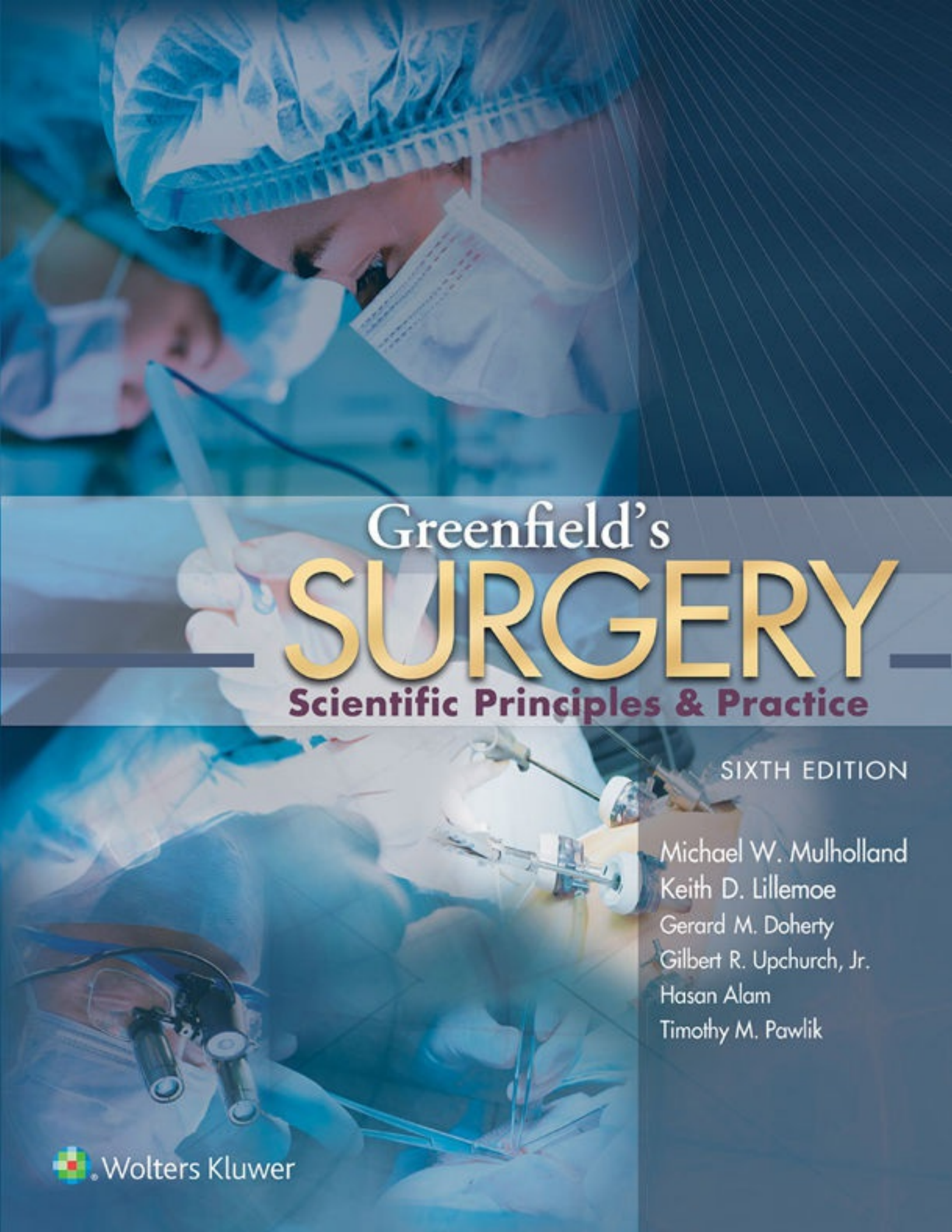

Greenfield's SURGERY

Scientific Principles & Practice

SIXTH EDITION

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Keith D. Lillemoe
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Gilbert R. Upchurch, Jr.
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Wolters Kluwer

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Preface

The editors are pleased to present the sixth edition of *Greenfield's Surgery: Scientific Principles & Practice*. The field of surgery has changed fundamentally in the years since the first edition of this text. Growth in the knowledge base of clinical surgery continues exponentially. Surgical practice has been transformed through advancements in physiologic and cellular investigation, integration of new techniques derived from imaging and robotics, from the concept of patient-centered care, and from the emerging field of biocomputation. The accelerating pace of scientific progress demands rapid adoption of new ideas into surgical therapy and a commitment to lifelong learning. Accordingly, the new edition of *Greenfield's Surgery* seeks to integrate new scientific knowledge with evolving changes in surgical care.

The sixth edition has been enhanced in every way, with changes to the book's editorial board, authorship, content, organization, and visual presentation. It reflects the founding principles and guidance of Lazar J. Greenfield, MD, whose perceptive wisdom helped to create a truly unique book that balances scientific advance with clinical practice. With this new edition, we welcome new editors—Hasan Alam, MD and Timothy Pawlik, MD. Their expertise, energy, and vision have invigorated this edition.

We have solicited contributions from well over 200 authors, all chosen because of their scientific and clinical sophistication. Each contributor is currently an active practitioner in the field of surgery. Moreover, many have presented seminal articles and developed the new concepts in their disciplines that are featured in the text. Advances ranging from patient safety to fetal surgery mark the book as truly unique.

Organizationally, the book begins with topics of broad relevance to the practice of surgery, followed with chapters arranged by organ system. Trauma and transplantation are presented in the form of separate sections rather than subdivided chapters. The content within each has been presented as individual chapters in appreciation of the significance of each topic.

The book has been designed to create a text that not only looks better but also works better. The text is produced in a full range of colors, creating both visual impact and more opportunity to convey information quickly and with greater meaning. We continue our commitment to superb medical art in the form of line drawings. These illustrations have been enhanced to ensure a presentation that maximizes teaching effectiveness and clinical utility. Each chapter begins with a series of highlighted key teaching points, which are referenced within the text that follows. Individually numbered decision-making algorithms are featured throughout the book to provide diagnostic and management information in a simplified format. Tables carry classification bars, such as diagnosis or results, useful both when scanning the text for information and when accessing the book's contents digitally. The most important articles and chapters on the topic are highlighted in the reference list.

The sixth edition continues to be highly integrated with electronic elements to provide supplemental educational material, including Morbidity and Mortality Case Discussions and an interactive question bank.

Today, *Greenfield's Surgery: Scientific Principles & Practice* has become the gold standard text in the field of surgery. The editors continue their commitment to the education of contemporary surgeons, and to improved care of the patients that they serve. We believe that with the many improvements implemented in this sixth edition, it will continue be the text by which all other surgery texts are judged.

Michael W. Mulholland, MD, PhD

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Chapter 1

Lifelong Learning

Gurjit Sandhu and Rebecca M. Minter

Key Points

1. Self-regulated learning is a skill that can be taught to trainees.
2. The Dreyfus model of skill development is helpful for understanding the growth and depth of self-regulated learning from novice to expert level.
3. As self-regulated learning solidifies and becomes habitual for the trainee, it enhances transitions into effective lifelong learning.
4. Lifelong learning is an essential component of safe patient care with up-to-date knowledge and skills.
5. Surgeons who are lifelong learners are better prepared to deal with the complexities of future practice.

LIFELONG LEARNING FOR PERSONAL, PROFESSIONAL, AND SOCIAL RESPONSIBILITY

The Accreditation Council for Graduate Medical Education (ACGME) Task Force on Quality Care and Professionalism has drawn a clear and explicit connection among professionalism, safe patient care, and lifelong learning.[1] This is a direct reference to ensuring that graduate medical education programs are graduating fully trained physicians who are prepared to practice independently.[1,2] In order to achieve this goal, *exposure* to the curriculum is insufficient. Surgeons in training must demonstrate that they are able to perform the activities of a specialist in that field. This becomes a complex feat of curriculum development and learner assessment when one considers that even as learners are graduating from their training programs, their specialties are evolving. With a patient population that is older, has higher acuity, greater number of chronic diseases and comorbidities, accompanied with unprecedented growth in medical knowledge, it is naive to assume that trainees will graduate with mastery of every facet of their discipline.[3,4] Hence, graduating physicians who are primed for lifelong learning becomes a salient professional and social responsibility of graduate medical education programs.

Ultimately, lifelong learning is about bringing together individual responsibility with safe patient care. The commitment to ongoing reflective learning lends itself to a practice where research, education, and experience come together to best serve the needs of the patient. ACGME emphasis on lifelong learning is evidenced in two concrete ways: (1) by the continuum with which milestones are developed – beginning with the pretrained novice and extending throughout the physician's career – reinforcing learning and growth beyond graduation; and (2) an explicit ACGME Common Program Requirement stating "residents must demonstrate the ability to investigate and evaluate their care of patients, to appraise and assimilate scientific evidence, and to continuously improve patient care based on constant self-evaluation and lifelong learning."[5,6] Several surgical specialties have gone on to include lifelong learning as a milestone within the practice-based learning and improvement competency.[7–10]

If lifelong learning is an outcome that is sought among high performing, safe, up-to-date surgeons, it is imperative that surgeons in training develop appropriate knowledge, skills, and attitudes during training that will foster this habitual behavior for when they are in professional practice. Just as management of complex problems or knowledge about postoperative complications of most essential operations are milestones that are met in a progressive manner, the same is true about lifelong learning as a milestone that is met in a progressive manner. As a trainee works toward honing and demonstrating expertise for lifelong learning, progressive development toward this goal while still in a residency program would be called self-regulated learning. In other words, the goal over time is for a resident/fellow to fully and intuitively adopt self-regulated learning and graduate from training entrusted to embrace lifelong learning. Before considering the development of self-regulated learning in a graduated manner across the continuum of graduate medical education, it is important to define and establish the relationship

between self-regulated and lifelong learning.

SELF-REGULATED LEARNING

1 Self-regulated learning has been used to describe students who are "metacognitively, motivationally, and behaviorally active participants in their own learning process."[11] This includes the ability to plan and organize self-instruction, monitor and assess self, and seek out optimal learning opportunities. White et al.[12] argue that these are not merely innate attributes, but skills that can be taught during medical training. Self-regulated learning is framed as a cycle of four phases[12]:

1. Planning
2. Learning
3. Assessment
4. Adjustment

Planning is about setting personal goals, establishing desired outcomes, and having the belief in one's ability to achieve those goals. In this phase, intrinsic motivation and extrinsic motivation are important considerations in the setting and reaching of learning goals. While extrinsic motivation is embedded in graduate medical education (e.g., passing certifying oral examinations), it is intrinsic motivation that is "key to the development of autonomy" and "autonomy is key to lifelong learning."[12] Therefore, during the planning phase, learners develop a sense of urgency for their own learning and an ability to plan and act on goals.

During the *Learning* phase, learners need clarity about how they learn most effectively. This includes developing awareness about one's personal beliefs toward acquiring knowledge, preferred ways of learning (e.g., visual, auditory), learning strategies (e.g., where and when studying happens), and finally aligning learning expectations with those of the educator.

Assessment requires timely, specific, and regular formative feedback (e.g., from supervisors, colleagues, medical students) as well as internal monitoring that compares one's progress against the goal that was set. Together these sources of feedback guide the learner's next steps toward reaching the goal.

Finally, *Adjustment* is where the learner synthesizes what has been gained through the planning, learning, and assessment phases and makes adjustments either in the nature of the goal or in the strategies needed to reach the goal. How learners integrate information about successes or failures could be seen as a matter of attribution – how performance is accounted for ranging from ability to effort. Examining the performance feedback that has been gathered to date, considering the validity of the information, and then determining how to make sense of it in relation to what they already know is a complex process of reflection.[13]

Through explicit teaching and practice at each phase, learners are guided toward sustaining strategies for ongoing, more effective self-regulated learning. Sustainable strategies form the basis for lifelong learning. White et al.[12] underscore sustainable strategies as a key to continuing medical education (CME) for the practicing surgeon and point to the link between CME and quality health care.

LIFELONG LEARNING

If the phases of self-regulated learning solidify for the trainee, they become **habitual** characteristics of effective lifelong learning. In the broadest sense, lifelong learning is about ongoing learning from cradle to grave. However, in the context of entering the workplace after graduate medical education, we look at physicians and lifelong learning more closely as the "ability to guide their own learning throughout their lives and in the wide variety of situations they will encounter after leaving formal education."[14]

This ongoing reflexive process of lifelong learning includes five characteristics[14]:

1. set goals
2. apply appropriate knowledge and skills
3. engage in self-direction and self-evaluation
4. locate required information
5. adapt their learning strategies to different conditions

These characteristics are meant to extend the physician's concept of ongoing learning from "lifelong schooling" to "life-wide learning" so that personal inquiry can happen, for example, at the bedside or in the community and is not constrained to formal educational opportunities.[14]

As a trainee transitions through different levels in residency, the nature of self-regulated learning will also change depending on the learner's needs. As learners meet increasingly more complex patient care milestones, the practice of self-regulated learning transforms accordingly. Solidifying the phases of self-regulated learning during graduate medical education feeds into establishing effective characteristics for lifelong learning that become a critical part of a physician's everyday practice (Table 1-1). As such, medical education programs have a social and professional obligation to further develop and deepen characteristics of self-regulated learning among learners so that graduating surgeons pursue professional learning throughout their careers.[5] It is critically important that a robust curriculum be established within graduate medical education for teaching, engaging with, and assessing practices for lifelong learning.

Table 1-1 Relationship Between Self-Regulated Learning and Lifelong Learning

Self-Regulated Learning Phases	Lifelong Learning Characteristics
Planning	Set goals
Learning	Apply appropriate knowledge and skills
Assessment	Engage in self-direction and self-evaluation Locate required information
Adjustment	Adapt their learning strategies to different conditions

Self-regulated learning evolving and deepening into lifelong learning is best understood using the Dreyfus model for skill development.[15] This is in keeping with the foundational framework from which the milestone frameworks have been structured to assess residents/fellows in surgical disciplines.[1]

DREYFUS MODEL FOR SKILL DEVELOPMENT

The Dreyfus model for skill development identifies five levels of skill development[15–17]:

1. Novice
2. Advanced Beginner
3. Competent
4. Proficient
5. Expert

On this continuum, learners pass from one level to the next as skills are acquired. At each level, there are "recognizable, qualitatively different ways of acting and performing in the process of learning a given skill. Individuals at a given level do better than individuals at the previous level."[18] Table 1-2 presents the five levels of the Dreyfus model with the addition of delineating each level along four characteristics of skill development: knowledge; decision-making; perception of context; and autonomy.[19–23] Increasing understanding, confidence, and independence associated with these characteristics is in keeping with higher levels of competency with the skill being measured. This delineated view demonstrates in a granular way how a learner progresses and performs differently at each level. Based on criteria, it is clear why not every learner reaches the highest level. The criterion-based foundation of the Dreyfus model makes it a widely adapted process for assessment.[23,24]

2 At the novice level, learners largely have textbook familiarity with a skill. After having advanced to the expert level, learners have extensive experiential knowledge with a skill and are seen to be highly intuitive. We understand self-regulated learning to be a skill that can be learned, will progressively grow and deepen over time, is carried out differently at each successive level, and ought to be carried out in the workplace. As the skill is honed and becomes habitual, self-regulated learning transitions into lifelong learning. This progression in skill development makes the Dreyfus model highly appropriate for understanding, teaching, and assessing self-regulated learning.

Table 1-2 Dreyfus Model of Skill Development: Novice to Expert Levels for Self-Regulated Learning

Level	Characteristics			
	Knowledge	Decision-Making	Perception of Context	Autonomy
1. Novice	Primarily textbook knowledge with few previous experiences Context free following of taught rules Unconscious incompetence	Considers everything and makes tentative judgments with no flexibility Unable to deal with complexity when something unexpected happens Rational	Understand each action as a separate entity Analytic	Close supervision and instruction Observes procedure being performed
2. Advanced Beginner	Gaining practical experiences and knowledge Beginning to apply rules based on context Conscious incompetence	Perception improving, but judgments continue to be largely limited Realizes complexity of situation, but still has difficulty with troubleshooting Rational	Understands actions as related steps Analytic	Requires supervision for overall procedure Assists with performing a procedure and receives opportunities to try some tasks on own
3. Competent	Well-developed background of understanding, conceptual models, and working knowledge in a specialty Led by guidelines that are specific to each situation, yet sees the larger context Conscious competence	Handles complex situations through deliberate planning and own judgment Able to troubleshoot on own, but seeks out expert consult for confirmation Rational	Relates actions to long-term goals Analytic	Direct supervision Able to perform an entire procedure under direct supervision
4. Proficient	Depth of knowledge in field of practice Increasingly working from intuition with less dependence on rules; using analytic approaches primarily to address unusual problems in context Unconscious competence	Merges intuitive and analytic approaches in complex situations Uses pattern recognition to determine essential elements in a situation and what is a deviation Rational	Considers context holistically and how individuals contribute to it Holistic	With indirect supervision, takes full responsibility for performing a procedure Reflects on personal performance and experiences of others for continuous self-improvement
5. Expert	Influential authority in the field Intuitive understanding outweighs reliance on rules, yet uses analytic approaches in novel circumstances Deep understanding	Manages complex conditions with confident decision-making Uses pattern recognition in context and for forward planning Intuitive	Sees larger context and alternative approaches to what may be possible Holistic	Independently performs the procedure without any supervision Takes full responsibility for going beyond maxims

DREYFUS MODEL OF SKILL DEVELOPMENT APPLIED TO SELF-REGULATED LEARNING IN SURGERY

The attributes and practice of self-regulated learning change as learners transition from one level to the next. In other words, as learners attain greater levels of responsibility, the goals they set for themselves, insights adopted about learning, feedback they require, and adjustments they make based on successes and failures will be different from one level to the next. This is in line with gradually more mature forms of reflection and insightful learning plans learners develop for themselves. Self-regulated learning will be described at each level in terms of the learner's skills, but also includes suggestions for educators on how to teach at the level of the learner and establish scaffolds to support the learner advancing to the next level.[23,24]

Novice

The novice learner is focused on figuring out how textbook knowledge applies to the current experience. The goals learners set for themselves are about making sense of uncertain or unfamiliar content by connecting it to existing familiar sets of knowledge. At this point, the learner adheres to step-by-step rules, regardless of context. Working through a methodical line of reasoning without situational awareness or discretion makes it difficult for the trainee to deal with exceptions and complexity.[24] The learner searches for absolute answers. Tendencies toward binary sets of knowledge reveal that learners at this level often do not know what they do not know (unconscious incompetence), suggesting they have an incomplete development of self-assessment.[25] After routine-guided observations of procedures being performed, novice learners are incrementally moved to close supervision with explicit instruction in order to complete tasks. Reflecting on their behavior during experiential opportunities along with the feedback received from faculty or more senior residents and fellows causes learners to revisit the knowledge they believed to be universally true and adjust their goals and views on learning.

Educators must be deliberate and specific in the feedback that is provided, even being explicit about the phases of effective self-regulated learning that should be developed. Educators become a resource as trainees learn to develop appropriate goals and establish a plan forward. Determining the existing level of the learner and learning preferences of the trainee is essential for educators so that they can guide the learner toward suitable challenges that will scaffold him/her to the next level.

Advanced Beginner

For the advanced beginner, emphasis is on gaining practical experiences and knowledge. The balance tilts from taking textbook knowledge and applying it to the context, to better understanding the context, patient indicators, and beginning to discern and apply rules. Although perception is improving, judgments are still quite limited. The advanced beginner continues to be rational and analytic, but now sees actions as related rather than a series of independent steps.[24] Developing an understanding of connectedness helps learners realize the complexity of situations and with that comes an appreciation for how much they do not know (conscious incompetence).[25]

Faculty provide trainees with structured opportunities and directly observe their skills. Under this closely guided practical experience, trainees assist with performing a procedure and receive some opportunities to try simpler tasks on their own. There is a high likelihood these trainees will be able to accomplish these simpler tasks successfully. With the learner starting to see steps as related, this is an opportunity for the educator to give feedback that will push the learner to be aware of more complex connections. Learners still require supervision for the procedure largely because they continue to have difficulty with troubleshooting. Educators should provide challenges just at the edge of the learners comfort level. The trainee's performance will help the educator identify where emphasis needs to be placed in the next educational encounter. It is important to debrief this experience with the learner so s/he can reflect back on emotions, thinking, and skills and establish subsequent goals. Educators simultaneously assess how much scaffolding learners require to extend them to the next level while also removing scaffolds as the learner demonstrates task competence.

Competent

At the competent level, the learner has well-developed conceptual models and fund of knowledge in a specialty. Although still primarily rational and analytic in decision-making, the learner is largely led by guidelines that are specific to the given context. In other words, through deliberate planning and judgment, the trainee can see the larger context and handle complex situations.[24] Trainees recognize what they know, for example, the limits of what they are able to troubleshoot on their own, and also know when to ask for guidance or help (conscious competence).[25] Safely progressing in a high-stakes environment while knowing when to slow down or stop is indicative of being able to reflect while in the moment. A competent level learner will reflect on actions and develop long-term goals.

Educators recognize that learners are able to complete an entire procedure independently to an optimal level. Nevertheless, educators still provide direct supervision to guide refinement, efficiencies, and standardization of procedures. With increasingly complex skills, educators will model specific methods. Learners at the competent stage ask for feedback and the response of the educator becomes less about general principles and more about fostering specific opportunities for individualized growth. While still under direct supervision, individualized instruction allows faculty to release greater degrees of responsibility for the full spectrum of patient care to residents/fellows so they can begin to take ownership and think ahead in developing a care plan.

Proficient

The proficient level represents a learner who sees context, actions, and interactions holistically. Physician core competencies (e.g., Patient Care and Professionalism), as outlined by the ACGME, are understood and enacted in an integrated way into the roles and responsibilities of the learner.[6] It is in seeing the bigger picture that the trainee is able to filter out extraneous materials and focus on essential information that results in less labored decision-making and consistently high levels of performance.[24] Residents/fellows are able to apply the depth of knowledge they have acquired in their specialty and increasingly become more intuitive with less dependence on rules (unconscious competence).[25] Trainees continue to be guided by maxims and rationale approaches to address unusual problems or deviations from expected patterns. The trainee reflects on personal performance with the goal of being able to efficiently merge intuitive and rationale approaches in complex situations.

Proficient residents/fellows have demonstrated that they reliably perform at an acceptable standard; therefore, there is a greater degree of indirect supervision. The role of faculty is to provide opportunities for learners to take full responsibility for performing a procedure, as well as work through uncommon cases. The feedback provided to learners is specific and formative (i.e., not scored) in helping them reach self-identified goals, as well as extend their critical thinking to unique problems and situations.

Expert

At the expert level, individuals have deep holistic understanding in their specialty. Depth of knowledge has provided them with intuitive understanding, confidence in decision-making, and ability to successfully manage complex situations with ease.[24] When faced with novel situations, they are able to seamlessly proceed with alternative approaches, consciously draw on guidelines and maxims, and consider innovative possibilities. Internal creative inquiry challenges these individuals to raise questions to themselves, put the mental brakes on what is familiar, and set goals that extend the field in new directions.[26] Experts are thought to be authorities in their specialties.

Individuals at this level rarely receive feedback unless they ask for it.[27] They adjust and adapt their learning with regular review of current literature, participating in CME, and pursuing and publishing research. As surgeons who independently perform procedures without any supervision, experts also rely on patient outcomes – by reflecting *in* action (e.g., adapting to unexpected conditions) and reflecting *on* action (e.g., follow-up care with patient) – as forms of feedback to inform practice.[13,28] The expert level does not represent completion in learning, rather it signifies that a learner has the skills to continue to stay informed through workplace-based learning. This transition into habitual, ongoing, life-wide learning illustrates that a learner has solidified skills for lifelong learning.

SELF-REGULATED LEARNING AND LIFELONG LEARNING IN SURGERY EDUCATION

3 4 The purpose of this discussion is to show that skills for self-regulated learning can be learned, developed, and transformed into lifelong learning. The Dreyfus model provides an accessible model for visualizing the development and progression of skills from self-regulated learning into lifelong learning. The implications for overlooking development of lifelong learning skills are less obvious while under the observation and guidance of a Surgery Education program. However, if the goal of Surgery Education programs is to produce surgeons who are able to practice independently, actively pursue safe patient care with up-to-date knowledge and skills, then the development of skills for lifelong learning cannot be easily overlooked while still in training. As such, the role of faculty educators to model and explicitly teach about self-regulated learning and lifelong learning is essential.

Educators of residents/fellows at early levels of skill development must be explicit and concrete when explaining how to set independent goals for advancing abilities, as well as provide specific instructions on how to pursue inquiry on their own. As trainees deepen their skills and apply those more routinely, the responsibility for stimulating habitual inquiry begins to shift from the faculty to the trainee. The faculty now looks for the ways in which surgeons in training seek, receive, and provide feedback as indicators of the awareness learners have about where they need to focus their attention for growth.[29] With still further development of self-regulated learning, learners will likely transition into lifelong learners.

5 When advancing in training and moving into careers as experts, there is a great deal of familiarity with procedures, processes, and knowledge. When there is unconscious competence or deep understanding, automaticity sets in. Individuals at this level have ingrained skills and habits that routinely incite internal creative inquiry causing them to challenge these familiar patterns. The lifelong learner purposefully "makes unconventional linkages (…) in order to reveal unseen aspects."[26] The lifelong learner also seeks, applies, and makes new meaning. These are the surgeons who are prepared to deal with the problems of today, but even better prepared to deal with complexities that are yet to be encountered.

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Chapter 2

Principles of Intermediary Metabolism

Steven E. Raper

Key Points

1 Intermediary metabolic pathways – the metabolic manipulation and balancing of ingested carbohydrate, fat, and protein – can process essentially all nutrients to acetyl coenzyme A (CoA) for energy production predominantly through aerobic glycolysis, the citric acid cycle, and oxidative phosphorylation.

2 Glucose must always be available for brain function; if not available directly from the diet, it can be mobilized for a brief period from glycogen stores and then derived from proteins in the liver and kidneys.

3 Free fatty acids are a direct source of energy for cardiac and skeletal muscles.

4 Hepatic protein synthesis, when excess amino acids are available, includes albumin, fibrinogen, and apolipoproteins and can reach 50 g/day.

5 The citric acid cycle includes a series of mitochondrial enzymes that transform acetyl CoA – itself derived from pyruvate or fatty acyl CoA – into water, carbon dioxide, and hydrogen-reducing equivalents. Each molecule of acetyl CoA that enters the citric acid cycle yields 12 molecules of adenosine triphosphate (ATP).

6 Oxidative phosphorylation converts the energy from NADH and $FADH_2$ into ATP by the electron transport chain and ATP synthase with a process called the proton motive force.

7 Biotransformation of potentially toxic, often hydrophobic, compounds into hydrophilic, excretable compounds occurs mainly in the liver by the cytochromes P-450, the uridine diphosphate-glucuronyl (UDP-glucuronyl) transferases, the glutathione (GSH) S-transferases, and the sulfotransferases.

INTERMEDIARY METABOLISM: AN OVERVIEW

Introduction

Intermediary *metabolism* – derived from the Greek word for change – is predominantly the fate of dietary carbohydrate, fat, and protein in a series of life-sustaining cellular chemical transformations. Although admittedly intricate, all surgeons should be familiar with the basics of the biochemistry by which nutrients are converted to energy. Understanding the major biochemical pathways is a prerequisite to making use of the rapid – and exciting – expansion of medical knowledge directed at managing human metabolic derangement and improving health by beginning at the cellular level.

1 Intermediary metabolic pathways – the metabolic manipulation and balancing of ingested carbohydrate, fat, and protein – can process essentially all nutrients to acetyl coenzyme A (CoA) for energy production predominantly through aerobic glycolysis, the citric acid cycle, and oxidative phosphorylation. The major intermediary metabolites are glucose, fatty acids, glycerol, and amino acids. Glucose is metabolized to pyruvate and lactate by glycolysis. Aerobic metabolism allows conversion of pyruvate to acetyl CoA. Acetyl CoA enters the citric acid cycle resulting in carbon dioxide, water, and hydrogen-reducing equivalents (a major source of adenosine triphosphate [ATP]). In the absence of oxygen, glycolysis ends in lactate. Glucose can be stored as or created from glycogen. Glucose can also enter the phosphogluconate pathway, where it is converted to reducing equivalents for fatty acid synthesis and ribose five-carbon sugars important in nucleotide formation. Glucose can be converted into glycerol for fat formation and pyruvate for amino acid synthesis. Gluconeogenesis allows synthesis of glucose from lactate, amino acids, and glycerol.

With regard to lipid metabolism, long-chain fatty acids arise from dietary fat or synthesized from acetyl CoA. Fatty acids can be oxidized to acetyl CoA by the process of beta-oxidation or converted to acylglycerols (fat) for storage as the main energy reserve. In addition to the fats noted previously, acetyl CoA can be used as a precursor to cholesterol and other steroids and in the liver can form the ketone bodies, acetoacetate and 3-hydroxybutyrate, which are critical sources of energy during periods of starvation.

Proteins are degraded in two major ways: an energy independent path, usually in lysosomes, and an energy requiring path, usually through the ubiquitin pathway. About three-fourths of the amino acids generated in protein catabolism are reutilized for protein synthesis and one-fourth is deaminated to form ammonia and subsequently urea. Amino acids may be divided into nutritionally essential and nonessential. Nonessential amino acids require fewer enzymatic reactions from amphibolic intermediates or essential amino acids. Each day, humans turn over 1% to 2% of total body protein.

CARBOHYDRATE METABOLISM

The products of intestinal carbohydrate digestion are glucose (80%) and fructose and galactose (20%). Fructose and galactose are rapidly converted to glucose, and the body uses glucose as the primary molecule for transport and uptake of carbohydrates by cells throughout the body. Despite wide fluctuations in dietary intake, blood glucose levels are tightly regulated by the liver. About 90% of portal venous glucose is removed from the blood by liver cells through carrier-facilitated diffusion. Large numbers of carrier molecules on the sinusoidal surface of the hepatocyte are capable of binding glucose and transferring it to the cytoplasm. The rate of glucose transport is enhanced (up to 10-fold) by insulin. Given the critical role of glucose in survival, complex metabolic pathways have evolved for the storage of glucose in the fed state, the release of glucose from glycogen, and the synthesis of new glucose.

Blood glucose is stored, primarily in liver and muscle, as glycogen. Glycogen is a complex polymer of glucose with an average molecular weight of 5 million. The liver can convert up to 100 g of glucose into glycogen per day by glycogenesis. The liver can also release glucose into the blood by glycogenolysis, (breakdown of glycogen), or gluconeogenesis, (formation of new glucose from substrates such as alanine, lactate, or glycerol). Hormones play a key role in the hepatic regulation of glycogen balance. Insulin, for example, stimulates glycogenesis and glycolysis; glucagon stimulates glycogenolysis and gluconeogenesis through cyclic adenosine monophosphate (AMP) and protein kinase A.[1]

Glycogenesis and Glycogenolysis

2 Glucose must always be available for brain function; if not available directly from the diet, it can be mobilized for a brief period from glycogen stores and then derived from proteins in the liver and kidneys. The first step in glycogen storage is the transport of glucose through the plasma membrane. Once in the hepatocyte, glucose and ATP are converted by the enzyme glucokinase to glucose-6-phosphate (G6P), the first intermediate in the synthesis of glycogen (Fig. 2-1). Because complete oxidation of one molecule of G6P generates 37 molecules of ATP, and storage uses only one molecule of ATP, the overall efficiency of glucose storage as glycogen is a remarkable 97%.

Glycogenolysis does not occur by simple reversal of glycogenesis. Each glucose molecule on a glycogen chain is released by glycogen phosphorylase (Fig. 2-2). Eventually, G6P is reformed. G6P cannot exit from cells and must first be converted back to glucose. The conversion of G6P to glucose is catalyzed by glucose-6-phosphatase, which exists only in hepatocytes, kidney, and intestinal epithelial cells. Brain and muscle both use glucose as a primary fuel source and do not contain the phosphatase enzyme. This lack of glucose-6-phosphatase ensures a ready supply of glucose for the energy needs of brain and muscle. Liver uses glucose primarily as a precursor for other molecules and not for fuel.

Glycolysis

Glycolysis is the mammalian cellular pathway by which glucose is converted to pyruvate or lactate (Fig. 2-3). The glycolytic pathway is interesting in that glucose can be metabolized in the presence (aerobic) or absence (anaerobic) of oxygen. Aerobic glycolysis is one of four stages in the oxidation of glucose and the only stage that occurs in the cytosol. As will be discussed below, stages II to IV occur in mitochondria; the citric acid cycle, electron transport generation of the proton motive force, and ATP synthase leading to generation of ATP.

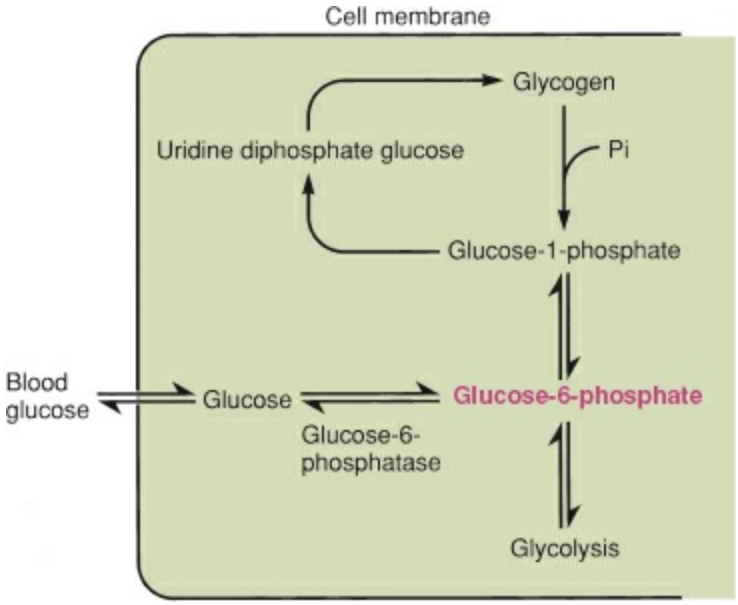

Figure 2-1. The chemical reactions of glycogenesis and glycogenolysis. Glucose-6-phosphatase allows hepatic glucose to be transported out of the hepatocyte for use in other tissues. Glucose-6-phosphate, in *red,* plays a central role in carbohydrate metabolism.

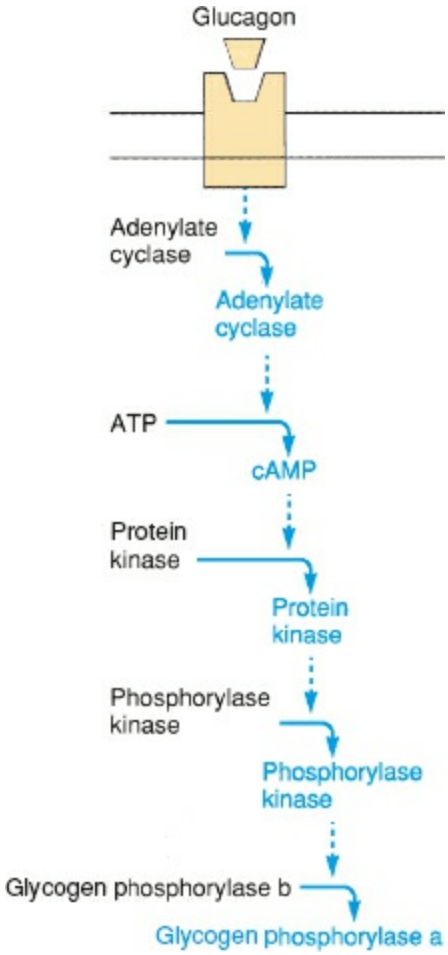

Figure 2-2. Glucagon-stimulated enzyme cascade, responsible for the control of glycogen metabolism. Inactive forms are shown in *black,* active forms in *blue.*

The aerobic conversion of glucose to pyruvate has three effects: (a) a net gain of two ATP molecules, (b) generation of two reducing equivalents of the nicotinamide adenine nucleotide (NADH + H^+), and usually, (c) conversion of pyruvate to acetyl CoA with subsequent conversion of acetyl CoA in the mitochondria to ATP. The conversion of glucose to pyruvate is regulated by three enzymes: hexokinase (glucokinase), phosphofructokinase, and pyruvate kinase, which are nonequilibrium reactions and as such, functionally irreversible.

Under anaerobic conditions, NADH cannot be reoxidized by transfer of reducing equivalents through the electron transport chain to oxygen. Instead, pyruvate is reduced by NADH to lactate. Glycolysis takes place in the cytoplasm, in contrast to the citric acid cycle and oxidative phosphorylation which are mitochondrial processes. During times of glucose excess, as in the fed state, hepatic glycolysis can generate energy in the form of ATP, but the oxidation of ketoacids is a preferred energy source in liver.

The conversion of lactate (through pyruvate) to glucose – a process possible only in the presence of oxygen – is an important means of preventing severe lactic acidosis. Active skeletal muscles and erythrocytes form large quantities of lactate. In patients with large wounds, lactate also accumulates. The liver is exceptionally efficient at converting lactate to pyruvate through the Cori cycle (Fig. 2-4). As a result, one would expect that only significant liver dysfunction would affect the Cori cycle and lead to hyperlactatemia. However, lactate levels are now widely used to assess shock – septic and otherwise.[2] The

hypothesis is that circulatory hypoperfusion impairs tissue oxygen delivery with resultant mitochondrial hypoxia. In the absence of adequate oxygen, mitochondria switch to anaerobic glycolysis and oxidative phosphorylation stops. As a result, serum lactate concentrations appear proportional to ongoing tissue oxygenation deficits; thus improved lactate clearance can be used as a surrogate for success of sepsis therapy.[3] Serum lactate can also be used to assess prognosis and triage patients to ICU level care.[4]

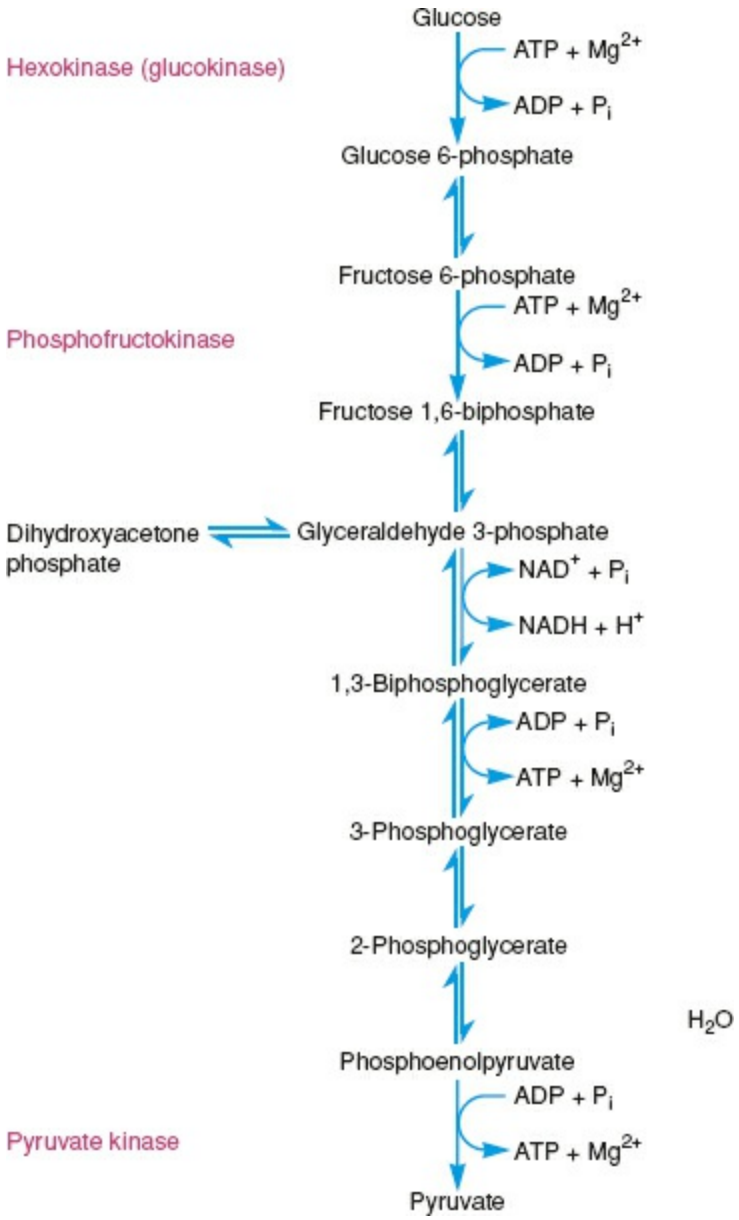

Figure 2-3. The glycolytic pathway. There is a net gain of two ATP molecules per glucose molecule. Phosphofructokinase is the key regulatory enzyme in this pathway; however, all the enzymes in *red* catalyze irreversible reactions. The pathway shown here is active only in the presence of aerobic conditions.

In erythrocytes, a unique variant of glycolysis enhances oxyhemoglobin dissociation. The first site in glycolysis for generation of ATP is bypassed, leading to the formation of 2,3-bisphosphoglycerate by an additional enzyme called bisphosphoglycerate mutase. Kinetics of the mutase present in erythrocytes allow the presence of high concentrations of 2,3-bisphosphoglycerate to build up. The 2,3-bisphosphoglycerate displaces oxygen from hemoglobin, allowing a shift of the oxyhemoglobin dissociation curve to the right.

Gluconeogenesis

There is an absolute minimum requirement for glucose in humans. Below a certain blood glucose concentration, brain dysfunction causes coma and death. When glucose becomes scarce, as in the fasting state, glycogenolysis occurs. Once glycogen stores have been depleted, the liver and kidneys are capable of synthesizing new glucose by the process of gluconeogenesis. Glucagon is produced in response to low blood sugar levels and stimulates gluconeogenesis.

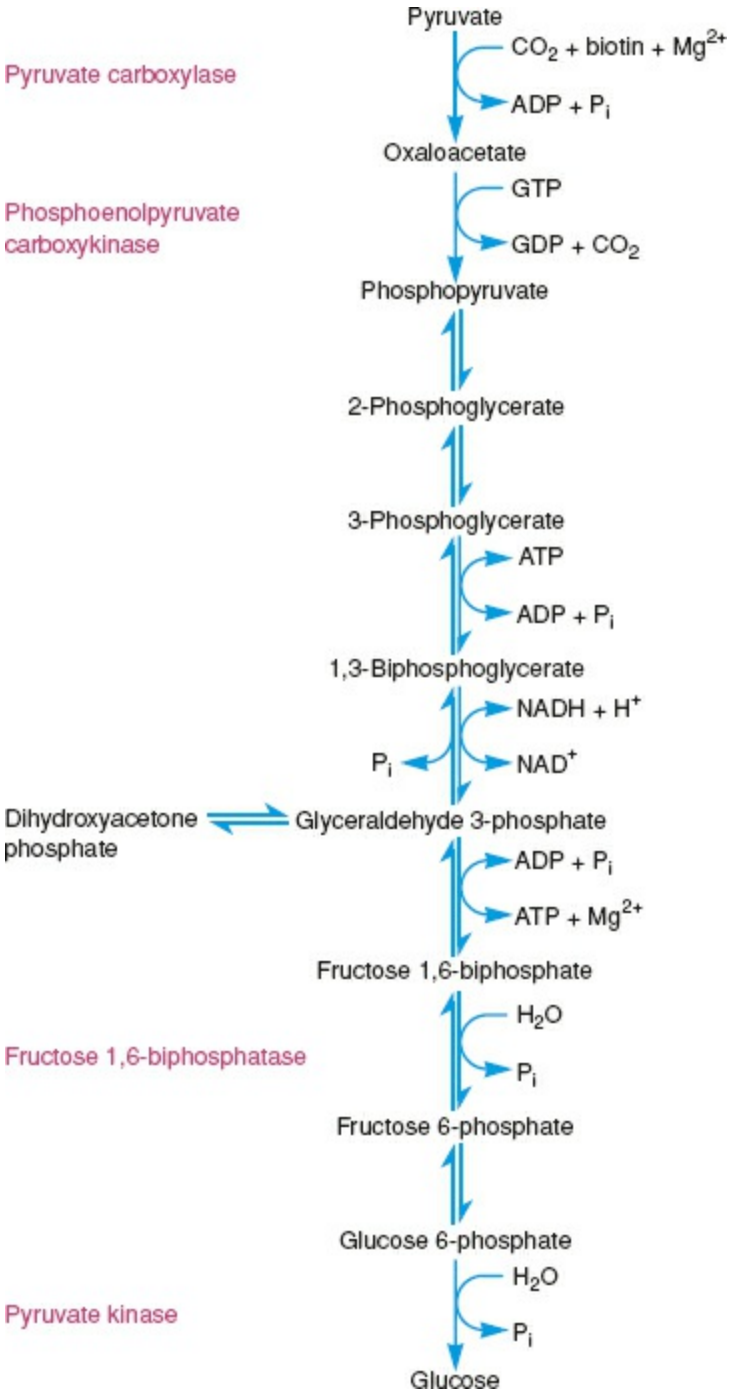

Figure 2-4. The gluconeogenesis pathway. The irreversible nature of the glycolytic pathway means that a different sequence of biosyntheses is required for glucose production. The enzymes in *red* catalyze irreversible reactions that are different from those in glycolysis. In mammals, glucose cannot be synthesized from acetyl coenzyme A, only from cytosolic pyruvate.

Gluconeogenesis is not a simple reversal of the glycolytic pathway. In glycolysis, as noted previously, the conversion of glucose to pyruvate is a one-way reaction. As a result, four separate, functionally irreversible enzyme reactions are required to convert pyruvate into glucose (Fig. 2-5). These enzymes are pyruvate carboxylase, phosphoenolpyruvate carboxykinase, fructose-1,6-bisphosphatase, and glucose-6-phosphatase. Other enzymes are shared with the glycolytic pathway.

About 60% of the naturally occurring amino acids, glycerol, or lactate can also be used as substrates for glucose production. Alanine is the amino acid most easily converted into glucose. Simple deamination allows conversion to pyruvate, which is subsequently converted to glucose. Other amino acids can be converted into three-, four-, or five-carbon sugars and then enter the phosphogluconate pathway (next section). Gluconeogenesis is enhanced by fasting, critical illness, and periods of anaerobic metabolism.

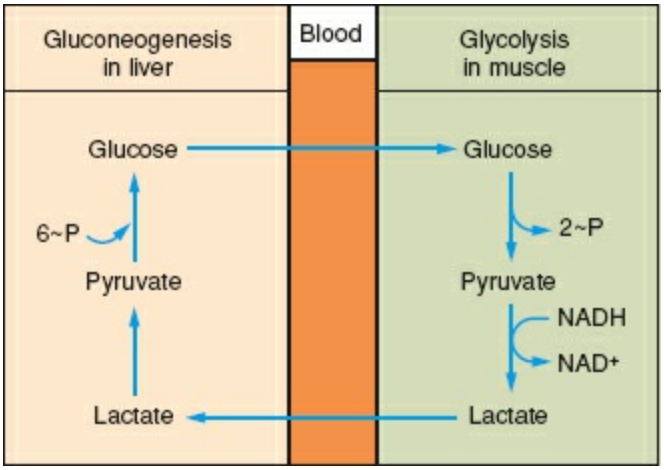

Figure 2-5. The Cori cycle, an elegant mechanism for the hepatic conversion of muscle lactate into new glucose. Pyruvate plays a key role in this process.

Phosphogluconate Pathway

When glucose enters the liver, glycogen is formed until the hepatic glycogen capacity is reached (about 100 g). If excess glucose is still available, the liver converts it to fat by the phosphogluconate pathway (also known as the pentose phosphate pathway) (Fig. 2-6). The cytosolic phosphogluconate pathway can completely oxidize glucose, generating CO_2 and nicotinamide adenine dinucleotide phosphate (NADPH) through what is known as the oxidative phase. Hydrogen atoms released in the phosphogluconate pathway combine with oxidized nicotinamide adenine dinucleotide phosphate ($NADP^+$) to form reduced nicotinamide adenine dinucleotide phosphate ($NADPH - H^+$).[5] The oxidative phase is present only in tissues, such as the adrenal glands and gonads, that require reductive biosyntheses such as steroidogenesis or other forms of lipid synthesis. Essentially, all tissues contain the nonoxidative phase, which is reversible and produces ribose precursors for nucleotide synthesis. In erythrocytes, the phosphogluconate pathway provides reducing equivalents for the production of reduced glutathione by glutathione reductase. Reduced glutathione can remove hydrogen peroxide, which increases the conversion of oxyhemoglobin to methemoglobin and subsequent hemolysis.

LIPID METABOLISM

Lipid Transport

Lipid transport throughout the body is made complicated by the fact that lipids are insoluble in water. To overcome this physicochemical incompatibility, dietary triglycerides are first split into monoglycerides and fatty acids by the action of intestinal lipases. After absorption into small intestinal cells, triacylglycerols are reformed and aggregate into chylomicrons, which then enter the bloodstream by way of lymph. Chylomicrons are removed from the blood by the liver and adipose tissue. The capillary surface of the liver contains large amounts of lipoprotein lipase, which hydrolyzes triglycerides into fatty acids and glycerol. The fatty acids freely diffuse into hepatocytes for further metabolism. Similar to chylomicrons, very low-density lipoproteins (VLDLs) are synthesized by the liver and are the main vehicle for transport of triacylglycerols to extrahepatic tissues. The intestines and liver are the only two tissues capable of secreting lipid particles. In addition to chylomicrons and VLDLs, there are two other major groups of plasma lipoproteins: low-density lipoproteins (LDLs) and high-density lipoproteins (HDLs). LDLs and HDLs contain predominantly cholesterol and phospholipid.

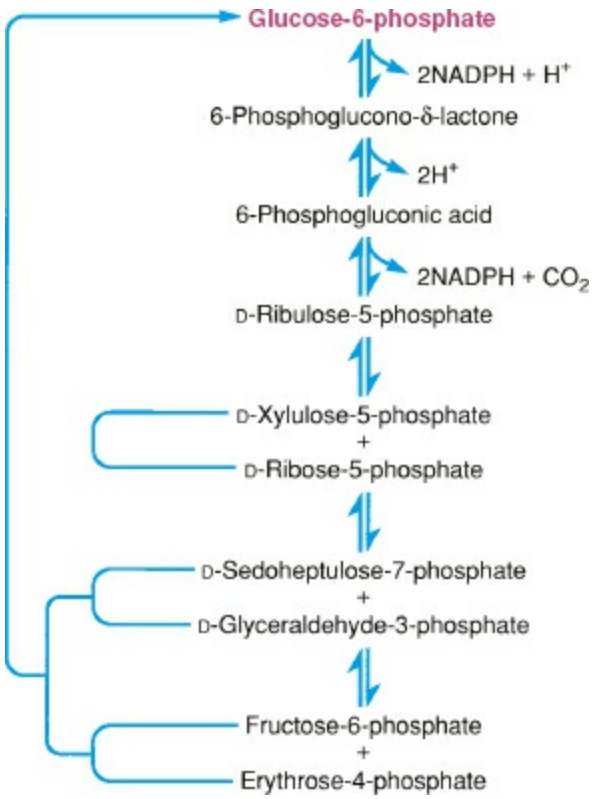

Figure 2-6. The phosphogluconate pathway. One of the major purposes of this pathway is to generate reduced nicotinamide adenine dinucleotide, which can serve as an electron donor and allow the liver to perform reductive biosynthesis. Glucose-6-phosphate, in *red*, plays a central role in carbohydrate metabolism.

The structure of all classes of lipoproteins is similar. There is a core of nonpolar lipids, either triacylglycerols or cholesteryl esters, depending on the particular lipoprotein. This nonpolar core is coated with a surface layer of amphipathic phospholipid or cholesterol

oriented so that the polar ends are in contact with the plasma. A protein component is also present. The A apolipoproteins occur in chylomicrons and HDLs. The B apolipoproteins come in two forms: B-100 is the predominant apolipoprotein of LDLs, whereas the shorter B-48 is located in chylomicrons. The C apolipoproteins can transfer between VLDLs, LDLs, and HDLs. Apolipoproteins D and E also exist. Apolipoproteins have several functions in lipid transport and storage. Some, such as the B apolipoproteins, are an integral part of the lipoprotein structure. Other apolipoproteins are enzyme cofactors, such as C-II for lipoprotein lipase. Lastly, the apolipoproteins act as ligands for cell surface receptors. As an example, both B-100 and E serve as ligands for the LDL receptor.[6]

Plasma variations in LDL cholesterol, HDL cholesterol, and triglycerides affect risk for atherosclerotic cardiovascular disease. As dyslipidemias are being identified and studied, new therapeutic approaches are needed. A convergence of human genetics and functional biology has led to recent advances in the study of lipoprotein metabolism. Genome-wide association studies have identified about 100 genes associated with plasma lipid phenotypes – many of which were not previously known to be associated with lipids. These genes are now being functionally validated through human genetic analysis such as deep targeted resequencing of kindreds with Mendelian lipid abnormalities or gene manipulation (over- or underexpression) in cultured cells and animal models.[7]

FATTY ACID METABOLISM

Most human fatty acids in plasma are long-chain acids (C-16 to C-20). Because long-chain fatty acids are not readily absorbed by the intestinal mucosa, they must first be incorporated into chylomicrons. In contrast, short-chain and medium-chain fatty acids are absorbed directly into the portal circulation and are avidly taken up by the liver. Free fatty acids in the circulation are noncovalently bound to albumin and are transferred to the hepatocyte cytosol by way of fatty acid–binding proteins. Fatty acid-CoA esters are synthesized in the cytosol after hepatic uptake of fatty acids. These fatty acid-CoA esters can be converted into triglyceride, transported into mitochondria for the production of acetyl CoA and reducing equivalents, or stored in the liver as triglycerides. The rate-limiting step in the synthesis of triglyceride is the conversion of acetyl CoA to malonyl CoA. Malonyl CoA, in turn, inhibits the mitochondrial uptake of fatty acid-CoA ester, favoring triglyceride synthesis. The liver also contains dehydrogenases that can unsaturate essential dietary fatty acids. Structural elements of all tissues contain significant amounts of unsaturated fats, and the liver is responsible for the production of these unsaturated fatty acids. As another example, dietary linoleic acid is elongated and dehydrogenated to the prostaglandin precursor arachidonic acid.

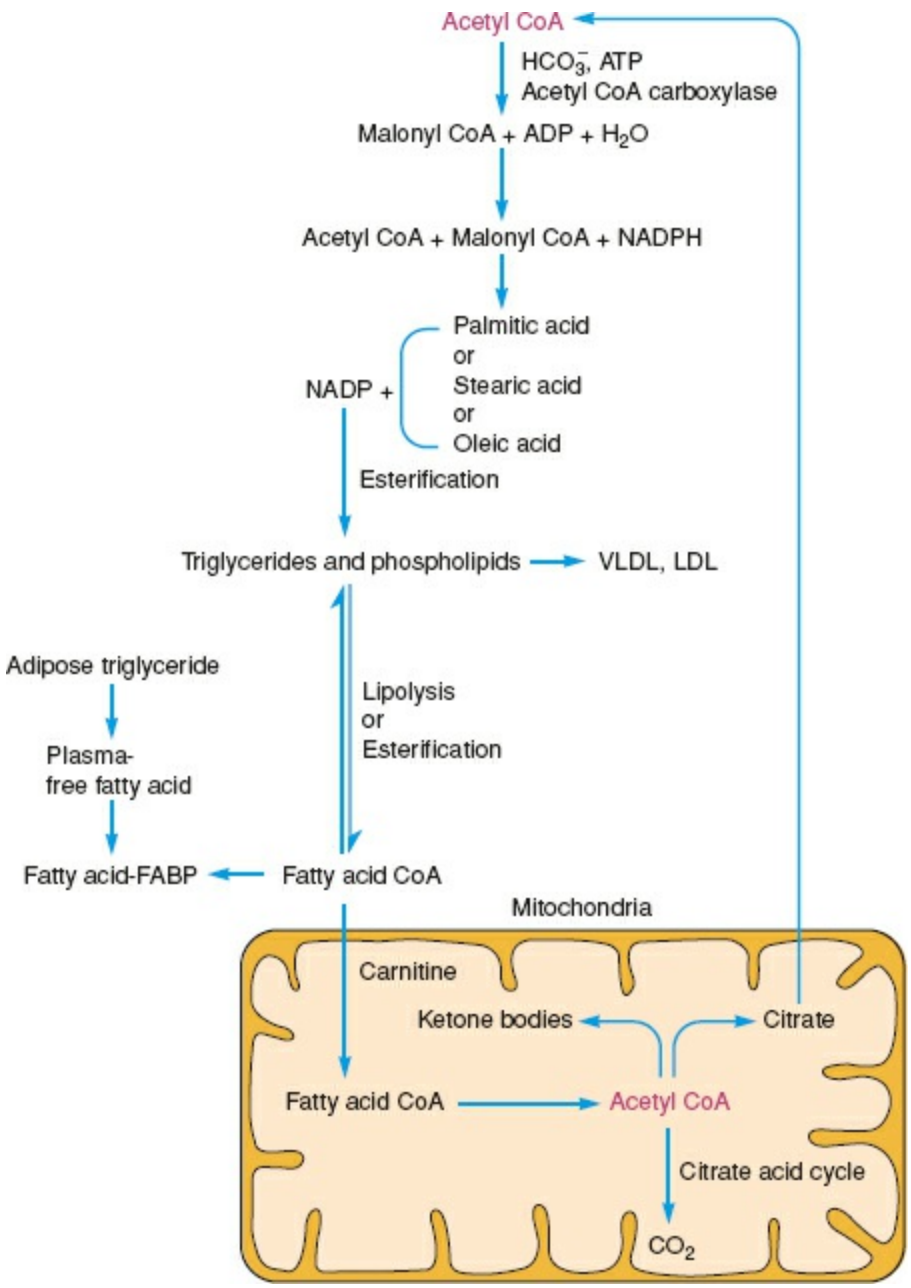

Figure 2-7. Diagram of hepatic fatty acid metabolism. Both dietary and newly synthesized fatty acids are esterified and subsequently degraded in the mitochondria for energy, first as reducing equivalents, then adenosine triphosphate via the electron transport chain. Acetyl CoA, in *red*, plays a central role in lipid metabolism.

3 Free fatty acids are a direct source of energy for cardiac and skeletal muscles and under basal conditions, most free fatty acids are catabolized for energy. Under conditions of adipocyte lipolysis, the liver can take up and metabolize fatty acids. Although fatty acid synthesis occurs in the cytosol, fatty acid oxidation occurs in the mitochondria. Fatty acid-CoA esters bind carnitine, a carrier molecule, and in the absence of cytosolic malonyl CoA, they enter the mitochondria, where they undergo beta-oxidation to acetyl CoA and reducing equivalents (Fig. 2-7). Acetyl CoA can then take one of the following routes: (a) enter the tricarboxylic acid cycle and be degraded to carbon dioxide, (b) be converted to citrate for fatty acid synthesis, or (c) be converted into 3-hydroxy-3-methylglutaryl CoA (HMG-CoA), a precursor of cholesterol and ketone bodies. The mitochondrial hydrolysis of fatty acids is a source of large quantities of ATP. The conversion of stearic acid to carbon dioxide and water, for instance, generates 136 molecules of ATP and demonstrates

the highly efficient storage of energy as fat. By a process called beta-oxidation, acetyl-CoA molecules are cleaved from fatty acids. The acetyl CoA is then metabolized through the citric acid cycle under normal circumstances.

In times of significant lipolysis – starvation, uncontrolled diabetes, or other conditions of triglyceride mobilization from adipocyte stores – the predominant ketone bodies 3-hydroxybutyrate and acetoacetate are formed in hepatic mitochondria from free fatty acids and are a source of energy for extrahepatic tissues. Ketogenesis is regulated primarily by the rate of mobilization of free fatty acids. Once in the liver mitochondria, the relative proportion of acyl CoA destined to undergo beta-oxidation is limited by the activity of an enzyme, carnitine palmitoyltransferase-1. Lastly, there are mechanisms that keep the levels of acetyl CoA entering the citric acid cycle constant, so that only at high mitochondrial levels will acetyl CoA be converted to ketone bodies. Even the brain, in times of starvation, can use ketone bodies for half of its energy requirements. At some point, however, the ability of liver to perform beta-oxidation may be inadequate. Under such circumstances, hepatic storage of triglyceride or fatty infiltration of the liver can be significant, leading to the development of nonalcoholic steatohepatitis. Triglyceride storage by itself does not appear to be a cause of hepatic fibrosis, but fatty infiltration may be a marker for the derangement of normal processes by alcohol or drug toxicity, diabetes, or long-term total parenteral nutrition. A specific type of microvesicular fatty accumulation is also seen in a variety of diseases, such as Reye syndrome, morbid obesity, and acute fatty liver of pregnancy.

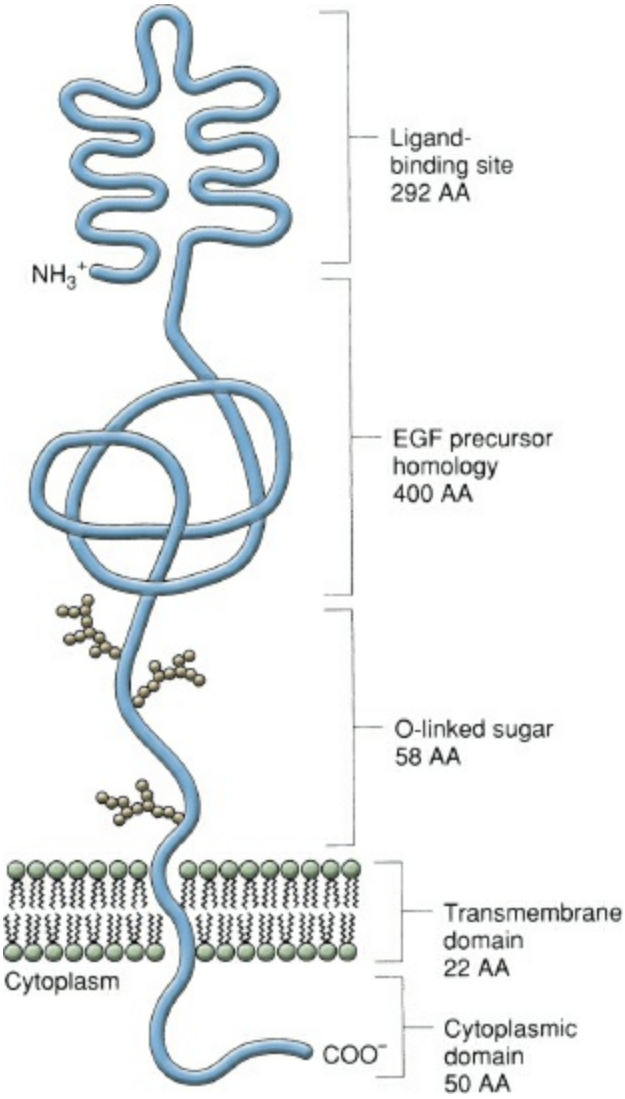

Figure 2-8. The LDL receptor, an example of a transmembrane receptor that participates in receptor-mediated endocytosis. The LDL receptor specifically binds lipoproteins that contain apolipoprotein B-100 or E. Once internalized, the lipoproteins are degraded. AA, amino acids; EGF, epidermal growth factor.

As noted above, fatty acids are critical elements of all mammalian cells; as energy substrate, in cellular structure, and for intracellular signaling. Evolutionarily, storage of excess fat in adipose tissue mitigated starvation. But in most modern societies the ready availability of calorie-dense foods has led to an epidemic of obesity as is discussed in detail in other chapters. In terms of intermediary metabolism, excess dietary fatty acids are now known to cause insulin resistance in muscle through intramyocellular triglyceride content leading to type II diabetes. This effect is likely due to intracellular perturbations in active lipid metabolites such as diacylglycerols or ceramides. Other studies have documented mitochondrial abnormalities possibly through interference with serine kinases.[8]

CHOLESTEROL METABOLISM

Cholesterol is an important regulator of membrane fluidity and is a substrate for bile acid and steroid hormone synthesis. Cholesterol may be available by dietary intake or by de novo synthesis. In mammals, mostly new cholesterol is synthesized in the liver from its precursor, acetyl CoA. Dietary cholesterol intake can suppress endogenous synthesis by inhibiting the rate-limiting enzyme in the cholesterol biosynthetic pathway, HMG-CoA reductase. A competitive antagonist, lovastatin, can also block HMG-CoA reductase and effectively lower plasma cholesterol by blocking cholesterol synthesis, stimulating LDL receptor synthesis, and allowing an increased hepatic uptake and metabolism of cholesterol-rich LDL lipoproteins. The structure of the LDL receptor is known and serves as a model for the structure and function of other cell membrane receptors (Fig. 2-8).

Cholesterol is lipophilic and hydrophobic, and most plasma cholesterol is in lipoproteins esterified with oleic or palmitic acid. The liver can process cholesterol esters from all classes of lipoproteins. Hepatocytes can also take up chylomicron remnants containing dietary cholesterol esters. Abnormally elevated levels of cholesterol in VLDLs or LDLs are associated with atherosclerosis, whereas high HDL levels are protective. Newly synthesized hepatic cholesterol is also used to synthesize bile acids for further intestinal absorption of dietary fats. A large proportion of the bile acids secreted by the liver into bile are returned to the liver via the enterohepatic circulation (Fig. 2-9).

Phospholipids

The three major classes of phospholipids synthesized by the liver are lecithins, cephalins, and sphingomyelins. Although most cells in the body are capable of some phospholipid synthesis, the liver produces 90%. Phospholipid formation is controlled by the overall rate of fat metabolism and by the availability of choline and inositol. The main role of phospholipids of all types is to form plasma and organelle membranes. The amphiphilic nature of phospholipids makes them essential for reducing surface tension between membranes and surrounding fluids. Phosphatidylcholine, one of the lecithins, is the major biliary phospholipid and is important in promoting the secretion of free cholesterol into bile. Thromboplastin, one of the cephalins, is needed to initiate the clotting cascade. The sphingomyelins are necessary for the formation of the myelin nerve sheath.

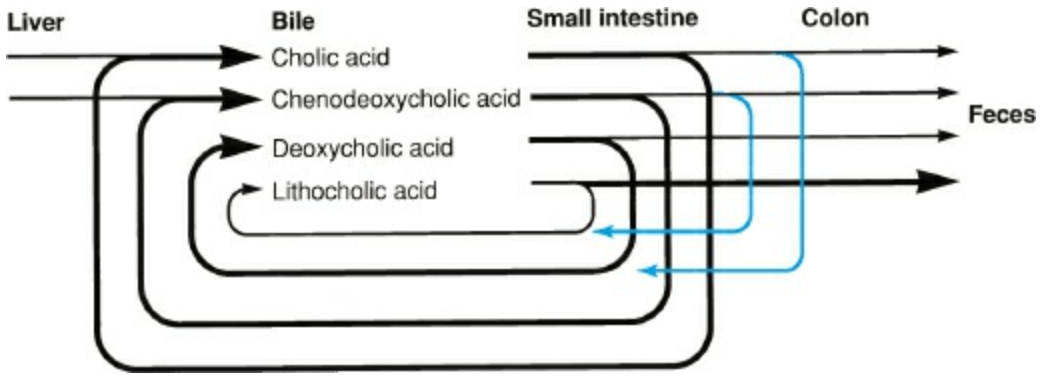

Figure 2-9. The enterohepatic circulation of bile acids. The primary bile acids, cholic acid, and chenodeoxycholic acid, are synthesized in the liver from cholesterol. Deoxycholic acid and lithocholic acid are formed in the colon (*blue lines*) during bacterial degradation of the primary bile acids. All four bile acids are conjugated with glycine or taurine in the liver. Most of the lithocholic acid is also sulfated, which decreases reabsorption and increases fecal excretion. Bile acids are absorbed passively in the epithelium of the small and large intestine and actively in the distal ileum.

PROTEIN METABOLISM

Formation and Catabolism of Plasma Proteins

4 Hepatic protein synthesis, when excess amino acids are available, includes albumin, fibrinogen, and apolipoproteins and can reach 50 g/day. Of the total hepatic protein synthesized, 75% is destined for export in plasma. Most newly synthesized proteins are not stored in the liver, and the rate of protein synthesis is primarily determined by the intracellular levels of amino acids. The tertiary structure of many proteins undergoes posttranslational modification after they have been synthesized in the liver's rough endoplasmic reticulum (ER). Glycosylation, or the addition of carbohydrate moieties, occurs in the smooth ER. Sialation, or the addition of sialic acid, occurs in the Golgi. Glycosylation is important in allowing some proteins to bind with specific receptors for subsequent hepatic uptake and processing. Removal of sialic acid residues, or desialation, from the terminal galactose molecules of glycoproteins allows them to bind to the asialoglycoprotein (ASGP) receptor in the liver and undergo degradation. Desialation, therefore, is important in the clearance of senescent proteins from the plasma.

Intracellular proteases hydrolyze proteins into peptides, and the peptides are in turn hydrolyzed by peptidases. Ultimately, free amino acids are generated. Unlike carbohydrate and lipids, excess amino acids are degraded if they are not immediately reincorporated into new proteins. Protein degradation occurs primarily by one of two routes. ASGPs are internalized into lysosomes via receptor-mediated endocytosis. The lysosomal enzymes do not require ATP and are nonselective in their activities; more than 20 known hydrolytic enzymes are present in lysosomes. A second pathway involves the covalent attachment of ubiquitin, named for the fact that it exists in all mammalian cells, targeting proteins for destruction. This pathway is ATP dependent and generally is used for proteins with shorter half-lives.[9]

Amino Acid Synthesis

Essentially, all the end products of dietary protein digestion are amino acids, which are absorbed by the enterocytes into the portal circulation in an ionized state. Liver amino acid uptake occurs by one of several active transport mechanisms. Amino acids are not stored in the liver but are rapidly used in the production of plasma proteins, purines, heme proteins, and hormones. Under certain conditions, the amine group is removed from amino acids, and the carbon chain is used for carbohydrate, lipid, or nonessential amino acid synthesis.[10]

Ten nutritionally essential amino acids must be obtained from dietary intake (Table 2-2). However, human tissues contain transferases, which convert the α-keto acids of leucine, valine, and isoleucine so that the corresponding α-keto acids can be used as dietary supplements. The remaining nutritionally nonessential amino acids can be synthesized in one to three enzyme-catalyzed reactions. Hydroxyproline and hydroxylysine do not have a corresponding tRNA and arise by posttranslational modification of proline or lysine by mixed function oxidases. Glutamate, glutamine, and proline are derived from the citric acid cycle intermediate α-ketoglutarate. Aspartate and asparagine are synthesized from oxaloacetate. Serine and glycine are synthesized from the glycolysis intermediate 3-phosphoglycerate. Cysteine and tyrosine are formed from essential amino acids (methionine and phenylalanine, respectively).[11]

Table 2-1 Amino Acids Required by Adult Humans

Nutritionally Essential	Nutritionally Nonessential	
	Amino Acid	Precursor
Arginine	Alanine	Pyruvate
Histidine	Asparagine	Oxaloacetate
Isoleucine	Aspartate	Oxaloacetate
Leucine	Cysteine	Methionine
Lysine	Glutamate	α-Ketoglutarate
Methionine	Glutamine	α-Ketoglutarate
Phenylalanine	Glycine	3-Phosphoglycerate
Threonine	Hydroxyproline	α-Ketoglutarate
Tryptophan	Hydroxylysine	Lysine
Valine	Proline	α-Ketoglutarate
	Serine	3-Phosphoglycerate
	Tyrosine	Phenylalanine

Catabolism of Amino Acid Nitrogen

Ammonia, derived largely from the deamination of amino acids, is toxic to all mammalian cells. The ammonia formed as a result of the deamination of amino acids is detoxified by one of two routes.[12] The most important pathway involves the conversion of ammonia to urea by enzymes of the Krebs–Henseleit, or urea cycle, which occurs only in the liver (Fig. 2-10). A second route of ammonia metabolism involves synthesis of L-glutamine from ammonia and glutamate by renal glutamine synthetase.

CELLULAR ENERGY GENERATION

Overview and Stage I

5 The citric acid cycle includes a series of mitochondrial enzymes that transform acetyl CoA – itself derived from pyruvate or fatty acyl CoA – into water, carbon dioxide, and hydrogen-reducing equivalents. Each molecule of acetyl CoA that enters the citric acid cycle yields 12 molecules of ATP. The fundamental mechanism by which mammalian cells generate energy is the aerobic conversion of sugars and fatty acids into ATP. There are four stages with stage I – glycolysis – (see glycolysis above) beginning in the cytosol, converting glucose into two molecules of pyruvate. Also, cytosolic fatty acids are converted to fatty acyl CoA. Pyruvate and fatty acyl CoA are transported to the mitochondrial matrix and converted to acetyl CoA; generating the electron carriers NADH or $FADH_2$ as well as CO_2. In stage II, mitochondrial acetyl CoA enters the citric acid cycle further generating NADH, $FADH_2$, additional CO_2, and GTP. In stage III, oxygen is reduced to water via the electron transport chain using previously generated molecules of NADH and $FADH_2$ as electron donors. The electron transport chain causes hydrogen ions to move from the mitochondrial matrix to the intermembrane space generating a proton motive force. Lastly, in stage IV, ATP synthase uses energy generated by the proton motive force to generate large amounts of ATP.[13]

Stage II: The Citric Acid Cycle: Integration of Metabolic Pathways and Oxidation of Acetyl CoA

One major function of the citric acid cycle (also known as the Krebs cycle or the tricarboxylic acid cycle) is to act as a common pathway for the oxidation of carbohydrate, lipid, and protein and generate energy in the form of ATP. Conversely, the citric acid cycle is important in gluconeogenesis, lipogenesis, and amino acid metabolism. In the fed state, a large proportion of ingested energy from foodstuffs is converted to glycogen or fat. The metabolism of sugars, fats, and proteins, then, allows adequate fuels for all tissue types under conditions from fed to fasting to starvation. The body accomplishes production of fuel substrates for organs and regulates intestinally absorbed nutrients for tissue consumption or storage by integrating three key metabolites: G6P, pyruvate, and acetyl CoA (Fig. 2-11). Each of these three simple chemical molecules can be extensively modified to allow a large number of metabolites.

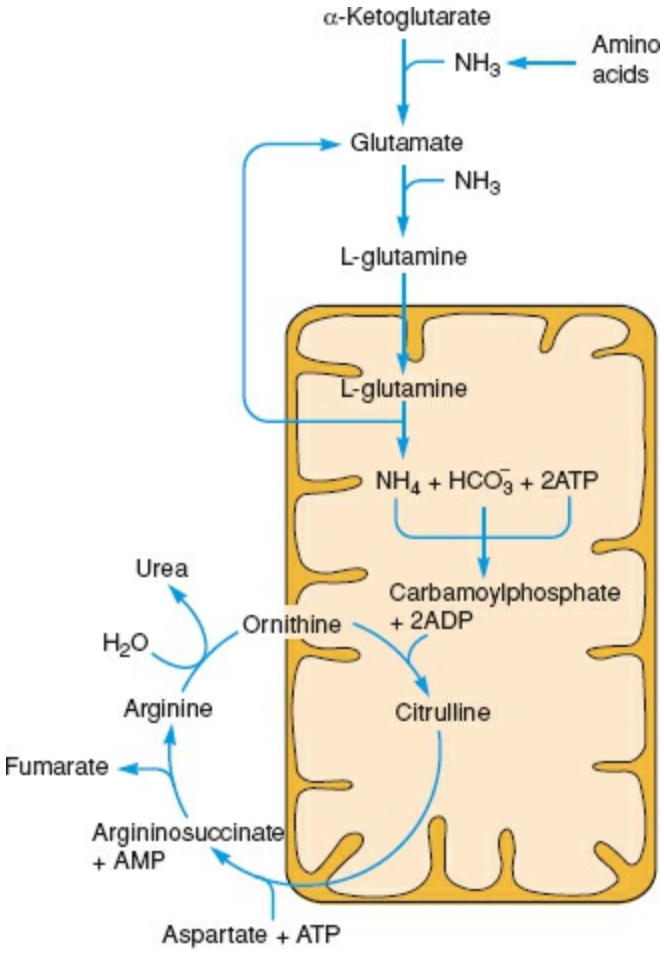

Figure 2-10. The urea cycle. Ammonia entering the urea cycle is derived from protein and amino acid degradation in tissues (endogenous) and the colonic lumen (exogenous).

G6P can be stored as glycogen or converted into glucose, pyruvate, or ribose-5-phosphate (a nucleotide precursor). Pyruvate can be converted into lactate, alanine (and other amino acids), and acetyl CoA, or it can enter the tricarboxylic acid cycle by conversion to oxaloacetate. Acetyl CoA is converted to HMG-CoA (a cholesterol and ketone body precursor) or citrate (for fatty acid and triglyceride synthesis), or it is