate (cyclic AMP). The hormone itself, in this case adrenaline, is known as the 'first messenger', which remains outside the cell, and it is cyclic AMP which brings about the actual changes seen. The actions of adrenaline are antagonized by insulin, which exerts a direct effect on the liver to inhibit

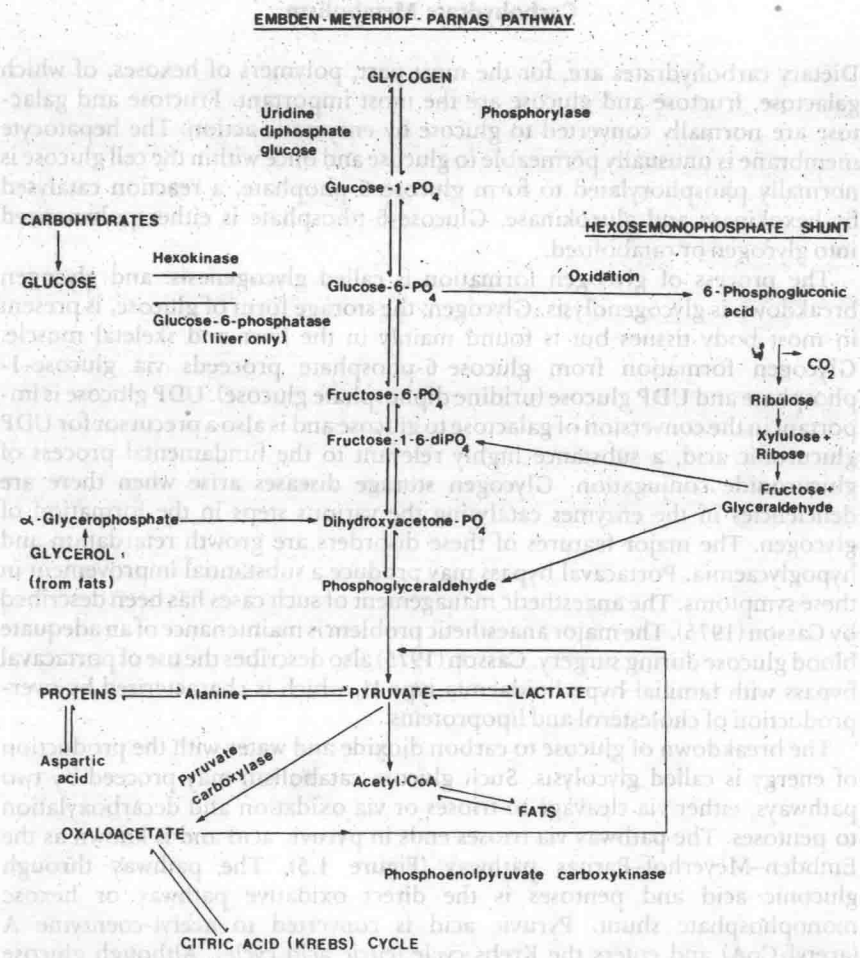

Figure 1.5. Embden–Meyerhof–Parnas pathway and the hexosemonophosphate shunt. Some steps are reversible (double arrows), some are not (single arrows), and the appropriate enzymes necessary are shown.

the production of glucose and urea. Potassium uptake is promoted, in contrast to adrenaline which leads to a loss of potassium from the liver. The effects of insulin may be partly due to a decrease in cyclic AMP in the liver. Glucagon increases the level of cyclic AMP within the liver and thus tends to produce effects opposite to those of insulin. The antagonistic actions of insulin and glucagon on glycogenesis, gluconeogenesis and glycogen synthesis in the liver provide an effective control system for glucose homeostasis and fuel consumption. By stimulating adenyl cyclase, adrenaline causes activation of the phosphorylase in liver and skeletal muscles, thus leading to a rise in blood glucose and lactic acid levels. Glucagon has a similar action, but it only exerts its effect on the phophorylase in the liver. Therefore although glucagon causes a rise in blood glucose there is no change in blood lactic acid. Any