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# Heart Dysfunction in Diabetes

Grant N. Pierce, Robert E. Beamish and Naranjan S. Dhalla

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Authors

**Grant N. Pierce, Ph.D.**
**Robert E. Beamish, M.D.**
**Naranjan S. Dhalla, Ph.D.**
Division of Cardiovascular Sciences
St. Boniface General Hospital Research Centre and
Department of Physiology, Faculty of Medicine
University of Manitoba
Winnipeg, Canada


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# DEDICATION

To Dr. Henry G. Friesen, Professor and Head, Department of Physiology and Distinguished Professor of Medicine, University of Manitoba in recognition of his important contributions to endocrinology, physiology, and in appreciation of his leadership, guidance, and friendship.

# PREFACE

It is widely recognized that heart disease is the leading cause of death in the industrialized world and is of increasing incidence elsewhere. What is not as well appreciated is the highly significant role that diabetes mellitus plays in the genesis of heart disease. It has been said that if the contribution of diabetes to cardiovascular mortality were taken into account, diabetes mellitus would rank third (behind heart disease and cancer) as a cause of death in the Western World. While, admittedly, the acceleration of coronary atherosclerosis is the main factor in the increased heart disease encountered in diabetes mellitus, there has, in the past decade, been increasing awareness of a unique cardiomyopathy associated with the disease. It is the purpose of this book to identify and describe the complex mosaic of factors involved in the genesis of cardiac dysfunction during diabetes mellitus.

In recent years there has been a tremendous increase in knowledge and understanding of the structure and functions of the heart muscle cell at very basic molecular and atomic levels. The myocardial cell is capable of contraction and relaxation in a periodic fashion which depends on energy derived from various metabolic processes. These processes are much disturbed in diabetes mellitus. Additionally there are pathological changes in the autonomic nervous system and the microvasculature and an augmentation of the atherosclerotic process. Very little is known regarding the exact relationships among metabolic, ultrastructural, electrical, and mechanical events in the heart in health and disease — and particularly not in diabetes mellitus. Since various membrane systems such as sarcolemma, sarcoplasmic reticulum, and mitochondria are known to influence the function of contractile proteins it has become particularly important to study the molecular and cellular properties of these organelles. The enormous literature, scattered through journals devoted to physiology, biochemistry, pharmacology, ultrastructure, and clinical medicine, together with the laboratory observations of the authors, is reviewed and integrated in an effort to portray the origin, evolution, and consequences of heart dysfunction during diabetes. All of these factors are influenced by various drugs and hormones and by relating their actions to the underlying metabolic abnormality, new methods of prevention and treatment may be identified. This too, this book has attempted to review.

# ACKNOWLEDGMENTS

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# THE AUTHORS

**Dr. Grant N. Pierce** undertook graduate training at Dalhousie University and the University of Manitoba from 1977 to 1983. After receiving his Ph.D. degree from the University of Manitoba in 1983, Dr. Pierce continued his training in cellular and subcellular physiology in the Cardiovascular Research Laboratories at the University of California at Los Angeles. In 1986, he returned to the University of Manitoba to assume the positions of Assistant Professor in the Department of Physiology, Faculty of Medicine and Scientist in the St. Boniface General Hospital Research Centre, Winnipeg, Canada. He is currently a Scholar of the Canadian Heart Foundation. Dr. Pierce has published many full-length research manuscripts and edited a volume on the subject of cardiovascular physiology. He is Assistant Editor of *Molecular and Cellular Biochemistry*.

**Dr. Robert E. Beamish** received his M.D. degree in 1942 from the University of Manitoba and joined the Department of Medicine at the Health Sciences Center in Winnipeg. He furthered his training in cardiology from 1947 to 1948 at the National Heart Hospital in London, England. Dr. Beamish served a Medical Director of Great West Life Assurance Company from 1970 to 1981. He is presently Professor, Faculty of Medicine, University of Manitoba and Consultant at the St. Boniface General Hospital Research Centre. Dr. Beamish has authored numerous research papers, edited several books, and currently serves as the Editor-in-Chief on the *Canadian Journal of Cardiology*.

**Dr. Naranjan S. Dhalla** studied at the University of Pennsylvania before graduating from the University of Pittsburgh with a Ph.D. degree in 1965. For 2 years Dr. Dhalla taught as an Assistant Professor at the St. Louis University before moving to the Department of Physiology, University of Manitoba. He is currently a Professor in this department and Head of the Division of Cardiovascular Sciences at the St. Boniface General Hospital Research Centre. He has chaired several international heart meetings and presently serves the cardiovascular community as Secretary General of the International Society for Heart Research. Dr. Dhalla has published about 300 papers in the field of myocardial biology, has edited 17 books on the subject, and has been serving on the editorial boards of several journals for the past 15 years and currently serves as Editor of *Molecular and Cellular Biochemistry*.

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Chapter 1

# CLINICAL PROBLEMS ASSOCIATED WITH DIABETES MELLITUS

## I. INTRODUCTION

Diabetes mellitus is a clinical disorder of major medical significance. Epidemiological findings indicate that a relatively large percentage of the population in the U.S. suffers from diabetes mellitus and it is a leading cause of death in North America today. As a result of these factors, the economic burden on our society of diabetes management is staggering. Several conditions must be met in order to lessen the effects of diabetes mellitus. Before we can treat the disease, we must recognize the clinical symptoms of the disease and acquire information about the factors that are required to ameliorate the condition. Before we can take steps to prevent the occurrence of diabetes, we must undertake further research to understand the cause of this disease. This chapter will focus on the problems of diabetes mellitus in America today. The reader is referred to several volumes for more extensive reviews[1-3] on the nature of the clinical and research challenge which diabetes mellitus presently poses.

## II. TYPES OF DIABETES MELLITUS

Diabetes mellitus is a disease involving an alteration in the glucose homeostasis of the body. The glucose intolerance can be immediately life threatening or detectable only when the glucose regulatory mechanisms in the body are challenged. Diabetes is also a disease with varied etiology and pathogenesis. As a result of this heterogeneity in the disease, classification of the various types of diabetes has been nonuniform, confusing, and, in some cases, inaccurate. This problem has been addressed by the National Diabetes Data Group[4] who proposed a more precise and consistent way to categorize subtypes of diabetes mellitus. This classification of diabetes has been adopted by the world diabetic community and represents a significant advance in clearly defining diabetes nomenclature for the clinician, researcher, and patient.

Glucose intolerance can be separated into three clinical classes:(1) diabetes mellitus, (2) impaired glucose tolerance, and (3) gestational diabetes. Two further categories describing classes at statistical risk for diabetes are previous abnormality of glucose tolerance and potential abnormality of glucose tolerance (Table 1). Diabetes mellitus can be further subdivided into three categories: insulin-dependent (IDDM), noninsulin-dependent (NIDDM), and various other types.

Insulin-dependent diabetics have a lack of pancreatic insulin and are dependent upon daily injections of insulin to control blood glucose levels, avoid ketotic coma, and stay alive. In most instances, IDDM appears in youth but this is not always the case. Thus, the nomenclature which was previously used, juvenile-onset diabetes, has been abandoned in favor of the IDDM terminology. Complex etiological factors appear to play a role in the onset of IDDM. Genetic determinants, environmental factors, and immune system abnormalities are thought to be involved in the genesis of this disease.

Noninsulin-dependent diabetics do not usually require insulin to regulate blood glucose levels and they are rarely ketotic. The vast majority of these patients are obese, though not always, and are frequently hyperinsulinemic and exhibit characteristics of insulin resistance. Genetic factors play a more important etiologic role in NIDDM than in IDDM. Environmental factors are also involved. Most of the diabetic patients in America are of the NIDDM type.

The third subclass of diabetics includes various types of diabetes which have known causes

**Table 1**
**CLASSIFICATION OF DIABETES MELLITUS AND GLUCOSE INTOLERANCE**

| Present terminology | Abbreviated present terminology | Former terminology |
|---|---|---|
| Diabetes mellitus | DM | |
| Insulin-dependent type, type I | IDDM | Juvenile diabetes, juvenile-onset diabetes, ketosis-prone diabetes, brittle diabetes |
| Noninsulin-dependent types, type II | NIDDM | Adult-onset diabetes, maturity-onset diabetes |
| Nonobese NIDDM | | Ketosis-resistant |
| Obese NIDDM | | Diabetes, stable diabetes |
| Other types associated with certain conditions: | | Secondary diabetes |
| Pancreatic disease | | |
| Hormonal | | |
| Chemically induced | | |
| Insulin receptor abnormalities | | |
| Certain genetic syndromes | | |
| Other types | | |
| Impaired glucose tolerance | IGT | Asymptomatic diabetes |
| Nonobese IGT | | Chemical diabetes |
| Obese IGT | | Subclinical diabetes |
| IGT associated with the same conditions seen above | | Borderline diabetes, latent diabetes |
| Gestational diabetes | GDM | Gestational diabetes |
| Previous abnormality of glucose tolerance | PrevAGT | Latent diabetes, prediabetes |
| Potential abnormality of glucose tolerance | PotAGT | Prediabetes, potential diabetes |

Adapted from National Diabetes Data Group, *Diabetes*, 28, 1039, 1979.

or strong etiologic relationships with certain agents or compounds. This type of diabetes is secondary to pancreatic disease, altered hormonal activity (due to, for example, conditions like pheochromocytoma, somatostatinoma, aldosteronoma, hypoparathyroidism, and dwarfism), chemical induction (via diuretics, hormonal agents, psychoactive drugs, neurological agents, antineoplastic, analgesic, antipyretic, and anti-inflammatory agents), insulin receptor defects, genetic manifestation, and diabetes associated with malnourishment.

The patients classified as having impaired glucose tolerance (IGT) exhibit mild glucose intolerance as exhibited by abnormal responses to a challenge by a glucose load. Fasting plasma glucose levels may be in the normal range. These patients may or may not be obese and its etiologic origin is, as with the NIDDM syndrome, associated with various conditions. The third clinical class of diabetes, gestational diabetes, is a condition of glucose intolerance which becomes apparent only during pregnancy. Diabetics who become pregnant are not included in this class. Its etiology is unknown but probably involves hormonal alterations.

Patients with a previous, but not present, glucose tolerance abnormality fall into the class of those at statistical risk of diabetes. Individuals who have recovered from gestational diabetes and obese diabetics whose glucose intolerance disappeared after losing weight are but two examples of subjects within this category. The second statistical risk class (potential

abnormality of glucose tolerance) includes those patients who have genetic, physical (obese), or racial (American Indian) factors which may predispose them in the future to glucose intolerance.

## III. CLINICAL RECOGNITION OF DIABETES MELLITUS

Three measurements have gained acceptance over the years for diagnosing abnormalities of glucose metabolism. Because of its simplicity, sugar content of the urine was the first indicator of diabetes, in a historical sense, to be employed. However, urine glucose concentration provides only an indirect measurement of glucose metabolism in the body. It is not sensitive enough nor immediate enough to detect subtle but significant changes in circulating glucose levels. The most recent method of evaluating glucose homeostasis, available to the clinician for only the past decade, involves the measurement of glycosylated hemoglobin.[5] Glucose can react nonenzymatically with red blood cell hemoglobin to form stable covalent linkages.[6] However, although high concentrations of glycosylated hemoglobin serve as a reliable indicator of chronic diabetes, they lack the sensitivity to detect patients with IGT or diabetes of recent onset.[5,7] Currently, glucose estimations from the blood are most commonly used by the physician. The blood is the most reliable indicator of glucose abnormalities.

It has been recommended that the diagnosis of diabetes should be based on (1) an unequivocal elevation of plasma glucose concentrations in conjunction with classic diabetic symptoms (like polydipsia, polyuria, and polyphagia), (2) evidence of elevated fasting plasma glucose concentrations after more than one testing, or (3) evidence of elevated plasma glucose levels after an oral glucose challenge from more than one testing.[4] The latter is the most commonly used clinical method to assess glucose tolerance in the patient. The oral glucose tolerance test should be performed in a seated position in the morning after 10 to 16 hr of fasting. A glucose load of 75 g dissolved in water at a concentration less than 25 g/d$\ell$ is now the standard recommended load to be administered to a nonpregnant adult. Children should receive 1.75 g/kg ideal body weight and pregnant women 100 g.[4] The test should begin by collecting the fasting blood sample, then again every 30 min for 2 hr. Samples should be collected in tubes containing sodium fluoride, centrifuged, and the plasma recovered and stored below 0°C for future analysis of glucose. Convenient, inexpensive assays for measuring glucose are available.[8] In nonpregnant adults, venous plasma glucose concentrations that are $\geq$140 mg/d$\ell$ would be diagnostic of diabetes. Venous plasma samples having a glucose concentration $\geq$200 mg/d$\ell$ 2 hr after the start of the oral glucose tolerance test would also constitute one indicator of diabetes.[4] Typical results from a glucose tolerance test administered to a nondiabetic and diabetic patient are shown in Figure 1.

It is also possible to measure blood glucose levels at home with the use of the commercially prepared Dextrostix® or Chemstrip®. These are chemically inpregnated strips which, when contacted with a drop of blood obtained by pinpricking the finger of the patient, changes color to indicate the blood sugar level. This is a useful, convenient method of measuring blood glucose levels and provides the patient with immediate information on glycemic status.

## IV. MEDICAL SIGNIFICANCE OF DIABETES MELLITUS

### A. Incidence of Diabetes

Diabetes mellitus is a relatively common disease. Its incidence in the general population is relatively high and dependent upon several factors. Racial and ethnic considerations, geography, the type of diabetes, and the age of the patient are all factors which affect the appearance of diabetes mellitus. In a 1976 report from the National Commission on Diabetes as many as 5% of the American population (or 10 million people) had diabetes.

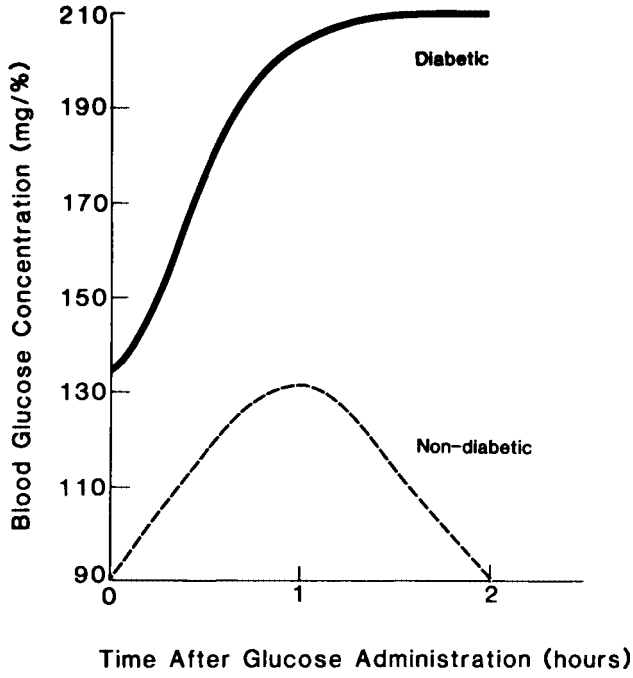


FIGURE 1. Typical blood glucose response of a nondiabetic man and a diabetic man to an oral glucose load. Note the elevated blood-glucose concentration even at rest in the diabetic and the abnormally high glucose levels up to 2 hr after administration of the load. In contrast, the nondiabetic subject has blood glucose values which have returned to resting values at the 2 hr time point. (Adapted from Guyton, A. C., *Textbook of Medical Physiology*, W.B. Saunders, Philadelphia, 1986.)

The race of a population has an important effect on the incidence of diabetes mellitus. These differences between races may reflect genetic and environmental factors. The native Indian and aboriginal people exhibit the most marked difference from most other populations in their incidence of diabetes. The Cherokee Indians of North Carolina have a prevalence of diabetes which is fivefold higher than the general population in the U.S.[10] The Pima Indians of Arizona exhibit a phenomenal 20-fold increase in the incidence of diabetes when compared to a representative cross-section of the American population.[11] Conversely, Eskimos in Greenland[12] and Alaska[13] have a six- to tenfold lower incidence of diabetes than the general population. In a study which would lessen but certainly not eliminate the geographical influence upon the above results, Marine and colleagues[14] found that the East Indian population of South Africa had a prevalence of diabetes which was almost threefold higher than the African or Malaysian ethnic groups in the same country.

In spite of the results from studies cited above, it is difficult to deny that geographical differences play a large part in statistics of incidence of diabetes. Perhaps the most striking example is the incidence rate for Chinese residents of China and those of Chinese ethnic origin who now reside in North America. Diabetes mellitus is a relatively rare disease in China;[15] however, Chinese Americans have similar diabetic characteristics as the general American population.[16]

The type of diabetes affects its frequency of appearance. Noninsulin-dependent diabetes has been reported to have an incidence rate of 2% or 2000 cases per 100,000 population.[3] Insulin-dependent diabetes occurs in 20 to 40 children per 100,000 children.[17,18] It is estimated that there are 150,000 diabetic children in the U.S. and tenfold more across the world.[18]

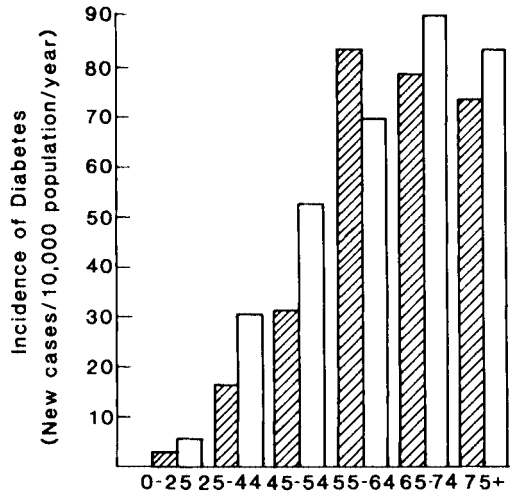


FIGURE 2. The incidence of diabetes mellitus examined as a function of age in men (▨) and women (□) in America, 1975. Note the peak incidence in men at 55 to 64 years of age and women at 65 to 74 years of age. (Adapted from National Diabetes Data Group.[19])

The incidence of diabetes is also affected by the age of the patient (Figure 2). Note that the incidence of diabetes increases rapidly with advancing age until settling at a plateau value at 55 years and older. A quite different pattern is observed for IDDM. As shown in Figure 3, the age at diagnosis of diabetes peaks at about 12 years of age, then steadily declines. The glycemic status of the parents also affects the incidence of diabetes in their children. IDDM was transmitted to children more frequently if the father was diabetic rather than if the mother was diabetic.[125] The reason for this is unclear.

### B. Complications of Diabetes

The primary focus of this text is to review one of the more serious complications of diabetes: heart disease. However, many other significant problems affect the diabetic patient. Disease of the eye is common during chronic diabetes. Manifestations of these ocular complications are varied and numerous (Table 2). Diabetes remains as one of the leading causes of blindness today. Renal disorders are also common in the diabetic. Glomerulosclerosis, nephrosclerosis, toxic nephropathy, urinary tract infections, and neurogenic abnormalities like hydronephrosis are the major complications affecting the kidney during diabetes.[27] Neuropathy is another complication of diabetes. This can have a serious impact upon a variety of bodily functions. Neural abnormalities during diabetes have been reported to alter function of the heart, GI tract, bladder, sex organs, eyes, various muscles, and the skin.[28] Peripheral vascular complications during diabetes can lead to gangrenous infection and result in amputation of the affected limb or body part. Skin problems and dental abnormalities are also observed during diabetes. All of these complications occur to a greater extent in the diabetic than in the general population.

### C. Mortality Related to Diabetes

After the discovery of insulin by Banting and Best, diabetes mellitus was thought to be "cured". Pharmaceutical companies spared no effort in making the hormone commercially available to the diabetic community as a prophylactic agent. In some ways, the early hopes for the success of insulin administration to the diabetic patient have been confirmed. Regular

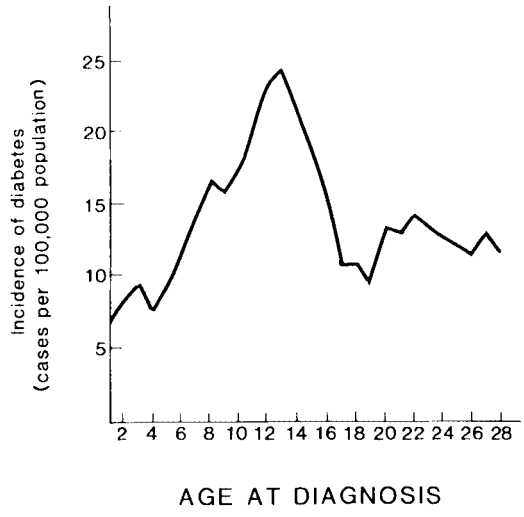


FIGURE 3. The incidence of IDDM in males and females in Denmark as a function of age. (Data from Cristau, B., Kromann, H., Christy, M., Andersen, O. O., and Nerup, T., *Acta Med. Scand. Suppl.*, 624, 54, 1979.)

**Table 2**
**DISEASE OF THE EYE ASSOCIATED WITH DIABETES MELLITUS**

| Complication | Ref. |
|---|---|
| Neuropathy of optic nerve and nerves to the extraocular muscle | 21,22 |
| Corneal damage | 23 |
| Retinopathy | 24 |
| Cataracts | 25 |
| Pupil abnormalities | 23 |
| Glaucoma | 26 |

insulin injections have increased the average life expectancy of the diabetic patient dramatically in comparison to the preinsulin era.[29]

However, the discovery and subsequent incorporation of insulin administration in the treatment of diabetes mellitus has not been a panacea. Diabetic patients still suffer from the symptoms and complications associated with diabetes and, although vastly improved over the last few decades, the diabetic population still has a lower life expectancy than the general population. A study done by Bale and Entmacher[30] in the late 1970s revealed that the diabetic population has from 7 to 9 years lower life expectancy than the general population. Separate studies which examined mortality rates of the diabetic population in each of the last 3 decades confirm this. Diabetics have a higher mortality rate than the general population.[33] This means that more diabetics died over an arbitrarily chosen period of time (e.g., from 1970 to 1979) per 1000 diabetics than did 1000 people from the general population over the same period of time. In the Framingham study, Garcia and co-workers[34] found the mortality rate in diabetics to be as much as three times as high as that of the general population. Goodkin[35] compared the rate of death in the general population (the expected death rate) to that observed

**Table 3**
**STATISTICAL ANALYSIS OF DIABETIC MORTALITY ACCORDING TO THE AGE OF THE PATIENT (1951—1970)**

| Age (years) | Number of patients | Av duration of diabetes (years) | Actual deaths | Expected deaths | Actual expected death ratio (%) |
|---|---|---|---|---|---|
| <15 | 1268 | 8.75 | 169 | 15 | 1127 |
| 15—19 | 846 | 8.69 | 111 | 12 | 926 |
| 20—29 | 1710 | 9.38 | 177 | 40 | 443 |
| 30—39 | 2161 | 8.32 | 250 | 73 | 344 |
| 40—49 | 2471 | 7.32 | 393 | 131 | 301 |
| 50—59 | 1537 | 6.73 | 276 | 129 | 213 |
| >60 | 342 | 5.64 | 85 | 36 | 234 |
| Total | 10335 | 8.01 | 1461 | 436 | 335 |

*Note:* Expected deaths based on Equitable's Select Mortality Table for the general population, 1958—1963.

Data modified from the study of Goodkin, G., *Trans. Assoc. Life Ins. Med. Direc. Am.*, 58, 271, 1974.

in the diabetic population across a full range of subject age (Table 3). The results demonstrate a marked increase in mortality rate in the diabetic population. This is especially magnified in the younger age groups.

Palumbo and co-workers[36] examined diabetic patients in Rochester, Minn. over a 25-year period and discovered survivorship was lower in this select group than in the general population. A study by Tokuhata et al.[37] examined the diabetic death rate as a function of age and civil subdivisions. They showed a curiously large difference between mortality rates in cities and townships. The death rate of diabetic patients was far higher if they lived in cities rather than towns. Another study has shown that the mortality rate is decreased with increasing age at diagnosis of diabetes and increased with the increasing duration of the disease.[38] Borderline diabetics also suffer from increased mortality rates.[126] Both Caucasian and Black diabetics suffer from increased mortality rates.[39] Estimates of the contribution of diabetes to death in America today are complicated when a significant number of cases are not reported by physicians as a contributory cause of death on death certificates.[37] In one recent study only 2639 persons were actually reported as having died from diabetes when, in fact, some 20,000 people died with diabetes in the course of a year.[37] The result is that diabetes remains as a significantly underestimated health problem in North America today. Its impact on society may be far more serious than present statistics imply.

### D. Economic Impact of Diabetes

The cost of diabetes involves expenses incurred while detecting and treating the disease as well as rehabilitation from its effects. Physicians, nurses (at the hospital and home), therapists, and other medical service personnel are all involved in the cost of caring for the diabetic. Medical supplies, drugs, and hospital expenses must also be considered. In addition to these direct costs of diabetes, indirect economic ramifications like lost earnings and lost productivity due to illness, disability, or shortened life expectancy must be included into the calculations. Entmacher[40] estimated these total costs to be over $4 billion for the U.S. in 1973. This reduces to a value of $1000 per diabetic in 1973. We can expect this amount to be significantly underestimated today for a number of reasons. First, inflation over a decade would raise the cost considerably. Second, there are far more diabetic patients in

America today which would inflate the total national cost. Third, Entmacher[40] calculated his values using figures for known diagnosed cases of diabetes. This may not accurately reflect the true incidence of diabetes. Estimations made for 1979, taking into account the possibility of the further economic cost of undiagnosed diabetes, resulted in a value of $15.7 billion/year or $2400 per known diabetic.[44] Fourth, as medical technology progresses, complex surgical procedures (bypass operations, organ transplantation) will cost far more than in the past. Fifth, an increase in the use of insulin[41] will inevitably escalate drug expenses. The economic cost of diabetes mellitus may be phenomenal in the very near future. The trend from recent data[42] would support this contention. In a study of diabetics hospitalized in New Zealand, the total costs rose over tenfold from $127,295 in 1975 to $1,381,575 in 1982.[42]

The importance of supporting research to find means of lowering this cost becomes paramount. Presently, such support needs strengthening if significant advances in diabetes research are to be achieved. In Canada, 1985 figures indicated that just under $7.5 million were provided by the government to support operating and equipment costs and personnel training on diabetes-related research.[43] This represented less than 3% of the total direct expenditure of the government on all biomedical research.[43] The economic commitment is in obvious disproportion to the incident, severity, and cost of the disease in Canada today.

## V. METABOLIC EFFECTS OF INSULIN AND INSULIN DEFICIENCY

The postabsorptive metabolism of glucose is almost entirely dependent upon insulin. Since diabetes is a disease of abnormal glucose metabolism, it is logical to conclude that one of the major problems in diabetes involves an aberration in the action of insulin. Insulin is, therefore, of primary concern to those interested in the characteristics and etiology of diabetes. The subsequent discussion will address the characteristics of insulin, its physiological role, and the metabolic effects on the body if it is not present or fails to function in a normal manner. Space limitations do not permit an extensive treatise on this topic and the reader is directed to several more detailed reviews on this subject.[1,2,44-46]

Human insulin is a small protein with a molecular weight of 5808. As shown in Figure 4, insulin is composed of two amino acid chains linked together by disulfide bonds. These disulfide linkages provide structural stability to the molecule. Insulin is released from the islets of Langerhans. The islets of Langerhans are one of two types of tissue in the pancreas. The islets are composed of two major cell types—α and β. The α cells secrete the hormone glucagon. The β cells secrete the hormone insulin. The β cells synthesize preproinsulin which is first converted to proinsulin and then to C-peptide plus insulin. The mechanism by which insulin is secreted from the β cells is not completely understood. Elevations in plasma glucose stimulate a release of insulin from the β cells. The glucose levels must rise to 50 to 90 mg% before detectable insulin secretion is observed; it peaks at glucose levels of about 300 mg%.[47] If the elevation in glucose concentration is acute, insulin release will subside within several minutes. However, if the glucose level remains elevated, insulin secretion will be maintained.[48] Certain amino acids, proteins, and hormones can also stimulate insulin secretion.[49] $Ca^{2+}$, cyclic AMP (cAMP)[46,50] and $K^+$-induced depolarization[51] have also been proposed to have direct or indirect roles in the release of insulin from the pancreatic β cells. Fasting plasma insulin concentrations are generally found to be in the range of 10 to 25 μU/mℓ in nondiabetic subjects. Insulin concentrations fluctuate widely in the blood during the course of a day with maximal values reported of nearly 200 μU/mℓ.[49] Insulin will circulate for a short time before interacting with target cell receptors ($t_{1/2}$ = 6 to 10 min).

In diabetes, pancreatic islet cells exhibit pathological changes dependent upon the type of diabetes. In IDDM, β cells are less numerous and may show evidence of lymphocytic

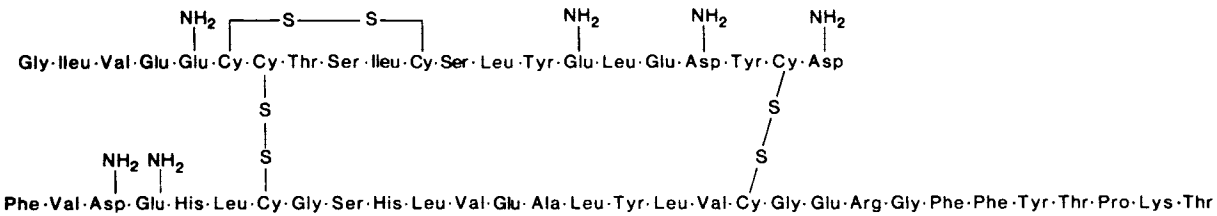


FIGURE 4. The amino acid composition of the insulin molecule from humans. The disulfide bridges maintain structural integrity between the two peptide chains.

infiltration.[52] These cells are significantly reduced in insulin content and islet disorganization is present. In NIDDM, β cell number may be reduced but to a more moderate extent than in IDDM. An increase in islet fibrotic tissue is also evident.[52]

Glucose is needed by the cell for energetic and biosynthetic reasons. The extracellular concentration of glucose is higher than the intracellular levels. Glucose can enter the cell without the need for insulin; however, insulin greatly facilitates this entry process. Insulin does this by increasing the $V_{max}$ for glucose transport without altering the affinity of the transporter.[53] This increase in the maximum velocity of glucose transport by insulin may not be due to a change in mobility of a fixed number of transport systems but instead may reflect an increase in the number of the glucose transport systems.[54] Earlier work has suggested that insulin or some fragment of it may be internalized and exert some intracellular action which would stimulate glucose entry. This is probably inaccurate and it is more likely that the binding of insulin to the receptor results in a more active complex.[55] This is reinforced by data which show that vanadate may stimulate glucose transport in an insulin-dependent manner.[56]

The precise mechanism by which insulin stimulates glucose transport remains unclear. Several intracellular second messengers have been proposed to couple the stimulus to the response. Intracellular $Ca^{2+}$ transients have been proposed as one way of regulating glucose transport in the muscle.[57] This hypothesis is attractive and much data support it;[57] however, it does not appear to account fully for the actions of insulin.[55] cAMP and cGMP have also been proposed as intracellular messengers for the action of insulin. Insulin can increase cellular cGMP and decrease cAMP in tissue preparations.[58,59] The intracellular concentrations of these cyclic nucleotides have been correlated with insulin action on glucose transport in most, but not all, circumstances. Phosphorylation of cellular proteins has also been suggested to account for the effects of insulin.[60] Recent data have also suggested that the cellular mediator of insulin action may be a peptide.[61] Obviously, many mediators for the cellular action of insulin have been proposed to explain its effects on glucose transport but none of them have been conclusively proven. It may be that elements of more than one of the mediators are involved in insulin effects.

In IDDM, the etiopathology of glucose intolerance usually involves the pancreas. In NIDDM, glucose intolerance usually results from defects at the tissue site rather than the pancreas. Similarly, insulin-receptor abnormalities have been reported in various disease states such as obesity, acromegaly, some insulinomas, and glucocorticoid excess.[62] In NIDDM and obese subjects, muscle and adipose tissue exhibit a decreased sensitivity to insulin.[63] The desensitization is due to a decrease in the number of insulin receptors in the muscle or adipose cell.[62-64] This reduction in insulin receptor number is caused by a "down regulation" response by the tissue to chronically elevated circulating insulin concentrations.[63] In addition to a change in sensitivity to insulin, NIDDM and obese patients have a depressed responsiveness to insulin.[63] The decreased responsiveness of the tissue to insulin is demonstrated by a relative lack of effect of even supramaximal concentrations of insulin. This depressed responsiveness of the tissue is not a result of receptor down regulation but instead is due to postreceptor defects.[64] The biochemical basis for this defect remains to be clarified; however, one may hypothesize that any of the intracellular messengers previously identified (cAMP, cGMP, $Ca^{2+}$, phosphorylation, peptide bodies) represent potential candidates. The obese individuals or noninsulin-dependent diabetics may have both receptor and post-receptor defects in varying degrees depending upon the severity of the disease. Those patients with mild insulin resistance have predominantly a receptor defect whereas patients with more severe insulin resistance usually exhibit the postreceptor defect.[64,65]

The metabolic effects of insulin are numerous and varied. It has an influence on carbohydrate, fat, and protein anabolic and catabolic pathways in liver, muscle, and adipose tissues of the body (Figure 5). Insulin promotes glucose entry into all three types of cells,

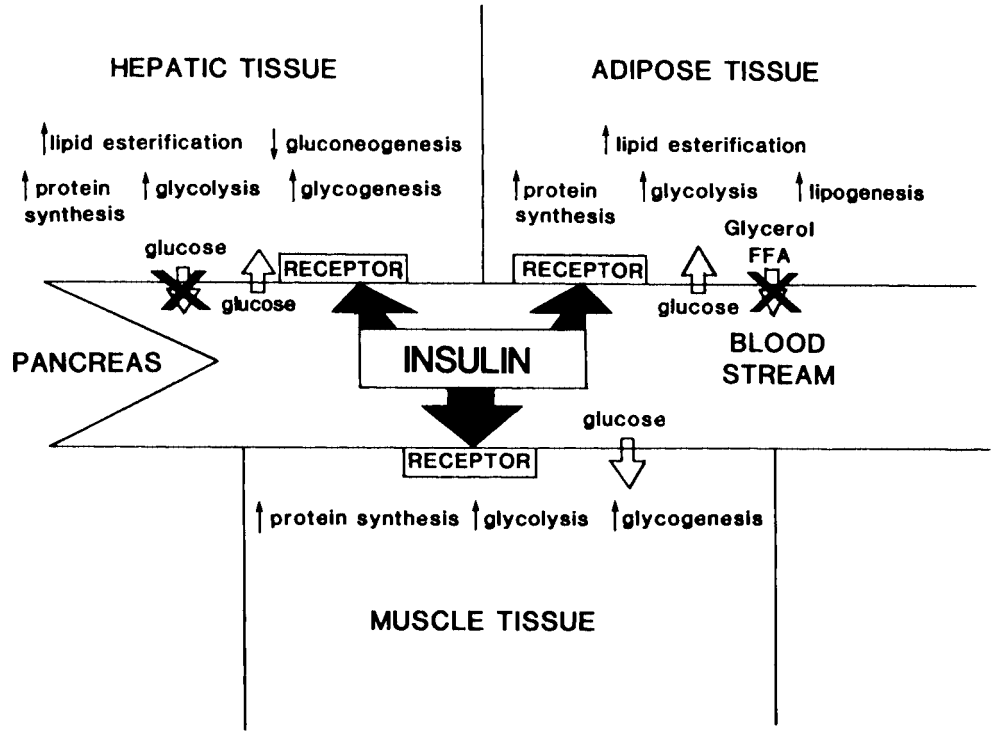


FIGURE 5. Physiological action of circulating insulin on fat, liver, and muscle in the body.

although its effect is only indirect in the case of liver through a stimulation of intracellular glucokinase activity.[66] Glucose release from the liver is inhibited. Cellular glycolysis and glycogenesis is enhanced. In muscle this is achieved by a stimulatory action of insulin on UDPG-glucosyltransferase, the regulatory enzyme for glycogen synthesis from glucose substrate. The conversion of amino acids to glucose is inhibited in the liver by insulin. Protein synthesis is uniformly stimulated by insulin in all three of these cell types.[67-69] RNA synthesis is also enhanced. Insulin increases the rate of triglyceride synthesis from glucose or acetate and fatty acid synthesis and esterification. Conversely, the release of lipids like glycerol and fatty acids from adipose tissue is inhibited by insulin.

With such an important pivotal role for insulin in substrate metabolism, it is not surprising to find serious metabolic consequences when circulating insulin concentrations become depressed as in IDDM. The effects of insulin which are shown in Figure 5 become reversed when there is a lack of insulin. Glucose transport into the cell is slower; thus, plasma glucose concentrations rise. Lipid release from adipose tissue is increased over control conditions and the plasma may become hyperlipidemic. Protein synthesis is impaired and protein degradation will dominate in severe insulin deficiency such that the body operates for a limited duration in a negative nitrogen balance.[70] Weight loss in severely insulin-dependent patients is an inevitable result.

## VI. MANAGEMENT OF DIABETES MELLITUS

### A. Insulin Injection

Therapeutic use of insulin should be under the supervision of a physician. Injection of insulin with the use of a needle and syringe is the most common and convenient method for a diabetic patient to receive insulin. It can be carried out quickly in the privacy of home

or anywhere the need arises and the appropriate material is available. Insulin is injected into the fatty s.c. tissue which lies just below the skin. The abdomen, thighs, triceps, and upper outer buttock areas of the body represent injection sites. The same injection area should not be used repeatedly. An injection site should be about 1 in. away from the last injection site and never used again for 4 to 6 weeks. One area of the body should be entirely used before using another part of the body for injections. By bunching the skin between the thumb and index finger, a fold of s.c. tissue is presented which provides easy access for needle insertion and insulin delivery. Depending upon the need, injections may be given one or more times daily. For more detailed information on insulin injection, the reader is directed to Reference 71.

Insulin was first used by Banting and Best in Canada to reduce blood sugar. The first pharmaceutical modification of insulin was carried out by Hagedorn in 1936[72] to slow the rate of absorption from the injection site. Insulin has no systemic biological effect until it is absorbed into the circulation from the s.c. injection site. The rate of absorption may be a critical factor to the diabetic patient depending upon the immediacy of the need for circulating insulin. Hagedorn's modification of insulin absorption was achieved by adding fish-sperm protamine to the insulin solution. In its current form this type of insulin is referred to as NPH insulin (neutral protamine Hagedorn). The addition of zinc to the insulin preparation was found to further reduce the absorption rate[73] and led to the commercial development of protamine zinc insulin (PZI) and the Lente insulins. Table 4 shows the various types of commercial preparations of insulin which are available and their rates of action.

Bottled insulin is commonly available in U100 concentrations (100 units insulin per milliliter). The needle is made of reusable steel or a single-use disposable needle can be purchased which is silicon coated. The insulin is drawn from the bottle through the needle into a disposable polypropylene syringe with a polystyrene plunger. All components are sterilized. If reused, the needle usually becomes dull after five or six injections and it can then be disposed.[74] It appears that reuse of the plastic insulin syringes results in no significant microbial contamination or skin infections.[75]

Complications do arise with the s.c. injection method of insulin delivery. Insulin-induced lipoatrophy (loss of s.c. fat) or lipohypertrophy (augmentation of s.c. fat) at the site of injection is well documented.[71] Changing the insulin to a purer preparation or to another species has been suggested to be helpful in alleviating these problems.[71] Local allergic reactions or infections of the skin at the injection site have also been observed.[76] Hypo- and hyperglycemia can occur if the dosage of insulin delivered is not adequately managed.[76] Most significantly, it has been found that s.c. delivery of insulin may result in insulin degradation by muscle or fat tissue which can lead to insulin resistance.[77] Whether this is an important clinical problem in insulin-dependent diabetics is debatable.[76]

### B. Insulin Pumps

Because of the aforementioned complications, s.c. injection of insulin may not represent the ideal method of insulin delivery to the diabetic. Furthermore, it was observed that in some IDDM diabetics who were predominantly young women, s.c. delivery of insulin was an unsuccessful method of managing diabetes.[78] Frequent episodes of ketoacidosis developed in these patients which required immediate hospital attention in the form of i.v. insulin infusion.[78] For these patients, an implantable insulin infusion pump was found to be a viable alternative to s.c. insulin injections. The pump was placed subcutaneously inferior to the left clavicle with the delivery catheter in the left cephalic vein. The pump could be refilled and simultaneously recharged by percutaneous needle injection into the pump. In patients who received the pump, the frequency of clinical ketoacidosis were reduced by 99% (from 32 episodes per year to 0.4). The average number of in-hospital days was reduced (89%) from a mean of 20.8 to 2.2 days/month. The estimated savings in cost was $10,000 per

**Table 4**
**COMMERCIALLY AVAILABLE INSULIN PREPARATIONS AND ABSORPTION CHARACTERISTICS**

| Short-acting | Intermediate-acting | Long-acting |
|---|---|---|
| Velosulin® | Lente® | Protamine zinc |
| Actrapid® | NPH | Ultralente® |
| Semilente® | Insulatard® | |
| | Monotard® | |

patient month. The quality of life in these patients was enhanced dramatically. Other investigators have reported that infusion pumps regulate glycemia better than conventional s.c. insulin injection.[79] The pump need not be implanted into the patient in some cases.[80]

Data regarding the use of insulin infusion pumps are not uniformly positive. Infusion pump treatment has been implicated in frequent hypoglycemia,[81] severe hyperkalemia, and ketoacidosis which may result in cardiac arrest[82] and pump malfunction and subsequent inadequate glycemic control.[83] Some concern regarding the psychosocial stress of having an implantable infusion pump has also been reported.[84]

### C. Transplantation

Pancreatic transplantation or islet cell transplantation represents a third method of regulating insulin levels in the diabetic when pancreatic malfunction is the primary lesion site in the diabetic. Organ transplantation is probably the most direct and logical solution to the problem of pancreatic malfunction. However, to date, progress in both islet cell transplantation[85] and pancreas transplantation[86] has been exceedingly slow. Nonetheless, some encouraging advances are being made which warrant continued study. Sutherland and colleagues[85] at the University of Minnesota reviewed the results from 86 clinical pancreas transplants from 1978 to 1983. Their preferred method of managing the pancreatic duct in surgery was the pancreaticojejunostomy. By 1984, 81% of the transplant patients were alive, 32% had functioning grafts, and 28% were not dependent upon insulin anymore. Most patients with functioning grafts were euglycemic; 12% of these patients were no longer ketosis-prone but did require insulin supplementation. One half of the functioning graft recipients had normal glucose tolerance tests and one half of the tests were abnormal. Of the grafts, 15 functioned for longer than 1 year. The graft survival rate was far higher if the pancreas graft was obtained from a relative of the recipient (43%) rather than a cadaver (18%). The transplantation results improved as the surgeons learned more about the factors which governed graft rejection and failure. The success rate from 1983 transplants was up to 50% functioning grafts.[85] Significantly, the diabetes-associated nephropathy in two long-term transplant recipients was regressing. Regulation of circulating insulin and glucose was reported to be acceptable and similar in pancreas transplant recipients and diabetics treated with continuous s.c. insulin infusion systems.[87] Islet cell transplantation surgery has proven to be far more difficult and its success rate low.[85] This has discouraged further work from some clinical groups into this area.[85]

### D. Pharmacological Treatment

Diabetes may also be managed pharmacologically in certain clinical cases. The sulfonylurea drugs are the most common measure to directly regulate diabetic hyperglycemia but other new experimental compounds are being examined. Other drugs which regulate the metabolic complications of hyperglycemia rather than the glycemic status may also be useful to the diabetic patient.