Chapter 11
Protein Synthesis and Nutrient Metabolism

Dennis D. Black

1 Introduction

The liver **produces and secretes most of the circulating proteins** in the body that function in an amazingly complex array of regulatory and metabolic processes. The liver also functions as a central metabolic way station for the **processing, partitioning and trafficking of nutrients**, including *lipids* and *carbohydrates*, as well as *vitamins*, at the intersection of the intestine and the rest of the body. It is remarkable that the regulatory mechanisms that have evolved to control these processes generally function in a highly responsive and coordinated manner. However, when dysregulation occurs due to genetic or environmental factors, such as in glycogen storage diseases or non-alcoholic fatty liver disease, significant morbidity may result. This chapter will highlight these functions of the liver and some of the disease processes that may occur.

2 Role of the Liver in Synthesis of Biologically Important Proteins

The majority of circulating plasma proteins is synthesized by the liver. A list of plasma proteins secreted by the liver and their characteristics and functions is shown in Table 11.1. To accomplish this task, the hepatocyte has a well-developed endoplasmic reticulum, Golgi system, and cellular cytoskeleton, all of which function in the synthesis, processing, and secretion of proteins. The most abundant plasma protein produced by the liver is **albumin**, which comprises

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Table 11.1 Partial list of plasma proteins synthesized and secreted by the liver

Protein	Mol. Wt. (kDa)	Function	Ligand binding
Albumin	66	Binding and carrier protein, osmotic regulator	Hormones, amino acids, steroids, vitamins, fatty acids
α-1-acid glycoprotein (orosomucoid)	40	Uncertain, may have role in inflammation. Acute phase reactant	
α-1-antitrypsin	54	General protease inhibitor	Proteases in serum and tissue secretions
α-fetoprotein	72	Uncertain, expressed in fetus and malignancy. Tumor marker	Possibly the same as albumin
α-2-macroglobulin	720	Serum endoprotease inhibitor	Proteases
Antithrombin III	65	Protease inhibitor of intrinsic coagulation system	Proteases
Apolipoprotein A-I	26	Lecithin:cholesterolacyl-transferase activator. Esterifies cholesterol in HDL	Major apolipoprotein of plasma HDL
Apolipoprotein B-100	500	Lipoprotein assembly and secretion, LDL receptor ligand	Component of plasma VLDL and LDL, binds to LDL receptor
Ceruloplasmin	134	Transport of copper	6 atoms copper/mol
C-reactive protein	105	Uncertain, may have role in inflammation. Acute phase reactant	Complement C1q
Fibrinogen	340	Fibrin precursor in hemostasis	
Haptoglobin	100	Binding and transport of cell-free hemoglobin	Hemoglobin
Hemopexin	57	Binds to porphyrins, particularly heme for recycling	Porphyrins
Transferrin	80	Iron transport	2 atoms iron/mol

Adapted from Zakim [16, p. 125]

55–60 % of the total plasma protein pool. Albumin serves as a ***binding and carrier protein*** for hormones, amino acids, steroids, vitamins, and fatty acids. It is also an important ***osmotic regulator*** in the maintenance of normal plasma oncotic pressure. Albumin synthesis is exquisitely sensitive to nutritional status and availability of amino acids, particularly *tryptophan*. Also, it has been demonstrated that albumin gene transcription is regulated by changes in **serum colloid osmotic pressure** to facilitate maintenance of osmotic homeostasis. This regulation appears to be mediated by the interaction of transcription factor HNF-1α with a specific site in

the albumin gene promoter region. Furthermore, it is interesting that expression of other genes with promoters containing the HNF-1α recognition site, such as α-1-antitrypsin and certain apolipoproteins, can be regulated by the serum colloid osmotic pressure. This is but one example of the complex regulatory mechanisms involved in hepatocyte gene expression. The other proteins synthesized and secreted by the liver are for the most part **glycosylated proteins (glycoproteins)**, which function in hemostasis, protease inhibition, transport, and ligand binding.

One especially interesting glycoprotein produced by the liver is important in both health and disease. **Alpha-1-antitrypsin (A-1-AT)** is a neutrophil protease inhibitor that is secreted and protects tissues, particularly *lung*, from damage by endogenous proteases. In **A-1-AT deficiency**, a point mutation produces an abnormal protein that accumulates in the ER and is susceptible to misfolding, polymerization and aggregation, resulting in toxicity to the hepatocyte. This disorder is a common cause of liver disease in infants and adults, as well as chronic lung disease in adults. Interestingly, only about 10 % of homozygotes develop clinically significant liver disease that may require liver transplantation. Genetic and environmental modifiers that impact on the adaptation to or degradation of the accumulated abnormal protein in the hepatocyte ER, through proteosomal and autophagic pathways, appear to play crucial roles in determining the severity of the liver disease. Development of new therapies has focused on targeting and enhancing these pathways.

3 Role of the Liver in Carbohydrate Metabolism

The liver plays a key role in the utilization of the **major monosaccharides**, ***glucose***, ***fructose***, and ***galactose*** (Fig. 11.1). The initial step in hepatic glucose metabolism is phosphorylation by **glucokinase**. Glucokinase synthesis is increased by high glucose diets and high insulin concentrations. Depending upon the metabolic need, the glucose may be utilized for energy production, synthesis of other substrates (i.e. amino acids, fatty acids), or stored as glycogen. **Glycogen** is a polymer of units of glucose (Fig. 11.2) with ***linear 1-4 linkages*** and ***branch points with 1-6 linkages***. Glycogen serves as a storage depot for glucose in the liver, which can be readily mobilized when glucose is in immediate demand. Because of its polymeric structure, glycogen has a low osmolality and is more easily stored in hepatocytes than the monomeric glucose. The liver can store up to 65 g of glycogen per kilogram of liver tissue.

Fructose is taken up by the hepatocyte and phosphorylated by **fuctokinase** (Fig. 11.1). It may then be stored as glycogen by conversion to **glucose-6-phosphate**. When used for energy production, phosphorylated fructose may actually traverse the glycolytic pathway more readily than glucose. Also, fructose is a better substrate for lipogenesis than glucose in the liver. Hepatic metabolism of fructose follows the **Leloir pathway** to form either ***glucose-6-phosphate*** to enter the glycolytic pathway or ***UDP-glucose*** to enter the glycogenesis pathway. **Galactose** can also be taken up and used by the liver after phosphorylation by **galactokinase** (Fig. 11.1).

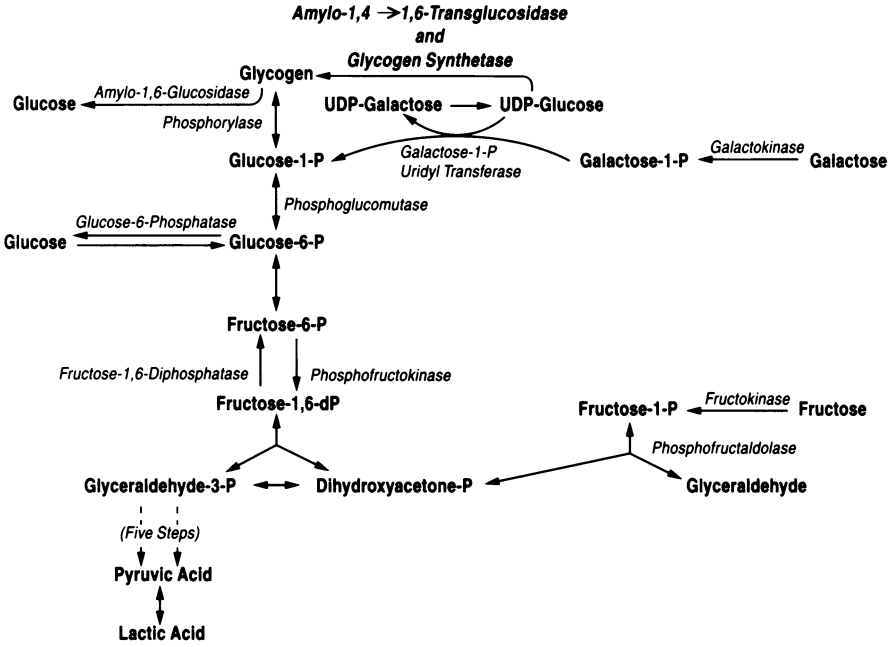

Fig. 11.1 Metabolic pathways for hepatic utilization of glucose, fructose, and galactose

Glycolysis is the only pathway by which glucose can be oxidized anaerobically with production of ATP. Under aerobic conditions the liver uses mainly fatty acids as substrates for oxidation, and the glycolytic rate is low. Higher rates of glycolysis result in lipogenesis from carbohydrate. Regulation of glycolysis in the liver is highly integrated with that of gluconeogenesis, lipogenesis, glycogen synthesis, and glycogenolysis.

Gluconeogenesis is the production of glucose from amino acids and lactate and is carried out solely in liver and renal cortex. **Two cycles** exist for hepatic gluconeogenesis from non-hepatic substrates (Fig. 11.3). These are the ***lactic acid (Cori) cycle*** and the ***glucose-alanine cycle***. In the Cori cycle lactic acid produced by working muscle is taken up by the liver and provides a substrate for gluconeogenesis to produce glucose. Alanine is also released from muscle and serves as a substrate for hepatic glucose synthesis. Regulation of gluconeogenesis is dependent on substrate availability and hormonal factors, particularly insulin and glucagon levels. Overall, **glucagon** and **epinephrine** stimulate and insulin inhibits gluconeogenesis.

As mentioned previously, glycogen is a storage form of glucose consisting of a polymeric form of glucose. The pathway for glycogen metabolism is shown in Fig. 11.4. Most substrates enter the glycogen synthetic pathway by conversion to **UDP-glucose**. The glucosyl units are linked linearly by 1-4 linkages by the enzyme **UDPG-glycogen synthetase**. Branch points with 1-6 linkages are formed by the branching enzyme **amylo-1-4, 1-6-transglucosidase**. Glycogen synthesis is

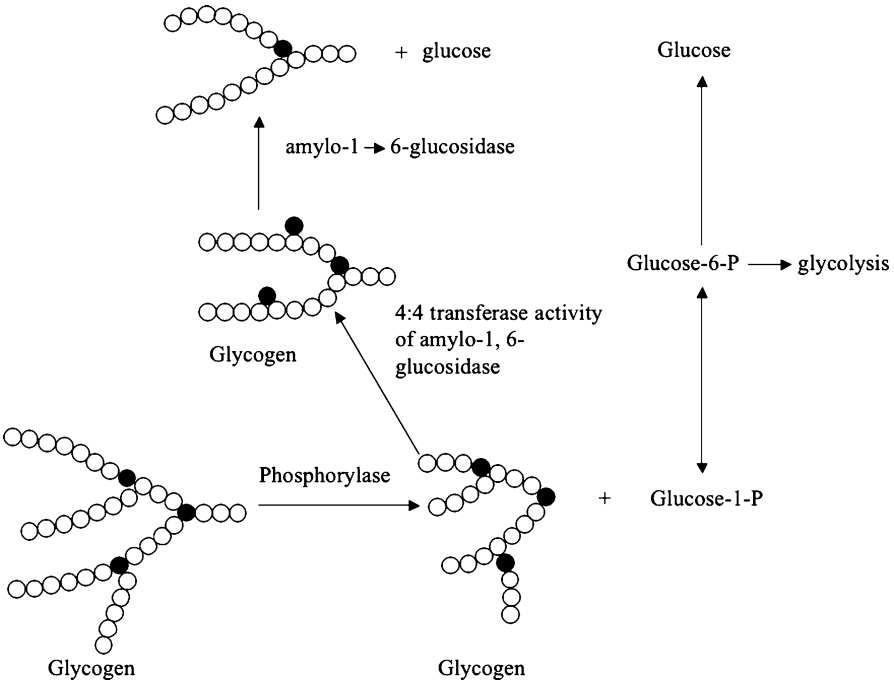

Fig. 11.2 Pathway for production of glucose from glycogen (glycogenolysis). Notice that the product of the phosphorylase-catalyzed hydrolysis of glycogen is glucose-1-phosphate. A small amount of glucose (about 6 % of the total produced) is released via action of the enzyme amylo-1,6-glucosidase. This last reaction removes the glucose residues that form branch points (*closed circles*) and occurs after the shortened oligosaccharide chain attached to a branch point (three glucose residues) is shifted to create a longer oligosaccharide. These reactions are required because phosphorylase will not catalyze hydrolysis of short oligosaccharide chains (Reproduced with permission from Zakim [16, p. 69])

promoted by insulin and glucocorticoids and by increased glucose concentrations. **Glycogen synthetase** is the ***rate-limiting step*** in glycogen synthesis and is converted from active to inactive form by phosphorylation by a **cAMP-dependent protein kinase. Glycogenolysis**, the breakdown of glycogen to release glucose units, is promoted by glucagon, epinephrine, vasopressin, angiotensin II, and oxytocin. Under conditions promoting glycogenolysis, **phosphorylase** catalyzes glycogenolysis by breakage of the linear 1-4 linkages. Phosphorylase is converted from the inactive to active form by phosphorylation by a cAMP-dependent protein kinase. Glucose molecules are removed from the 1-6 linkage branch points by the debrancher enzyme **amylo-1-6-glucosidase** (Fig. 11.2). Several inherited defects in various steps of glycogen metabolism have been identified, as shown in Fig. 11.4, and result in a clinical spectrum of glycogen storage diseases with the abnormal accumulation of glycogen in the liver.

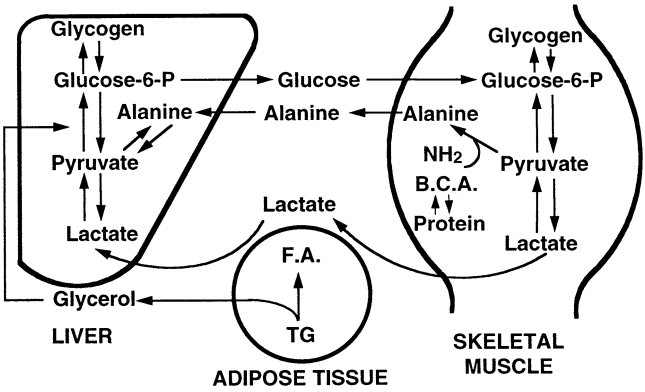

Fig. 11.3 The lactic acid (Cori) and glucose-alanine cycles. Lactic acid produced by working muscle is taken up by the liver and provides a substrate for gluconeogenesis to produce glucose. Alanine produced in muscle as a result of protein breakdown, is released and deaminated in the liver to form pyruvate. Glucose is formed from pyruvate and is released to be metabolized by muscle, where it is reconverted to pyruvate and alanine, respectively, completing the cycle. *BCA* branched-chain amino acids, *FA* fatty acid, *TG* triglyceride (Reproduced with permission from Van Thiel [13])

4 Role of the Liver in Lipid Metabolism

Fatty acids are synthesized in the liver from carbohydrate precursors by conversion of these precursors to **acetyl-CoA** by the **cytosolic fatty acid synthase complex**. Hepatic fatty acid synthesis is stimulated by carbohydrate feeding and insulin. Fatty acids are generally stored in the liver as **triglycerides**, consisting of three fatty acids esterified to a glycerol backbone. Fasting, starvation, and diabetes mellitus with insulin deficiency cause increased hepatic fatty acid oxidation and production of **acetoacetate** and **D-3-hydroxybutyrate** (also known as ketones), which can be used as an energy source by muscle and brain. This process is known as **ketogenesis.** Lipolysis of adipose tissue triglycerides provides a major source of substrate fatty acids to the liver for production of ketones. The **plasma glucagon to insulin ratio** is probably the main regulator of ketogenesis.

The liver is a major site of **fatty acid β-oxidation**, which results in the production of energy using fatty acids as substrates. There are **two postulated regulatory mechanisms for β-oxidation** when carbohydrate is in short supply: regulation at the level of ***pyruvate formation*** and regulation at the level of ***fatty acid entry into the mitochondria***, the site of most fatty acid oxidation, by way of **carnitine acyltransferase I**. Another site of fatty acid oxidation in the hepatocyte, particularly for saturated long chain fatty acids, is the **peroxisome**. Peroxisomal fatty acid oxidation is regulated only by fatty acid substrate concentration. This pathway may provide a mechanism for the production of acetyl CoA outside the mitochondria without the participation of citrate formed in the mitochondria.

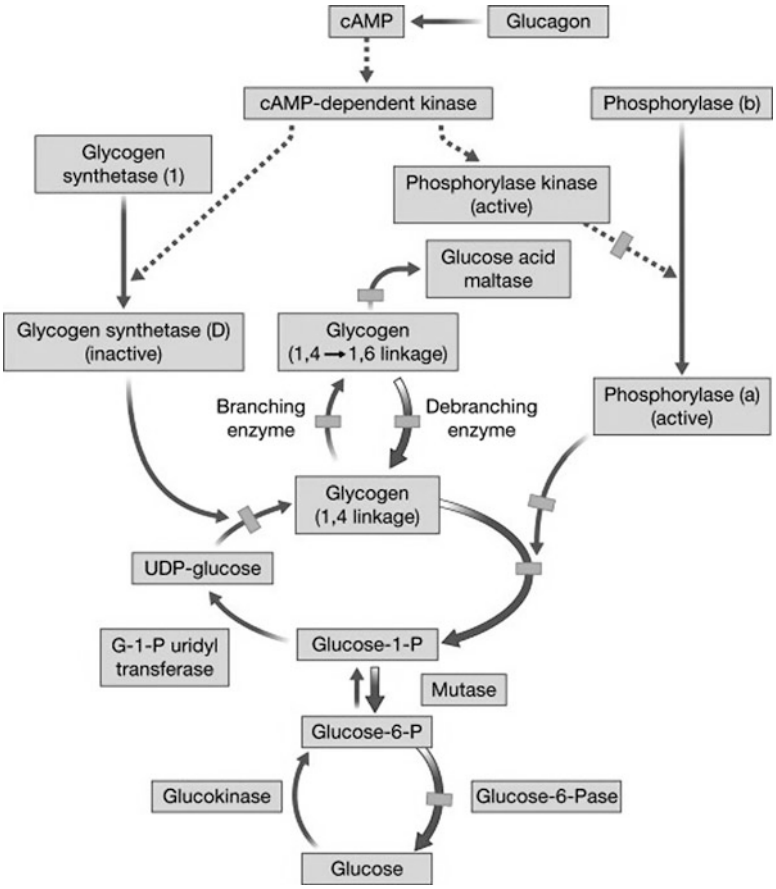

Fig. 11.4 Pathways for glycogen formation and glycogenolysis. *Broken lines* indicate enzymatic activation after glucagon stimulation; *thick arrows* indicate glycogen degradation from glucagon infusion, and *hatched boxes* indicate points in the metabolic sequence where enzymatic defects have been identified (Reproduced with permission from Elsevier [6])

Peroxisomal β-oxidation is inducible in rats by feeding a high-fat diet and treatment with certain hypolipidemic drugs that cause peroxisome proliferation.

The liver is a major site of **cholesterol synthesis** from **acetyl CoA**. In fact, all of the carbon atoms in cholesterol are derived from acetate. Cholesterol is ubiquitous throughout the body as a structural component of cell membranes and is a substrate for synthesis of several steroid hormones. Cholesterol is important in the liver as the precursor for bile acid synthesis. The **rate-limiting step** in cholesterol synthesis is the ***cleavage of CoA from the synthetic intermediate* β-hydroxy-β-methylglutaryl (HMG) CoA** with the ***simultaneous reduction to* mevalonate**. The enzyme which catalyzes this reaction is **HMG-CoA reductase**. Although the regulation of hepatic cholesterol synthesis is complex, several regulatory factors

have been defined. In general, synthesis is **up-regulated** by ***any event that depletes the hepatocyte of cholesterol***. For example, depletion of the bile acid pool by interruption of the enterohepatic circulation by biliary diversion, ileal resection or administration of a bile acid sequestrant such as *cholestyramine* will increase cholesterol synthesis, since bile acids are synthesized from cholesterol. Increased secretion of very low density lipoproteins (VLDL) stimulated by an influx of free fatty acids or carbohydrate requires cholesterol for packaging and depletes intracellular cholesterol resulting in increased synthesis. ***Hormones*** such as *thyroid hormone*, *corticosteroids*, and *glucagon* also up-regulate synthesis. Cholesterol synthesis is **down-regulated** by ***events that increase cellular cholesterol***, such as the influx of cholesterol from receptor-mediated uptake of dietary cholesterol in chylomicron remnants and endogenous cholesterol in low density lipoproteins (LDL). The most potent down-regulators of cholesterol synthesis are ***oxidation products of cholesterol***, ***7-ketocholesterol*** and ***25-hydroxycholesterol***. Bile acid synthesis and biliary secretion of cholesterol are the major secretory pathways for cholesterol and will be subsequently discussed.

Triglycerides synthesized by the liver are secreted as particles called **very low-density lipoproteins (VLDL)**. Lipoproteins are spherical particles, which serve as thermodynamically stable circulating packages for the transport of lipids through the aqueous environment of the bloodstream. The ***core*** of the particle contains hydrophobic, non-polar lipids, triglycerides and cholesteryl esters, and the ***surface*** coating consists of hydrophilic, polar lipids, phospholipid and free cholesterol, and lipid-binding peptides called **apolipoproteins**. Apolipoproteins generally serve important functions in the assembly, secretion, and peripheral metabolism of lipoprotein particles. The secreted hepatic VLDL serves to transport lipid from the liver to peripheral tissues. In humans, a large portion of the VLDL secreted is converted to **low density lipoproteins (LDL)**, which are the major transporters of cholesterol to various tissues throughout the body. This pathway is summarized in Fig. 11.5.

Carbohydrate feeding stimulates hepatic fatty acid production; thereby driving increased triglyceride and VLDL production and secretion. Secreted VLDL triglyceride is hydrolyzed by the enzyme **lipoprotein lipase** to liberate fatty acids for storage by adipose tissue and energy production by muscle. Lipoprotein lipase is bound to the *endothelium of capillary beds* in primarily adipose tissue and muscle and requires the apolipoprotein **apo C-II**, produced by the liver, as a cofactor. A related lipase produced by the liver, **hepatic lipase**, resides on *sinusoidal endothelial cells*. Hepatic lipase is important in HDL metabolism and in the hydrolysis of lipid in chylomicrons, VLDL and intermediate density lipoproteins (IDL).

The liver not only functions in the secretion of lipoprotein particles, but also is an essential organ for the **uptake and metabolism of lipoproteins. Chylomicrons** of intestinal origin, which carry mainly exogenous fatty acids and cholesterol, are metabolized by **lipoprotein lipase** to produce triglyceride-depleted, relatively cholesteryl ester-enriched remnants which are cleared by a receptor-mediated mechanism in the liver. This receptor-mediated clearance involves the **LDL receptor**

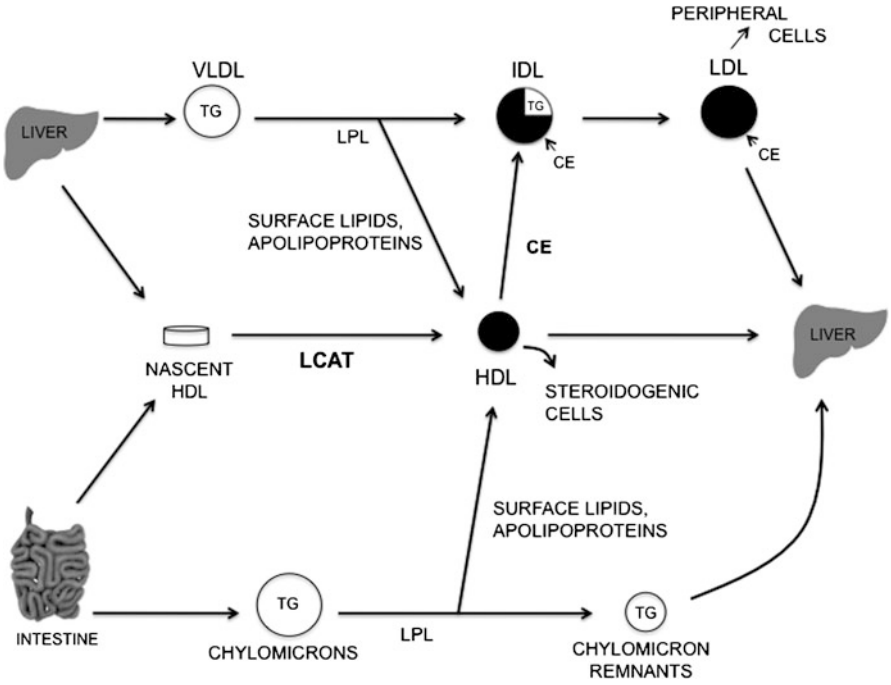

Fig. 11.5 Simplified scheme of plasma lipoprotein metabolism. Key events are the hydrolysis of triglyceride-rich lipoproteins by lipoprotein lipase (*LPL*), the conversion of VLDL to IDL, the movement of surface lipids and apolipoproteins released during lipolysis by LPL to HDL, the progressive enrichment of IDL and LDL with cholesteryl esters (*CE*) transferred from HDL as a result of the LCAT reaction, and the removal of LDL and chylomicron remnants by peripheral cells and the liver (Reproduced with permission from Glickman and Sabesin [7])

and the **LDL receptor-related protein**, a membrane receptor, which binds and internalizes a wide variety of ligands. A significant proportion of plasma LDL particles are taken up by the liver via the LDL receptor, as the liver contains over half of the body's total LDL receptors. Receptor-mediated LDL uptake results in an increase in esterification of the incoming cholesterol for storage, down-regulation of the number of LDL receptors, and suppression of cholesterol synthesis by the cell (Fig. 11.6). Finally, it has been demonstrated that the liver takes up a portion of VLDL particles shortly after they are secreted.

Recently, another key protein that regulates cellular cholesterol homeostasis in the liver through interaction with the LDL receptor was identified, **proprotein convertase subtilisin kexin type 9 (PCSK9)**. Originally, PCSK9 was identified as a protein up-regulated during apoptosis of nerve cells. Subsequently, **mutations of the PCSK9 gene** associated with hypercholesterolemia were noted leading to identification of its role in cholesterol metabolism. **Gain-of-function mutations** result in ***increased plasma LDL cholesterol levels*****,** and **loss-of-function mutations** cause the ***opposite***. The normal function of PCSK9 appears to be interaction with

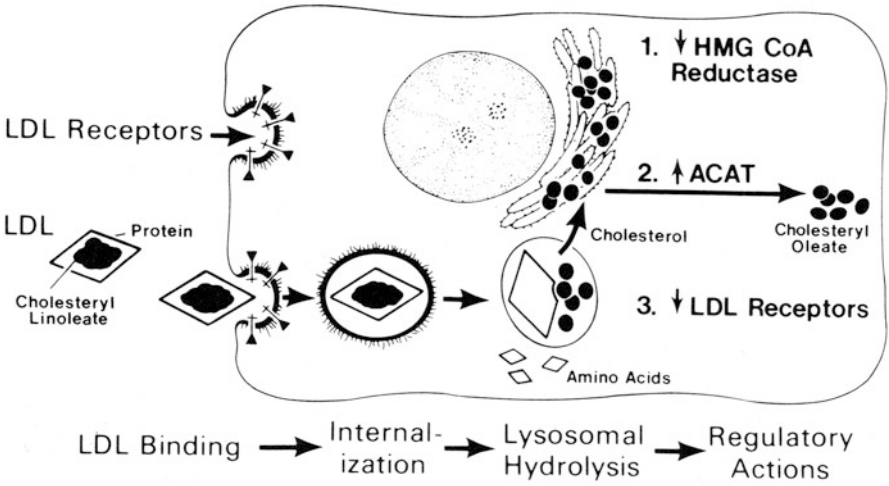

Fig. 11.6 Sequential steps in the LDL pathway. The numbers indicate the regulatory actions of LDL: *1* decrease in 3-hydroxy-3-methylbutyryl coenzyme A reductase (HMG CoA reductase) and cholesterol synthesis, *2* increase in acyl coenzyme A:cholesterol acyltransferase (ACAT) and cholesterol esterification, *3* decrease in the number of cell surface receptors for LDL (Reproduced with permission from Brown and Goldstein [4])

the LDL receptor protein on the cell surface to interfere with normal recycling of the protein and direct it to a degradative pathway. This role of PCSK9 in cholesterol metabolism makes it an attractive **therapeutic target for the treatment of hypercholesterolemia**.

Another lipoprotein produced by the liver is **high-density lipoprotein (HDL)**. This particle is secreted as a discoidal bilayer consisting primarily of phospholipid and free cholesterol. The major apolipoprotein is **apo A-I**, a cofactor for **lecithin:cholesterol acyltransferase (LCAT)**, which is produced by the liver and catalyzes the transfer of a fatty acid from lecithin to free cholesterol to produce cholesteryl ester. These HDL particles acquire free cholesterol from peripheral tissues, which is then esterified and thereby moves into the core of the particle to change the shape from discoidal to spherical. This esterification is a driving force to effect net movement of cholesterol from tissue membranes to HDL. A portion of the cholesteryl ester in the HDL core may be transferred to a chylomicron, VLDL, or LDL particle through the action of a plasma **cholesteryl ester transfer protein (CETP)** to allow transport of the cholesterol to a variety of tissues throughout the body. The cholesterol from mature HDL particles is ultimately taken up by the liver via **scavenger receptor-BI (SR-BI).** Thus, HDL function in "**reverse cholesterol transport**" to effect cholesterol movement from peripheral tissues to the liver. Serum levels of HDL cholesterol correlate ***inversely*** with risk for atherosclerotic coronary artery disease.

4.1 Regulation of Hepatic Lipid Metabolism

Many of the regulatory processes described above for hepatic lipid metabolism are mediated by transcription factors called **nuclear receptors** that regulate the transcription of key proteins and enzymes in response to physiological cues, such as cellular lipid and substrate levels. One family of such receptors is that of the **sterol regulatory element binding proteins (SREBPs)**. Key enzymes involved in ***de novo* lipogenesis**, such as *acetyl-CoA carboxylase*, *fatty acid synthase,* and *stearoyl-CoA desaturase*, are regulated by **SREBP-1c**, and genes involved in cholesterol metabolism, including those of *HMG-CoA synthase* and *reductase*, the *LDL receptor* and *PCSK9*, are regulated by **SREBP-2**. Another regulatory transcription factor, **carbohydrate responsive element binding protein (ChREBP)**, mediates activation of several glycolytic and lipogenic regulatory enzymes, including *fatty acid synthase*, *acetyl CoA carboxylase* and *pyruvate kinase*. It is translocated to the nucleus and binds to the carbohydrate response element in the promoter of its target genes. Activation of ChREBP occurs by dephosphorylation in the presence of high levels of glucose-6-phosphate (glucose-responsive), leading to nuclear translocation.

The **lipid-sensing property of SREBP-2** occurs via a unique cellular mechanism called **regulated intramembrane proteolysis.** For example, in the case of cholesterol, SREBP-2 precursor protein is anchored to the membrane of the ER and complexed to the cholesterol sensing **SREBP cleavage activating protein (Scap)**, which in turn is bound to ER proteins, Insig-1 and -2. When cellular cholesterol falls below a certain level, Scap and the Insigs no longer bind to each other. The **Scap/SREBP precursor protein complex** then moves to the Golgi, where a **site-1 protease (S1P),** followed by a **site-2 protease (S2P)**, cleave the SREBP precursor protein to produce two N-terminal fragments that dimerize to form the active transcription factor. The active SREBP then translocates to the nucleus and binds to the promoter of a target gene, such as the LDL receptor, and activates transcription. Subsequently, the increased number of LDL receptors takes up circulating LDL and raise intracellular cholesterol levels, while lowering plasma cholesterol levels.

Another class of nuclear receptor transcription factors, the **liver X receptors (LXRs)**, also play a major role in hepatic lipid metabolism, and exist in two forms, **LXR-α**, abundant in liver and other tissues, including intestine, and **LXR-β**, ubiquitous in many tissues. When activated by binding of a ligand, LXRs heterodimerize with the **retinoid X receptor (RXR)** and bind to specific response elements, as well as coactivator and corepressor proteins, in the promoters of their target genes to modulate cholesterol metabolism at several sites to avoid cholesterol overload. Interestingly, LXR-α has an LXR response element in its gene promoter and can autoregulate its own transcription. The LXRs promote transcription of genes that have wide-ranging effects on cholesterol homeostasis, including efflux of cholesterol from peripheral cells, such as macrophages involved

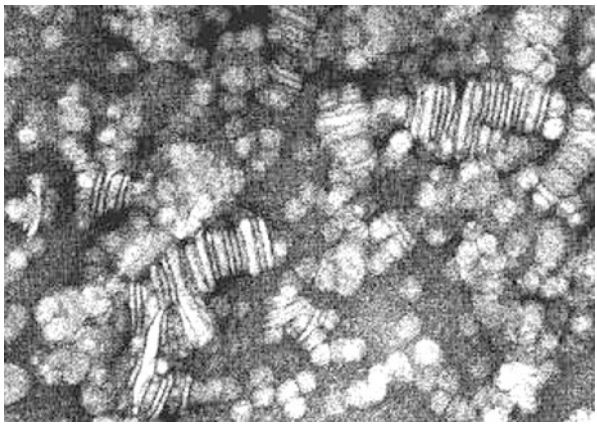

Fig. 11.7 Electron photomicrograph of negatively stained lipoprotein-X from an infant with biliary obstruction. Original magnification 100,000× (Reproduced from Williams et al. [15])

in atherosclerosis via **ATP binding cassette (ABC) proteins ABCA1** and **ABCG1**. They also regulate hepatic excretion of cholesterol into bile and intestinal absorption of cholesterol by inducing **ABCG5** and **ABCG8**. The endogenous ligands for LXRs are **oxysterols**, formed by the oxidation of cholesterol and present in proportion to the amount of intracellular cholesterol, thus enabling these receptors to function as cholesterol sensors. The gene for the rate-limiting enzyme in bile acid synthesis from cholesterol, **Cyp7α1**, is also regulated by LXRs. Recently, LXRs have been implicated in the regulation of target genes involved in glucose metabolism and inflammation. Adverse effects of LXR activation, including hepatic triglyceride overproduction via up-regulation of fatty acid synthesis, have hampered the development of small molecule LXR agonists to prevent atherosclerosis and treat other diseases. However, recent evidence suggests that exclusive targeting of extrahepatic LXRs may bypass this problem.

4.2 Hepatic Lipid and Lipoprotein Metabolism in Liver Disease

In **cholestatic liver disease**, particularly *biliary obstruction*, hyperlipidemia occurs with often striking elevation of plasma cholesterol and phospholipid levels. Furthermore, the majority of this cholesterol is unesterified, in contrast to the normal situation in which most plasma cholesterol is esterified. Much of this excess cholesterol and phospholipid is contained in an abnormal plasma lipoprotein, **lipoprotein-X**, which accumulates in individuals with cholestasis (Fig. 11.7). Lipoprotein-X is isolated in the low density lipoprotein (LDL) density range in the ultracentrifuge and consists mainly of free cholesterol and phospholipid. The major protein components of lipoprotein-X are **albumin** and the **apo C and E peptides**. Although the presence of lipoprotein-X in plasma is a sensitive marker for cholestasis, it cannot reliably discriminate intrahepatic from extrahepatic cholestasis. Interestingly, although certain cholestatic liver diseases may result in

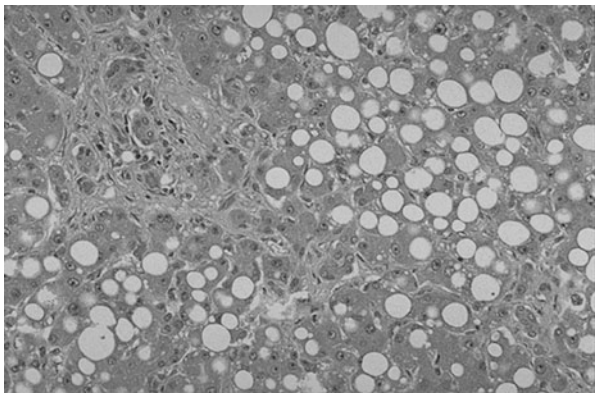

Fig. 11.8 Photomicrograph of a liver biopsy from a patient with NAFLD. Note the hepatocytes distended with large lipid droplets. Hematoxylin and eosin stain, original magnification 100×

markedly elevated lipoprotein-X levels with total serum cholesterol levels above 1,000 mg/dL, unlike LDL, this particle does not appear to be atherogenic and does not increase the risk for cardiovascular disease.

Mild to moderate **parenchymal liver disease**, such as *typical acute viral hepatitis*, usually results in an increase in plasma triglycerides, a less striking increase in cholesterol (mostly free cholesterol), and a decrease in HDL. These changes are thought to result from decreases in hepatic lipase, LCAT, and possibly peripheral lipoprotein lipase. With **severe parenchymal liver injury**, such as *fulminant hepatitis* disappearing HDL fraction portends an especially poor prognosis.

The most common plasma lipid abnormality with acute and chronic ethanol ingestion is hypertriglyceridemia contained in the triglyceride-rich very low density lipoprotein fraction (VLDL) and results from increased hepatic synthesis and secretion of VLDL. Chronic mild ethanol ingestion may result in only an elevation of plasma HDL levels. In the presence of **alcoholic hepatitis**, in addition to the abnormalities described for parenchymal liver disease, there is accumulation of an abnormal discoidal HDL particle **deficient** in ***apolipoprotein A-I*** and **rich** in ***apolipoprotein E.*** This may represent a nascent HDL particle persisting in the circulation due to **LCAT deficiency** caused by the ethanol-induced liver injury.

The current obesity epidemic in adults and children has resulted in a dramatic increase in the accumulation of lipid in the liver, termed **non-alcoholic fatty liver disease (NAFLD)** (Fig. 11.8). In many cases, the steatosis of liver cells is also associated with ***inflammation***, which is then termed **non-alcoholic steatohepatitis (NASH),** and the development of cirrhosis. This disorder often accompanies the **metabolic syndrome**, a constellation of abnormalities that includes *insulin resistance*, *hypertension*, *abdominal obesity*, *hypertriglyceridemia*, *low HDL cholesterol levels*, and the presence of *abnormal*, *highly atherogenic small*, *dense LDL particles*. In the presence of insulin resistance, free fatty acids are mobilized from adipose tissue and are taken up by the liver, where they are re-esterified to triglyceride and packaged into VLDL particles. These particles are secreted and result in hypertriglyceridemia. However, overproduction often overwhelms the secretory

pathway, and triglyceride accumulates in the hepatocytes. Local events, such as lipid peroxidation coupled with a systemic inflammatory state, may result in hepatic inflammation (the so-called "**second hit**") to produce **NASH** and progressive liver disease with **cirrhosis** and, in some cases, the development of **end-stage liver disease**, requiring transplantation, or **hepatocellular carcinoma**.

Recently, the contribution of the **intestinal microbiome** to progression of NAFLD and other liver diseases has been more clearly defined. The liver's location at the interface between portal blood from the gut, which carries bacteria and bacterial products, such as lipopolysaccharide (LPS) and metabolites, that have breached the intestinal barrier, and the rest of the body, places it in an ideal position to react to perturbations in the composition of the microbiome. The liver contains **immune cells**, such as the Kupffer cell, and **innate immune response receptors** that function in the initiation and modulation of inflammation, which plays a role in diverse pathologic processes, including the metabolic syndrome, progression of NAFLD to NASH, autoimmune liver diseases and others associated with immune dysregulation. **Future therapies targeting the gut microbiome** may result in prevention or amelioration of these diseases.

5 Role of the Liver in Substrate/Energy Processing and Distribution During the Fed, Postabsorptive, and Fasting States

The liver plays a pivotal role as a metabolic distribution center for the body in the face of very different metabolic conditions characterizing the **fed**, **postabsorptive**, and **fasting states**. In the **fed state**, nutrients absorbed from the small intestine are abundant. ***Glucose*** is readily available as an energy substrate for brain and red blood cells, which have no capacity for storage of glucose as glycogen. In **muscle**, the glucose is taken up for ***storage as glycogen*** when needed for energy production. However, unlike liver glycogen, muscle glycogen does not contribute to maintenance of blood glucose levels. In the **liver**, the incoming glucose is stored as glycogen. When glycogen stores are saturated, glucose is used for ***fatty acid synthesis***. As previously discussed, these fatty acids are esterified into triglycerides and incorporated into VLDL, which are secreted and supply fatty acids to peripheral tissues. Also as previously discussed, dietary lipid is distributed to peripheral tissues and liver by intestinal chylomicron metabolism. These events are summarized in Fig. 11.9.

In the **postabsorptive fasting state**, the influx of dietary glucose is interrupted, and the liver releases glucose from glycogen to maintain blood glucose levels between meals for use by the brain. ***Amino acids*** released by muscle are substrates for ***hepatic gluconeogenesis***. Also, adipose tissue releases fatty acids into the circulation, rather than storing them as triglycerides. Oxidation of glucose, as

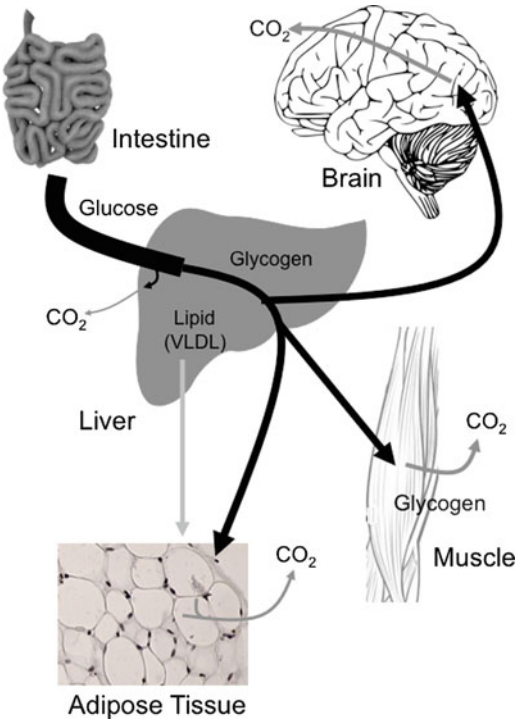

Fig. 11.9 Glucose metabolism in the fed state. Glucose is absorbed from the gut. A small fraction is used within the liver for immediate hepatic energy needs and for lipid and glycogen storage. The rest is utilized by muscle, brain, and other tissues (Adapted with permission from Van Thiel [13])

an energy source begins to decline and fatty acid oxidation by liver and muscle increases. This scheme is summarized in Fig. 11.10.

With **prolonged fasting**, hepatic glycogen stores are depleted within 48 h in adults and more rapidly in children and infants. **Gluconeogenesis** in the liver becomes more important as an energy source for brain and red blood cells. ***Amino acids from muscle*** are the predominant substrates for this gluconeogenesis. As fasting continues, fatty acids released from adipose tissue are oxidized to ***ketones*** by the liver to supply alternative energy to the central nervous system. The factors regulating these metabolic adaptations include *liver sinusoidal glucose concentrations* and *hormones* (insulin, glucagon, and catecholamines).

Glucose is readily taken up by the hepatocyte predominately by the glucose transporter, GLUT2, that is regulated by glucose levels via SREBP-1c, and the intracellular glucose concentration is generally the same as the sinusoidal concentration. The velocity of the conversion of glucose to glucose-6-phosphate by glucokinase is dependent therefore on the **sinusoidal glucose concentration**. The amount of the enzyme glucokinase is transcriptionally regulated by insulin concentrations. Therefore, during and immediately after a meal, insulin and sinusoidal glucose levels are high, and glucose is rapidly taken up, phosphorylated, and incorporated into glycogen for storage and used as a substrate for fatty acid and amino acid synthesis when glycogen stores are fully repleted. **Increasing sinusoidal concentrations of**

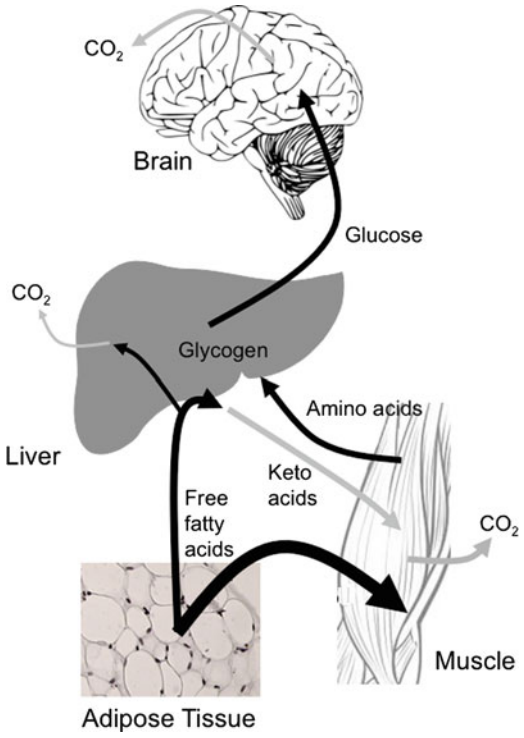

Fig. 11.10 Energy metabolism in the fasting state. Glucose is formed from amino acids released from muscle and from hepatic glycogen. The bulk of the energy requirement is satisfied as a result of lipolysis and fatty acid oxidation (Adapted with permission from Van Thiel [13])

glucose result in activation of glycogen synthetase; this incorporates glucose into glycogen, and decreased activity of the phosphorylase that breaks down glycogen to release glucose. This process is reversed when sinusoidal glucose concentrations are low. **Glycogen synthetase and phosphorylase** are activated by enzyme protein dephosphorylation and phosphorylation, respectively. A **cAMP-responsive protein kinase** is responsible for phosphorylating and thereby inactivating glycogen synthetase directly. This same protein kinase activates a phosphorylase kinase which in turn phosphorylates and activates phosphorylase. Regulatory factors involved in this complex scheme involve *glucagon* and *epinephrine*, as well as hormones and neural stimuli that affect *intracellular calcium concentrations*.

6 Role of the Liver in Vitamin Metabolism

6.1 Vitamin A

Vitamin A is essential for normal **vision**, normal **reproductive** function, and **maintenance of epithelia** throughout the body, including a role in processing cell surface glycoprotein receptors. Dietary vitamin A from ***animal sources*** is present in

the intestine primarily as **retinyl esters**, which undergo cleavage prior to absorption of the free retinol. **Carotenoids** from ***plant sources*** are converted to **retinal**, then to **retinol**, prior to intestinal absorption. **Retinol** is a fat-soluble vitamin, requiring bile salt solubilization for absorption. Although a portion of carotenoids is absorbed intact, this fraction does not represent functional vitamin A. The absorbed retinol is esterified with a fatty acid in the enterocyte, and the resultant retinyl esters are incorporated into intestinal chylomicrons. Ultimately, the retinyl esters enter the hepatocyte with chylomicron remnant uptake. After uptake, hydrolysis, and reesterification by the hepatocyte, retinyl palmitate (over 90 % of total body reserve) is stored mainly in hepatic non-parenchymal fat-storing (stellate) cells. Retinol is mobilized as the **free alcohol (retinol)** bound to **retinol binding protein (RBP)**, which is synthesized by the hepatocyte. Nutritional retinol status regulates hepatic RBP secretion. Also, an **intracellular retinol binding protein (CRBP)** is present in hepatocytes and fat-storing cells. Retinol binding protein circulates complexed with prealbumin **(transthyretin)**, which also transports thyroid hormones and functions to deliver retinol to peripheral tissues. **Excess vitamin A intake** results in stellate cell overload with activation of these cells and production of excess collagen resulting in ***liver fibrosis***.

6.2 Vitamin D

Vitamin D is essential for normal **calcium metabolism** and maintenance of proper **bone mineralization**. Vitamin D_3 is produced in the ***skin*** and absorbed from ***dietary sources***, requiring bile salts for absorption. **Vitamin D3 (cholecalciferol)** is produced in the skin from the precursor 7-dehydrocholesterol in a reaction requiring ultraviolet light. **Vitamin D_2 (ergocalciferol)** is found to a limited extent in ***plant products*** and is the major form of ***dietary vitamin D supplementation***. **Vitamin D_3** is abundant in ***fish oils*** and ***eggs***. Although vitamin D is incorporated into chylomicrons, which are secreted into intestinal lymphatics, a significant proportion is absorbed directly into the portal circulation. In the blood, vitamin D binds to **vitamin D binding protein (DBP)** for transport to liver for 25-hydroxylation. After hepatic 25-hydroxylation, 25-OH vitamin D is transported bound to DBP to kidney for final hydroxylation to **1,25-$(OH)_2$ vitamin D**. The liver does not significantly store vitamin D. Reduced levels of 25-OH vitamin D may be seen in liver disease because of reduced absorption of vitamin D with cholestasis and/or reduced hepatic synthesis of DBP. Liver disease generally does not result in significantly reduced vitamin D hydroxylation. Regulation of vitamin D metabolism occurs primarily at the level of the ***kidney***. Production of 1,25-$(OH)_2$ vitamin D is enhanced by parathyroid hormone and inhibited by elevated blood levels of calcium and phosphorus. The **metabolically active 1,25-$(OH)_2$ vitamin D** regulates intestinal absorption of dietary calcium and recruits stem cells to mature into osteoclasts, which mobilize calcium from bone.

6.3 Vitamin K

Vitamin K is produced by ***intestinal bacteria*** and requires bile acids and pancreatic secretions for the most efficient absorption. Other significant dietary sources of vitamin K include ***liver***, ***eggs***, ***butter***, ***cheese***, and ***green***, ***leafy vegetables***. Vitamin K is incorporated into chylomicrons in the enterocyte and is ultimately delivered to the liver in chylomicron remnants. In the liver, vitamin K is incorporated into VLDL, which are secreted from the liver with a significant proportion of the VLDL being converted to LDL, allowing distribution of vitamin K throughout the body. The liver synthesizes the **vitamin K-dependent clotting factors,** ***prothrombin*** and ***factors VII, IX, and X,*** as well as ***protein C and S***. Vitamin K is required for the **posttranslational formation of γ-carboxyglutamic acid** from specific glutamic acid residues on these proteins during hepatic synthesis. Without this carboxylation, the secreted factors are not functional in the clotting cascade. Whenever one observes a coagulopathy in an individual with liver dysfunction, particularly cholestatic liver disease, vitamin K should be administered parenterally. If the coagulopathy corrects, it was likely due to ***vitamin K deficiency***. If not, the coagulopathy is probably ***secondary to severe liver synthetic failure***.

Clinical Correlations

Case Study 1

A three and a half month-old male infant is brought to the emergency room having a generalized seizure. The infant was born to a 22-year-old G1P0Ab0 female after an uneventful term pregnancy. The vaginal vertex delivery went smoothly, and there were no perinatal problems. The birth weight was 8 lb and 12 oz. The infant was breast-fed from birth and has had no apparent problems until approximately 20 min before arrival at the hospital when he was noted to be poorly responsive and began having generalized jerking movements, prompting the parents to call an ambulance. In the emergency room a blood glucose is found to be 13 mg/dL. The infant is given an intravenous push of glucose, and the seizure activity stops within seconds. On examination the infant is postictal, but responsive. The baby is noted to have a "doll-like" appearance with chubby cheeks, a protuberant abdomen, and thin extremities. Abdominal examination reveals a massively enlarged liver extending down into the right pelvis and the left lobe extending across the midline to the left upper quadrant. Both kidneys are detectable and felt to be enlarged on deep palpation. There is no splenomegaly.

Laboratory studies: Hematocrit 36 %; hemoglobin 11.5 g/dL; white blood cell count 3,600 cells/mm^3 (5,000–190,500) with a neutropenia reflected in the differential; 180,000 platelets/mm^3 (150,000–350,000); prothrombin time 13.0 (control 12.4 s); glucose (before glucose infusion) 13 mg/dL (60–105 mg/dL); albumin 4.5 g/dL (3.7–5.6); total bilirubin 1.3 mg/dL; direct bilirubin 0.3 mg/dL; ALT 91 IU/L (10–54), AST 85 IU/L (25–75); GGTP 41 IU/L (5–65); alkaline phosphatase 296 IU/L (150–400); blood ammonia 59 μmol/L (29–70); sodium

135 mEq/L (135–145), potassium 5.5 mEq/L (3.5–5.0), chloride 101 mEq/L (94–106); carbon dioxide 11 mEq/L (22–29); blood urea nitrogen (BUN) 21 mg/dL (5–25); creatinine 0.3 mg/dL (0.2–0.4); lactic acid 79 mg/dL (5–20); uric acid 12 mg/dL (2.0–7.0) triglycerides 920 mg/dL (less that 99); and cholesterol 280 mg/dL (less than 203). The urine is negative for ketones.

Questions:

1. **What is the most likely diagnosis in this patient?**
   Answer: The constellation of ***hypoglycemia, lactic acidosis, hyperuricemia, hyperlipidemia, nephromegaly,*** and ***massive hepatomegaly*** in an infant with "***cherubic" facies*** with ***normal liver synthetic function*** and ***minimally elevated transaminases*** suggests a diagnosis of **glycogen storage disease type I (von Gierke's disease, glucose-6-phosphatase deficiency),** an *autosomal recessively inherited disorder.* The presence of ***neutropenia*** would suggest further classification as **type Ib**, which is caused by **mutations in the glucose-6-phosphate translocase gene**, resulting in defective microsomal membrane transport of glucose-6-phosphate. Inability to generate glucose from glucose-6-phosphate results in a block in the final steps of the glycogenolytic and gluconeogenic pathways, which causes the ***fasting hypoglycemia*** observed in these patients. There is generally no ketosis in the face of profound hypoglycemia. Accumulation of glucose-6-phosphate results in increased shunting of this substrate into the glycolytic pathway with generation of lactic acid. ***Hyperuricemia*** is caused by both decreased renal clearance and increased production. Lactate competes for uric acid excretion by the kidney, and hepatic accumulation of phosphate esters causes increased degradation of adenine nucleotides with resultant increased uric acid production. ***Hyperlipidemia*** is caused by increased hepatic production of triglycerides and VLDL due to overproduction of NADH, NADPH, acetyl-CoA and glycerol by the glycolytic pathway, which serve as the co-factors and substrates for lipogenesis.

   These patients are generally ***hyperinsulinemic,*** which results in decreased activity of peripheral lipoprotein lipase and decreased lipolysis of triglyceride-rich lipoproteins. Striking ***hepatomegaly*** is caused by accumulation of glycogen and triglyceride in the hepatocytes. ***Renal enlargement*** is found early in life, and renal disease is a late complication with ***hypertension, proteinuria,*** and ***nephrolithiasis***. Most patients have growth retardation and delayed puberty. Diagnosis of this disorder requires **liver biopsy** with demonstration of **decreased glucose-6-phosphatase activity (type Ia)** or **deficiency of one of three microsomal translocase systems (type Ib)**. Genetic diagnosis is also available. There are other types of glycogen storage disease involving various steps in the synthesis and breakdown of hepatic and muscle glycogen. A photograph of an infant with glucose-6-phosphatase deficiency is shown in Fig. 11.11.
2. **How would you treat this patient?**
   The cornerstone of therapy is **maintenance of normoglycemia**. This may be accomplished by the ***ingestion of raw cornstarch***, which acts as a timed-release form of glucose in the GI tract, or use of ***continuous nasogastric drip***

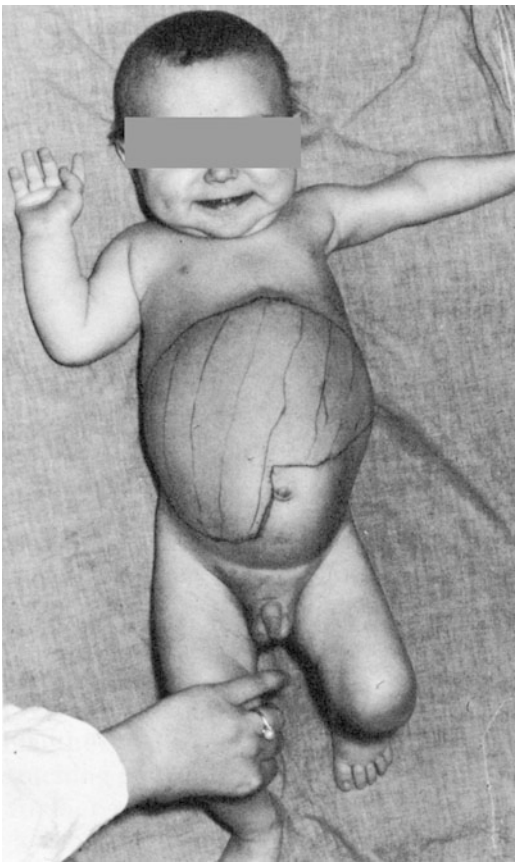

Fig. 11.11 Eight-month-old infant with glucose-6-phosphatase deficiency. Note the massive hepatomegaly and "cherubic" face (Reproduced with permission from Alagille and Odievre [1])

feedings. These measures usually result in improved growth, prevention of hypoglycemia, and lowering of lactic acid and lipid levels. The development of hepatic adenomas may necessitate ***liver transplantation***.

Case Study 2

A 12-year-old female is referred for evaluation of hypercholesterolemia detected after her new family physician saw her for the first time and noticed xanthomata on her extremities. She has apparently had these lesions since early childhood. She has also previously been followed by several dermatologists for severe chronic pruritis resulting in extensive excoriations, sub-ungual hematomas, and inability to sleep at night or function in school. Further physical examination reveals short stature (<3rd percentile for height), peculiar facies with a broad forehead, deep-set eyes, and pointed chin. There is no jaundice. Cardiac examination demonstrates a grade III/VI systolic murmur compatible with pulmonic stenosis. Abdominal examination reveals a liver edge 4 cm below the right costal margin, which is firm. There is no splenomegaly, ascites, or signs of chronic liver disease or portal hypertension. Skin

examination reveals diffuse excoriation from itching and extensive xanthomata on palmar creases and extensor surfaces of the upper and lower extremities. There is a family history of the deceased father having similar symptoms, although much milder.

Laboratory studies: Hematocrit 43 %; hemoglobin 14.5 g/dL; white blood cell count 9,600 cells/mm^3 (4,500–13,500); 220, 000 platelets/mm^3 (150,000–350,000); prothrombin time 15.1 s (control 12.4 s); albumin 4.7 g/dL (3.7–5.6); total bilirubin 1.6 mg/dL; direct bilirubin 1.1 mg/dL; ALT 112 IU/L (10–30), AST 102 IU/L (15–30); GGTP 660 IU/L (14–25); alkaline phosphatase 550 IU/L (50–375); blood ammonia 43 μmol/L (29–57); fasting total serum bile acids 310 μmol/L (0–6); sodium 135 mEq/L (135–145), potassium 4.2 mEq/L (3.5–5.0), chloride 99 mEq/L (94–106); carbon dioxide 25 mEq/L (22–29); blood urea nitrogen (BUN) 39 mg/dL (5–25); and creatinine 0.6 mg/dL (0.5–1.0); total serum cholesterol 1,140 mg/dL (<202); triglycerides 212 mg/dL (<125), and HDL cholesterol 25 mg/dL (32–70).

Questions:

1. **What is the most likely diagnosis in this patient?**
   The **Alagille syndrome** or **arteriohepatic dysplasia** consists of the findings of ***cholestasis*** with ***intrahepatic ductal paucity, short stature, peculiar facies, peripheral pulmonic stenosis*** or more ***complex heart lesions, failure of complete vertebral body*** or ***arch fusion*** resulting in **"butterfly" vertebral bodies** on X-ray, ***posterior embryotoxon*** on slit lamp eye exam, and ***renal abnormalities***. This disorder is inherited as an *autosomal dominant disorder* with variable penetrance, as well as a high spontaneous mutation rate, accounting for the frequent finding of an asymptomatic or minimally symptomatic parent or lack of one or more characteristic features in probands. The disorder is due to **mutations of the *JAG1* or *NOTCH2* genes** that are involved in intercellular signaling during embryonic development. Although cholestasis may be severe, most patients do not develop cirrhosis and liver failure. However, some patients eventually require liver transplantation. **Two striking features** of this disease are the ***severe cholestasis*** with markedly elevated serum bile acids and ***pruritis*** in the face of a normal or only slightly elevated bilirubin and the resulting marked hypercholesterolemia with xanthoma formation. The majority of the serum cholesterol is unesterified and contained in lipoprotein-X. These patients also often have low HDL cholesterol levels. It is interesting that even though these patients may have serum cholesterol levels many fold higher than individuals with familial hypercholesterolemia and elevated LDL cholesterol, premature atherosclerosis is not observed. However, a patient with primary biliary cirrhosis and severe cholestasis with an extremely high lipoprotein-X level has been reported with complications from a resultant **hyperviscosity syndrome with neurologic and cardiovascular impairment**. Also, these patients have a **vasculopathy** that may result in blood vessel rupture and spontaneous bleeding, and may be fatal, especially with an intracranial site of bleeding.

2. **How would you treat this patient?**
   Chronic administration of oral ursodeoxycholic acid appears to result in improvement in the cholestasis and pruritis, as well as the serum lipid profile, in some patients. This non-toxic, water-soluble bile acid acts as a **choleretic** to increase bile flow and after chronic administration may make up 40 % or more of the bile acid pool, displacing more toxic bile acids, which may contribute to the liver disease. Some patients may achieve the same result by **chronic external biliary diversion** using a ***cholecystojejunal conduit*** or ***ileal diversion*** for bile acid pool depletion. **Fat-soluble vitamin supplementation** is a necessity with particular attention to vitamin E. Severe vitamin E deficiency may develop in these patients with resultant neurologic symptoms, including *weakness*, *opthalmoplegia*, *ataxia*, *areflexia*, and *decreased vibratory and proprioceptive sensation*. This patient's prothrombin time corrected to normal within 24 h after a **parenteral injection of vitamin K**.

Case Study 3

A 48-year-old white male is referred for evaluation of the recent onset of chest pain with exertion. He works as an investment banker, has a very sedentary lifestyle with no regular exercise and smokes two packs per day. He eats out frequently with high-fat and high-sugar foods. He drinks an average of 1–2 beers per day. On physical examination his weight is 88 kg with a BMI of 27.8 (overweight range) and blood pressure of 152/103. His waist to hip ratio is 1:4 (normal <1.0), indicating abdominal obesity. The cardiovascular exam is otherwise normal. The abdominal exam is normal except for hepatomegaly with the liver edge 5 cm below the right costal margin.

Laboratory studies: Hematocrit 46 %; hemoglobin 15.3 g/dL; white blood cell count 10,600 cells/mm^3 (4,500–13,500); 289, 000 platelets/mm^3 (150,000–350,000); prothrombin time 11.1 s (control 12.4 s); fasting glucose 160 mg/dL (<120); glycosylated hemoglobin 9 % (<6 %); fasting insulin 48 μU/mL (<25), C-reactive protein 3.2 mg/dL (<1); albumin 4.2 g/dL (3.7–5.6); total bilirubin 1.1 mg/dL; direct bilirubin 0.4 mg/dL; ALT 199 IU/L (10–30), AST 180 IU/L (15–30); alkaline phosphatase 89 IU/L (25–100); total serum cholesterol 260 mg/dL (<202); triglycerides 493 mg/dL (<150), and HDL cholesterol 26 mg/dL (>40); LDL cholesterol 146 mg/dL (<100); apo B 209 mg/dL (<125).

Questions:

1. **Is this patient at high risk for serious health problems?**
   Yes, he fits the criteria for **metabolic syndrome:** ***abdominal obesity*****;** ***hypertension*****;** ***insulin resistance*** that is now manifest as frank ***type 2 diabetes***, as indicated by elevated glucose, glycosylated hemoglobin and insulin levels; and ***hypertriglyceridemia*** and ***low HDL cholesterol levels***, as well as ***elevated LDL cholesterol with apo B levels*** (a reflection of LDL particle number) consistent with highly atherogenic small, dense LDL particles. He also has ***elevated CRP levels***, a marker for inflammation, which may be a component of the

metabolic syndrome. His **chest pain** may be due to ***angina from atherosclerotic coronary artery disease***, and the patient needs a comprehensive evaluation by a cardiologist. Finally, the h**epatomegaly** and **elevated transaminase levels** are consistent with the presence of ***NAFLD***.

2. **How would you approach making the diagnosis of NAFLD?**
   Other causes of liver disease, including viral hepatitis, alcoholic liver disease, A-1-antitrypsin deficiency, hemochromatosis, and Wilson disease, should be ruled out. **Imaging of the liver with CT or MRI** (Chap. 10) may be used to detect ***fatty liver***. **Serum markers for fibrosis or elastography** may be helpful in detecting ***advanced liver fibrosis or cirrhosis***. Finally, a **percutaneous liver biopsy** will help confirm ***steatosis***, as well as ***degree of fibrosis*** and the ***presence of inflammation***, which would indicate progression to NASH.
3. **How would you treat this patient?**
   Treatment of metabolic syndrome encompasses comprehensive lifestyle changes, including **weight reduction**, **regular exercise**, and **dietary reduction of total calories** with particular attention to **eliminating sugar**, especially fructose-containing foods, and refined carbohydrates. Effective medications are available to treat insulin resistance, type 2 diabetes and hypertension. Treatment with **vitamin E supplementation**, as an antioxidant, reduces serum transaminase levels and improves liver histology (but not fibrosis). However, at higher doses this therapy may be associated with significant adverse effects. **Insulin sensitizers**, such as *thiazolidinediones*, may also be an effective therapy, but may also be associated with serious adverse effects with long-term use. Recent data suggest that the intestinal microbiota may play a role in the development of NAFLD, and **alteration of the microbiome by the use of probiotics** may prove to be a useful therapeutic approach. **Bariatric surgery for morbid obesity** improves insulin resistance and diabetes and may also improve NAFLD, but more study is needed to define associated risks.

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