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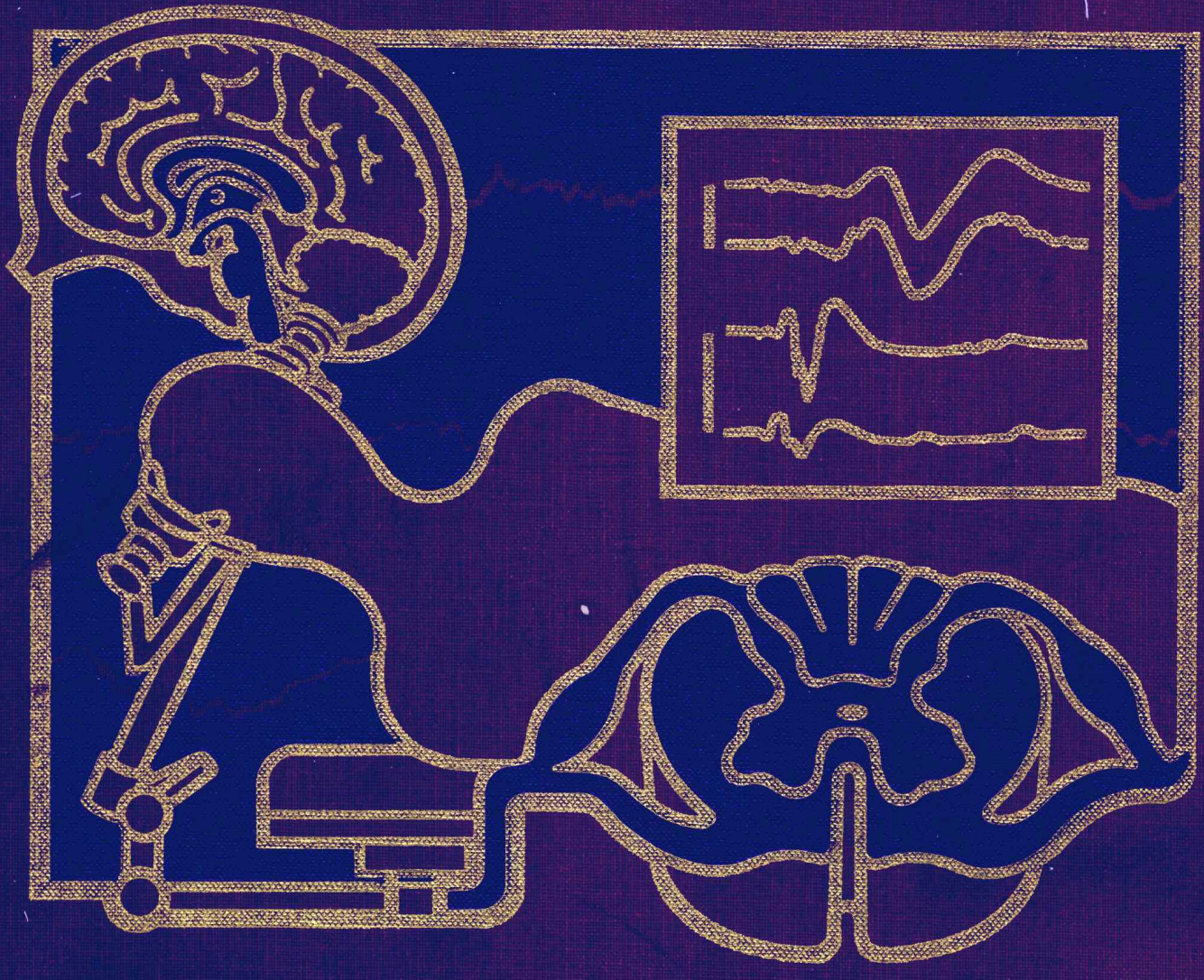
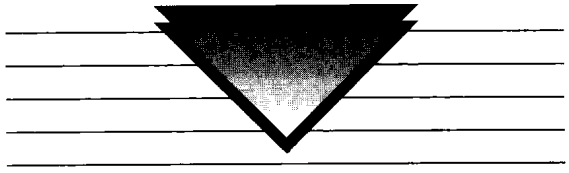
Anesthesia and Neurosurgery



JAMES E. COTTRELL • DAVID S. SMITH

Anesthesia and Neurosurgery



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THIRD EDITION

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Executive Editor: Susan M. Gay
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Cover Design: Renée Duenow

THIRD EDITION

Printed in the United States of America
Composition by the Clarinda Company
Printing/binding by Walsworth Publishing Company

Mosby–Year Book, Inc.
11830 Westline Industrial Drive
St. Louis, MO 63146

Library of Congress Cataloging in Publication Data

Anesthesia and neurosurgery / [edited by] James E. Cottrell, David S. Smith.—3rd ed.
p. cm.
Includes bibliographical references and index.
ISBN 0-8016-6573-6
1. Nervous system—Surgery. 2. Anesthesia in neurology.
I. Cottrell, James E. II. Smith, David S. (David Stuart), 1946-
[DNLM: 1. Anesthesia. 2. Nervous System—surgery. WO 200 A578 1994]
RD593.A5 1994
617.9'6748—dc20
DNLM/DLC
for Library of Congress 94-3103
CIP

95 96 97 98 / 9 8 7 6 5 4 3 2

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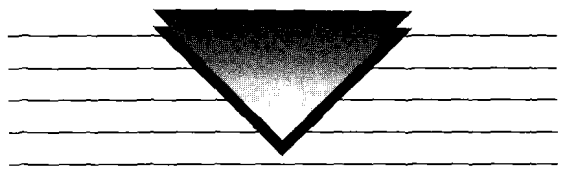

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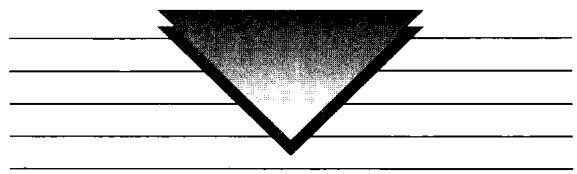
Foreword to the Third Edition



Since publication of the second edition of *Anesthesia and Neurosurgery*, the field of anesthesiology has been significantly enhanced by advances in technology, the manufacture and clinical validation of new equipment, and the development of new pharmacological agents. In combination with advances in electrophysiologic monitoring, these tools have expanded the research base upon which neuroanesthesiology is built. That enriched foundation has, in turn, resulted in a greater understanding of neuropharmacology and neuropathology.

Advances in neuroanesthesiology have also enabled neurosurgeons to expand their own field while anesthesiologists provide more appropriate perioperative management, superior postoperative care, and improved management of acute and chronic pain. Indeed, as our expanding abilities become applicable to a larger and more diversified patient population, neuroanesthesiologists are now faced with new challenges in providing assistance to colleagues in radiology, neonatology, critical care, and other specialities.

Subspecialities emerge as a result of an expansion of knowledge. The Oxford English Dictionary defines a "specialist" as an "authority who particularly or exclusively studies a single branch of his profession or subject." The editors of this volume have certainly devoted their lives to becoming masters in the subspecialty of neuroanesthesiology. Jim Cottrell was a founder and subsequent President of the Society of Neurosurgical Anesthesia and Critical Care. In addition, he initiated the *Journal of Neurosurgical Anesthesiology*, recognizing the need to bring the subspecialty's literature, previously fragmented across many journals, under one cover. David Smith, the new co-editor of this volume, has worked for many years in one of the leading research centers in neuroanesthesiology and is also a past President of the Society of Neurosurgical Anesthesia and Critical Care.

Outcome is the most important attribute of any anesthetic intervention of critical care experience. Brain damage can cause severe emotional and financial consequences—consequences which we can most fully appreciate when the damage affects someone close to us—a colleague, a friend, or, in particular, a member of our own family. I am certain that this third edition of *Anesthesia and Neurosurgery* will be an indispensable source of up-to-date knowledge and practical clinical advice for all anesthesiologists who strive to provide neurosurgical patients with the most appropriate care and the best possible outcome.

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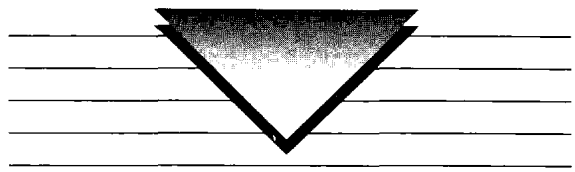
Preface



The nineties have been declared "The Decade of the Brain" and the third edition of *Anesthesia and Neurosurgery* will serve this decade well. When a subspecialty advances as rapidly as neuroanesthesiology, most material that was current just eight years ago must be left behind. Accordingly, with a preponderance of new chapters, new authors, and even a new co-editor, this edition of a once familiar text is essentially a new book with a 14-year legacy. That legacy has paralleled the development of the field itself, and we owe a debt of gratitude to Dr. Herman Turndorf for the contributions he made to previous editions of this text and to the foundations on which modern neuroanesthesiology has been built.

Putting first things first, Part I covers relevant biochemistry and physiology, including brain metabolism, cerebral and spinal cord blood flow, metabolically induced brain injury, cerebrospinal fluid, intracranial pressure monitoring, the blood-brain barrier and cerebral edema, and the effects of anesthetics on ICP and CBF. Part II reviews basic aspects of neuroradiology and neurophysiologic brain monitoring.

Part III focuses on the perioperative period, including fluid management; care of the acutely unstable patient; surgical and anesthetic management of supratentorial masses, the posterior fossa, aneurysms, and arteriovenous malformations; interventional neuroradiology; induced hypotension; blood-brain barrier disruption; occlusive cerebrovascular disease; seizure surgery; pediatric neurosurgery; neurologic diseases of the spine and spinal cord; and neuroendocrine disease.

Finally, Part IV takes us to the postoperative period and intensive care management of the neurosurgical patient. It covers management of severe head injury, spinal cord injury, and includes an innovative discussion of ethical considerations.

The new format of *Anesthesia and Neurosurgery* provides quick orientation, focused reading, and an index that facilitates comprehensive access to specific subjects. There is liberal use of color for emphasis. The international group of authors has been chosen for their ability to communicate and for their expertise. They have generously lived up to their reputations, and we, the editors, are grateful for their contribution.

Everyone involved hopes this book will serve its readers by helping them to better serve their patients.

JAMES E. COTTRELL
DAVID S. SMITH

ACKNOWLEDGMENTS

The editors would like to acknowledge the efforts of many individuals who, in addition to the authors of each chapter, spent hours in helping prepare this book for publication. These include Iris Karafin who was central to manuscript revision; Kathleen Grugan, R.N., M.S.N., David Bowden, B.A., and Cara Grugan who spent many hours reading chapters for flow and content; and Anne Miniadis, Dr. Cottrell's administrative assistant, and several associates, including Cynthia Cohen, Ph.D., J.D., Theodore Cheek, M.D., Ira Kass, Ph.D., John Hartung, Ph.D., and Audrée Bendo, M.D., who reviewed various chapters. The editors would also like to thank Susan Gay of Mosby–Year Book for her guidance and patience during the production of this text.

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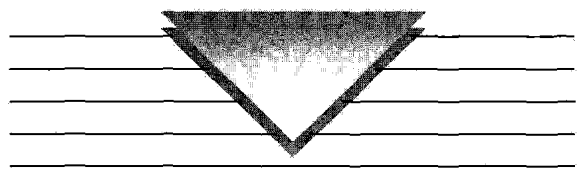

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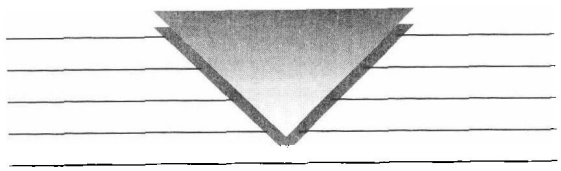
Brain Metabolism



WILLIAM FITCH

The brain is a *converter* of energy: It converts substrates supplied as metabolic fuel (mainly D-glucose and oxygen) into the usable forms of energy with which it supports and regulates its many synaptic connections, voltage-dependent and agonist-operated ion channels, and the synthesis, transportation, and packaging of neurotransmitters. The brain is also a substantial *consumer* of energy. In humans, the central nervous system receives about 15% of the resting cardiac output (750 ml/min) and consumes about 20% (170 μmol/100 g/min) of the oxygen required by the body at rest (on average, the weight of the brain is only 2% to 3% of the total body weight). Moreover, one quarter (31 μmol/100 g/min) of the glucose consumed by the body is used by the brain. Fortunately, the brain is also a *conserver* of energy. Under physiologic conditions, the expenditure of energy is controlled by the activity of the cells: The consumption of fuel is related to the work done and not the reverse.

This chapter describes how the brain obtains energy from its supply of metabolic substrates, details why the brain consumes energy, and discusses briefly the clinical importance of its ability to conserve energy. In addition, the chapter considers those means by which the metabolic activity of the brain may be assessed, either relatively or absolutely, and their clinical applicability.

THE BRAIN AS A CONVERTER OF ENERGY

The brain's energy requirement is substantial; paradoxically, its store of energy-generating substrates (glycogen, glucose, oxygen) is small—so small, in fact, that at normal rates of ATP production the available stores of glycogen would be exhausted in less than 3 minutes. Thus the normal functioning of the central nervous system depends on the continuous provision of appropriate energy substrates and the adequate removal of the waste products of metabolism.

The requirement of the central nervous system for metabolic fuel is provided almost exclusively, at least under physiologic conditions, by the glycogenolysis of the glycogen stored in the liver (mainly), muscle, and, to a limited extent, other organs (per unit mass, muscle stores 10 times as much glycogen and liver 100 times as much as the brain),

and the complete oxidation of the released glucose to carbon dioxide and water. In the absence of ketosis (such as may occur in association with starvation or diabetes), the adult brain uses glucose as its sole metabolic substrate. Although glucose may be formed from noncarbohydrate sources (certain amino acids, the glycerol portion of fat molecules), gluconeogenesis does not contribute much to the brain's energy supply. With starvation (perhaps also during the fast prior to anesthesia), gluconeogenesis—a process requiring the expenditure of significant quantities of energy in its own right[20]—is essential because the ability of the brain to metabolize ketone bodies depends on a basal input of glucose with which to regenerate certain of the intermediary substrates required by the citric acid cycle.[43] Under certain circumstances, the energy released by the oxidation of ketone bodies by the brain is important, such as under physiologic conditions in the neonate and during starvation in the adult. It has been recognized for some time that, with prolonged starvation, ketone bodies, acetoacetate, and beta-hydroxybuterate will replace glucose as the predominant metabolic substrate in the brain. More recent studies have shown an increase in the uptake of ketones by the brain (in proportion to their concentration in blood) in *healthy* individuals who have fasted for as little as 12 to 16 hours. However, even when ketone bodies are the predominant source of metabolic fuel, the brain cannot tolerate hypoglycemia; a supply of glucose, albeit small, is necessary.

Glucose is transported via facilitated diffusion from the blood into the brain by membrane-based carrier mechanisms specific for D-glucose, which exhibit the properties of saturability and competition.[22] At rest, the brain extracts from the blood around 10% of the glucose delivered to it. Obviously, there is some reserve, and more will be extracted if the blood flow decreases. However, because the concentration of glucose in the brain is lower than that in the blood, there is no "safety device" with which the brain can supplement its supply in the presence of systemic hypoglycemia.[22] The properties of the intact blood-brain barrier (as well as those of the membrane-based transporters) restrict the substrates used by the brain to the few mentioned previously. However, when blood-brain barrier function is absent or impaired, compounds such as various intermediaries of the citric acid cycle and dicarboxylic acids may be able to enter brain tissue and be metabolized.[3]

The oxidation of glucose occurs in every cell in the body with the exception of red blood cells, which lack mitochondria, and provides the cell's major source of energy. It occurs in three successive stages: glycolysis, the citric acid cycle, and the electron transport chain (Fig. 1-1).

Glycolysis is the term given to a series of 10 chemical reactions that occur in the cytoplasm of the cell and convert the six-carbon molecule of glucose into two three-carbon molecules of pyruvic acid (Fig. 1-2). Because two molecules of adenosine triphosphate (ATP) are required to initiate the glycolytic reactions and four molecules of ATP are generated to complete the process, there is a net gain of two molecules of ATP for each molecule of glucose oxidized (Table 1-1). The fate of the pyruvic acid depends on the availability of oxygen. Under anaerobic conditions, the pyruvic acid is reduced by the addition of two hydrogen atoms to form lactic acid. This may be transported back to the liver, where it is reconverted to pyruvic acid, or it may remain in the cell until aerobic conditions are restored.

In the presence of adequate amounts of oxygen, the complete oxidation of glucose continues in the mitochondria, where, in a cyclic series of reactions, the pyruvic acid (now as acetyl co-enzyme A) is oxidized to form carbon dioxide

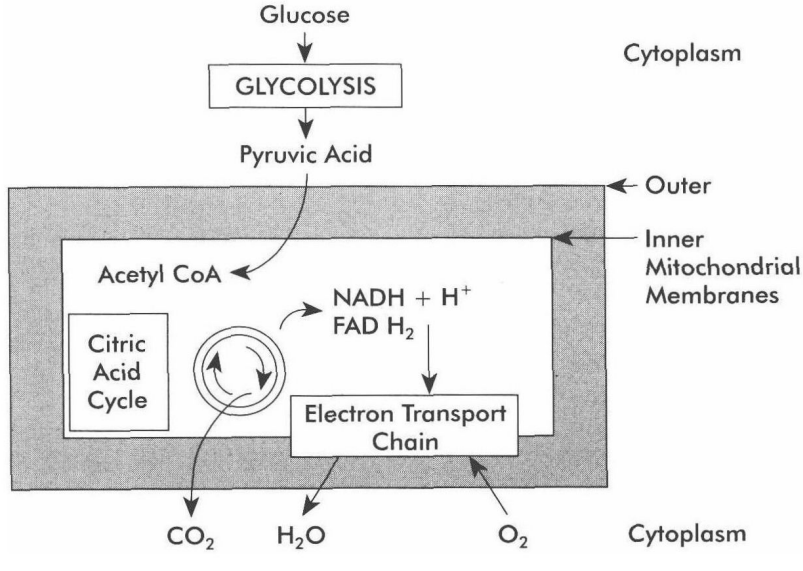


FIG. 1-1 Schematic representation of complete oxidation of glucose.

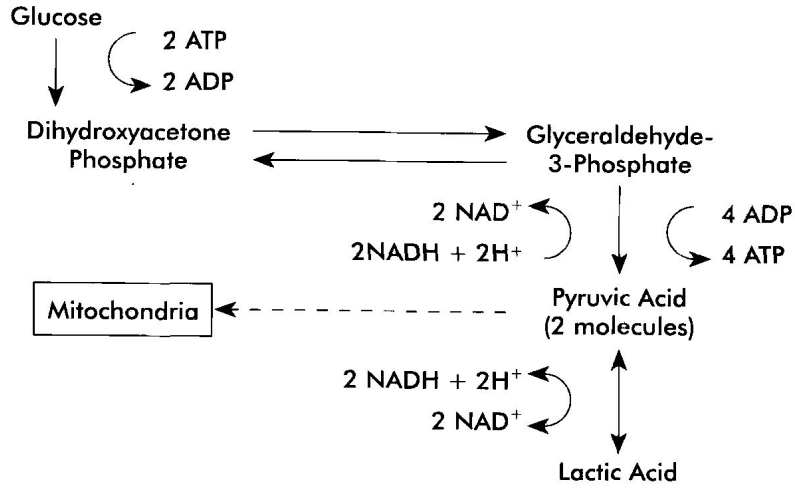


FIG. 1-2 Simplified version of biochemical reactions involved in glycolysis. *(Modified from Siesjo BK*: Brain energy metabolism, *New York, 1978, Wiley.*)

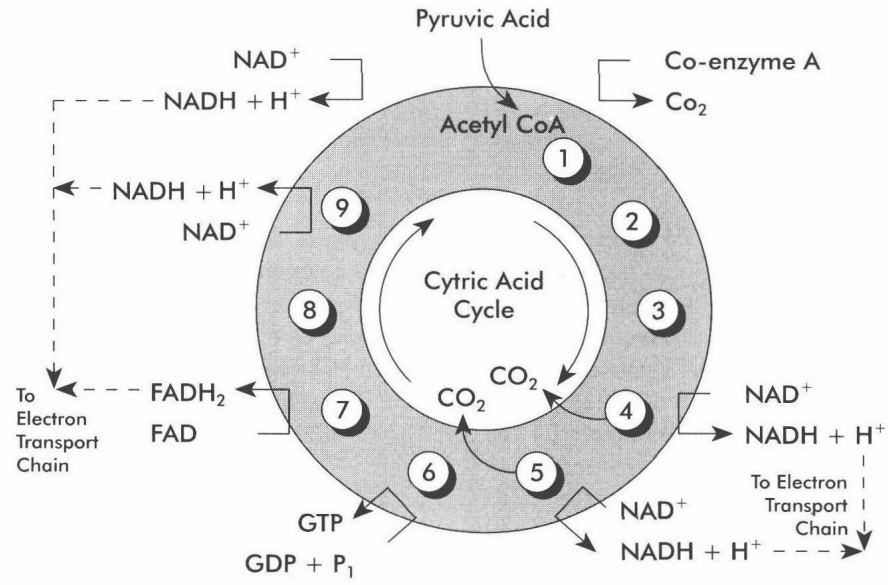


FIG. 1-3 Simplified version of biochemical reactions involved in the citric acid cycle. *(Modified from Siesjo BK*: Brain energy metabolism, *New York, 1978, Wiley.*)

TABLE 1-1
Summary of ATP Production (Aerobic Metabolism) from One Molecule of Glucose

Source	Yield of ATP
Glycolysis	
Oxidation of glucose to pyruvic acid	2
Krebs cycle	
Oxidation of succinyl CoA to succinic acid	2 (GTP)
Electron transport chain	
1. 2 Nicotinamide adenine dinucleotide (NADH) + 2 H^+ (glycolysis)	6
2. 2 NADH + 2 H^+ (acetyl CoA)	6
3. 6 NADH + 6 H^+ (Krebs cycle)	18
4. 2 Flavin adenine dinucleotide ($FADH_2$)	4
Total	38

and water. The citric acid (Krebs) cycle is a series of biochemical reactions in which the large amount of potential energy, stored in the intermediate substances derived from the pyruvic acid, is released in a stepwise manner (Fig. 1-3). A series of oxidations (pyruvic acid derivatives) and reductions (coenzymes) transfers the potential energy, in the form of electrons, to a number of coenzymes. The net result of the citric acid cycle is that for every two molecules of acetyl CoA that enter the cycle there is the liberation of four molecules of carbon dioxide, which are excreted via the lungs, the production of reduced coenzymes (six nicotinamide adenine dinucleotide (NADH) + $6H^+$ and two flavin adenine dinucleotide ($FADH_2$)), which contain stored energy, and the generation of two molecules of GTP,

a high-energy compound that is used to produce ATP. The reduced coenzymes (NADH, H^+, and $FADH_2$) are the most important end-products because they contain most of the energy stored originally in the glucose and subsequently in the pyruvic acid (Table 1-1).

During the third component of aerobic metabolism, the energy stored in the coenzymes is transferred to adenosine diphosphate (ADP) and inorganic phosphate to form ATP, a high-energy molecule that releases large amounts of *usable* energy (E) when it is hydrolyzed:

$$ATP + H_2O \rightarrow ADP + Pi + E \quad (1)$$

Because the supply of ATP is limited and the energy released by the breakdown of ATP is being used by the cell constantly, the ATP is replenished as a phosphate group and is added to ADP:

$$ADP + Pi + E \rightarrow ATP + H_2O \quad (2)$$

The carriers of the electron transport chain are organized into three complexes within the cristae of the inner membrane of the mitochondrion (Fig. 1-4): the NADH complex (which contains flavin mononucleotide [FMN]), the cytochrome b-c complex (which contains cytochromes b and c), and the cytochrome oxidase complex (which contains cytochromes a and a_3). Coenzyme Q transfers electrons between the first and second complexes and cytochrome c between the second and third. The NADH dehydrogenase complex, coenzyme Q, and the cytochrome b-c_1 complex are the three components of the system that pump (actively transport) hydrogen ions from one side of the membrane to the other and, as a result, establish a hydrogen ion gradient across the membrane and a "store" of potential energy. As the hydrogen ions on the side of the membrane with the higher hydrogen ion concentration diffuse back across the membrane with the help of ATPase, the energy is released and used by the enzyme to synthesize ATP from ADP and Pi. The various transfers of electrons in the electron transport chain generate 34 molecules of ATP from each molecule of glucose oxidized, 3 from each of the 10 molecules of NADH + H^+ and 2 from each of the two molecules of $FADH_2$. Thus, theoretically, 38 molecules of ATP (usable energy) can be generated by aerobic metabolism (Table 1-1) from each molecule of glucose supplied as metabolic fuel:

$$C_6H_{12}O_6 + 6\ O_2 + 38\ ADP + 38\ Pi \rightarrow 6\ CO_2 + 6\ H_2O + 38\ ATP \quad (3)$$

However, in reality, one molecule of glucose probably yields no more than 30 to 35 molecules of ATP. There are other (alternative) pathways by which small amounts of glucose and pyruvate are metabolized. Some of the glucose is required for the synthesis of nucleotides and is diverted into the pentose phosphate pathway,[38] some is used to sustain the store (albeit small) of glycogen in the brain, and 5% to 8% is metabolized to lactate.

The ATP generated by these reactions in the mitochondria next must be transported into the cytoplasm for use elsewhere in the cell. This is achieved by transport proteins in the inner membrane of the mitochondria that couple the outward movement of ATP with the passage of ADP (formed from metabolic reactions in the cytoplasm) into the mitochondria.

Glycolysis, the citric-acid cycle, and the electron transport chain normally provide all of the ATP required by cellular activities. Because the citric acid cycle and the electron transport chain are *aerobic* processes (and yield 17 to 18 times as much ATP as glycolysis alone), *anaerobic* metabolism clearly cannot satisfy the energy requirements of the brain (Table 1-1). Hence the central nervous system depends fundamentally on the continuous provision of oxygen.

The brain is an obligate aerobe; it cannot store oxygen, and its high metabolic requirements *(vide infra)* consume 40 to 70 ml O_2/min. Fortunately, under normal circum-

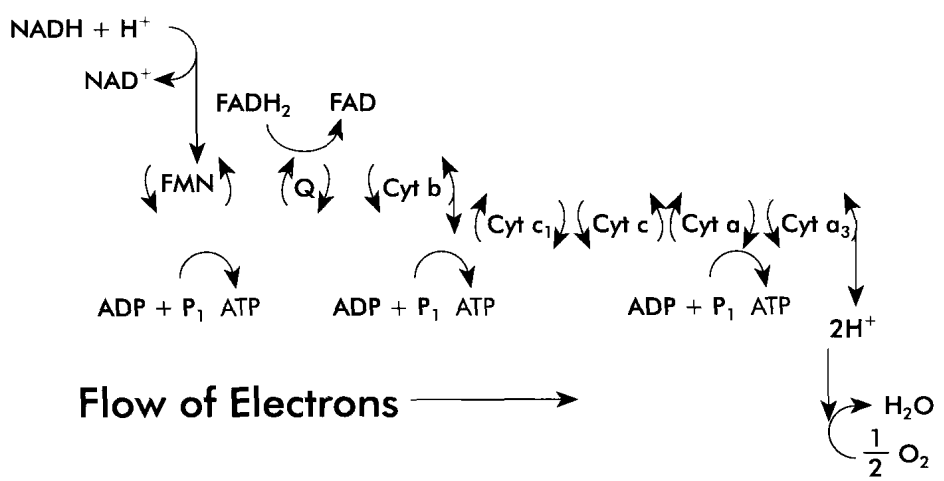


FIG. 1-4 Simplified version of reactions involved in the electron transport chain. (*Modified from Siesjo BK*: Brain energy metabolism, *New York, 1978, Wiley, and* J Neurosurg *60:883-908, 1984.*)

BOX 1-1
SUMMARY OF BALANCE BETWEEN DEMAND FOR AND DELIVERY OF OXYGEN UNDER PHYSIOLOGIC CONDITIONS

Demand for Oxygen

3-5 ml per 100 g brain tissue per minute (i.e., 40-70 ml per min)

Delivery of Oxygen

20 ml per 100 ml blood

50 ml blood per 100 g brain tissue per min (i.e., 150 ml per min)

stances, there is a substantial safety margin and the delivery of oxygen ($CaO_2 \times CBF$) is considerably greater than demand (Box 1-1). As a result, any decrease in delivery (unaccompanied by any decrease in demand) will be counteracted, at least initially, by an increase in the amount of oxygen extracted from the blood, with the preservation of aerobic metabolism and normal clinical function. If necessary, certain emergency reactions that delay the depletion of ATP or increase glycolysis can be brought into play. Ultimately, however, after the supply of oxygen at cellular level has become insufficient to support the continuing synthesis of adequate amounts of ATP, there is failure of those energy-requiring processes that sustain the normal function of the cell and its integrity.

It was conventionally taught that mitochondrial oxidations involve the acceptance by oxygen of a package of four electrons (with the formation of water) and that the production of ATP is coupled to the flow of electrons. On balance, it is now accepted that other reactions exist in which the univalent reduction of oxygen occurs with the subsequent formation of superoxide radicals, hydrogen peroxide, and hydroxyl radicals.[39] Fortunately, this liberation of free radicals does not appear to disadvantage the normal cell. However, this may not be the case under pathologic conditions in which the increase in the concentrations of these free radicals may threaten the survival of the cell.

THE BRAIN AS A CONSUMER OF ENERGY

Unlike muscle, the brain does no mechanical work. Nevertheless, as has been discussed previously, its consumption of energy is substantial. In this section, we will consider some anatomic and biochemical reasons for this.

Neurons are the basic information processors of the central nervous system. They are also responsible for the conduction of nerve impulses from one part of the body to another in a nondecremental manner. Most neurons consist of a cell body, dendrites, and an axon. The cell body contains a well-defined nucleus and a nucleolus surrounded by the cytoplasm, in which there are typical organelles (the Golgi apparatus, endoplasmic reticulum, mitochondria, Nissl bodies, and lysosomes). Dendrites are branched extensions of the cytoplasm that conduct nerve impulses toward the cell body. The axon is usually a single, long, thin, specially adapted process that conducts the nerve impulses away from the cell body to other neurons, muscles, or glands. The specialized terminals of the axon (synaptic terminals) contain unique structures that are usually vesicular in nature. These are believed to contain thousands of molecules of a transmitter substance that has been synthesized in the whole neuron and then packaged in remarkably regular amounts (quanta) within the vesicles. In most instances, a neuron synthesizes, stores, and releases only one neurotransmitter. Recently, some neurons have been identified that apparently produce two. However, as a general rule, it is possible to define a neuron by the type of transmitter released from its terminal(s) (acetylcholine, norepinephrine, dopamine, 5-hydroxytryptamine, gamma-aminohydroxybutyric acid, glutamate, and others). Until recently, it was believed that all neurotransmitters were small molecules; however, it is now clear that many neurons secrete peptides (e.g., substance P, enkephalins).

Macromolecules and macromolecular assemblies are being synthesized constantly in the cell body and transported peripherally to replace those lost or degraded. Although the rate at which this "wear and tear" occurs is not known with any degree of accuracy, it has been estimated that the cell body may reproduce up to 2000 mitochondria and renew its population of macromolecules in 1 day.[48] Moreover, it has been suggested that synaptic vesicles are used on only a few occasions before being degraded. Clearly such estimates are uncertain; nevertheless, they do highlight the fact that synthetic tasks must consume a significant proportion of the energy generated.[39]

Every living cell has a potential difference across its membrane because of the fact that charged particles are separated by a semipermeable membrane that prevents the charged particles from redistributing themselves randomly. The special feature of the so-called "excitable cells" (nerve, muscle) is that membrane permeability can be changed by processes that either increase (hyperpolarize) or decrease (depolarize) the potential difference. The cell membrane is formed of a double layer of phospholipid molecules (polar heads outside, hydrophobic fatty-acid tails inside) into which cholesterol molecules and specialized protein molecules (e.g., ATPases, adenylate cyclases, cytochrome oxidases) are inserted. Some of the proteins penetrate the membrane completely and are structured to form channels that permit the passage of water and ions. In addition to these specialized channels, there is an active pumping mechanism that transports sodium ions out of and potassium ions into the cell. Although the structural basis of the pump is unknown, the actions of certain metabolic inhibitors indicate that its carrier molecules are driven by energy derived from the metabolic processes within the cell, most likely by energy released when ATP is hydrolyzed by Na-K-ATPase.