Nestlé Nutrition Workshop Series
Volume 35

DIABETES

EDITED BY

RICHARD M. COWETT

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Volume 35

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Editor

Richard M. Cowett, M.D.
Professor
Department of Pediatrics
Brown University School of Medicine
Providence, Rhode Island, USA

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DIABETES

The 35th Nestlé Nutrition Workshop, Diabetes, *was held in Athens, Greece, April 18–21st, 1994.*

Workshop participants: *(left to right, first row):* A. Drash-USA; F. A. Van Assche-Belgium; R. Assan-France; F. W. Scott-Canada; R. N. Bergman-USA; O. Crofford-USA; P. M. Catalano-USA; G. F. Bottazzo-U.K.; R. M. Cowett-USA; P. R. Guesry-Switzerland; R. Schwartz-USA; J. Girard-France; E. Marliss-Canada; J. J. Hoet-Belgium; G. Chiumello-Italy; K. Papadatos-Greece; C. Bartsokas-Greece; K. Unachak-Thailand; C. Dakou-Voutetaki-Greece; (*second row*) G. Jiang-China; P. Steenhout-Switzerland; J. Batubara-Indonesia; A. Carrascosa-Spain; E. Borrajo-Spain; M. Bueno-Sanchez-Spain; M. Nattrass-U.K.; C. Zoupas-Greece; K. Choo-Malaysia; M. Ratti-Malaysia; R. Jegasothy-Malaysia; S. Sampurno-Indonesia; G. Zoppi-Italy; V. Tripodi-Italy; A. Quinto-Italy; C. Panpitpat-Thailand; G. Biscatti-Italy; (*third row*) P. Swift-U.K.; F. Vargas Torcal-Spain; M. Oyarzabal-Spain; S. Batuna-Indonesia; F. J. Dorca-Spain; P. Beauvais-France; A. Otten-Germany; I. Barberi-Italy; L. Giuffre-Italy; A. Latronico-Italy; J. Rodriguez Pereira-Portugal; J. Sales Marquez-Portugal;' R. Carolino-Portugal; U. Vetter-Germany; A. Martins Mota-Portugal; H. Geiger-Germany; Lai-Italy, V. Tripodi-Italy; H. Grobe-Germany.

Preface

The 35th Nestlé Nutrition Workshop, *Diabetes Mellitus*, surveyed recent exciting discoveries in one of the major chronic diseases of our time. Diabetes mellitus has fascinated the curious since antiquity where, as discussed by one of the participants, it was first described in the Egyptian Papyrus Ebers in 1500 BC. The name of the disease is derived from the ancient Greek word for siphon as recorded by Aretaeus of Cappadocia (AD 81–138). The continuing importance of the disease is emphasized by its mention by medical giants through the ages including Galen, Avicenna, Claude Bernard, Langerhans, Minkowski, and von Mering. Of course, the modern era dates back to Banting and Best who, with MacLaod and Collip, are credited with the discovery of the pancreatic extract "insulin" in 1923. They named it after the Latin root for the islet cell of the pancreas.

Interest has focused on this disease for numerous reasons. Not only is it a major cause of morbidity and mortality, but it also affects the multiple stages of human existence from the fetus and neonate, the child and adolescent, the pregnant woman, to the middle aged and the elderly. Advances in medicine in general have paralled the successes in the understanding of diabetes mellitus by the various disciplines. These include studies of epidemiology, physiology, biochemistry, molecular biology, pathology, immunology, nutrition, genetics, and clinical evaluation at the various ages noted above. Many of these areas have been eloquently discussed in the chapters that comprise this volume.

This workshop conference brought together investigators who have contributed significantly to the advances of the recent past and are contributing to the potential for the immediate future.

We trust the interested reader will share the workshop's enthusiasm for the current successes in the understanding of this ancient malady.

RICHARD M. COWETT, M.D.
Professor
Department of Pediatrics
Brown University School of Medicine
Providence, Rhode Island, USA

Foreword

From the time of the first revolution of the 1920s when Banting and Best discovered insulin therapy, and that of the second revolution (at least for pediatric diabetologists) of the 1950s when the free diet was proposed and insulin treatment adapted to the level of blood glucose, urinary glucose, and ketones, no breakthrough occurred for the following 30 years in the field of diabetes mellitus. It has been only during the last 10 years that a tremendous number of discoveries and new concepts have reawakened interest in the subject.

The prevention of the complications of diabetes is now directed less toward acute hypoglycemia or hyperglycemia with acidosis; these should be avoided by strict monitoring and good education of the patient, even a young child. The current focus is more on the prevention of long-term complications such as blindness, renal insufficiency or, more generally, early atherosclerosis, and is based on the monitoring of glycosylated hemoglobin. The use of genetically engineered human insulin prevents some cases of immunologically induced insulin resistance. The use of a portable insulin pump may help to equilibrate the treatment in difficult circumstances, and pancreas transplant or transplant of islet cells may offer a better way of avoiding hyperglycemia and its long-term consequences.

But the most recent work consists of trying to identify the population of children and adolescents genetically at risk of developing insulin-dependent diabetes mellitus (IDDM), and to prevent autoimmune destruction of the β cells by different drug or diet therapy.

That bovine serum albumin (BSA) shares some epitopes with a protein of the β cell seems to be accepted, but the possibility of preventing insulin-dependent diabetes mellitus by a diet devoid of BSA in infancy is far from proved, and seems to be in contradiction with the observation that the two countries in the world where insulin-dependent diabetes mellitus is most frequent (Finland and Sweden) are also the two countries where use of cow's-milk-based infant formulas during the first months of life is the lowest among all the industrialized countries.

For prevention of non-insulin-dependent diabetes mellitus (NIDDM), diet is, in contrast, now well established through a weight reduction plan based on lowering the fat content of the diet rather than on a calorie count. This offers interesting possibilities for a food company to work in collaboration with the medical profession to reduce the incidence of this disease with its severe consequences and rapidly increasing incidence. This workshop and its publication is an important step forward.

PIERRE R. GUESRY, M.D.
Vice President of Research
Nestlé Research Center
Vers-Chez-Les-Blanc
Switzerland

Contributors

Speakers

Roger Assan
C.H.U. Bichat
Assistance Hôpitaux Publiques de Paris
46, rue H.-Huchard
75877 Paris, Cedex 18 France

Marian Benroubi
Polikliniki Anthinon
Pireos Str. 3
Athens, 10552 Greece

Richard N. Bergman
Department of Physiology and Biophysics
Univeristy of Southern California
School of Medicine
1333 San Pablo St., MMR 626,
Los Agneles, California 90033, USA

Gian F. Bottazzo
Department of Immunology
The London Hospital Medical College
Turner Street
London, E1 2AD England

Patrick M. Catalano
Department of Reproductive Biology
Case Western Reserve University
MetroHealth Medical Center
2500 MetroHealth Medical Center
Cleveland, Ohio 44109-1998, USA

Richard M. Cowett
Department of Pediatrics
Brown University School of Medicine
101 Dudley Street
Providence, Rhode Island 02905-2401, USA

Oscar B. Crofford
D-3100 Medical Center North
Vanderbilt University
Nashville, Tennessee 37232-2358, USA

Allan L. Drash
The Children's Hospital of Pittsburgh
Rangos Research Center
3705 Fifth Avenue
Pittsburgh, Pennsylvania 15213, USA

John H. Fuller
University College London Medical School
Department of Epidemiology and Public Health,
1-19, Torrington Place,
London, WC1E 6BT England

Edwin A. M. Gale
Department of Diabetes and Metabolism
St-Bartholomew's Hospital
Centre for Clinical Research
59, Bartholomew Close
West Smithfield
London, EC1A 7BE England

Jean Girard
Centre de Recherche sur l'Endocrinologie Moléculaire et le Développement. CNRS
9, rue Jules Hetzel
92190 Meudon, France

Joseph J. Hoet
Cell Biology Laboratory
Catholic University of Louvain
5, Place Croix du Sud
1348 Louvain-la-Neuve, Belgium

Nicholas Katsilambros
1st Department of Propedeutic Medicine
Athens University Medical School
Laiko General Hospital
17 Agiou Thomas street (Goudi)
Athens, 11527 Greece

Errol B. Marliss
McGill Nutrition and Food Science Centre
Royal Victoria Hospital
687 Pine Avenue West
Montréal, Quebec H3A 1A1 Canada

Robert Schwartz
Department of Pediatrics
Rhode Island Hospital
593 Eddy Street
Providence, Rhode Island 02903 USA

Fraser W. Scott
Nutrition Research Division
Bureau of Nutritional Sciences Food Directorate
Health Canada Sir Frederick Banting Research Centre
Tunney's Pasture
Ottawa, Ontario K1A 0L2 Canada

David Sutherland
Department of Surgery
University of Minnesota
420 Delaware Street SE
Minneapolis, Minnesota 55455 USA

F. A. Van Assche
U.Z. Gasthuisberg
Department of Obstetrics and Gynecology
Herestraat 49
3000 Leuven, Belgium

Session Chairmen

J. Alivisatos / *Athens, Greece*
Ch. Bartsocas / *Athens, Greece*
G. Chiumello / *Milan, Italy*
Richard Cowett / *Providence, RI, USA*
C. Dakou-Voutetaki / *Athens, Greece*
Robert Schwartz / *Providence, RI, USA*
Ch. Zoupas / *Athens, Greece*

Invited Attendees

J. Alivisatos / *Athens, Greece*
Ignazio Barberi / *Messina, Italy*
Ch. Bartsokas / *Athens, Greece*
Jose Rizal Latief Batubara / *Jakarta, Indonesia*
Sander Batuna / *Jakarta, Indonesia*
Paul Beauvais / *Mulhouse, France*
Giuliano Biscatti / *Cantù, Italy*
Emilio Borrajo / *Murcia, Spain*
Manuel Bueno Sanchez / *Zaragoza, Spain*
Rui Carolino / *Ess, Portugal*
Antonio Carrascosa / *Barcelona, Spain*
Giuseppe Chiumello / *Milan, Italy*
Keng Ee Choo / *Kota Bharu, Kelantan, Malaysia*
P. Christakopoulos / *Athens, Greece*
C. Dakou-Voutetaki / *Athens, Greece*
Syahrir Dullah / *Surakarta, Indonesia*
H. Geiger / *Schwäbisch Hall, Germany*
Liborio Giuffre / *Palermo, Italy*
H. Grobe / *Nürnberg, Germany*
Ravidran Jegasothy / *Seremban, Malaysia*
Guoyan Jiang / *Beijing, China*
Ahmad Jufri / *Lhokseumawe, Indonesia*
B. Karamanos / *Athens, Greece*
Amilcar Joaquim Martins Mota / *Lisbon, Portugal*

Malcolm Nattrass / *Birmingham, England*
A. Otten / *Hamm, Germany*
Mirentxu Oyarzabel Irigoyen / *Pamplona, Spain*
Chanathip Panpitpat / *Udontani, Thailand*
C. Phenekos / *Athens, Greece*
Anna Quinto / *Napoli, Italy*
S. Raptis / *Athens, Greece*
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Jorge Rodriguez Pereira / *Aveiro, Portugal*
Giorgio Rondini / *Pavia, Italy*
Jorge Sales Marquez / *V.N. Gaia, Portugal*
Gian Paolo Salvioli / *Bologna, Italy*
Slamet Iman Sampurno / *Palembang, Indonesia*
Francesca Severi / *Pavia, Italy*
Ahmad Siadati / *Tehran, Iran*
Peter Swift / *Leicester, England*
N. Thalassinos / *Athens, Greece*
Ch. Theodorides / *Athens, Greece*
Mahmoud Touhami / *Oran, Algeria*
Vittorio Tripodi / *Napoli, Italy*
Kevalee Unachak / *Chiang Mai, Thailand*
Fernando Vargas Torcal / *Elche, Spain*
U. Vetter / *Berlin, Germany*
Giuseppe Zoppi / *Verona, Italy*
Ch. Zoupas / *Athens, Greece*

Nestlé Participants

Francisco Javier Dorca, *Barcelona, Spain*
Bianca-Maria Exl, *Münich, Germany*
Pierre R. Guesry, *Vers-chez-les-Blanc, Switzerland*
Alberto Latronico, *Milano, Italy*
George Makridimitris, *Athens, Greece*
Constantin Papadatos, *Athens, Greece*
Philippe Steenhout, / *Vevey, Switzerland*

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Hormonal Control of Glucose Metabolism

Jean Girard

Centre de Recherche sur l'Endocrinologie Moléculaire et le Développement, CNRS, 9 rue Jules Hetzel, 92190 Meudon, France

Plasma glucose concentration is normally maintained within a narrow range despite wide fluctuations in the supply (meal) and demand (exercise) for nutrients. In adult humans, plasma glucose concentrations throughout a 24-hour period average 90 mg/dl, with maximum values 60–90 minutes after meals, usually not exceeding 140 mg/dl, and values during a moderate fast or exercise usually remaining above 50 mg/dl. This relative stability contrasts with the situation for other fuels such as glycerol, lactate, free fatty acids (FFA), and ketone bodies (acetoacetate and β-hydroxybutyrate), the fluctuations of which vary more widely. The reason why plasma glucose concentration must be maintained in a narrow range of concentration is related to the deleterious effects of both hypoglycemia and hyperglycemia. Acute hypoglycemia is well known to have harmful effects on the brain. Glucose is usually the main fuel used by the brain; this is because plasma concentrations of one of the alternative fuels (ketone bodies) are low, while transport across the blood-brain barrier of the other alternative fuel (free fatty acids) is limited. As the brain has low energy stores, it is markedly dependent upon circulating glucose for its energy metabolism. When plasma glucose levels fall below 60 mg/dl, brain glucose uptake decreases and cerebral function is impaired. More severe and prolonged hypoglycemia can cause convulsions, permanent brain damage, and death. Chronic hyperglycemia also has deleterious effects. The functional and vascular changes in the eyes, nerves, aorta, and kidneys of diabetic patients seem to be related to increased metabolism of glucose via the polyol pathway. To maintain plasma glucose concentrations within a normal range, the changes in the dietary or endogenous glucose supply must be precisely matched by comparable changes in tissue uptake. Conversely, the changes in tissue glucose uptake (for example, during exercise) must be matched by appropriate changes in the exogenous or endogenous glucose supply.

The aim of this chapter is to review briefly the mechanisms by which the rate of glucose production and uptake is finely regulated during a 24-hour period in normal resting humans, and how they are coordinated by hormones and alternative substrates to maintain the plasma glucose level within a normal range. The cellular mechanisms by which hormones alter the rate of hepatic glucose production and peripheral tissue glucose utilization will also briefly be discussed.

OVERALL GLUCOSE HOMEOSTASIS IN HUMANS

In a normal human living in a Western society, the 24 hours of a normal day can be divided into three periods of approximately 4 hours, corresponding to the absorption and assimilation of the principal meals and to a postabsorptive period corresponding to the 12-hour overnight fast. During these periods, systemic glucose homeostasis is profoundly modified, as described in a recent review (1).

The Postabsorptive State

The postabsorptive period generally refers to the 12 hours following the last meal of the day during which transition from the fed to the fasting state occurs. At the end of this period, tissue glucose utilization in resting humans is approximatively 2 mg/kg/min. Approximatively 1 mg/kg/min is due to the obligatory uptake of glucose by the brain and other non-insulin-dependent tissues. Glucose uptake by insulin-dependent tissues (skeletal muscle, adipose tissue) accounts for less than 30–50% of glucose utilization. Tissue glucose uptake is precisely matched by the liver glucose output, and plasma glucose concentration remains constant.

The Postprandial State

Postprandial hyperglycemia is dependent upon the amount and form of carbohydrate ingested and on the amount of accompanying protein and fat [reviewed in (1)]. In general, complex carbohydrates are absorbed more slowly than simple sugars, and protein and fat delay absorption; both of these factors reduce postprandial glucose excursions. The time of the day when carbohydrates are ingested is also important since glucose tolerance is better in the morning than in the evening.

After a carbohydrate meal, plasma glucose levels increase after 15 minutes, glucose production is inhibited, and glucose utilization is enhanced. Plasma glucose, glucose production, and glucose utilization return to basal levels after 180 minutes. These changes are associated with a parallel increase in plasma insulin and a decrease in plasma glucagon. Plasma glucose concentrations after a meal are determined by the relative changes in the rates of glucose delivery and removal. The magnitude of these changes is largely determined by the secretion of insulin and glucagon.

The major tissues responsible for glucose removal after a carbohydrate meal are the liver, small intestine, brain, skeletal muscles, and adipose tissue [reviewed in (1)]. Skeletal muscles and splanchnic tissues (liver, small intestine) each probably account for 30%, brain for 20%, and adipose tissue for 10% of glucose taken up. The uptake of glucose by skeletal muscles and adipose tissue is influenced by both plasma glucose and insulin levels, whereas the uptake of glucose by the brain is only influenced by plasma glucose levels. Adipose tissue lipolysis and lipid oxidation are suppressed after carbohydrate ingestion. Of the glucose taken up by tissues, 60% is used for replenishment of liver and muscle glycogen stores, 30% is oxidized, and 10% is

released as lactate into the circulation for further uptake by the liver for indirect glycogen formation.

CONTROL OF HEPATIC GLUCOSE PRODUCTION

The only tissues that contain significant amounts of glucose-6-phosphatase, the enzyme necessary for hydrolysis of glucose-6-phosphate to glucose and the subsequent release of glucose into the circulation, are liver and kidney. The liver is the main source of circulating glucose except in two situations: 1. after a prolonged fast, when kidney may provide up to 10% of circulating glucose; 2. after meals or administration of exogenous nutrients (for example, intravenous infusions, parenteral nutrition).

The liver provides glucose to the circulation through two metabolic pathways: 1. glycogenolysis, the breakdown of glycogen stores, and 2. gluconeogenesis, the formation of new glucose molecules from amino acids, glycerol, and lactate. The contribution of each of these pathways in humans has been estimated from different types of studies: the rate of decrease in glycogen from serial liver biopsies, balance of gluconeogenic precursors across the splanchnic bed, and incorporation of isotopically labeled gluconeogenic precursors into circulating glucose [reviewed in (1)]. It was initially estimated that glycogenolysis accounts for 70% of overall hepatic glucose output in the postabsorptive period. However, recent studies employing nuclear magnetic resonance to measure depletion of hepatic glycogen stores suggest that glycogenolysis may account for only 30% of overall hepatic glucose output (2). If fasting is prolonged to 48–60 hours, gluconeogenesis accounts for virtually all of the hepatic glucose output.

On a minute-to-minute basis, glucose, insulin, and glucagon are the major factors regulating hepatic glucose production. After ingestion of a meal, plasma insulin and glucose concentrations increase, plasma glucagon levels are suppressed, and hepatic glucose production is reduced. Conversely, as one proceeds from the fed into the fasted state, plasma insulin and glucose levels decrease, plasma glucagon levels increase, and hepatic glucose production is increased. Under stressful conditions, circulating epinephrine from the adrenal medulla and neurally released norepinephrine become involved and augment hepatic glucose production through β-adrenergic receptors in humans (3). Glucocorticoids have no direct effects on hepatic glucose production, but they markedly potentiate the effects of glucagon and adrenaline (permissive role).

By using the "pancreatic clamp" technique, it has been possible to delineate the respective role of glucose and different hormones in hepatic glucose production in dogs in the postabsorptive state [reviewed in (4–6)]. This technique involves the infusion of somatostatin into a peripheral vein to inhibit the secretion of insulin and glucagon and the infusion of the two pancreatic hormones into the portal vein to replace their endogenous secretion. It is thus possible to fix the levels of plasma glucose, insulin, glucagon, catecholamines, and cortisol to the desired values. The