Management of Diabetes Mellitus
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We dedicate this book to our mentor, Dr. Robert Jackson, to our three daughters (Laura, Joyce, and Tammy), and to our parents for what they have sacrificed to support us in this work.
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Diana Rhiley, EdS, LCMFT, CDE contributed to the chapter on the psychologic effects of diabetes in people with Type 2 diabetes. She is a marriage and family therapist and approved supervisor for students in this field for Friends University. She has passionately worked with people who have diabetes since the 1980’s, both in private practice and with Mid-America Diabetes Associates.
Foreword

Practice-changing events are rare in diabetes, but the Guthries have often been the forerunners in education, research, and practice of diabetes over the past 40 years.

Having the opportunity to learn diabetes and practice with Drs. Richard and Diana Guthrie is one of those rare events. Richard and Diana have dedicated their lives to people with diabetes. They are passionate about good diabetes control and independence through self-management.

The Guthries’ careers in health care began nearly a half-century ago. Their diabetes work began almost immediately thereafter. Both began their training at the University of Missouri–Columbia.

Richard Guthrie was recruited to Wichita to Chair the Department of Pediatrics for the University of Kansas School of Medicine–Wichita Branch. He has been driven to do diabetes work. Long before the Diabetes Control and Complications Trial (DCCT) results verified it, he believed good glycemic control was imperative. Being a fourth generation preacher, Dr. Guthrie has always been articulate and persuasive about sharing his convictions about good control. He and Diana built a diabetes team of which I am proud to be the first to join. The University supported their efforts in research. Early muscle biopsies documented normal blood glucose levels reversed early basement membrane thickening, a precursor to microvascular disease.

The first injection in the world of rDNA Lilly insulin was given to a person with diabetes in Wichita by Dr. Richard Guthrie. Publications, state, local, and international lectures, burgeoning clinical practice, and professional education created a reputation for both Dr. Richard and Diana Guthrie.

Diana’s additional work on the Nursing Faculty at Wichita State University was the launching pad for the development of the first graduate program in diabetes. She later consulted with Yale to help them develop their program. Diana took the lead in creating group patient education programs that taught self-management and insulin adjustments to patients in the days when urine testing was the only method for self-monitoring.

Both Dr. Guthrie and Diana have mentored literally thousands of students, many of them doctors, nurses, dietitians, physician assistants, and others. Dr. Guthrie has received lifetime achievement recognition by way of the American Diabetes Association’s Outstanding Clinician Award and Diana by way of the Outstanding Non-physician Educator’s Award. Diana is one of only a handful of Kansans admitted as a Fellow of the American Academy of Nursing.

This book is an example of their labor of love to ensure that people are well educated to take better care of people with diabetes. Now in their 70s, they show...
no signs of slowing down. Rather than retire and do international medical mis-
mission work, they have declared their diabetes work in Kansas to be their mission.
Truly that is the case. Thousands of people with diabetes and health profession-
als are grateful for that commitment as they travel to the far corners of the state
every month to see patients in outreach clinics.

This book, now in its 6th edition, reflects the current practice of diabetes
and the diabetes management philosophies of many in the heartland. I know
you will find it enlightening.

Enjoy!

Deborah Hinnen, RN, MN, ARNP, FAAN, BC-ADM, CDE
Preface

Our mentor, the late Dr. Robert L. Jackson, felt that the treatment of diabetes should be as physiologic as possible, matching the treatment to the actual functioning of the pancreas. He determined that patterns, even those obtained with the archaic use of urine tests, were useful in determining the correct dose of medication to cover the food and activity of the active child (and adult). As machines are now made available to match the body’s functioning release of insulin in real time, and the blood glucose levels after a period of time, knowledge of these values will be useful in directing the algorithms used in the pump, the artificial pancreas, or the injected or oral diabetes medications. A rapid, reactive response is needed when the person is in diabetic ketoacidosis (DKA), in hyperglycemic hyperosmolar nonketotic syndrome (HHNS), or having a severe hypoglycemic reaction. Daily use of diabetes medications to maintain a hemoglobin A1c lower than 6.5% (American Diabetes Association, 7%) does not need to be as dramatic, especially when the decision making is done by the patient or family member. The physiologic or pattern approach to management not only gives a safety factor, but also has proven quite useful in maintaining a high degree of control over long periods of time (evidence by the average, from the worst to the best hemoglobin A1c in our tertiary care diabetes clinic, is 7.4%). As a tertiary care clinic, we get individuals with newly diagnosed diabetes, people who are failing on oral agents, people who have already developed complications, and others that are difficult to control. We therefore have had extensive experience with numerous patients for more than 40 years.

We have attempted to put our years of experience in this book and to make this book user friendly for a variety of health professionals. Although the first edition was written as a guide for the working nurse who cared for a patient with diabetes, we recognized, over the years, that the book has become a working reference for all health professionals, including those professionals specializing in the field, and as a textbook for professionals wanting to know more about the disease and how to manage it by using the pattern approach.

I am reminded of an airplane ride in which I became involved in a conversation with a physician seated close by. During the course of the conversation I found that she was using our book as a guide for managing patients with diabetes. When I disclosed that I was one of the authors, tears welled up in her eyes and she thanked me for the help it had given her and her patient population.

When Richard and I discovered that some physicians, in addition to nurses and other health professionals, were using this book, we decided to develop the edition for broader use and for better ease of use. What you will find in the proceeding pages is the result.
The introduction takes you from the beginning to the present, including history, statistics, criteria for diagnosis, etiology, and physiology of the disease itself. Although acute care treatment (Chapter 6: In-Hospital Management of Diabetes Mellitus) perhaps should have been placed first, for handy reference, we decided to include some background to aid the reader in recognizing why a particular treatment is espoused. Treatment of diabetes when one has an infection and the effect of sleep apnea related to diabetes management (Management in the Clinic), along with treatment of hypoglycemia and school issues (In-Home Management), are also included. In this light, a reader interested in aspects of acute care or general diabetes treatment could read only the first two parts (Part I Introduction and Part II Management) or just Part II and obtain the immediate information desired.

The decision to separate Type 1 (Part III Ongoing Treatment and Care in Type 1 Diabetes) and Type 2 management (Part IV Type 2 Diabetes in Children and Adults), despite some controversy that one type is an extension of the other type, highlights major concerns and interventions associated with each of these conditions. If some of the information is a bit repetitive here, which we hope it is not, we trust it will be useful in the learning process.

A key addition to Part III is the particular focus on the needs and responses of children through adulthood; for example, the response of one unit of insulin to a 40-pound child is different than one unit of insulin to a 140-pound adult. Children with Type 2 diabetes, included in Part IV, remind us of the epidemic proportions of diabetes occurring in persons who are not yet adult.

We have coined the term “intermediate complications” to represent those conditions of a limited duration (refer to Part V). Pregnancy goes from pre-conception counseling through to labor and delivery and follow-up. Sexual dysfunction might be “cured” with today’s medications or might require some surgical intervention. Surgery needs some prior considerations with blood glucose control before, during, and after the procedure. Pain management interventions are essential to maintain more normal blood glucose levels and for the healing to best take place. Poor control may lead to gingivitis and other dental problems that, with adequate interventions, may be resolved.

Part VI emphasizes chronic complications and is intended as an overview of the four specific classifications. Books are written on each topic for in-depth coverage of the pathophysiology and treatments involved. Cardiovascular disease includes the large-vessel problems and is placed first in relation to its impact on society and the need to keep blood glucose levels, cholesterol, and triglyceride levels in check to prevent damage from occurring. The retinopathy chapter includes more than just the problems related to the retina of the eye, but also related to those other conditions that might occur in a more frequent manner in someone who has diabetes. The nephropathy chapter was conveniently placed after the retinopathy chapter. If you have small-vessel disease in the eye, you are more apt to have small-vessel disease in the kidneys. Neuropathy not only includes the various types of neuropathy, but also the discomfort or pain management that may be needed to accompany the “healing” condition.

There is so much to cover in relation to diabetes that a special subjects section (Part VII) was a must. Self-management education tops the list as do barriers to care. Reference to standards of care and the two most useful journals to have on hand are recommended here. Interaction of social drugs and alcohol, including smoking, is also in need of attention. Complementary
and alternative therapies are of importance and, although this chapter is not intended to be exhaustive, it will form a basis from which to gain further insight and knowledge to use when counseling patients. In addition, being prepared and knowing what to do in a disaster may save lives.

Breaking developments, and those soon to come, also continue to give hope to professionals and patients alike.

Finally, the promise of breaking developments and potential of those soon to come give hope to professionals and to the “whole person” who has diabetes (Part VIII). This, in a sense, is the most important section of all. At the same time, what is it like to be a parent of a child (or an older person) with diabetes? We trust that this section will continue to provide insight into what occurs when a person is diagnosed with a potentially life-threatening disease.

The Appendices should bring you fingertip information that we trust will be of ready assistance, especially the various protocols and listing of diabetes-related websites.

Diabetes is not the patient—the person with diabetes is the patient. Diabetes is a disease that affects every organ and organ system of the body; moreover, it affects and is affected by the emotions. This requires a cadre of professionals: a team effort (the individual with diabetes, the family and significant friends, and the family physician, the diabetes specialist, the acute care nurse, the nurse educator, the dietitian, the psychologist, counselor, social worker, podiatrist, physical therapist, or exercise specialists). This book is dedicated to the proposition that diabetes can and should be controlled through the coordinated interdependency of the health care professionals and the person with diabetes.

All of us join together in wishing that diabetes may soon be cured and, even better, prevented, so that one day this book will become unnecessary. Until that time, we hope that the book will assist those who are afflicted with this chronic problem, those who care for them professionally, and those they are close to, family and friends alike.
Acknowledgments

Appreciation is expressed to numerous people that have contributed to various chapters found in the five previous editions of this book. They are Elizabeth L. Burke on assessment; Betsy S. Desimone and Diana Rhiley on psychologic implications; Liddy Dye and Belinda Childs on surgery; Dr. Ronald James and Colleen Sheets on the older adult; Judy Jordan on complications and hygiene; Ben Leedle and Jayne McDaniel on exercise; Maria Smith on diagnosis and intermediary metabolism; Rita Nemchick and B. J. Maschak-Carey on the development of an education program; Donna Nickerson on urine testing, hygiene, and oral hypoglycemic agents; Virginia Stucky and Judy Friesen on meal planning; Deborah Hinnen on pregnancy, with Dr. Joseph Hume, and self-monitoring of blood glucose levels; and Ida Unsain, Michael Goodwin, and Marvel Logan on the effect of diabetes on sexual functioning. We also thank those that have challenged us to accomplish more, and most importantly, we thank the patients and their families from whom we have learned so much.

A special note of thanks goes to Joan Hoover, president of Diabetes Consultants, Inc., and mother of a daughter with diabetes, on “The Parents’ and Patients’ Perspectives,” a chapter included in each edition of this book, and to Dr. Carle Lee and her fine contributions to a better understanding of the physiology of glucose metabolism.
Introduction
Diabetes is a metabolic disease or group of diseases of unknown cause resulting from an alteration in the availability and use of the pancreatic hormone insulin and irregularities in the endocrine system that may involve other hormones and the body’s ability to use insulin. The disease has been known for centuries, and although research has elucidated many of the mysteries and resulted in the design of lifesaving treatments, the cause and the prevention of diabetes has remained elusive. The word *diabetes* is derived from the Greek word meaning *to siphon* and refers to the most obvious sign of the disease—marked loss of water by urination, or polyuria. The word *mellitus* comes from the Latin word for *sweet* or *honey* and thus differentiates diabetes mellitus (sweet urine disease) from diabetes insipidus (bland urine disease), a disease associated with the posterior pituitary gland (see Appendix A). In 1490, Paracelsus was the first to record that when a container of urine from a person with diabetes was allowed to evaporate it changed from a syrupy consistency to one that appeared to be a salt (the term for solids). He noted that it attracted flies. By allowing the urine to ferment, Thomas Willis, born in 1621, proved that its taste was sweet, because of sugar rather than salt.
From early times, dietary intake was viewed as a treatment. If a person did not eat as much, the person did not urinate as much. If a person ate certain foods, such as lentils or meats, they did not urinate as much as when they ate sweets. Around the 1790s, it was determined that foods contained certain amounts of carbohydrate, and they were organized into 3%, 6%, and 12% groups. Diets, at that time, consisted of guidelines to eat animal foods (proteins) and just 3% or 6% carbohydrate foods. Out of this type of thinking came other diets such as a diet composed of rancid meat or just composed of eggs, or vegetables cooked three times, or rice cooked, drained, and recooked several times to “cook all the carbohydrate out.” Other programs included a week of fasting (no foods, just water) followed by an alternate week of feeding. One diabetes center on the East Coast actually had a small hut with bars on the windows for patients to stay when they had difficulty with the fasting week.

Scientific progress in our knowledge of diabetes began in the eighteenth century with the development of the microscope and Langerhans’s descriptions of the islets in the pancreas that contain the beta cells. The “most celebrated diabetes clinician in the world,” at that time, was Bouchardat of France (1806–1886). He is perhaps the first to associate the pancreas with diabetes. Pathologists such as Virchow (1821–1902) and others subsequently described the lesions of the pancreas, leading Minkowski (1858–1931) and von Mering in Germany in 1889 to prove that diabetes was caused by this gland. They did this by removing the pancreas from a dog and observing the resulting severe diabetes. This experiment led to the speculation that the pancreas contained an internal secretion whose deficiency was responsible for the disease. Many experienced investigators searched in vain for the internal secretion of the pancreas. All efforts were thwarted because the enzymes of the exocrine pancreas digested the beta cells.

Bernhard Naunyn (1839–1925) is one of the early scientists to report on a clearer understanding of the pathophysiology of the disease and the role of glucose “derived from protein, gluconeogenesis, and that control of plasma glucose levels in diabetic children required dietary limitations on both carbohydrates, and protein” (Loriaux, 2006). Dr. Naunyn published some of the first works on diabetes, promoting the treatment of “near starvation” to control blood sugars. One of his students (Hallevorden) noted in the urine large amounts of ammonia, which was later determined to be an acid (which Minkowski found to be butyric acid)—or the first understanding of ketone bodies.

In the dramatic summer of 1921, Dr. Frederick Banting devised a way of rid- ding the body of the exocrine pancreas while preserving functioning beta cells. Charles Best, a young graduate student working with Dr. Banting that summer, developed the alcohol techniques for extracting the hormone from the remaining pancreatic tissue and for measuring blood glucose. In August 1921, after several failures, Banting found that an extract of pancreas produced a dramatic drop in the blood glucose level of a dog that they had made diabetic by removing its pancreas. Thus, the internal secretion of the pancreas was isolated. This secretion, named insulin, was soon purified and concentrated, and a new era dawned for the unfortunate victims of diabetes.

Hagedorn, in Copenhagen, Denmark, noted that the insulin developed only lasted a few hours, so he sought to remedy this defect. He did so by using protamine, which had been discovered in 1868 (by Miescher in Germany) in fish
sperm. Dr. Hagedorn experimented with many protamines and found the one that would cause a precipitation of insulin, resulting in a compound that absorbed so slowly that it acted twice as long as the initial insulin (neutral protamine Hagedorn, or NPH). Later, Scott and Fisher, in Canada, found they could prolong the action of insulin for more than a day by adding a very small amount of zinc (protamine zinc insulin, or PZI).

Insulin has since been further refined, concentrated (from U10 to U20 to U40 to U80 to present day use of U100; and also available directly from the companies in concentrations of U400 or U500), and humanized (to alter the chain of amino acids from beef [eight amino acids different from humans] or pigs [one amino acid different from humans] to human insulin with a same sequence in the chain of amino acids). It has been modified to alter the duration of action and designed to change its rate of absorbability (by altering and/or adding to the sequence and addition of another amino acid). The continuing discovery of various oral agents, the further alterations of insulin, and the discoveries of the kinds and causes of diabetes have all opened new avenues of research.

Throughout this period, a variety of approaches to the dietary management of persons who had diabetes developed. Already noted are the types and amounts of foods (the near starvation) used in treatment. One of these later programs was the point system, which was developed by Dr. Roland T. Woodyatt, who became involved with diabetes in the early years after insulin was discovered. His method of calculating the teaching diet involved the use of points and colored symbols and was originally developed for a non-English-speaking population in Chicago. This program was further defined by Virginia Stucky, the author of this chapter as it appeared in the first and second editions of this book. Judy Friesen, who studied with Dr. Stucky, has continued to refine and update this material. The exchange program of the American Diabetes and American Dietetic Associations has been the commonly used method of diet calculation and patient education. The exchange system often places foods of diverse content into an arbitrary category. For instance, peanut butter would be placed in the meat list, with some notice of its fat content. The point system overcomes some of the problems of the exchange system by assigning carbohydrate points for its carbohydrate content, fat points for its fat content, and protein points for its protein content or calorie points for the total caloric content. Carbohydrate counting is another major program. It is a variation of the point system without counting the fat and giving protein recognition when the advanced level of this program is taught. The point system, like the exchange system and carbohydrate counting, is not perfect but does represent an alternative method of meal planning, which should be carefully considered by the health care team. The pros and cons of various programs are discussed.

With the discovery of insulin in 1921, certain complacency settled over the diabetes world—diabetes was “cured.” After a few years, however, it became evident that insulin treatment was not the final answer. Insulin extended the life span, but within a few years, people with diabetes began to go blind and die of vascular disease. Thus began the most important of the many controversies concerning diabetes, one that continued until the report of the Diabetes Control and Complications Trial study (DCCT, 1993).

The previous controversy was briefly stated as follows. Is the vascular and neuropathic disease that results in most of the morbidity and mortality when
diabetes mellitus is diagnosed a genetic concomitant of diabetes or of the control of blood sugars? Or, is the vascular disease and neuropathy a complication of diabetes, somehow related to insulin deficiency and hyperglycemia, and thus preventable by control? If the first position were correct, diabetes control would be of little importance because the vascular disease was inevitable and unalterable. Little effort should be made to achieve control and diabetes education would be unnecessary. If the latter position were correct, as found to be true by many scientists and health care professionals, every effort should be made to effect control. Then, the burden is put on the diabetes specialists to educate the person who has diabetes, his or her family, the public, and other health care professionals who care for patients with diabetes in order to accomplish the goal of normalizing blood glucose levels as much as safely tolerated. This controversy, thought to have been settled by the DCCT study, has now been reactivated by the findings of the recently released ACCORD study, which shows that persons with preexisting cardiac disease have a higher mortality rate when the diabetes is very tightly controlled (A1c < 6%) than do people whose blood glucose levels are less tightly controlled. Further research is being carried out to finally settle this issue.

In 1946, the U.S. Public Health Service was developed. This unit of the government expanded to all states and internally developed sections, such as the Centers for Disease Control and Prevention (CDC). The CDC then developed a subsection devoted to diabetes mellitus.

The American Diabetes Association was founded in 1940 and also expanded to be the large, influential organization that it is today. Other significant organizations also developed programs, influenced legislation, and supported research such as the Juvenile Diabetes Foundation and the International Diabetes Federation (1952; the first congress was held in Holland with 15 countries represented) and the International Society for Pediatric and Adolescent Diabetes (started in 1973). What followed was input, coordinated research, and education to lessen the impact of this disease on individuals and society and to improve the treatment, care, and education of professionals and the people with diabetes and their families and significant friends. This is why the brief discussion of some of the controversies in diabetes was included—to put this book in proper perspective.

A Historical Review of the Pattern Approach

The three-meal, three-snack eating pattern with four doses of regular insulin was devised more than 60 years ago (Jackson & Guthrie, 1986). It was a time when a number of physicians, especially in Europe, recognized that the results of a blood glucose test represented what had passed rather than just what was occurring.

Jackson, as a pediatric resident at the University of Iowa, noted that children, despite receiving insulin, were not growing well and continued to have high blood sugars. He logically assumed that if children were given the nutritious foods for appropriate growth and development and adequate insulin to “cover” the food in relation to the child’s activity level, they would maintain weight for height as the children who did not have diabetes. With this logic in
mind, he then set about to observe more than 200 children who did not have diabetes. He noted what they ate, how often they ate, and when they ate.

What he observed was the three-meal, three-snack eating pattern. This same meal pattern was applied to children with diabetes, and insulin doses were administered in such a way that externally administered insulin levels would cause the child’s blood glucose levels to be within the normal range as much as safely possible for 24 hours a day without the child experiencing any significant hypoglycemia. The percentages of 35%, 22%, 28%, and 15% of the total daily insulin or regular insulin with meals and at midnight were initially determined—from bedside research on children eating three meals and three snacks and controlled by four doses per day of short-acting insulin.

When intermediate insulin became available, Dr. Jackson completed the same meticulous, around-the-clock testing and developed the program to have a mixture of 2 parts intermediate-acting insulin and 1 part regular insulin before breakfast (globin was the only intermediate-acting insulin available then) and one part each short-acting (crystalline) insulin, and intermediate-acting insulin before supper (at that time and with that population, the largest meal was at noon). The evening meal was small, so intermediate insulin alone 2 hours before the meal without the use of short-acting insulin could be used to result in acceptable blood glucose levels at bedtime and before the morning meal the next day.

In the 1960s and with a different population of families that ate their larger meal at supper time, Dr. Guthrie (Jackson & Guthrie, 1986) added regular insulin to the supper-time intermediate-acting insulin (now NPH insulin, because globin insulin had been removed from the market). Premixing of the insulins had been started for the purpose of safety and stability of the dosing. Globin, an early intermediate-acting insulin, and regular were compatible. Later when NPH and regular had the same pH and globin insulin was subsequently taken off the market, the mixing of insulin continued. Eventually, with the recognition that when the insulin was purified it seemed to have a shorter duration of action, the short-acting insulin was “broken out” and administered before supper and the intermediate-acting insulin was used at bedtime.

Changes continued over time as insulin was humanized and attained an even shorter duration of action. So, a mixture before breakfast, a short- or rapid-acting insulin before supper, and an intermediate-acting insulin at bedtime became popular. One thing was still noted, even with the advent of long-acting insulin (which appeared to work better with adults than children—Ul- tralente and PZI or protamine zinc insulin): the use of multiple doses of insulin increased the flexibility of the lifestyle and decreased the possibility of hypoglycemia because smaller amounts of insulin were needed at each dosing.

When insulin analogs became available, not only was increased blood glucose level control possible, but insulin was made available to the body in a way similar to the physical response of the release of insulin when a person without diabetes ingests food. The addition of continuous subcutaneous insulin infusion (CSII), blood glucose sensing, etc., has led to safer and more effective management of the disease.

The three-meal, three-snack program for children has become a popular phenomenon. Small children gravitate to such an eating pattern because of their small glycogen stores. Adults have found that the body handles food better
when given in small, frequent feedings (especially helpful for weight loss). Numerous studies have noted that 87% of teenagers eat in a three-meal, three-snack pattern, although the composition of the snacks may not be as nutritious as might be desired. Some states have instituted a midmorning nutrition break in the public schools, and teachers and parents have reported to us, by observation, a marked increase in effective teaching time.

Children are not able to hold as much food because of the small size of their stomachs; yet their caloric needs for activity and growth are larger than those of adults. Adults have coffee breaks, which often include caloric intake. Why then restrict the child with greater needs and decreased stomach capacity to fewer meals and snacks than are taken by adults? As children become adults, their lifestyles may change and variations may be needed. Medication is then adjusted to cover the needs of the food intake in relation to the activity to follow.

The increased incidence of Type 2 diabetes (T2DM) in children is especially noteworthy. Obesity and a sedentary lifestyle go hand in hand with the potential for an increasing number of children to be diagnosed with diabetes. Good nutrition and exercise are essential to having healthy children, and their being healthy requires the input of a variety of health professionals whether or not they have a chronic disease. The team approach (the multidisciplinary approach) is a need as much as for those youngsters with T2DM as for the youth with Type 1 diabetes (T1DM; Hall & Jacques, 2007). Hall and Jacques state, “Health care providers must understand this disease to insure proper management. A multidisciplinary approach is advocated . . . to help prevent the disabling and often incapacitating complications associated with T2DM.”

The Goal

The goal of diabetes therapy should be to safely achieve normal blood glucose levels around the clock. This should take into account school, physical activity (such as gym or play), sleep and rest times, and stage in development (initial treatment, metabolic recovery, middle childhood, pubescent growth spurt, post puberty, and early, middle, and late adulthood). This objective may only be achieved with adequate education. The parents and adults as well as the youth must learn to adjust diabetes medication and/or insulin dosages and food intake to control glucose on a 24-hour basis. The child, the adolescent, and the adult must also be able to participate in activities with friends and at school or work without fear of hypoglycemia. As the family adjusts to the fact that the one who has diabetes mellitus has a chronic condition and as the individual adjusts to the same fact, methods must be devised to support continued understanding, good judgment, self-discipline, and motivation in order to obtain optimum health.

The principles are based on the following:

1. Food intake should be adjusted with exercise.
2. Insulin dose and/or oral agents should be adjusted and individualized as needed to match food intake and activity/exercise.
3. Food intake should conform to the needs of each individual and should be in relationship to the medication and blood glucose values noted in regard to the patterning of that person.
It is of utmost importance, therefore, to use the correct blood glucose values to adjust the insulin, oral agents, and food. Utilization of the wrong blood glucose values for adjustment of insulin (e.g., sliding scales) appears to be the most common error in diabetes management today and often leads to erratic blood glucose level control.

Summary
We have always believed that control of diabetes has been and is important in the prevention of both acute and chronic complications. Data from the DCCT and studies carried out in other countries have confirmed this belief. They also have found that education of the person with diabetes is a vital part of the control program.

It is also our belief that people with diabetes and/or their significant others should understand their disease so well that they can make their own individual adjustments (self-management) in their program. Health professionals should assist these individuals when necessary in altering their program to meet changing needs, but basically if diabetes is to be well controlled, it should be self-managed.

Knowledge and motivation are needed if such a self-management program is to be effective. Motivation must come from within the person, but self-motivation is facilitated by knowledge. Rarely will individuals do what they should unless they understand why they are being asked to do it. Thus, emotional support and ongoing educational programs are clearly needed to assist in attaining both the motivational force necessary to control the diabetes and the information needed to carry out the prescribed program safely.

Diabetes is not the patient—the person with diabetes is the patient. Diabetes is a disease that affects every organ and organ system of the body; moreover, it affects and is affected by the emotions. Diabetes can be difficult to control under the best of circumstances, but in the presence of emotional disturbance, home instability, or lack of a will to try, it is impossible. Control of diabetes requires a team effort, involving the cooperation of individuals with diabetes, the family and significant friends, physicians, nurses, dietitians, pharmacists, podiatrists, psychologists and/or counselors, and often social workers, exercise specialists, and physical therapists. The team must be alert to prevent or handle problems as they arise or, more importantly, to prevent problems.

This book is dedicated to the proposition that diabetes can and should be controlled through the coordinated interdependency of the health care professionals and persons with diabetes and their families.

References
Diabetes mellitus encompasses a heterogeneous group of diseases with various etiologies. All of these diseases affect the ability of the endocrine pancreas to produce, or the body to use, the hormone insulin. All of the diseases of the diabetes mellitus syndrome are characterized by variable and chronic hyperglycemia and other disturbances of carbohydrate, lipid, and protein metabolism. Diabetes mellitus is also associated chronically with a variety of vascular and neurologic changes that result in considerable morbidity and mortality as well as economic loss.

Because of the variety of diabetes syndromes and the varying definitions of what constitutes diabetes, authorities have disagreed not only on the incidence or prevalence of diabetes mellitus, but also on the terminology. To bring some order to the ambiguous terminology of diabetes syndromes, such as borderline diabetes, asymptomatic diabetes, chemical diabetes, latent diabetes, and prediabetes, the National Institutes of Health (NIH) appointed a select international committee on definition and terminology, the National Diabetes Data Group.
**Classification**

The various forms of diabetes, by present terminology, are divided into diabetes mellitus, gestational diabetes, other types of diabetes, and the various early or asymptomatic states of abnormal carbohydrate metabolism.

Diabetes mellitus is defined as a symptomatic or asymptomatic state of altered carbohydrate metabolism characterized by two or more fasting plasma glucose levels of 126 mg/dl (7.0 mmol/L) or greater or a value of 200 mg/dl (11.1 mmol/L), or greater, at 2 hr, on an oral glucose tolerance test. A diagnosis of diabetes can also be made with a random blood glucose value of 200 mg/dl (11.1 mmol/L) or greater, if it is associated with symptoms (polydipsia, polyuria, polyphagia, and unexplained weight loss). If the fasting plasma glucose is above normal (100 mg/dl or 5.6 mmol/L), but less than 126 mg/dl (7.0 mmol/L), the diagnosis is impaired fasting glucose, or IFG. If an oral glucose tolerance test is performed (and it is rarely needed) and the 2-hr value is greater than normal (140 mg/dl or 7.9 mmol/L), but less than 200 mg/dl (11.1 mmol/L), the diagnosis is impaired glucose tolerance, or IGT. IFG and IGT are now called prediabetes. The term borderline diabetes is obsolete and should never be used. (See Appendix B for etiological classification.)

**Type 1 Diabetes Mellitus**

What we once called juvenile or insulin-dependent diabetes mellitus is now simply called Type 1 diabetes mellitus, or T1DM. This is an insulinopenic state of the disease usually seen in young people, but it can occur at any age. Individuals with T1DM depend on exogenous insulin for life and become ketotic when insulin is removed, and most of these individuals have classic symptoms and certain human leukocyte antigen (HLA) haplotypes. They may also have islet cell antibodies early in their disease. Subgroups of T1DM include autoimmune and nonautoimmune forms (Imagawa, Hanafusa, Miyagawa, & Matsuzawa, 2000). Anything that can produce absolute insulin deficiency can be classed as T1DM. This form of diabetes accounts for about 5%–10% of the people with the disease in the United States.

**Type 2 Diabetes Mellitus**

What we used to call non-insulin-dependent diabetes mellitus, or NIDDM, is now simply referred to as Type 2 diabetes mellitus, or T2DM. This form of the disease occurs predominantly in adults, especially in persons older than 30 years of age, but it may occur at any age. In the past 10 years there has been a dramatic upsurge of T2DM in children, some younger than 4 years of age. The disease was formerly called adult or maturity-onset diabetes, but with the increasing prevalence of the disease in children, we can no longer use age-related terminology. Use of the term NIDDM was also awkward because many of the individuals with NIDDM required insulin for control. With these problems in mind, the 1997 committee decided to simplify the terminology by adopting the acronym T2DM and the etiological classification of diabetes (Report, 1997).

These individuals are not initially insulin deficient but are insulin resistant and hyperinsulinemic. With time, they will usually develop a relative insulin
deficiency and require insulin, especially during periods of stress (e.g., during infection or surgery). T2DM is a genetic disease and the gene or genes are prevalent in all societies, but the disease becomes manifest primarily as societies industrialize (i.e., as calorie intake increases and calorie expenditure decreases) (Harris, 1995).

Other Types of Diabetes Mellitus

Other types of diabetes mellitus were formerly referred to as secondary diabetes as opposed to the familial or genetic forms of the disease. There are several subgroups of the class:

1. Pancreatic causes—pancreatectomy, pancreatitis, cystic fibrosis, hemochromatosis, and others.
2. Hormonal causes—acromegaly, Cushing’s syndrome, etc.
3. Drug-induced causes—phenytoin (Dilantin), steroids, birth control pills, and others.
4. Receptor site abnormalities—acanthosis nigricans, congenital lipodystrophy.
5. Other causes—Turner’s syndrome, Prader-Willi syndrome, progeria.

Some of these individuals are insulin dependent and occasionally massively dependent (i.e., receptor site abnormalities). Insulin dependency may be temporary, however. In drug-induced syndromes, the diabetes may remit if the drugs are discontinued. This category of diabetes causes accounts for less than 1% of all diabetes.

Gestational Diabetes

Gestational diabetes is diabetes in pregnant women who were previously healthy. This classification does not refer to the woman with T1DM or T2DM who becomes pregnant, but to the individual whose diabetes becomes known during pregnancy. Women with gestational diabetes were called Class A diabetics in the old White classification. Many are obese and, in the past, were managed by diet alone. The disease may be mild and even asymptomatic, but the incidence of fetal and perinatal complications is increased. Diagnosis of this condition is based on the criteria of O’Sullivan, Mahan, Charles, and Dandrov (1973). After pregnancy, the disease of these individuals must be reclassified as T1DM or T2DM, impaired glucose tolerance or prediabetes, or previous abnormality of glucose tolerance as determined by postpartum testing.

Asymptomatic States of Carbohydrate Intolerance

Impaired Glucose Tolerance

The term impaired glucose tolerance (IGT), now called prediabetes, applies to persons with abnormal results on a glucose tolerance test who have a fasting plasma glucose level that is normal or only slightly elevated (less
Glucose tolerance testing and the criteria for interpretation will be dealt with later. Most individuals with prediabetes are asymptomatic. This condition has been called by many names: asymptomatic diabetes, chemical diabetes, borderline diabetes, latent diabetes, and other ambiguous names. All of these incorporate the word diabetes. When that term is used, insurance companies and some employers do not differentiate these mild forms of carbohydrate intolerance from full-blown diabetes mellitus. Because many of these individuals do not progress to diabetes mellitus and many revert to normal glucose tolerance, especially if they lose weight, and because most do not seem to develop the microvascular complications of diabetes mellitus, it is unfair to classify them with the word diabetes. Because diabetes is occurring in epidemic proportions, it is now considered best to identify such individuals as having prediabetes, a codeable diagnosis. These patients have a very great risk of macrovascular disease when they do not receive a diagnosis or remain untreated. In August 2001, data from the Diabetes Prevention Program, reported by the *New England Journal of Medicine* (Fodor & Adamo, 2001), confirmed that lifestyle changes and weight loss can prevent full diabetes in many of these individuals and thus prevent or delay macrovascular disease.

On July 21–22, 2008, a conference was held in Washington, DC. This was a consensus conference involving the American Association of Clinical Endocrinologists, the American College of Endocrinology, the American Diabetes Association, the Centers for Disease Control, and a representative for the Food and Drug Administration. The purpose of the conference was to develop a consensus on whether prediabetes was a problem that should be recognized and treated. Several questions were asked, including: Did prediabetes lead to diabetes? Did people with prediabetes have a higher likelihood of developing micro- or macrovascular disease? If so, should people with prediabetes be diagnosed earlier and should they be treated? And finally, would treatment of people with prediabetes be cost-effective? The final report from this conference will not be available until fall 2008, but the preliminary report was released July 23, 2008. This preliminary report answered all of the questions above as “yes” and recommended guidelines for diagnosis and treatment. In essence the discussion at this conference leads to the conclusion that prediabetes really does not exist. Prediabetes, IGT, and IFG are just stages of diabetes, and we should probably just call it diabetes any time the blood glucose level is above normal. The problem is determining what exactly normal is. An analogy would be blood pressure. If blood pressure is above normal, we do not say the person has prehypertension, we say they have hypertension. Again, the problem is: What is a normal blood pressure? Most values considered normal are norms, that is, an average of a population. This does not mean this is truly normal, as another population might be different. An analogy here might be cholesterol. We call less than 200 normal but is it normal? It is the average + 2 standard deviations above the mean for the American population, but is that normal? We don’t have the answers to these questions yet, but work will continue to find the proper values. Until then we need to do the best we can to keep blood glucose levels as low as possible without harming the patient. The final report of the consensus committee will be awaited with great interest.
Classifications Recognized in Other Parts of the World

Protein-Deficient Pancreatic Diabetes
Individuals with protein-deficient pancreatic diabetes (PDPD) have fasting blood glucose levels at or greater than 126 mg/dl (7.0 mmol/L), or a 2-hr glucose tolerance test value at or greater than 200 mg/dl (11.1 mmol/L). They are usually very thin (cachexia), and they might be insulin dependent at some times and not at others. PDPD was once known, by some, as Jamaican diabetes.

Fibrocalculus Pancreatic Diabetes
The characteristics of individuals with fibrocalculus pancreatic diabetes fit the description of PDPD, but they have pancreatic calcification. The only other diagnostic criterion is having a fasting blood glucose level at or above 126 mg/dl (7.0 mmol/L). In Africa and the Mediterranean region, this is often referred to as Type 3 diabetes.

Facts and Figures
The facts and figures regarding diabetes are constantly changing and those presented here may be obsolete by the time this book is published. The data we present here was up to date at the time the manuscript was submitted to the publisher. Data were obtained from the American Diabetes Association (ADA), the National Institutes of Health (NIH), the International Diabetes Federation (IDF), the Centers for Disease Control and Prevention (CDC), and numerous other sources.

It is difficult to estimate the prevalence of diabetes in the world. Many countries do not report diabetes data. In many underdeveloped countries people with diabetes die without a diagnosis being made. This is particularly true of T1DM in children who live in countries where early medical care for chronic disease is unavailable. It is also difficult to report world data because the data are changing rapidly in many countries. In countries such as China, India, and others where the standard of living is changing rapidly, so is the prevalence of diabetes, particularly T2DM. The IDF has estimated that there are more than 200 million people in the world with diabetes. This is probably a low estimate. The World Health Organization (WHO) has estimated that there will be 350 million people with diabetes in the world by 2012. A United Nations resolution in November 2007 (Silink, 2007) acknowledged these facts and asked the WHO to develop a program for worldwide diabetes control. T2DM is increasing rapidly in China and India and other countries where the standard of living is increasing in association with their increase in obesity. T1DM is increasing not only in the Western world, as it has been for many years, but also in Middle Eastern countries for reasons that are unclear.

The highest prevalence of T1DM in the world is in Finland. In general, the prevalence of T1DM is lowest at the equator and increases as you go north. There are exceptions to this generalization, such as the island of Sardinia in the Mediterranean where the prevalence of T1DM is about the same as in Finland. This may represent a genetic input from old Viking seamen raiding and then settling in Sardinia in centuries past. It may also be due to a change in feeding
that occurred about the time of the turn of the twentieth century. At that time, there was a change from using milk from Brahman cattle to northern European cattle. There is some evidence that a protein found in the milk of Northern European cattle may be diabetogenic, though this is far from proven.

The increase in the prevalence of T2DM in the world is understandable in light of the increased industrialization and more sedentary lifestyle occurring in much of the developing world. In China, bicycles are being replaced by cars. Food supply is increasing as is income, and exercise is decreasing. Obesity is on the increase as is T2DM. The increase of T1DM is harder to understand, especially in Middle Eastern countries where there has been little change in food supply or customs. The increase in T1DM is about 3.5% per year in the United States but it is greater than 7% per year in many countries. It is unfortunate that the increase in the United States is in the younger children, usually under school age. Studies are under way in Europe and through TrialNet in this country to find the causes of the increase in T1DM and various treatments are being tested.

The increase in diabetes in the United States has caused a marked increase in health care costs, but statistics on diabetes mellitus are difficult to acquire for many reasons. Questionnaires, for example, can be misleading because many persons with diabetes do not want the fact of their disease to be known and they will deny having it. In the past, criteria for diagnosis have been highly variable from one center to another. The new criteria, as explained earlier, will change the data in the future. Unless otherwise noted, the data reported here are from National Diabetes Fact Sheet (ADA, 2008; CDC, 2008), Diabetes Facts and Figures (IDF, 2008a, 2008b), and Diabetes Public Health Resources (National Institute of Diabetes and Digestive and Kidney Diseases, 2008).

Prevalence

The prevalence of a disease is defined as the frequency of the disease in the population at the time of the survey. In 1973, there were 4.2 million people with diagnosed diabetes in the United States—2% of the noninstitutionalized population. In 1987, there were 6.51 million known persons with diabetes in the United States for a prevalence of 2.8%. Based on the National Health Interview Survey (NHIS) from 1993, there were 7.8 million persons with a diagnosis of diabetes at that time. This is a rate of 3.1% of the population of the United States and is more than a threefold increase from the prevalence of 0.93% in 1958. Part of this increase is attributable to better diagnosis, but much of it results from an actual increase in the incidence and prevalence of this disease (Margolis & Saudedk, 2001). The change in diagnostic criteria in 1997 resulted in a shift in classification with more people in the diagnosed class and fewer in the undiagnosed and IFG and IGT (prediabetes) classes, but the total numbers of people with diabetes did not change at that time. In 2002, the estimate was a total of 17 million people in the United States. The present estimate is 23.8 million (ADA, 2008) or 24 million (CDC, 2008a) diagnosed and undiagnosed. Of these, 5.7 million are undiagnosed. This total constituted 5.9% of the population in 2000 and increased to 8% in 2008. It has been estimated that there are another 57 million
Facts and Statistics

people in the United States with prediabetes and/or the metabolic syndrome. The following is a summary of the latest data from the ADA and CDC:

TOTAL ADA 23.8 million (7.8%), CDC 24 million (8%).
Undiagnosed—5.7 million.
Prediabetes 57 million.
New cases per year—1.6 million in persons over 20 years of age.
Prevalence under 20 years of age—186,000 or 0.22%. This equals about 1 in every 400–600 children with T1DM.
Prevalence in persons age 20 and older—23.5 million or 10.7% of all people in this age group.
Prevalence in persons age 60 and older—12.2 million or 23.1% of all people in this age group.
Prevalence in men age 20 and older—12 million or 11.2%.
Prevalence in women age 20 and older—11.5 million or 10.2%.
Non-Hispanic Whites—14.9 million or 9.8%.
Non-Hispanic Blacks—3.7 million or 14% of this group.
American Indians and Alaskan Natives—16.5% (total), 6.0% (Alaska), and 29.3% (Southern Arizona) of these populations have diabetes.
Adjusting again for age 20 or above—6.6% of non-Hispanic Whites, 7.5% of Asian Americans, 10.4% of Hispanics, and 11.8% of non-Hispanic Blacks have diabetes mellitus.

Many people without diabetes now will develop diabetes sometime in their lives. In children born after the year 2000, 1 in 3 will develop diabetes. In some ethnic groups the number is 1 in 2 (Lee, Herman, McPheeters, & Gurney, 2006). The increase in the number of persons with diabetes in the United States and in the world seems to be accelerating. The number of people with diabetes in the United States will double every 9–11 years. This fact is of concern because of the high prevalence of vascular and neurologic complications, and the high cost of these complications. Of particular concern in the United States is the high prevalence of diabetes in certain racial and ethnic groups. The prevalence of diabetes in African Americans is nearly twice that of Whites and even higher in Latinos, Asians, Pacific Islanders, and Native Americans. The Latinos and Asians are the most rapidly growing groups in the United States today.

Incidence

Incidence of a disease is defined as the frequency of new cases of the disease developing during a specified time interval. The incidence of T1DM in the United States in persons younger than 20 years of age has been estimated to be 18.2/100,000/year, and for those older than 20 years of age, 9.2/100,000/year. This represents a total of 29,713 new cases per year. For T1DM the risk is twice as high for Whites as for Blacks. A useful comparison of the burden of diabetes is found in a comparison with childhood AIDS. The number of children who develop diabetes is 14 times higher than those who develop AIDS and the
economic impact is large, with a cost to age 40 of nearly $40,000 per case. The incidence and prevalence of T1DM varies with race and geographic area, with the increasing incidence in Asians and the highest in people of northern European extraction.

For T2DM, the incidence varies with age, diagnostic criteria, and the sampling system. For all ages, the incidence was between 8.2 and 17.6/1,000 population/year in 1991. In the United States, the incidence and prevalence of diabetes is highest in the Pima Indians, slightly less in other Native Americans, next highest in Asians and Pacific Islanders, next in Mexican Americans, slightly less in Puerto Rican and Cuban Americans, next highest in Blacks, and lowest in Whites. Based on the 2008 data, there are about 1,600,000 people under age 20 years, with newly diagnosed diabetes in the United States each year. This represents about 4,384 people diagnosed with diabetes every day. This number was 2,500 persons/day or 912,500 people with a diagnosis of diabetes mellitus per year in 2005.

Undiagnosed Diabetes
The number of persons with undiagnosed diabetes in the United States cannot be determined with great accuracy. Various projections indicate that there are from 4 to 6 million persons with undiagnosed diabetes in the population at any given time. The number of 24 million people with diagnosed and undiagnosed diabetes indicates that this disease is one of the most common chronic diseases in American society today. In addition to the diagnosed and undiagnosed diabetest in the U.S. population, there may be as many as 48–57 million people in the population with prediabetes and/or dysmetabolic syndrome (hyperinsulinemic syndrome). Most of these people will go on to develop diabetes in the future. Since the complications of diabetes begin to develop in the prediabetic state and develop rapidly in the diabetic but undiagnosed state, it is imperative that the health care system develop methods to bring all these people into the system and under treatment. If this could be done the cost savings would be tremendous.

Diabetes Mortality
The exact mortality rate for diabetes is unknown because diabetes is infrequently listed as the cause of death even for those known to have the disease. Cardiovascular disease is the immediate cause of death in most cases, usually listed first on the death certificate, and usually recorded as the diagnosis for statistical purposes. Diabetes may or may not even be listed as a comorbidity. T2DM is thought to account for at least 17.2% of all deaths in the United States for persons over the age of 25. In 1987, there were 40,018 deaths attributed directly to diabetes (diabetic ketoacidosis, hypoglycemia, and so forth).

In 1986, estimates of the number of cardiovascular, cerebrovascular, and renal deaths in which diabetes was the underlying cause of the vascular disease that led to death indicated that there were probably some 342,000 deaths/year caused by diabetes mellitus and its associated complications. In 1993, about 385,000 deaths from diabetes and its complications were estimated. The official
number of deaths attributable to diabetes listed in 1996 was 198,140, but this does not account for the associated deaths where diabetes was not listed on the death certificate but was the underlying cause of the mortality.

The number of deaths due to diabetes are increasing at an alarming rate and represent a major epidemic of disease in the United States and in the world. Diabetes is now the sixth leading cause of death by disease and accounts for more than 233,619 deaths per year based on death certificate data in 2005. It is estimated that diabetes is the underlying cause of death, or listed as a secondary or tertiary cause of death, on death certificates in more than 440,000 people.

Mortality from diabetes mellitus is primarily from cardiovascular and renal disease. Morbidity is also a result of vascular diseases, coronary artery disease, cerebral artery disease, arterial occlusion of the arteries of the lower extremities, small-vessel disease as evidenced by retinopathy and nephropathy, and of neuropathy. Both vascular disease and neuropathy contribute to ulcers and gangrene of the lower extremities. Diabetes mellitus is now the leading cause of new cases of adult blindness, renal disease with dialysis and transplant, and amputation of the lower extremities.

Diabetes Costs
All of the aforementioned problems contribute to the massive economic costs of diabetes. The economic loss to the nation in 1975 in direct medical care costs, direct costs from complications, and indirect costs from loss of productivity was estimated to be $56 billion. This $56 billion figure was surpassed in 1992, reaching $90 billion when the increased numbers and costs plus inflation were taken into consideration. In 1992, $37 billion was spent on hospital care. Indirect costs based on premature death cannot be estimated but would also be in the billions. Direct costs for medical care and supplies, in 1997, were estimated at $44 billion. Indirect costs for short-term morbidity, long-term disability, and premature mortality estimated at $54 billion make the total cost $98 billion. This estimate was published by the ADA (1997) and was probably a conservative estimate. Some estimates for 1999 ran as high as $140 billion. In 2002, the costs were still increasing (ADA, 2003).

Today, the cost exceeds $174 billion dollars (ADA, 2008). One of every 7 health care dollars in the United States is spent on diabetes. For Medicare, 1 of every 4 health care dollars is spent on diabetes. This economic loss is especially appalling because much of it is avoidable. Several studies have indicated that the economic loss from diabetes can be greatly reduced by careful medical control of the diabetes, careful continued medical surveillance, and patient education programs. In one of the first comparative reports, Miller and Goldstein (1972) in Los Angeles were able to save Los Angeles County $53 million/year in direct hospitalization costs by such a program. Diabetes Control and Complications Trial data (1993) confirm these savings by showing a reduction in microvascular disease of 50%–76%. A consensus conference on diabetes (1999) revealed similar savings and a marked reduction in amputations because of improved patient programs. In their update of the ADA report (2003) of the economic costs of diabetes in the United States, D’Souza and Padiyara (2008) revealed that diabetes costs have gone up 32% since 2002.
Projected nationally, interventions would result in savings and could reduce the national loss from diabetes by at least half. This projection makes it difficult to understand why the national government and third-party payers fail to cover some of the costs for patient education and follow-up programs, and, in some cases, to pay for glucose-monitoring equipment and supplies. This problem was being corrected by national and state legislation, some of which has been too easily negated by budgetary crunches.

Summary

The high incidence, prevalence, morbidity, and mortality of diabetes mellitus are a national tragedy that should be attacked immediately in a concerted effort. The only bright spot in these dreadful statistics is a reduction in emergency hospital admissions and hospital days per year of individuals with diabetes. Narayan, Boyle, Geiss, Saaddine, and Thompson (2006) estimated the increased prevalence of diabetes would be 48.3–51 million people by 2050. This would make the financial burden of the disease in the United States by 2050 $369,750,000 a year without including a correction for inflation. Intervention should occur now with the recognition that more research is needed to reduce these costs.

References

Facts and Statistics


The diagnosis of diabetes mellitus was simplified by the National Institutes of Health (NIH) consensus criteria of 1995 (Harris, 1995) and the select committee of 1997 (Diabetes Quality Improvement Project [DQIP] and Health Plan Employer Data and Information Set [HEDIS] Guidelines, 1999; Report of the Expert Committee, 1997). Other diagnostic criteria, such as the World Health Organization (WHO) criteria, are available and have been used in many studies. All data should always be scrutinized in light of the diagnostic criteria used.

Diabetes mellitus may be extremely easy to diagnose or extremely difficult. In the ketosis-prone individual (Type 1, T1DM), the onset of diabetes is usually sudden and fulminating. Signs and symptoms are usually present, and the fasting blood glucose level is usually elevated, but occasionally the onset can be insidious. Diagnosis can be made on the basis of a fasting plasma glucose of 126 mg/dl (7.0 mmol/L) or greater or a random plasma glucose level of 200 mg/dl (11.1 mmol/L) when symptoms are present. If, for example, the child has polydypsia, polyuria, polyphagia, weight loss, and a fasting blood glucose level of 600 mg/dL (33.3 mmol/L), no further testing is needed. Likewise, if the child presents in diabetic ketoacidosis and coma, no further testing is needed. Occasionally, however, a child may present for an annual school or athletic physical
examination and a routine urinalysis may show mildly elevated glucose levels. Further testing is needed.

Diabetes in the ketosis-resistant person (Type 2, T2DM) may be without symptoms and, at times, difficult to diagnose. The earlier and milder forms of the disease with impaired glucose tolerance are often very difficult to diagnose, even in relation to the consensus criteria. A fasting plasma glucose level of less than 126 mg/dl (7.0 mmol/L) but more than 100 mg/dl (5.5 mmol/L), or value of less than 200 mg/dl (11.1 mmol/L) but more than 140 mg/dl (7.7 mmol/L) at 2 hr on the oral glucose tolerance test are the criteria for the diagnosis of prediabetes. The standard values previously mentioned lead to a diagnosis of diabetes whatever the type of diabetes mellitus, including those in the Spanish population (Valdes, Botas, Delgado, Alvarez, & Cadorniga, 2008).

Who Should Be Tested for Diabetes?

In adults, testing for the presence of diabetes should be carried out when there is glycosemia, glycosuria, a history of diabetes, a strong family history of diabetes, a history of fetal loss or large babies (babies more than 9 lb at birth), symptoms of hypoglycemia, presence of obesity, evidence of neuropathy, retinopathy, premature coronary artery disease, or early peripheral arteriosclerosis, evidence of lipid abnormalities (such as hypercholesterolemia or hypertriglyceridemia), or older age (Harris, 1995). There should also be a high index of suspicion for diabetes in Mexican Americans, Native Americans, or African Americans.

In children, testing should be carried out when there is a strong family history of diabetes, obesity, the presence of acanthosis nigricans (Jones & Ficca, 2007), symptoms of hypoglycemia, or glycosuria.

Women who are pregnant should be screened at 24–28 weeks’ gestation for gestational diabetes (American College of Obstetricians and Gynecologists [ACOG], 2000). Screening is by means of 1-hr glucose level of 140 mg/dl (7.8 mmol/L) or higher after a 50-g glucose load. If the screening value is elevated, a 100-g glucose tolerance test is performed and interpreted according to the criteria of O’Sullivan (1967).

If children are obese, they should be suspected of having diabetes until proven otherwise (Franks et al., 2007; Jones, 2008). If the values fall within what used to be called the impaired glucose tolerance range (now, prediabetes), all risk factors should be addressed to aid in preventing the progression to frank T2DM, that is, instituting preventive interventions such as diet and exercise (Weiss, 2007). Gao, Dong, Nan, Tuomilehto, and Qiao (2008) were concerned with the “clinical and social implications of labeling,” such as might influence marriage ability in some countries and employment and health insurance in others. Recent legislation in the United States is being proposed to address this type of discrimination.

Recommended Tests

A variety of tests are available for screening for diabetes. They are discussed here in the order of their effectiveness from least to most sensitive.
Urine Testing for Glucose Values

Testing of the urine for levels of glucose or reducing substances is one of the oldest and least effective methods of screening for diabetes. The urine glucose test has the advantage of being inexpensive, quick, and painless, and it is insensitive. The urine test will be positive for glucose only after the blood glucose values have become sufficiently elevated to allow glucose to spill into the urine, usually blood glucose values of 160–180 mg/dl (8.9–10 mmol/L) or more. Thus, the urine test will be positive, especially in adults, only in the advanced stages of the disease and has no value for detection of the early stages of the disease.

Blood Testing for Glucose Values

Random Blood Sampling

Random sampling (i.e., the taking of blood samples at any convenient time) is performed without standardization. Values obtained by random sampling are difficult to interpret because there are no norms with which to compare them. Again, if the values are grossly abnormal, they may be meaningful, but normal or mildly abnormal values are meaningless without standardization. Random blood sampling is being used extensively by public health departments, some diabetes associations, pharmacists, fairs, and so on for mass screening because of its simplicity, relative inexpensiveness, and convenience to the population being screened, but it is of limited sensitivity. Because the 2-hr postprandial glucose level goes up in T2DM before the fasting blood glucose level does, there is some support for developing standardized criteria for this value for diagnosis.

Fasting Blood Glucose Test

The fasting blood glucose test is the standard laboratory test for the diagnosis of diabetes mellitus. The fasting plasma glucose (FPG) value of 126 mg/dl (7.0 mmol/L) or greater is diagnostic for diabetes mellitus. An FPG of more than 100 mg/dl (5.5 mmol/L) is prediabetes. Values between 110 and 126 mg/dl (6.1 mmol/L and 7.0 mmol/L) may still be called impaired fasting glucose (IFG) along with impaired glucose tolerance but are now in the category of prediabetes. This category may assume more diagnostic significance in the future because people with prediabetes are more prone to macrovascular disease than the general population. FPG is a poor diagnostic tool for persons with impaired glucose tolerance (IGT); however, because the fasting blood glucose values usually remain relatively constant early in the course of the disease, the ability to handle a glucose load declines.

Oral Glucose Tolerance Test

The most sensitive method for detecting diabetes mellitus or impaired glucose tolerance is some modification of the oral glucose tolerance test. Properly standardized and performed, this test will detect early-impaired glucose tolerance and mild overt diabetes with great accuracy. There are many pitfalls, however, to accurate glucose tolerance testing. The individual to be tested should receive
a high-carbohydrate diet for 3 days before the test. For adults, the diet should contain 80 g of protein, 150 g of carbohydrate, and the rest fat. For children, the diet should contain 60%–65% of carbohydrate and the appropriate amount of calories for size and age. A high-carbohydrate intake standardizes the glycogen reserves and sensitizes the beta cell to the glucose stimulus. Artificial diabetes can be created by starvation or carbohydrate deprivation because of a loss of beta cell sensitivity to the glucose stimulus.

After an overnight fast of 8–10 hr, the adult is given 75 g of glucose in a palatable base. For the child, the fasting period should be standardized to 10 hr; a snack is given at 10 p.m., and the test is started at 8 a.m. the next day. Failure to standardize the fasting period in children will result in an abnormal baseline (fasting) value. The child is given 1.75 g of glucose/kg ideal body weight for height, which is administered as a 30% solution in a palatable, carbonated base.

The glucose solution should be consumed within 5 min. Samples of blood and urine are obtained while the person is fasting and then 30, 60, 90, 120, and 180 min after oral glucose is administered. Some investigators extend the test to 4, 5, and even 6 hr. Standardization of the oral glucose tolerance test to the 2-hr test for the diagnosis of diabetes and the 5-hr test for confirmation of reactive hypoglycemia are now the established protocol. The criteria call for a 2-hr test with samples every 30 min using only the 2-hr value for diagnosis. A value of 200 mg/dl (11.1 mmol/L) or greater at 2 hr is diagnostic for diabetes mellitus and a value between 140 and 200 mg/dl (7.9–11.1 mmol/L) is diagnostic for impaired glucose tolerance. Medication should not be given during the test, and smoking or drinking anything (except water) should not be allowed. Simple, light activity is desirable.

Various drugs will affect the outcome of the oral glucose tolerance test. The following drugs elevate the blood glucose levels: glucocorticoids, which stimulate gluconeogenesis; thiazide diuretics, which diminish insulin secretion and total body potassium levels and aggravate existing diabetes; birth control pills containing mestranol, which impairs glucose metabolism; and nicotinic acid, which may damage liver cells. The following drugs decrease blood glucose levels: salicylates; alcohol, which inhibits the release of glucose by the liver; monoamine oxidase inhibitors (MAOs), which are “mood elevators” that stimulate insulin release; and propranolol.

**Other Carbohydrate Tolerance Tests**

Other diagnostic tests for carbohydrate tolerance are the cortisone-primed oral glucose tolerance test and the intravenous glucose tolerance test. Of these tests, the cortisone-primed oral glucose tolerance test is most useful for early diagnosis. This test is more sensitive than the standard test because it adds cortisone to glucose as an additional stress to the insulin-producing mechanism. It will diagnose impaired glucose tolerance in the earliest stages, but it has not been standardized for children and is most useful in a research setting. It is rarely used in the clinical setting.

The intravenous glucose tolerance test (IVGTT) is the most useful tool for studying persons with impaired glucose tolerance—especially for studying the insulin reserve; however, it is not as sensitive as the oral glucose tolerance test.
for diagnosis. This test was used in the National Diabetes Screening Program, known as DPT 1 and 2 (Diabetes Prevention Trial 1&2), for testing the insulin secretory capacity of the pancreas in persons who screen positive for islet-cell antibodies. IVGTT is now being used for the same purpose in TrialNet (an NIH-sponsored program to detect children with early diabetes or susceptibility to diabetes and test measures to prevent progression of the disease).

Testing for Serum Insulin Values
Since the advent of the radioimmunoassay for insulin in the early 1960s, it has been possible to measure the insulin-secreting ability of the pancreas during glucose tolerance testing. Testing for insulin-secreting ability increases the reliability of the oral glucose tolerance test. When the laboratory has the capability for measuring serum insulin values, this measurement should always be part of the oral glucose tolerance test for the diagnosis and definition of hypoglycemia but is rarely needed or useful for the diagnosis of diabetes mellitus. Fajans and Conn (1959) have published norms for serum insulin values for adults, and Pickens, Burkeholder, and Womack (1967) have published norms for children.

Screening Tests
Human leukocyte antigen (HLA) gene typing and anti-beta cell and anti-insulin antibodies are newer ways to screen for T1DM and impaired glucose tolerance (Eisenbarth, 1986). These tests are expensive if obtained commercially, and their use is usually confined to a research setting. They are more often used in research studies such as the Diabetes Prevention Trials and TrialNet.

Another consideration concerns the metabolic syndrome (dysmetabolic syndrome, cardiovascular risk syndrome, syndrome X), which, in the past, had only been noted when all of the following are found: hypertension, hypertriglyceridemia, obesity, impaired fasting glucose, and low high density lipoprotein (HDL). On further study, in a joint statement, the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) found that the criteria used for defining the syndrome were not complete and somewhat ambiguous. They also found that the criteria differed between the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) and the World Health Organization (Kahn, Buse, Ferrinnini, & Stern, 2005). The major question was the inclusion of patients with cardiovascular disease (CVD), and they noted that other factors were involved such as C-reactive protein as an inflammatory marker. They concluded that more studies needed to be done regarding the criteria for a diagnosis of metabolic syndrome, the definition of the syndrome, the decision of whether to remove CVD factors or not, and the examination of underlying causes of such a grouping of risk factors.

The ADA is proposing the concept of “cardiometabolic risk” (as global diabetes/CVD risk) as an alternative name for metabolic syndrome and the inclusion of, besides obesity and hypertension, abnormal lipid metabolism, inflammation/hypercoagulation, smoking, age, race, sex, family history (genetics), and insulin resistance syndrome—insulin resistance/elevated cholesterol/hypertension/hyperglycemia (Bectly, 2006).
Summary

The oral glucose tolerance test is the most sensitive test for the diagnosis of diabetes mellitus—especially in the earlier and asymptomatic stages (i.e., impaired glucose tolerance). Properly standardized and interpreted, this test, combined with serum insulin determinations, is an extremely sensitive tool for the diagnosis and study of diabetes. Its only disadvantage to the patient is expense and inconvenience. When symptoms suggestive of diabetes are present, the fasting plasma glucose or 2-hr postprandial blood glucose determination may be all that is needed for diagnosis, as noted in Gavin’s report of the “new” classification and diagnostic criteria for diabetes (1998), and in keeping with the clinical practice recommendations for the Diagnosis and Classification of Diabetes Mellitus (2008). When these are negative or when diabetes is suspected in an asymptomatic individual, an oral glucose tolerance test combined with serum insulin values, when available, should be performed under rigidly controlled conditions and the results compared with the carefully selected appropriate norms for age, especially in children.

Caution must be taken not to overdiagnose diabetes. It is important to detect diabetes as early as possible because treatment will prevent complications. A false diagnosis of diabetes though has serious implications in employment, insurability, and emotional impact. The standard oral glucose tolerance test properly performed and rigidly controlled and interpreted should lead neither to false-positive nor to false-negative tests, but to a proper diagnosis of diabetes mellitus or impaired glucose tolerance. It should be remembered, however, that the correct criteria for the diagnosis of actual diabetes mellitus are based on the fasting plasma glucose values, not on oral glucose tolerance testing, although oral glucose tolerance criteria can be included.

References

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The cause of diabetes mellitus remains unknown, but new research is leading us toward the concept that diabetes may have many causes. Indeed, diabetes is a syndrome, not a single disease, yet a few thinkers have recently suggested that the older concept of one disease may be right after all. Type 1 diabetes mellitus (T1DM) might be a telescoped form of diabetes manifesting somewhat differently between Type 1 and 2 because of age and environment on the genetic background. Age, body size, and other environmental factors affect the genetic background differently, causing the disease to be manifest differently in different people, as T1DM in younger patients and T2DM in older patients. This is called the acceleration theory (Wilkin, 2008). Epidemiologic studies are under way to prove or disprove this theory, but only one piece of supporting data is, as yet, available. At diagnosis, adolescents with T1DM appear to be heavier than expected even though they may have lost weight. Thus, body weight may be a factor in the etiology of T1DM as it is in Type 2 diabetes mellitus (T2DM) (Jones, 2008).

Diabetes is, then, one of many diseases that ultimately cause beta cell failure and/or peripheral insulin resistance. Diabetes has always been thought of as a genetic or inherited disease, although the mode of inheritance has not been
characterized. In general, this is true because a genetic marker for the disease in nondiabetic relatives of persons with diabetes has not been found. Genomic studies are identifying many genes on many different chromosomes as possible markers for the diabetes diseases but no one gene or group of genes has as yet been identified as the cause of the diseases. Data are now beginning to emerge to indicate that diabetes is an inherited disease with many modes of inheritance. These modes of inheritance are different in different families; moreover, the different environmental factors that determine (at least in part) the manifestations of the inheritance may be different for the different inheritance patterns. The inheritance of T1DM and T2DM is probably different, and the inheritance of different types of T2DM and other types of diabetes are most likely also different.

**Type 1 Diabetes Mellitus**

Genetic markers are being developed for T1DM mostly in the human leukocyte antigen (HLA) system that controls immunity in humans. Though no consistent HLA patterns have been found in T2DM, several HLA antigens have been found consistently in T1DM. The HLA-B8 and HLA-B15 antigens were first identified as genetic markers for this type of diabetes. These genes are on the short arm of the number 6 chromosome. B-8 and B-15 antigens are not very specific, so a search began for more specific genes perhaps linked to B-8 and B-15.

Persons with T1DM have been found to also have at least 2 antigens in the D locus of the HLA system—DR3 and DR4 (Kolb, 1999). Data presented by Lernmark (1989) indicate that these genes are linked to alleles in the DQ band on the number 6 chromosome that encodes for Class II antigens, and may be more closely associated with the development of diabetes than the neighboring DR genes. This locus codes for variants of the HLA-DQ antigen, two glycoproteins labeled alpha and beta (or A and B), which are involved in the immune system’s recognition of antigens and their presentation to macrophages. Antigen recognition and presentation is a vital step in immunity to foreign bodies such as bacteria and viruses. These alleles must also recognize self in order to differentiate self from foreign bodies. If an abnormality exists in these alleles, they may not be able to differentiate self, allowing the immune system to attack self, that is, an autoimmune process resulting in destruction of self-tissue such as the beta cells of the pancreas-T1DM.

Several abnormalities in the DQ band of the number 6 chromosome have been found that are related to the development of T1DM. One amino acid difference in the sequence of the glycoprotein can alter the ability of the locus to encode for recognition and presentation of foreign antigens and differentiation of self. Several such abnormalities have been found, in particular, deletion or substitution for aspartic acid at the number 57 position in several alleles. Such abnormalities have been found in loci labeled DQA1*0301, DQB1*0302, DQA1*0501, and DQB1*0201. Other amino acid deletions or substitutions have also been found, especially in other racial groups, in particular East Asians (Japanese and Chinese), so these abnormalities can be quite diverse. There are also some protective loci such as DQA1*0102 and DQB*0602. How all of these loci work to facilitate or protect against T1DM is unknown, but
this opens possibilities for further research that may soon provide not only immune markers for the diagnosis of T1DM, but also immune system therapies that may cure or prevent this disease (Sperling, 2008). The form of diabetes now known as Type 1A is usually associated with islet cell antibodies (Juneja & Palmer, 1999).

**Genetic Abnormalities**

Genetic abnormalities in other genes on other chromosomes have also been identified in small populations of families with T1DM. Fifteen such forms of T1DM have been identified and are labeled IDDM1–15. Three of these (IDDM5, -9, and 15) are located on chromosome 6 like Type 1A, but at other loci. IDDM2 and -4 are located on chromosome 11. IDDM3 is on chromosome 15, IDDM6 is on 18, IDDM7, -12, and -13 are on 2; IDDM9 is on 3; IDDM10 is on 10; and IDDM11 is on 14. The locus for IDDM14 has as yet not been defined. These forms of T1DM are phenotypically similar to the classic form, but they are genetically different and are limited to a few families each. In some of them, there are chemical markers in the blood facilitating identification.

The abnormalities of the HLA system may cause several abnormalities of the immune system. Some of the abnormalities may cause an underreaction of the immune system so that an environmental antigen (such as a virus) can invade the beta cells of the pancreas and destroy them before the immune system can react. Another abnormality can cause overreaction of the immune system or interfere with the immune system’s ability to recognize self, resulting in an autoimmune problem. With the latter problem, the onset of diabetes is slower than with the former and an association is often seen with other autoimmune diseases such as Hashimoto’s thyroiditis, Addison’s disease, pernicious anemia, alopecia areata, vitiligo, celiac disease, and, perhaps, autoimmune hepatitis, which are autoimmune diseases of the thyrogastric cluster. In all types of T1DM, there must be an environmental trigger before the immune system abnormality is activated. We know this because of twin studies. Identical twins have the same genetics but in a classic study, Tattersall, Pyke, Ranney, and Bruckheimer (1975) demonstrated that less than 50% of the second twins will develop the disease even after many years. These environmental triggers are discussed below.

**Islet Cell Antibodies**

In Type 1A diabetes, islet cell, insulin, and GAD 65 antibodies are present in the serum often for many years before the onset of the disease. Evidence from studies of siblings of people with diabetes suggests that early identification of these individuals could lead to prevention of this disease. Additional evidence for this is the remission or honeymoon phase of T1DM in which early treatment with insulin seems to arrest the beta cell destruction for a time and even promotes recovery of beta cell function. People with pancreatic antibodies and declining insulin secretory capacity have been given small doses of insulin and have slowed or stopped their beta cell destruction as measured by insulin requirement and C-peptide secretion. These provocative but limited observations have
led to the development of a national prevention program known as Diabetes Prevention Trial (DPT 1 and 2).

In DPT 1, first-degree relatives of people with known T1DM were screened for islet cell and insulin antibodies. Those with a positive titer were then given an intravenous glucose tolerance to define their first-phase insulin-producing capacity. Those with a decreased insulin-producing capacity that had normal or only slightly abnormal oral glucose tolerance tests were entered into a treatment protocol for treatment with low doses of insulin. The purpose of this study was not to treat blood sugar with insulin but to administer small doses of insulin to immunize the person, thus creating antibodies that could block the immune system’s attack on the beta cells and prevent the development of diabetes. Unfortunately, the procedure, at least in the insulin dosage and distribution used in the study, did not work and this portion of the DPT study was terminated in the spring of 2001 (Pozzilli, 2002). In DPT 2 similar screening procedures are carried out on second-degree relatives as well as first-degree relatives. In this study, the person with positive results was treated with an oral form of insulin (an insulin that is coated by a substance that will not break down until past the stomach and small intestine). Again, this insulin is not to control blood glucose but to immunize. This study was also unsuccessful but has led to a new trial with a different oral preparation. This study is a part of TrialNet, a network of groups across the country and in Europe testing various methods of solving the immune system problems and preventing diabetes.

## Immune Mechanism of Diabetes

A simplified but unifying concept of the immune mechanism of diabetes is as follows. The immune system may be thought of as having an on and an off switch. When the DR4 and its associate DQ allele genes are present, there is a defect in the on switch in which the system does not properly turn on. It does not recognize the presence of the virus or other insult and so does not destroy it. The defect may be in cellular or humeral immunity or both ("Lazy T" cells is one hypothesis). In any event, the insulting force is not destroyed and is allowed to penetrate the beta cell and destroy it. This form of the disease, with an early and explosive onset and poor beta cell recovery with treatment, is increasing worldwide and in the United States mostly in children under the age of 6 years.

When the DR3 and its associate DQ allele genes are present, the defect is in the off switch. The environmental insulting agent such as a virus activates the on switch of the immune system and the virus is destroyed. The problem in these individuals is that the immune system is not turned off. The T-killer cells remain activated and attack the beta cells in an autoimmune type reaction. This form of the disease comes on later and is slower in onset. Islet cell, anti-insulin, and GAD 65 antibodies may be present for years before the actual onset of the disease. These people have a more profound remission phase of the disease indicative of less initial beta cell loss. Continued autoimmune assault and/or repeated assaults result in slow loss of beta cell function over several months or years. This form of the disease becomes manifest in later childhood usually during the preadolescent growth spurt or even later in life and has a better recovery or remission period. It is also associated with other
autoimmune diseases. This has been a very simplified explanation of the process. Obviously, it is much more complex with many intervening steps and chemicals, including a variety of lymphocytes, cytokines, and other immune substances and cells. New research is clarifying these steps, identifying environmental triggers, and bringing new understandings that, in the future, may allow for interventions that will prevent T1DM.

Various treatment strategies are currently being developed to attack the immune system in new-onset T1DM and to preserve beta cell function. Immune therapy has had only marginal success so far, but much new knowledge is being gained and the immune theory of the etiology of T1DM is being proved. The first successful use of immunosuppressant was with cyclosporin A (Dupre et al., 1988). Extensive studies in Canada and Europe have shown the drug to be somewhat effective in preserving beta cell function, but cost and toxicity have been a problem. The effect is only temporary and when therapy is stopped, beta cell function is lost. Several other forms of immunotherapy such as the use of monoclonal antibodies to T cell proteins to deliver toxic enzymes specifically to the T cells and the use of monoclonal antibodies to block interleukin-2 receptors and other cytokines are being tried. All such therapies are experimental and should not be used except in carefully controlled research studies.

Other new approaches to the prevention or early treatment of diabetes are the administration of nicotinamide, restriction of cow’s milk feeding in susceptible infants, heat-shock proteins, thalidomide derivatives, CD-3 or 4 monoclonal antibodies, and many others. Researchers are also looking for the genome for diabetes so that diabetes might be prevented (Pani & Badenhoop, 2000) or perhaps reversed, along with the early recognition of HLA typing (Morwes sel, 1998). For treatment, researchers are trying almost every substance known in non-obese diabetes mice (NOD) mice, a species that develops an insulin-dependent diabetes very similar to that in humans, and the substances that show promise without severe toxicity are then proposed for human experimentation. Other than insulin and nicotinamide very few of these chemicals have as yet been cleared for trial in humans. Nicotinamide trials have been completed in Australia and New Zealand, and are under way in Europe, but nicotinamide, like many other chemicals, which have shown potential in NOD mice have not shown the same protective effects in humans.

Cow’s Milk

Cow’s milk has an interesting story in the understanding of the etiology of T1DM. It was reported several years ago from Scandinavia that breast-fed infants had a lower incidence of diabetes than those fed cow’s milk (Dahl-Jørgensen, Joner, & Hanssen, 1991). It was proposed that human milk contained certain antibodies that protected the infant from the viruses that could initiate the immune problem, and that substance was not found in cow’s milk or was destroyed by the preservation process in formula. Later research in Canada and New Zealand, however, showed that it was not a protective effect of human milk but an antigenic effect of cow’s milk. Cow’s milk seemed to contain something that triggered the immune attack on the beta cell. Further studies are under way to delineate that substance. Many researchers believe that it is bovine albumin
and that this protein is incompletely digested in the infant’s intestinal tract. The incomplete protein fragments are absorbed and trigger an immune response that is retained in the memory of the immune system. Later in life proteins form on the beta cells, which are similar to the cow protein fragments, and are then recognized by the immune system as foreign bodies. The immune system then attempts to eliminate these proteins and in the process kills the beta cells, causing diabetes. This same process is thought to be responsible for the increase of asthma in children where the foreign substance is the too early feeding of solid foods. An interesting sidelight of this issue is that milk from cows common to northern Europe (the milk used in Europe, United States, Canada, etc.) will cause the problem, but milk from Brahman cattle used commonly in Asia and Africa does not.

If the theory of a heat-resistant protein in cow’s milk is true, then human infants, especially those who are genetically susceptible to diabetes, should not be exposed to cow’s milk until they are at least one year of age. Further studies are needed to unravel this story, which may give us clues to other environmental triggers or insulting agents that may be involved with the etiology of T1DM. A study from Denver refutes the milk connection (Norris et al., 1996). The final story is not yet in.

Extensive studies are under way in Finland to delineate the role of cow’s milk and other potential triggers in the etiology of diabetes. Viruses, especially the Coxsackie viruses and perhaps other intestinal viruses, have been implicated as etiologic agents, but other environmental factors such as other foods, methods of cooking, environmental contaminants, and so on, are likely in some cases as well (Knip & Akerbloom, 1999).

Additional Theories

Two additional theories for T1DM have been proposed. The first of these was mentioned earlier (the accelerator hypothesis). It was proposed by Wilkins, who is an immunologist who has worked on the immune theory of diabetes for more than 30 years, without success in unraveling it. He has proposed that T1DM and T2DM are the same disease. There are genetic differences in the 2 types of diabetes which impact the age of onset but environment triggers are the same. Some evidence for this is the observation that children who develop T1DM have previously been heavier than children who do not develop diabetes at comparable ages. Another bit of evidence is the observation that there is an impairment of beta cell mass and function early in T2DM and may be the primary defect rather than insulin resistance (Florez et al., 2007). If this is true, loss of beta cell mass and function is the initial common denominator in both types of diabetes, and they may be the same disease.

An additional theory has been labeled the germ theory. An observation during the polio era was that polio and certain other intestinal viruses were more common in cleaner people and societies than in poorer societies and the “slums.” The idea was that in the less clean societies the infants were exposed to germs or viruses in infancy while they still had transplacental antibodies to protect them. They then developed immunity and had no disease. Infants in cleaner societies were not exposed while protected; thus, they had no immunity
and when exposed later in life developed the disease. At the border between Finland and Russia, there is a population of Finns who are genetically the same but of higher socioeconomic status on the Finnish side. These two populations are being studied to see if there is a difference in the prevalence of diabetes between them that might be explained by environmental exposure early in life. Data from this study are not yet available. This study is part of extensive studies in Finland on the epidemiology of T1DM because this nation has the highest prevalence of T1DM in the world. We eagerly await the results of all of the studies on the cause of T1DM, so that we may more intelligently develop ways to prevent this disease.

**Type 2 Diabetes Mellitus**

The etiology of T2DM is even less well understood than the etiology of T1DM. It is genetic, but it has nothing to do with the immune system and the genes are not located on the same HLA locus on the number 6 chromosome. Indeed, there are probably many genes causing T2DM, located on several chromosomes. Some candidate genes have been identified but most have not. We also know that there is a strong environmental influence in the development of T2DM. The gene or genes seem to be widespread throughout the world and in every race and culture. But we see the disease manifest only in developed or developing countries where it is associated with increased caloric intake and decreased caloric expenditure (obesity). Underdeveloped countries have a very low incidence and prevalence of the disease and it occurs primarily in the elderly. When these countries begin to industrialize or the people immigrate to more developed countries, a virtual explosion of diabetes occurs. How this change in lifestyle interacts with the genetic precursor is not known.

**Insulin Resistance and Obesity**

We do know that obesity is involved in insulin resistance and hyperinsulinemia, yet not all obese people develop diabetes. Insulin resistance may therefore not be the primary, or at least the genetic, defect. As previously noted, there appears to be a loss of insulin secretory ability by the beta cells and a loss of beta cell mass (Florez et al., 2007). This is probably the main genetic defect. When insulin resistance develops, the person without the gene can increase insulin secretion and compensate. Those with the gene cannot compensate and develop a relative insulin deficiency and consequent elevated blood glucose levels. This scenario is fairly well understood. What is not understood is why. The gene or genes for T2DM are very widespread throughout the world and even occur in animals. If it is an undesirable gene, why has it been bred in instead of being bred out over time? Perhaps it had a function. Human history is one of recurrent famine, not the plenty we see today. The gene may have been evolved as a thrifty gene to improve energy utilization during times of famine. In other words, the gene allows us to get more miles to the gallon. During times of famine then, it was the people with the diabetic gene who survived, thus perpetuating the gene. Today, we still see little T2DM in countries with low caloric intake.
Introduction and high caloric expenditure. When those people increase caloric intake and decrease activity by improving economic conditions or moving to developed nations, diabetes develops, often at alarming rates. The key to prevention of T2DM, then, is to prevent obesity, a finding recently confirmed by the Diabetes Prevention Program (Fodor & Adamo, 2001).

The obesity associated with T2DM is not generalized, but centralized, obesity. It is not only central, it is also primarily intra-abdominal obesity. Fat tissue was once thought to be inactive tissue, but it is now known to be an active organ producing many hormones and cytokines. Some of these hormones, such as leptin, are beneficial. They reduce appetite and enhance metabolism and insulin utilization. Other substances produced by fat tissue are harmful especially in increasing food intake and causing insulin resistance. Subcutaneous fat tends to produce more of the good substances, and intra-abdominal fat the harmful substances. Much research remains to be done on fat hormones. This is a fruitful area of research that may lead to better treatments in the future. Genetic defects in diabetes may lead to the production of abdominal fat as well as decreased beta cell function and mass. The insulin resistance of diabetes may also be caused by genetic defects in insulin receptors on cells and/or the cascade of kinase reactions inside the cells. This remains to be established.

Metabolic Syndrome

Whatever the name given to this syndrome, the metabolic syndrome has taken a major role in association with diabetes mellitus. Pradhan (2007) relates this syndrome to an inflammatory basis of glucose disorders, whereas McGill, Molyneaux, Twigg, and Yue (2008) question whether the metabolic syndrome exists, even whether it matters when concerning T2DM. DeFerranti and Osganian (2007) discuss, in length, the epidemiology of pediatric metabolic syndrome and its relation to T2DM. They contend that the prevalence of this syndrome is increasing in children and especially adolescents. Their fear is if not caught early enough, the associated complications will occur in younger individuals, leading to an increase in morbidity and mortality in this age population. In any case, whether it is called syndrome X, or even the more recent name of cardiovascular syndrome, hypertension, hyperglycemia, hyperlipidemia, and obesity as such relate to potential problems that have an endpoint in disability or death whether controlled in part or in whole.

Maturity Onset of Diabetes in the Young

In the 1960s, Fajans and Conn (1960) studied some families in Michigan who had an unusual form of diabetes. In 1989, Fajans reviewed this field of study and reported on his findings accumulated over the years. These were non-insulin-dependent children with diabetes resembling T2DM. He called this maturity onset diabetes in the young (MODY). MODY has now been identified as a group of genetic diseases primarily involving enzyme defects in the liver. A number of diseases labeled MODY have been identified genetically, but the numbers are small and each form is usually confined to one family group.
Recently, another form of non-insulin-dependent diabetes has been re-ported. Occasionally there are newborn infants with diabetes. They have always been treated with insulin but may not need to be so treated. Research has shown that these babies have a gene that results in a defect in the potassium receptor on the beta cell that is involved in signaling of the beta cell to produce insulin. This is the receptor that is activated by sulfonylurea drugs. These infants can therefore be treated with oral drugs instead of insulin (Rafig et al., 2008).

Other Forms of Diabetes
Gestational diabetes will be discussed in Chapter 23 dealing with diabetes in pregnancy. Other forms of hyperglycemia (see Appendix B) may be caused by a variety of rare syndromes. They may also be associated with stress, steroid use, and ingestion of some drugs that are toxic to beta cells. This group of diseases, labeled other, accounts for less than 1% of the total number of people with diabetes.

Etiology of Complications
Basement Membrane Biochemistry
One of the primary lesions seen in the vasculature of people with poorly con-trolled diabetes is thickening of the capillary basement membrane. This mem-brane surrounds the blood vessels and serves as a filtration system. It contains slit pores that filter small molecules out of the vessels and into the interstitial tissue and prevent the loss of protein from the blood. When these membranes thicken, the slit pores increase in size and lose their electrical activity. The membranes then can leak protein into the tissue (as in the eyes) or in the urine (as in the kidney). Thickening of the membrane occurs because of glycation of the membrane proteins by glucose. This process may occur via enzymatic glycosylation (Spiro & Spiro, 1971) or by nonenzymatic glycosylation, a process widespread in nature. The blood glucose levels drive both these processes, that is, poor diabetes control.

Polyol Pathways of Glucose Metabolism
The polyol pathway of glucose metabolism leads to other changes in the body when kept metabolically imbalanced by high glucose levels that lead directly or indirectly to problems in oxygen availability to the cells. The polyols are sugar alcohols and represent an alternate pathway of glucose metabolism when insulin-dependent pathways are blocked. Winegrad, Morrison, & Clements (1973) have demonstrated the presence of enzymes of the polyol pathway (aldose reductase and sorbitol dehydrogenase) in various tissues of the body, including capillaries, large vessels, nerves, and the lens of the eye. When glucose levels are high and the normal insulin-dependent glycolytic pathways are blocked by low insulin levels (poor control), the polyol products are formed and accumulate in the re-spective tissues. The accumulation of polyols decreases the absorption into the
cell as myoinositol, an important compound in oxidative metabolism. A myoinositol deficiency can develop and result in cellular death by oxidative stress in the vascular endothelium and nerve tissue.

The Process of Glycosylation

The use of the HgbA1c as a clinical tool in the assessment of diabetic control will be discussed in chapters 6, 7, and 8 in Part II regarding treatment. Here, we discuss this phenomenon as a model of tissue damage. HgbA1c is hemoglobin to which glucose has become attached at the terminal amino acid of the beta chain of the hemoglobin. The initial reaction is a loose bonding of the terminal nitrogen of the amino acid with the number one carbon of glucose to form a Schiff base. This reaction is reversible if glucose levels decline. However, if glucose levels are high, the law of mass action keeps the glucose in contact with the amino acid and an internal rearrangement of the double bond occurs (an Amadori rearrangement) resulting in a permanent bonding of the glucose to the amino acid (HgbA1c). This process is called glycosylation and is widespread in nature. The toasting of bread and the browning of fruit are examples of glycosylation of proteins in nature.

In humans, glycosylation of tissue has now been described not only for hemoglobin but also in red blood cell membranes, serum albumin (fructosamine—another test of glucose control), serum globulins and other plasma proteins, lens tissue, and collagen and elastic tissue. Glycosylation of collagen and elastic tissue in blood vessel walls is responsible for the stiffening of the vessels that, along with glycosylation and stiffening of red blood cells, may be responsible for, or associated with, large vessel disease in diabetes. The glycosylation of tissue proteins is a non-enzymatic process that is directly related to the blood and tissue glucose levels and causes acceleration of the aging process. Because the process is non-enzymatic and is directly related to the glucose level, there is a direct need to keep blood and tissue glucose levels as low as possible to prevent this reaction.

The common denominator of the glycosylation and other reactions of tissue with glucose is the permeability of that tissue to glucose without the presence of insulin. Only in tissue into which glucose may enter without the presence of insulin (such as vascular tissue, lens tissue, and nerve tissue) does damage occur in diabetes mellitus. Apparently, in those tissues permeable to glucose without the presence of insulin, the glucose level inside the cell will be the same as the ambient or blood glucose level. The cell must dispose of this glucose in some way. The normal glycolytic pathway for glucose disposal through the Kreb’s cycle is blocked, because the enzymes necessary for the chemical degradation of glucose are insulin dependent. The cell in some manner must dispose of the accumulating glucose by alternate pathways of metabolism. Spiro and Spiro (1971) described a pathway called enzymatic glycosylation. The polyol pathway was described by Morrison and Winegrad (1971) (operative in tissues that contain aldose reductase enzymes). The third pathway of glucose disposal is the glycosylation of tissue proteins, which is non-enzymatic and is directly proportional to blood glucose levels.
Recent Advances in Nonenzymatic Glycosylation

A recent addition to the non-enzymatic glycosylation story has been the discovery of advanced glycosylation end products (AGEs). The AGEs are the final stage in the glycosylation process after the formation of the Amadori product. These two stages of glycosylation are progressive spatial rearrangements of the amino acid-glucose-bonded molecule. The bonding is permanent and alters the properties of the protein. Indeed, the AGE is now in a configuration where it can bond to the same amino acids with which the glucose bound. This can result in cross-linkage of proteins such as collagen and elastic tissue that, when cross-linked, lose their elasticity and become rigid. Low density lipoprotein (LDL) cholesterol also contains the same amino acid complexes as collagen and can bond to the AGE, resulting in permanent infiltration of the tissue with lipid (an atheromatous plaque). Elevated blood glucose is the driving force in these reactions, which also happens in persons without diabetes, but to a much lesser extent because the glucose level is lower.

Summary

All of the mechanisms of glucose disposal are related either to elevated blood and tissue glucose levels or to deficiencies of tissue insulin. It therefore becomes apparent that it is vitally important to keep blood and tissue insulin and glucose levels normal or near normal to promote the normal disposal of glucose and to prevent tissue damage from the alternative methods of glucose disposal. This is called physiologic diabetes control and requires that insulin therapy in the insulin-dependent individual be carried out to simulate normal insulin secretion patterns, that is, to maintain a 24-hr basal tissue insulin level accompanied by a burst of insulin with each feeding. This is the rationale for the multiple-dose insulin administration regimens and for the use of insulin minipumps. As explained earlier, clinical data confirm the benefit of such forms of treatment. Biochemical, morphologic, and clinical data are consistent, indicating the need for a high degree of metabolic control of diabetes mellitus to prevent or at least slow and, in some cases, reverse microvascular and perhaps macrovascular and neurologic diseases in diabetes mellitus.

References


Care of individuals with diabetes requires an understanding of metabolism. Metabolism is a complex process of interrelationships between multiple regulatory factors and receiving sites and tissues. This process is essential to life, as all systems and their constituent cells rely on the maintenance of a balance, which is often, in addition to being complex, a delicate mechanism in healthy states. Also, the metabolic process is built to respond to nonmaintenance conditions, such as starvation, stress, injury, and inflammation. This response is predicated on the understanding of the need for restitution and replacement therapy undergirded by an understanding of the adaptive mechanisms of the human organism (Guthrie & Guthrie, 2004).

**Metabolism**

Metabolism can be described as a combination of the anabolic and catabolic processes of metamorphic stages of cellular life. Anabolism is the process of cellular production and tissue building, which relies on many factors, including the intricacies of the glucose–insulin relationship. This relationship
is paramount to supplying cells with energy resources. In a disorder such as diabetes mellitus, this derangement must be attended to carefully.

Catabolism, in contrast, refers to the breaking down processes of cellular metabolism. In normal situations, a balanced state exists between anabolism and catabolism. Imbalanced states, such as uncorrected diabetes states that are not managed carefully, result in multiple degenerative effects. The degenerative effects elicit negative nitrogen balance states and tissue destruction. Examples in persons with diabetes are microvascular disease, neuropathy, and muscle wasting. In recapitulation, metabolism and its concomitant stages are the essence of life.

The human body is built for the maintenance of functions based on a stable metabolic state. In contrast to stable states, the human body contains adaptive mechanisms that use various chemicals and other factors to adjust to conditions of starvation, stress, injury, and trauma. This chapter discusses the mechanisms of carbohydrate, protein, and fat metabolism as well as concepts of fluid, electrolyte, and acid–base balance as they relate to diabetes. The physiologic role of insulin, the consequences of insulin deprivation, and the special nutrient conditions related to diabetes are described.

Blood glucose is maintained in the human body in very narrow ranges (fasting blood glucose of 60–100 mg/dl [3.3–5.6 mmol/L] and post meal glucose of 80–125 mg/dl [4.4–6.94 mmol/L]) through a dynamic, delicate homeostatic mechanism. A delicate balance is necessary between the release of insulin by the beta cells of the pancreas, the secretion of catecholamines (epinephrine and norepinephrine) by the adrenal medulla, glucocorticoids by the adrenal cortex, glucagon by the alpha cells of the pancreas, and growth hormone by the pituitary as well as pancreatic polypeptide and somatostatin, hormones of the islets of Langerhans that mediate and balance the secretion and action of insulin and glucagon. Another hormone, amylin, is also secreted by the beta cells and functions to decrease glucagon secretion by the alpha cell of the pancreas to slow gastric emptying and depress appetite. With nutrient intake (i.e., in the postprandial condition), glucose load is increased; therefore, insulin is secreted by the beta cells of the islets of Langerhans. The net effect is to mediate the hormonal balance between insulin and glucagon secretion to decrease the serum blood glucose level, facilitate storage of excess glucose in liver, muscle, and lipid tissue, and encourage synthesis of muscle proteins. Thus, insulin has crucial effects on the metabolism of the three major nutrients: carbohydrates, fats, and proteins. In other words, insulin does not just affect sugar, but also fat and protein metabolism. When insulin secretion is compromised, and the body can no longer use glucose from carbohydrates, it then uses fat and protein by also converting some of the protein to glucose. This process is known as gluconeogenesis. A decline in insulin and the concomitant increased metabolic needs call for the release of fatty acids from fat storage depots (adipose tissues) and amino acids from muscles. Consequently, both fatty acids and amino acids are transported to the liver to be used for energy. Special conditions of starvation, stress, and trauma will also be discussed, enumerating the variations from the homeostatic mechanism.

Altered metabolism leads to and is threatened by obesity. With the current rise of obesity in children, an association of metabolic complications has occurred (Nathan & Moran, 2008). The metabolic syndrome clusters insulin resistance, hypertension, dyslipidemia, hyperglycemia, and obesity, and the
cardiovascular disease found in childhood and adolescence is the outcome if homeostasis is not accomplished.

Pathogenesis of Diabetes Mellitus

Diabetes is a disease of the derangement of metabolism. It is now regarded as a syndrome of multiple diseases with common symptoms but different etiologies and pathogenesis. To date, the only common denominator used to define diabetes operationally is an abnormal blood glucose level.

Diabetes mellitus may be caused by defects of insulin secretion and/or insulin resistance. There are two major types. Type 1 (T1DM) is an absolute deficit of insulin with elevated fasting blood glucose levels and increased postprandial blood glucose levels. This lack of insulin causes depletion of lipid and protein stores. In Type 2 (T2DM), insulin receptors in the peripheral tissues, enzymatic reactions within the cell, and the insulin secretion from the pancreas are compromised. Both types, then, are defined based on the relationship to insulin, not to an age classification (i.e., juvenile onset or adult onset).

The third type of diabetes mellitus is referred to as other types of hyperglycemia and encompasses a wide variety of genetic syndromes, pancreatic diseases, hormonal abnormalities, chemical exposures, and insulin-receptor abnormalities.

Carbohydrate–Insulin Relationship

Glucose is the primary fuel for all body tissues. The brain uses 50% of the total body glucose—an especially high demand. Because brain energy stores are small, a constant supply of glucose must always be available to maintain adequate brain function. It is therefore imperative that the blood glucose level be maintained in the 60–120 mg/dl (3.3–6.6 mmol/L) range to prevent central nervous system compromise.

Insulin is the primary hormone for regulating blood glucose levels and does so by controlling the rate at which blood glucose is taken up by muscle, fat, and liver cells. Each of these three types of cells uses glucose in a different way, as determined by specific enzyme systems and glucose uptake proteins on the cell membrane. Many of the principles of diabetic management and control are based on the intricate interaction of insulin and other hormones with these three cellular processes.

Fat Cell–Lipid Metabolism

The primary function of the fat cell is to provide energy storage. It contains unique enzymes that convert glucose into triglycerides as well as enzymes that convert triglycerides to fatty acids, which are released as needed and converted to ketones in the liver.

The conversion of glucose to triglycerides and the breakdown of triglycerides to free fatty acids occur continuously and simultaneously within the same fat cell, and both processes are regulated by insulin. High blood insulin levels
stimulate the uptake of glucose by fat cells to form triglycerides; thus, there is a net gain of storage fat. During low blood insulin levels, glucose uptake into the fat cell is poor; thus, fewer triglycerides are formed. Triglyceride breakdown, then, exceeds formation, resulting in a net loss of the storage fat. Thus, by regulating glucose uptake into fat cells, insulin influences net fat metabolism.

Insulin also inhibits the enzyme, lipase, which breaks down storage fat into fatty acids and glycerol. When insulin is high and lipase is inhibited, there is a net increase in storage fat. A net decrease in storage fat occurs when insulin is low, because lipase becomes activated and fat is then broken down.

Muscle Cell

The muscle cell has two primary functions. It converts glucose into the energy needed for muscle function, and it serves as a reservoir for protein and glycogen. When a person starves, the protein of the contractile apparatus itself can be made available in the form of amino acids, which can then be converted into glucose in the liver to maintain blood glucose at an adequate concentration for brain function (gluconeogenesis).

In the muscle cell, as in the fat cell, insulin promotes the uptake of glucose. The muscle cell, however, has different enzymes that control two metabolic pathways for glucose. First, glucose can be converted into contractile energy. Second, glucose can be converted to glycogen, a storage form of glucose that is more readily available than triglycerides in times of glucose insufficiency. When blood glucose levels are normal, insulin also assists muscle cell enzymes to maintain muscle mass by promoting the uptake of amino acids and preventing the breakdown of protein.

Liver Cell

Liver glycogen is another storage form of glucose. As mentioned earlier, glycogen is more readily available for use than are triglycerides, which first have to be converted to free fatty acids and then converted to ketones. The liver monitors these conversions and also converts amino acids to glucose when necessary. The latter process is called gluconeogenesis (new glucose formation). Although insulin is not required for the transport of glucose into the liver, insulin directly influences the liver to promote the uptake of glucose by reducing the rate of glycogenolysis (glycogen breakdown), increasing glycogen synthesis, and decreasing the rate of gluconeogenesis.

Beta Cell

Insulin is secreted by the beta cells of the islets of Langerhans in the pancreas, which continually monitor glucose levels. The beta cells function first as a sensor of blood glucose levels, then they secrete enough insulin to regulate the carbohydrate load, maintaining the blood glucose level within a narrow range. A feedback system exists whereby a small amount of carbohydrate stimulates a
small amount of insulin release. The liver responds to increased insulin secretion by stimulating glycogen synthesis (glycogenesis) and suppressing glycogen release (glycogenolysis). The formation of new glucose (gluconeogenesis) is likewise suppressed. A large carbohydrate intake stimulates a greater insulin response, and the peripheral and liver cells take up glucose. When glucose levels are low, insulin release is suppressed and glycogenolysis and gluconeogenesis occur to feed glucose into the system and maintain the blood glucose levels.

Although the process of beta cell stimulation and insulin release is not entirely understood, it is recognized that glucose metabolism signals the synthesis of the precursor of insulin called proinsulin. Proinsulin is transformed into insulin within the beta cell, and the insulin is then stored in granules and released in response to several stimuli. Glucose is the most profound stimulus to insulin release. Other stimuli include amino acids, hormones, vagal stimulation, sulfonylureas, and ketones. Those substances diminishing insulin secretion are epinephrine, norepinephrine, thiazide diuretics, starvation, and hypoxia. Pancreatic insulin is secreted directly into the portal circulation to the liver, the central organ of glucose homeostasis, where 50% of the insulin is degraded. The peripheral circulation then transports insulin to body cells and to the kidney, where 25% is degraded, and excretion occurs.

Intracellular Functioning Through Second Messengers

Insulin affects glucose, lipid, and protein metabolism in all tissues, as discussed earlier. In fat cells, insulin promotes the uptake and enhances triglyceride stores. In muscle cells, glucose enters via the cell membrane made permeable by insulin, and is converted to glycogen stores or used for energy. In liver cells, glucose is stored as glycogen. The intracellular effects of hormones are accomplished by second messengers, which are activated by receptors on cell membranes that determine whether or not the cell responds to the hormones. Specific enzymes then allow the cell to perform its functions in response to hormones and second messengers. The second messenger for most hormones is cyclic adenosine monophosphate (cAMP), which is activated by the enzyme adenyl cyclase in the cell membrane. Insulin suppresses adenyl cyclase and cAMP and activates other second messengers. These messenger enzymes are activated by closure of the potassium channels and opening of the calcium channels so that calcium can flow into the cell and activate formation of cAMP.

One enzymatic mechanism that insulin-responsive cells have is the phosphorylase–kinase system. Insulin stimulates the cells by interaction with a specific receptor on the cell surface, and this stimulates a series of enzymatic phosphorylation reactions within the cell. Finally, this phosphorylase cascade activates the PPar gamma enzyme in the cell nucleus. This enzyme activates the gene for the formation of the RNA, which synthesizes a protein called a glucose transporter to facilitate the uptake of glucose by the cell. Glucose transporter proteins modify the cell membrane to absorb the glucose into the interior of the cell for utilization. These transporters are manufactured inside the cell and carried to the cell membrane under the control of insulin and the subsequent enzyme reactions within the cell. Insulin also controls the reabsorption and degradation of the transporters that are numbered to differentiate the proteins
of different cells—GLUT 4 (Glucose Transporter 4 is found within muscle cells). A hexokinase enzyme inside the cell is also stimulated to facilitate the glycolytic process for the metabolism of glucose to CO₂, water, and energy (the Kreb’s cycle). This hexokinase enzyme is the only enzyme of the glycolytic pathway activated by insulin. It catalyzes the initial step of this process that is the phosphorylation of glucose to form glucose 6-phosphate.

This catalysis is a vital step in the metabolism of glucose for energy, and insulin deficiency will result in blockage of the entire glycolytic pathway for energy production. The enzymatic system for lipogenesis (to fats) is specific to the fat cell, whereas the enzymatic system for conversion of glucose to energy occurs in all cells. By a separate set of enzymes, the fat can, of course, also convert glucose to energy for its own metabolic processes, because the conversion of glucose to fat is an energy-requiring process. All of these specifics are probably mediated by a second messenger through an activation of the sodium potassium pump and by the calcium flux.

Hormones Relative to Metabolism

Epinephrine
Epinephrine works to prepare the body for many different kinds of stress. Its effect on glucose is rapid and can produce continuous changes in blood glucose levels. Stress stimulates epinephrine release, and the hormone then serves to mobilize glycogen to yield a higher blood glucose level. This part of the fight-or-flight mechanism supplies the energy needed by the body to meet emergencies.

Corticosteroids
Corticosteroids increase gluconeogenesis (new glucose) from protein (amino acids) by the liver. Glucocorticoids can respond to acute stress but are more generally associated with chronic stress. Treatment with high-dose steroids is a potential trigger to the development of hyperglycemia and diabetes especially if the genetic component is already present.

Growth Hormone
Growth hormone, together with insulin, promotes body growth. Its effect on blood glucose levels is much slower than epinephrine or glucocorticoid hormones. Epinephrine acts in seconds, glucocorticoids in minutes, and growth hormone in hours. Growth hormone elevates blood glucose, making it available for the growth process, but its physiologic role in glucose control is unknown. Although growth hormone elevates blood glucose levels and hypoglycemia will increase growth hormone levels, it is now doubtful that growth hormone plays any meaningful role in continuous regulation of blood glucose levels.

Metabolism in Starvation, Stress, and Injury
Normal metabolism within the context of homeostasis occurs as described earlier. In starvation, stress, and injury states, however, the mechanisms can
alter, escalate, or compensate in various ways. Each of these states is discussed, as they are germane to the maintenance of a balanced or steady state in the person with diabetes.

### Insulin Deficiency

The abnormal state of insulin deprivation as observed in individuals with unknown or uncontrolled diabetes is similar to a state of severe starvation. The degree of lack of insulin will influence the extent of this process. If untreated, complete insulin deprivation, as often observed in the young child with diabetes, will terminate in ketoacidosis and coma. The adult with diabetes with a minimal lack of insulin may not even experience symptoms of the disease.

An immediate consequence of insulin deficiency is the lack of glucose uptake by cells. In fat cells, triglyceride stores are liberated in the absence of insulin, yielding free fatty acids that are ultimately converted into ketones and glycerol. In muscle cells, glycogen stores are activated and protein is degraded to amino acids that are then converted into glucose in the liver.

**Diabetes mellitus** may be defined as an absolute or relative lack of insulin that results in aberrations of fat, protein, and carbohydrate metabolism. Absence of insulin production initially affects the uptake of glucose in muscle and fat cells. As glucose’s entry into cells diminishes, the body signals for fuel, and glycogen is released from the liver. The blood glucose level is thereby further elevated. As the glucose levels approach 180 mg/dl (10 mmol/L) of blood, the capacity of the renal tubules to reabsorb glucose (renal threshold) is exceeded, and glucose is excreted into the urine (glucosuria). The renal threshold is known to be lower in women during pregnancy and in children. It may be elevated in the older patient or in persons with a long history of diabetes. Because glucose is an osmotic diuretic, water and salts are also excreted in large quantities, and cellular dehydration occurs. Prolonged, excessive diuresis (polyuria) combined with caloric loss causes polydipsia (increased thirst), polyphagia (increased hunger), and fatigue, the classic symptoms of diabetes mellitus. Despite polyphagia, there may be weight loss because the food ingested cannot be used in the absence of insulin.

In addition to the classic symptoms mentioned, others may also be present. Weight loss, commonly seen in the child with diabetes, is uncommon in the adult, who is often obese. Fluctuation in blood glucose levels with changes of osmotic pressures may change the shape of the lens of the eye and the content of the vitreous humor, resulting in refractive changes manifested by blurred vision. Headache is often a major complaint and may be related to the vision problems. Faintness, nervousness, and hunger, experienced chiefly by adults, occur 1 or 2 hr after a meal; these problems are caused by rapid gastric emptying in the absence of the hormone amylin and the intestinal hormones GIP and GLP1 with a delayed insulin release, resulting in immediate hyperglycemia and later hypoglycemia. Weight gain, skin infection, and recurrent vulvovaginitis are fairly common complaints in the adult with diabetes.

Individuals with stable T2DM are often asymptomatic, and the diagnosis is made incidentally by routine blood or urine laboratory tests. These individuals frequently have the chronic complications of diabetes, such as recurrent
infection, atherosclerosis, peripheral vascular disease, neuropathy, and ocular complications, at diagnosis because the diagnosis is delayed.

When the onset of diabetes continues unchecked, especially in younger, ketosis-prone individuals, cells attempt to respond to glucose deprivation initially by metabolizing protein, resulting in the liberation of amino acids in large quantities. Some of these amino acids are converted into urea in the liver and are excreted, which results in a negative nitrogen balance. Other amino acids are converted to glucose, further enhancing the hyperglycemic state.

In the absence of insulin, fat cells attempt to provide fuel by mobilizing fat stores. The free fatty acids are initially used for energy production, but the majority reach the liver in which three organic acids are formed: acetoacetic acid, beta hydroxybutyric acid, and acetone. The keto acids are ultimately excreted by the kidney along with sodium bicarbonate. The combination of keto acid accumulation and bicarbonate excretion causes a fall in plasma pH, resulting in acidosis. The body attempts to correct the acidosis by the characteristic Kussmaul’s respiration, which is deep, labored respiration caused by the body’s effort to convert carbonic acid (H₂CO₃) to carbon dioxide and water, and to excrete the carbon dioxide via the lungs. In an unchecked state, acidosis, dehydration, and electrolyte imbalance ultimately affect brain function, and coma results. Death may occur if insulin deficiency remains untreated.

Total body potassium may be decreased because of cellular breakdown and excretion. Dehydration, however, may cause the serum potassium to be concentrated in less body fluid, resulting in low, normal, or elevated serum potassium levels. Potassium may also show a false positive because of pH-buffering mechanisms. Sodium is lost along with water in the urine, and serum sodium is almost always severely depleted, indicating a water (cellular) deficit.

Insulin treatment reverses the catabolic state created by insulin deficiency. Blood glucose levels fall, fats cease to break down, ketones are no longer produced, serum bicarbonate and pH levels rise, and potassium shifts intracellular as anabolism (tissue rebuilding) begins.

Incretins (GLP-1 and GIP) are hormones secreted by the gut that mediate insulin release and glucagon suppression (Fujioka, 2007). Glucagon suppression is most noticeable in individuals with T2DM, although it is present in various forms in T1DM. Glucagon-like peptide-1 (GLP-1) has an insulinotropic effect, and appears to preserve this ability when enhanced by medication. Glucose-dependent insulinotropic polypeptide (GIP) is inactivated in persons with T2DM. Both GLP-1 and GIP are inactivated by dipeptidyl peptidase 4 (DPP-4). The use of DPP-4 inhibitors and GLP-1 and GIP analogs have aided in glucose processing in the presence of adequate insulin.

Starvation
Insulin deficiency in the pathogenesis of diabetes mellitus was initially reported by many people in the 19th century from studies in pancreatectomized animals. The hormone itself was not discovered until long after it had been named. The name of the hormone insulin comes from the discovery by such men as Bernard, Vircow, Minkowski, and others that it came from the islets of Langerhans in the pancreas (islands in Latin is insular; thus the name insuline initially).
Historically, Banting and Best (Banting, 1925), more than 80 years ago (1921), are credited with the epoch-making discovery of insulin. Further investigation by many other investigators showed the relationship of pituitary and adrenal hormones interfering with insulin action and contributing to hyperglycemia. This latter finding relates to the stress mechanism, a discussion to follow. In the 1960s hormonal analysis through radioimmunoassay studies to measure polypeptide type hormones was developed. This technique has further confirmed that insulin deficiency characterizes T1DM and some people with T2DM.

In general, the body’s basic response to starvation is to lose nitrogen compounds in the urine. The person with diabetes and without appropriate treatment is in a state of metabolic response to starvation, because glucose and other nutrients are not properly transported to cells and metabolized. Calories to sustain life in a starvation state are derived from fat stores (80%–90%) and the remaining calories are taken from protein catabolism. Survival is related to the body’s ability to enhance oxidation of lipids and reduce breakdown of proteins.

The usual hallmark of starvation is progressive weight loss, seen as flaccid skin, lean body mass, poor skin turgor, and flaking skin. Initial weight loss reflects a disproportionate loss of water. A healthy individual can lose 5%–10% of normal body weight in water without loss of function; 40% loss is incompatible with life. After initial water loss, overall tissue loss occurs in the visceral organs (i.e., liver, pancreas, and gut). Studies of prolonged starvation show that the greatest weight loss is in visceral organs with least loss occurring in skeletal and orbital tissue. Additionally, increased glucagon and protein catabolism increases sodium, potassium, and magnesium losses. In later stages, urinary loss of sodium and potassium may buffer increased urinary ketone levels. The excretion of sodium and potassium in early starvation is decreased by administering glucose and insulin.

Changes in body composition from starvation include increased extracellular fluid (saline), loss of intracellular fluid (water), disproportionate loss of fat, and lesser losses of lean body tissue. Bone minerals are usually maintained. The tissue lost in early starvation is thus a mixture of fat, protein, and water, a caloric equivalent of 2,000 kcal/kg. Untreated or prolonged starvation could result in losses of up to 8,000 kcal/kg. The metabolic response is to use any available glucose (provided insulin is available), then fat stores, then proteins. With the exception of nervous tissue, body organs lose fat in proportion to their original lipid content (from fat stores). Protein loss follows, and it is important to note that there is no protein depot or stored protein as such. Every protein molecule serves a vital function. Thus, the use of protein (even 5%–10%) for energy results in loss of protein molecules essential to enzymatic and cellular functions. Skeletal muscle is first catabolized raising the blood urea nitrogen and urinary nitrogenous compound excretions, in a mean output of 12 g/day during 3–5 days. If this initial rate continued, death would quickly ensue. So the adaptive responses in long-term starvation result in the sparing of body proteins. Urinary losses decrease to 3–4 g/day.

Further, starvation reduces energy expenditure by neuroendocrine responses discussed in the stress section. Cardiac load is reduced, noted by bradycardia and decreased triiodothyronine (T₃). Skeletal energy needs are decreased with decreased glycogen, resulting in decreased muscle tone. Examination shows loss of more red muscles than white muscle (Levenson & Seifter, 1983).
In summary, the overall effect of starvation is as follows:

1. Initial rise of urinary nitrogenous excretion.
2. Increase in blood fatty acids, keto acids, and ketones, producing metabolic acidosis and ketonuria.
3. Increased blood glucose levels in persons with diabetes (lowered in persons without diabetes).
4. Increased urinary excretion of sodium, potassium, and other minerals.

Thus, persons with untreated diabetes experience a complicated starvation state and are particularly vulnerable, because compensatory mechanisms are often compromised in the absence of insulin and its multiple effects.

Stress

Stress states are ubiquitous with life. Persons with diabetes are additionally challenged, however; because much of the stress response mechanism is geared toward hyperglycemia to provide energy for the fight-or-flight syndrome (Cannon, 1953). The stress mechanism is a complex quality control system, in general, a negative feedback system that is directed to respond to increased body demands. It is a complicated neuroendocrine-mediated response to a trigger event. A discussion of the intermediary relationships between various neurologic and endocrine enzymes follows.

The stress response functions through intermediaries called hormones. The master hormones are secreted by the pituitary gland and the hypothalamus, which stimulate specific target glands throughout the body. Because diabetes is a metabolic disorder and because the insulin–nutrient relationships are impaired, stress phenomena make the person with diabetes additionally vulnerable. Consequently, stress (such as surgery, infection, or major psychosocial events) must be acknowledged in the medical management regimen. Most of the neuroendocrine hormones are involved in the stress mechanism, but some are more specifically involved.

The stress mechanism, a normal metabolic reaction, regularly triggers the hypothalamus area of the brain that in turn stimulates the anterior pituitary gland to produce the following hormones: growth hormone (HGH) also known as somatotropin (STH), thyrotropin (TSH), adrenocorticotropic hormone (ACTH), the gonadotrophic hormones (follicle-stimulating [FSH] and luteinizing hormone [LH]), and prolactin. The posterior pituitary secretes two additional hormones for stress, antidiuretic hormone (ADH) and oxytocin, involved in blood pressure control and childbirth. All of these master gland hormones are facilitated for secretion by intermediaries released in the hypothalamus called releasing hormones. After release by the pituitary, the hormones are transported via the bloodstream to stimulate target receptor sites in biologically programmed glands. The target glands (e.g., the adrenal cortex, thyroid gland, gonads, kidney, and so on) respond by secreting additional hormones, such as steroids, thyroxin, cortisol, and so on.

Hormones mediate the metabolism of nutrients. Persons with diabetes are affected not only regarding the insulin (a hormone) and glucose relationship
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previously discussed, but also in other hormone–nutrient relationships: growth hormone–protein synthesis and cellular factors; thyrotropin-thyroxin-cellular metabolic rate; adrenocortical hormones, glucose, and fluid and electrolyte metabolism (primarily salt balance); and antidiuretic hormones and water balance. Gonadotrophic hormones and the stress of pregnancy in the person with diabetes must be closely managed.

Stress, as a normal metabolic process, as well as increased stress, is important to the metabolic management of people with diabetes. Increased stress, or distress as defined by Selye (1976), prepares the body for fight or flight by release of adrenal medullary hormones, catecholamines, specifically epinephrine and norepinephrine. Each of these hormones facilitates specific effects. The hypothalamus is also stimulated by stress, causing the release of the pituitary hormones. In persons with diabetes, balance is particularly precarious, as multiple nutrient relationships are affected, especially glucose, sodium-potassium, and water balance. Glucose metabolism is affected by ACTH release (glucocorticoids and mineralocorticoids), thyroxin, and growth hormone. Glucocorticoids increase release of proteins and stimulate their conversion to glucose by the liver (gluconeogenesis), increasing blood glucose levels. Additionally, the release of epinephrine for additional stress mobilizes glycogen (glycogenolysis) to yield higher blood glucose levels. Thus, all hormones except insulin contribute to an increased blood glucose level, which requires more insulin production to facilitate transport of glucose into the cell; without sufficient insulin, hyperglycemia results. Additionally, the catecholamines suppress insulin release as does the stress of starvation and hypoxia.

Thus, the general effects of stress are a response to hormonal metabolism. Concurrently, the responses of the autonomic nervous system are elicited. Further information on this response follows in the discussion on injury and inflammation.

Injury and Inflammation

Adaptations to body changes caused by injury and inflammation elicit a set of characteristic responses. This challenge is particularly arduous for the person with diabetes. Thus, all goals in diabetic management are directed toward prevention of injury, trauma, surgical and critical illness, and infection.

The neuroendocrine mechanisms undergirding the human body’s response to injury and inflammation are altered, causing a profound effect on the person with diabetes. Injury elicits an autonomic nervous system response escalating to a central nervous system response, thus connecting with the pituitary for mediation. The autonomic nervous system mediates internal homeostasis, with the sympathetic branch being the chief effector in stress, injury, and inflammation. This response accentuates release of catecholamines, which, in turn, increase glucose and free fatty acids and suppress the expected elevation in insulin.

In injury, the characteristic shifts of fluids and electrolytes are directed at fluid and electrolyte balance (preservation of intravascular fluid and therefore tissue perfusion). Obligatory retention of sodium and water is mediated by ACTH and ADH, respectively. Initially, this results in saline excess (lowered
hematocrit) and water excess (lowered serum sodium). If shock or hypoxia occurs, metabolic acidosis ensues (pH lowered and serum carbon dioxide lowered because of lactic acidosis). The stress raises the blood glucose, and catecholamines suppress insulin release, resulting in hyperglycemia. Normally, wound healing depends on aerobic energy. The person without diabetes has a strong response to stress; a person with diabetes has an aggravated stress response, resulting in the use of lipids and protein for cellular energy, leading to ketoacidosis and delayed wound healing. Profound effects (severe metabolic acidosis) of combined lactic and metabolic acidosis can occur.

In the postinjury and postinflammatory phases, adequate energy is required to maintain bodily functions, to free reparative processes, and to respond to pathologic energy demands. Sources of energy are either exogenous or endogenous, and the caloric, fluid, and electrolyte needs in the individual with diabetes must be closely monitored. Typically, as is the case of uncomplicated starvation, lipid stores will supply approximately 80%–85% of energy needs. Long-term protein stores will be challenged to provide the remaining 20%. Protein use for energy can result in as much as a 10% weight loss. Thus, the potential for muscle wasting is metabolically increased in the person with diabetes.

In injury, without shock, proteins from lean tissue are mobilized, which is reflected in increased urinary nitrogen. It is unclear if proteins are mobilized because of increased muscular protein catabolism or reduced protein synthesis; this may depend on the severity of injury. In severe injury, sulfur-containing amino acids are elevated, indicating increased protein breakdown. Exogenous glucose can reduce loss of nitrogen. Therefore, treatment of hyperglycemia and supplying glucose is important in decreasing nitrogen loss. Additionally, decreased insulin levels inappropriate to plasma glucose levels favor lipolysis and release of fatty acids—again, emphasizing the propensity for ketoacidosis of the person with diabetes.

In comparison, the metabolic response to starvation, in general, differs from the metabolic response to injury in relation to nitrogenous losses, gluconeogenesis, and resting energy expenditure. In general, responses are augmented in injury and are diminished in starvation. The starvation response is directed to conserve tissue to prolong life, whereas injury accentuates tissue loss. The person with diabetes is particularly vulnerable to both.

**Altered States: Acidosis and Hyperglycemia**

Acidosis, a serious and critical state in diabetes, is a result of the primary pathogenesis of diabetes—insulin deficiency. The inability to transport glucose to cells and to metabolize cellular glucose leads the body to burn fats (lipids) for energy. The stored lipids are split into free fatty acids, then to ketone derivatives. Thus, this disorder is named ketoacidosis. Lipids are split to acetoacetic acid, beta hydroxybutyric acid, and acetone that rise in the extracellular fluid. Consequently large quantities of ketones are excreted in the urine, sometimes as much as 500–1,000 mmol/day. Diabetes acidosis results, then, primarily from the presence of keto acids (measured as ketones in blood and urine). This high acidic state (high hydrogen ion concentration) causes chemoreceptors to increase respiratory rate and depth; a key diagnostic sign
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is called Kussmaul’s respiration. Diabetes acidosis also results from the loss of large amounts of sodium bicarbonate, the alkaline half of the bicarbonate–carbonic acid buffer system (measured as a low serum carbon dioxide level, less than 22 mEq/L, and a large anion gap). Metabolic acidosis often results in profound reduction of serum carbon dioxide in contrast to respiratory acidosis. The major effect, which is death producing if unattended, is depression of the central nervous system, ranging from lethargy, dulled sensorium, disorientation, to coma. In persons with diabetes, the central nervous system depression and shock caused by metabolic acidosis progresses to a comatose state (McCance & Huether, 1998).

This hyperosmolar state created by high levels of glucose, free fatty acids, and ketones also results in excessive urinary excretion of saline fluids, thus leading to a saline depletion state, a type of hematogenic shock. The concomitant altered metabolic state can be prevented by adequate ammonia secretion by renal tubules, as hydrogen ions combine with ammonia and thereby release sodium for tubular reabsorption. When the total amount of acids (i.e., keto acids) entering the tubules exceed the rate of ammonia secretion, the excess acid transports sodium with it into the urine rather than allowing it to reenter the extracellular fluids as sodium bicarbonate.

Additionally, levels of potassium must be concurrently evaluated as the acidotic state increases. Cells, the third of the four-part buffering system (plasma, lungs, cells, and kidneys), will absorb hydrogen (acids) from the extracellular fluids to decrease the acidity of the plasma and therefore decrease the severity of the acidosis. This reaction results in the release of potassium from the cell to the plasma, however, resulting in a redistribution hyperkalemia. If the extracellular levels rise above 6.0 mEq/L, a toxic state is created and must be treated accordingly. Key diagnostic signs of potassium alteration are specific configurations in electrocardiogram tracings, such as high tented T waves in hyperkalemia, widening of the QRS complex, lowering and flattening of P waves leading to bradycardia and atrial arrest and flattened T waves, and the appearance of U waves in hypokalemia.

Buffering Mechanisms

Because the maintenance of acid–base balance is crucial to equilibrium, the body has several levels of defense or compensatory mechanisms against changes in pH. Physiologic compensatory mechanisms or compensation enables the adjustment by the organs to stress or physiologic disruption. These mechanisms can be total, partial, or noncompensatory in action, and they include the action of four regulatory systems: chemical serum buffers, lungs, cells, and kidneys.

The four mechanisms are triggered by a stressor, an event leading initially to physiologic imbalance, such as the excess of hydrogen ions (acids), which might result from ketoacidosis in uncontrolled diabetes (metabolic condition) or hypoventilation (respiratory condition). This state of excess of hydrogen ions (acidemia–acidosis) subsequently triggers the buffering mechanisms to respond. The response is time sequenced as follows: serum chemicals (seconds to minutes), lungs (10–30 min), cells (2–4 hr), and kidneys (hours to days).
Serum Chemical Buffers

A buffer is a certain combination of chemicals contained in the fluids of the extracellular compartment that act as a deterrent against spontaneous and critical changes in the hydrogen ion concentration. A buffer is sometimes conceptually likened to a “chemical sponge,” because it can “soak” up surplus hydrogen ions or release or donate them to calibrate or balance the fluctuations in pH. A buffer is composed of a “weak” acid combined with one of the salts of that acid. Although there are several buffering mechanisms in the human body, the most important one is the carbonic acid–sodium bicarbonate system in the serum.

The chemical serum buffers are the first level of defense against changes in the body’s acid–base balance. They begin to react immediately to counteract the slightest change in pH balance. Chemical buffers are paired compounds—a weak acid is paired with a weak base or salt. The weak acid separates to neutralize strong bases. The weak base separates to neutralize strong acids. Once the chemicals have reacted, they are consumed and cannot be used again as a defense until the body has had time to replenish them. Three primary (serum) chemical buffers function in the donor–acceptor pattern: bicarbonate, hemoglobin, and plasma proteins. The bicarbonate buffer is the key compensating mechanism in diabetes.

Bicarbonate Subsystem

One part of carbonic acid exists in relationship to 20 parts of bicarbonate. The base bicarbonate system must maintain this ratio of 20 parts bicarbonate to 1 part carbonic acid in the blood to keep a slightly alkaline pH (normally pH 7.4). Bicarbonate is produced when carbonic acid dissociates into hydrogen and bicarbonate. For example, if a strong acid like hydrochloric acid enters the bloodstream, the weak base sodium bicarbonate combines with it to form the weak carbonic acid and salt, sodium chloride. The salt does not affect the pH level, and the weak acid only slightly reduces the pH.

Hemoglobin Subsystem

When the bicarbonate or carbonic acid is consumed, the bicarbonate buffers can no longer react, and the next level of the blood chemical buffer regulatory system, hemoglobin, is challenged. The chloride in hemoglobin shifts in and out of the red blood cells as the level of oxygen changes in the blood. Chloride also leaves the cell in relation to pH changes. As the plasma becomes more alkaline, chloride shifts out of the cell. As a result, bicarbonate moves in. Conversely, if chloride moves into the red blood cells, bicarbonate moves out. In this way the body has another level of chemical control. The chloride shift corrects acidosis, or alkalosis, by varying the level of bicarbonate available to handle the stress. In acidosis, chloride may also combine directly with hydrogen. For example, a person whose system has become acidic from a starvation diet or a fad high-protein, low-carbohydrate diet may develop mild acidosis. This mild state of acidosis usually ranges from pH 7.34 to pH 7.30 and can be corrected by the chemical buffer bicarbonate. If slightly more bicarbonate is needed than is
available in the bloodstream, the oxygen level decreases. The reduced oxygen causes chloride to shift into the red blood cells and the bicarbonate to move into the bloodstream to buffer the excess acid that is not neutralized by bicarbonate. Chloride shifts occur in acute diabetic coma.

**Protein Subsystem**

The third chemical buffer is plasma protein, primarily albumin and globulin. Plasma protein, functioning in conjunction with the liver, has the ability to attract or release hydrogen ions. For example, alkalosis is diagnosed in a person having gallbladder problems with a pH range of 7.47 to 7.55 because of the loss of hydrochloric acid resulting from vomiting. In this case, the liver reacts to a decrease of acid by breaking down the plasma protein, thereby releasing more hydrogen ions that add acid to the blood and neutralize excess base. If the alkalosis or acidosis is too severe, the chemical buffers can reduce it only slightly.

**Lungs**

If serum chemical buffering systems are not able to correct the pH change, the second buffering mechanism is stimulated (i.e., the lungs). The lungs are unique in that they can regulate only the problems caused by metabolic acid–base imbalances. They cannot compensate for respiratory acid–base problems because the lungs themselves are part of the problem. The lungs initially assist the chemical buffers to maintain the correct metabolic base balance and act directly as a regulator system after the chemical serum buffers are consumed. During acidosis, the lungs aid the base bicarbonate and chloride chemical buffers. Bicarbonate neutralizes the excess strong acid into the weaker acid (i.e., carbonic acid). The lungs then break the carbonic acid, a volatile acid, into carbon dioxide and water, which is exhaled as a gaseous substance. In this way, the lungs act as a facilitator to the bicarbonate buffer system.

When the chemical buffers are consumed, the lungs react either to the excess or deficit in the ratio of bicarbonate to carbonic acid in the bloodstream by changing breathing patterns. With normal body pH, respiratory depth and speed are constant. When there is too much base or too little acid in the blood, resulting in a pH greater than 7.45, the lungs automatically reduce depth and speed of respiration to compensate for metabolic alkalosis. This slowing action (hypoventilation) causes carbonic acid to build up in the bloodstream. The retained carbonic acid neutralizes the excess base in the blood, thus reducing the metabolic alkalosis. If there is too much acid or too little base in the bloodstream and the pH drops below 7.35, the lungs increase the depth and speed of respiration, exhaling (hyperventilation) the excess acid in the form of carbon dioxide and water. This compensates for metabolic acidosis. An example of acidosis regulation is seen in patients who are hyperventilating as a result of diabetic acidosis. The lungs respond in 10–30 min to decrease the amount of acid in the bloodstream. Because the lungs can only exhale or retain carbon dioxide and water, they are only able to neutralize the hydrogen ions of carbonic acid. Fixed acid imbalances must be corrected by other regulatory systems, the cells and kidneys, especially in diabetic acidosis.
Cells

The cells regulate acid and base imbalances by exchanging potassium ions for hydrogen ions. Normally, 98% of the potassium is located inside the cell with only 2% in the serum. During acidosis, however, hydrogen ions move into the cell to reduce the acid in the serum. Potassium ions move out of the cell into the interstitial fluid and eventually into the serum to allow room for the hydrogen ions.

Although this hydrogen potassium exchange temporarily relieves the acidosis, it has the potential of creating a toxic state. As the quantity of potassium outside the cell increases, it rapidly becomes toxic causing a potassium excess called hyperkalemia. The hydrogen potassium exchange causes the level of potassium in the serum to increase six tenths for each one-tenth decrease in the pH reading. At this rate, the potassium rapidly reaches the toxic level (especially on the heart) of 6.0 mEq/L; consequently acidotic persons may evidence hyperkalemia or a “false” normal, with excessive gastrointestinal losses in diabetic acidosis. The excess serum potassium may be reduced by renal excretion causing a total body potassium deficit.

Kidneys

The kidneys are the last level of defense the body has against acid–base imbalances. The kidneys control the acid–base balance by regulating bicarbonate, converting phosphate to phosphoric acid, and changing ammonia to ammonium. The kidneys can control the amount of bicarbonate in the body by selectively secreting hydrogen ions into the urine and retaining bicarbonate ions, or excreting bicarbonate and retaining hydrogen. In the normally functioning kidneys with a normal serum pH, proportional amounts of hydrogen and bicarbonate are secreted into the kidney tubules. The tubules select whether to retain bicarbonate or hydrogen. The electrolytes not retained are excreted in the urine. Normal urine pH is 5.5 to 6.5. If the extracellular fluid becomes acidic, bicarbonate is used in the extracellular fluid to reduce acidosis, resulting in more hydrogen ions in the kidney tubules than bicarbonate. These excess ions, combined with the tubular fluid, are then excreted in the urine. In this way, hydrogen ions are removed from the body, and acidosis is reduced. This is primarily a kidney compensation for respiratory acidosis. Although it takes hours to days, this process can also help reduce severe metabolic acidosis. Bicarbonate is also used if the extracellular fluid becomes alkaline. The excess bicarbonate in the kidney tubules combines with sodium and is secreted in the urine in the form of sodium bicarbonate. This process is primarily a correction for severe metabolic alkalosis.

A buildup of phosphoric acid (H₂PO₄⁻) from a kidney dysfunction can also create an acid–base imbalance. A chemical reaction, phosphate and hydrogen, in the kidney tubules allows both to be excreted in the urine as H₂PO₄⁻, which reduces the acid in the serum.

Another mechanism by which the kidneys control the amount of acid in the extracellular fluid is a combined function with the liver called the ammonium mechanism. When the acidotic state becomes so severe that the kidneys cannot control the acidosis with buffers in the kidney tubules, the distal tubules begin to
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secrete ammonia. Ammonia combines with hydrogen ions to form ammonium. This combination hooks to chloride and is excreted in the form of a salt. Both phosphoric acid and ammonium are fixed acids and are only excreted through the kidneys. The kidneys are slower to react than any of the other defenses against acid–base imbalances, but they are also more thorough. The kidneys take from several hours to several days to respond. The pH level of the serum is controlled by the regulatory systems in both health and disease states. During a disease state, the regulatory systems are less effective and medical intervention is usually needed. Observation of urinary responses to metabolic imbalanced states in diabetes is important. Attention to renal responses in acute diabetes shock and coma is paramount.

Summary

Metabolic balance is the challenge that all persons face. This is particularly crucial to the patient with diabetes, however, and therapeutic regimens may be necessary to achieve this balance. The body works to maintain a balanced state (pH 7.35 to 7.45 arterial blood gases) by use of the buffering mechanisms just described. Thus, stages of buffering in acidotic and ketoacidotic states follow a usual pattern, assisting in the assessment of worsening or improving states. The therapeutic regime is predicated on the knowledge of these buffering mechanisms in metabolic balance.

The diagnosis of acidosis is made from physical findings and laboratory assessment. Major clinical findings center on the following metabolic conditions present (new or concurrent) or escalated because of stress: hyperventilation (a compensatory mechanism), stupor leading to coma, neurologic hyperirritability with twitching and convulsion in uremia, and stupor and acetone breath in ketoacidosis. Laboratory findings show plasma bicarbonate less than 22 mEq/L, arterial blood gases show lowered pH (<7.35, more reduced than with respiratory acidosis), bases lowered, and elevated or false normal potassium (cellular compensatory mechanism). Note that persons with diabetes mellitus are primarily vulnerable but may also have other conditions concomitantly with diabetes. Fluids such as normal saline are used to correct the fluid and sodium losses and potassium is added when renal blood flow is established. Other fluids can be administered depending on the etiology of the imbalance. Fluid and electrolyte administration will be further discussed with the discussion of DKA in Chapter 6. Metabolic acidosis is a major derangement of metabolism. Attention to early recognition, return to balance, and prevention of complications is paramount for the person with diabetes. Diabetes mellitus is a complex disease based on the pathogenesis or the creation of a catabolic state caused by a deficiency (absolute, T1DM, or relative, T2DM) of insulin. Deficiency of insulin leads to inhibition of normal body functions, improper cellular metabolism, and tissue degeneration leading to a ketoacidotic state. Fluid, electrolyte, and keto acid balances are critical to blocking serious metabolic derangements affecting almost every body organ and its constituent functioning (Kee, Paulanka, & Pur nell, 2004 [a programmed instruction manual]; Lee, Barrett, & Ignatavius, 1996; Reusens, Host, & Remacheo, 2001). The metabolic processes, including the altered states of starvation, stress, and injury, have been described. Administration

Giugliano, Ceriello, and Esposito (2008) note that not one, but all three measures of glycemic control (HbA1c, fasting glucose levels, and postmeal glucose peak), must be taken into account to achieve normal blood sugars the majority of the time and as safely as possible. If an imbalance occurs in the body, there are likely to be complications associated with that imbalance. The sooner this “rebalancing” is achieved, the sooner homeostasis delays or prevents complications.

References