EDITORIAL

Looking at 25 years of star-studded achievements in diabetology
Retour sur 25 ans d’avancées prestigieuses en diabétologie
C. E. Mogensen, Denmark

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In diabetology, as in medicine generally, discoveries are rarely planned. Instead they often depend on research centers fostering a culture of active serendipity while engaged on more routine work. To cite Pasteur (and the Medicographia motto): “Chance favors only the prepared mind.” This editorial focuses on some of the discoveries that have changed the diabetes world. Although inevitably a personal account,1-3 it may prompt readers interested in the long and fascinating story of diabetes to refer to the comprehensive new book Diabetes. The Biography4 by Robert Tattersall, Professor of Metabolic Medicine at the University of Nottingham. One such prepared mind was that of the immunologist Dr Samuel Rahbar (born in 1929), who obtained his medical degree and PhD in pre-Revolutionary Tehran. A famous example of an unexpected discovery is the one he made of a “new” molecule in diabetes, HbA1c (glycated hemoglobin), a marker of long-term glycemic control.5 Studying rare variants of the hemoglobin molecule endemic in the Middle East, he came across a fast moving variant that, to his surprise, occurred only in patients with diabetes and often poor glycemic control. This “serendipitous discovery” (to use Dr Rahbar’s own words) opened up a new field in medical research. The use of HbA1c along with miniaturized blood glucose meters revolutionized the monitoring and self-care of diabetes. Many other discoveries in diabetology have been made in similar fashion. Unlike standard problem solving, unexpected findings of this type often create paradigm shifts.6

The natural history of diabetes comprises a more or less silent prodromal period followed by progressive deterioration of glucose tolerance to overt or even severe diabetes. Yet despite all the progress made in diabetes research and treatment, we are increasingly aware of gaps in our basic understanding of the disease, whether type 1 or type 2. It can thus be argued that our treatment is compensatory, trying to counteract hyperglycemia (related to insulin resistance and progressive loss of β-cell function). In the last 25 years, we have discovered that multifactorial intervention plays a key role in preventing cardiovascular and renal complications, meaning that more than glucose is involved. Antihypertensive and lipid-lowering treatment may sometimes be more important than glucose lowering, particularly as the latter can be difficult to implement effectively. We are also now intensifying care of patients with early complications such as microalbuminuria, and its associated abnormalities.”

Until the results of two landmark diabetes trials—the Diabetes Control and Complications Trial (DCCT),7 planned by the Vanderbilt diabetologist Oscar Crofford (born in 1930), and the United Kingdom Prospective Diabetes Study (UKPDS),8 planned

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by Robert Turner (1938-1999) in Oxford, were published in 1994 and 1998, respectively—it was still uncertain whether glycemic control was really that important. Skeptics were always able to argue that they had seen patients with poor long-term glycemic control yet limited late-stage diabetic complications (without realizing the importance of other factors involved, such as the protective effect of low blood pressure).

In type 1 diabetic patients, DCCT demonstrated the long-term effect of glycemic control on diabetic complications. The prepublication results, which I vividly remember being announced at the American Diabetes Association meeting in Las Vegas in June 1993, were consistent with the meta-analysis published a month earlier by Wang et al in The Lancet.9 No less vivid a memory was the announcement 5 years later of the UKPDS data at the European Association for the Study of Diabetes (EASD) meeting in Barcelona.

The question of glycemia’s impact in type 2 diabetes became crucial after American UGDP (University Group Diabetes Program) data in the early 1970s suggested that glycemic control with sulfonylureas might even be harmful. In 1976, Robert Turner attended the debate at the International Diabetes Federation meeting in New Delhi and shortly thereafter planned the UKPDS. The investigators in Oxford still keep a small piece of paper on which he scribbled the very rough outlines of the UKPDS (the “UKPDS Museum”).

Some of us half-anticipated the results of UKPDS, in my case because I was writing an editorial on blood pressure-lowering for the British Medical Journal and clearly remember contributors’ general awareness that glycemic control was likely to be important in preventing microvascular disease. We were less sure about the relationship with macrovascular disease, but a 10-year follow-up in the New England Journal of Medicine showed a positive “legacy” effect in UKPDS. It soon became apparent that blood pressure-lowering was also crucial (high blood pressure and high blood glucose being “bad companions”). The combination of glycemic control and optimized blood pressure-lowering came to be seen as a key strategy, helping to delay progression to end-stage renal disease (ESRD). These results were later confirmed by Hans-Henrik Parving from the Steno Diabetes Center in Denmark,10 and Ed Lewis at Vanderbilt using an angiotensin-converting enzyme (ACE) inhibitor.11 Further confirmation came from the MDRD (Modification of Diet in Renal Disease) study, published in 1994, the primary results of which show a protective effect derived from low blood pressure rather than a low protein diet.

The next relevant megatrial, published in 2007, was ADVANCE (Action in Diabetes and Vascular Disease: PreterAx and Dia-microN MR Controlled Evaluation),12 a kind of continuation of UKPDS in that it included patients diagnosed some 8 years previously, in contrast to the newly diagnosed patients of UKPDS. ADVANCE confirmed the benefit of combining glycemic and blood pressure control. It found no lower limit to the values of either parameter in conferring benefit, in sharp contrast to the ACCORD (Action to Control Cardiovascular Risk in Diabetes) and VADT (Veterans Administration Diabetes Trial) studies.

This was probably because of the more specific effect of perindopril/indapamide and gliclazide MR in comparison to that of metformin and rosiglitazone, respectively, which were used in the other two trials. In an interesting, but controversial, study by Currie et al published in The Lancet in 2010,13 longest survival time was associated with intermediate HbA1c values around 7.5%, while high and low values were associated with shorter survival times. However, a variety of treatment strategies were used in this retrospective cohort study, in contrast to the controlled clinical trial conditions of ADVANCE, which found no lower limit. The once-daily medication used in ADVANCE was also extremely important for compliance (“Drugs don’t work in patients who don’t take them,” to cite ex-US Surgeon General C. Everett Koop [1916-]).

The therapeutic armamentarium against type 2 diabetes was complemented a decade ago by the introduction of a new class of insulin sensitizer, thiazolidinediones. One of these, troglitazone, was soon withdrawn because of severe liver toxicity. In September 2010, the European Medicines Agency recommended that rosiglitazone be suspended. Pioglitazone is also crucial (high blood pressure and high blood glucose being “bad companions”). The combination of glycemic control and optimized blood pressure-lowering came to be seen as a key strategy, helping to delay progression to end-stage renal disease (ESRD). These results were later confirmed by Hans-Henrik Parving from the Steno Diabetes Center in Denmark,10 and Ed Lewis at Vanderbilt using an angiotensin-converting enzyme (ACE) inhibitor.11 Further confirmation came from the MDRD (Modification of Diet in Renal Disease) study, published in 1994, the primary results of which show a protective effect derived from low blood pressure rather than a low protein diet.

Insulin is clearly the cornerstone of type 1 diabetes treatment, but it is also increasingly being used in type 2 diabetes, especially since UKPDS data made optimal glycemic control essen-
tial. Conventionally, this is best achieved by frequent injection or insulin pump (inhaled insulin has proven a major and very expensive failure, to be ranked alongside the concepts of aldose reductase inhibition and the inhibition of advanced glycation end product formation in preventing complications). Insulin analogs, rapid-acting insulin, and intermediate-acting (eg, NPH [neutral protamine Hagedorn]) insulin are now widely used. The long-acting analogs, insulin detemir and insulin glargine, are also popular, particularly in Europe.

It is not always easy to document better glycemic control than that obtained with NPH insulin, let alone differences in long-term complications. All the same, patients appreciate the new analogs and their 24-hour glucose curves are likely to be smoother and more stable.

The development of analogs is a sign of positive progress, but we must not forget that progress should be made conscientiously. The old dictum, “Don’t change basic clinical strategy on the strength of a single study,” is valid in diabetes, too.

In 2001, Greet Van den Berghe and her colleagues in Louvain proposed using insulin to fully normalize blood glucose in intensive care patients. Many centers implemented this approach before awaiting confirmation from further trials. In 2009, the NICE-SUGAR (N ormoglycemia in Intensive Care Evaluation–Survival Using Glucose Algorithm Regulation) study conducted in over 6000 randomized patients in Australia, New Zealand, and North America reached a diametrically opposite conclusion.

The important predictive role of microalbuminuria was documented both in type 1 and type 2 diabetes in 1982 and 1984, respectively. It has since featured as a major risk marker in many studies, including the PREMIER (PREterax in albuMini-uria rEgRession) study, which used the same antihypertensive agents (perindopril and indapamide) as ADVANCE. Although blockade of the renin-angiotensin system has been a key feature in most studies, it is clear that blood pressure lowering per se is crucial. Giuseppe Remuzzi (1949-) in Bergamo has been instrumental in demonstrating the contribution of ACE inhibition in incipient nephropathy, whether diabetic or nondiabetic. ADVANCE showed the benefit of perindopril/indapamide at all stages of chronic kidney disease. Improved glycemic control with gliclazide MR had a similarly positive impact on microalbuminuria. As discussed in detail by John Chalmers in this issue of Medicographia, the combined effect of blood pressure and blood glucose control is even more impressive and should help to further reduce the ever increasing burden of vascular complications in type 2 diabetes. This remains the biggest challenge of the new century.

I can’t end this editorial without highlighting the most serious and costly complication in diabetes, namely ESRD. Around 2 million people worldwide are on dialysis, mainly in the USA, Japan, and Germany, and the US government spends $24 billion a year on this treatment. The majority of recipients are diabetics, mostly type 2. In the USA, dialysis is free to those who need it under the Medicare ESRD program. Better control of blood glucose and blood pressure are key to reducing these alarming figures.

**References**


**Keywords:** glycated hemoglobin; paradigm shift; serendipity; microalbuminuria; multifactorial intervention; ACE inhibition; sulfonylurea; insulin; thiazolidinedione
En diabétologie, et d’une manière générale en médecine, les découvertes sont rarement planifiées. En revanche, elles dépendent souvent de centres de recherche ayant adopté une culture du « découverte fortuite » active dans le cadre de leurs activités plus routinières. Pour citer Pasteur (et la devise de Medicographia) : « La chance ne sourit qu’aux esprits bien préparés ». Cet éditorial concerne certaines des découvertes qui ont changé le monde de la diabétologie. Bien que l’angle de vue ne puisse être que personnel1-3, il pourra néanmoins inciter les lecteurs intéressés par la longue et fascinante histoire du diabète à se reporter au nouvel ouvrage remarquablement documenté du docteur Robert Tattersall, professeur de médecine métabolique à l’Université de Nottingham, intitulé Diabetes. The Biography4 (Biographie du diabète).

Le Dr Samuel Rahbar, immunologiste, (né en 1929), qui a obtenu son diplôme et son doctorat de médecine dans le Téhéran prérévolutionnaire, était sans conteste un esprit « bien préparé ». Un exemple célèbre d’une découverte inattendue est celle qu’il a faite d’une « nouvelle » molécule dans le diabète, l’hémoglobine glyquée (HbA1c), un marqueur du contrôle glycémique à long terme5. En étudiant des variantes rares de la molécule d’hémoglobine endémiques au Moyen-Orient, il a mis en évidence une variante à évolution rapide qui, à sa surprise, n’était présente que chez les patients diabétiques, et en particulier ceux présentant souvent un mauvais contrôle glycémique. Cette « découverte fortuite » (selon les propres termes du docteur Rahbar) a ouvert un nouveau champ de recherche médicale. L’utilisation de l’HbA1c, avec les lecteurs de glycémie miniaturisés, a révolutionné le contrôle et l’autosurveillance du diabète. De nombreuses autres découvertes ont été effectuées de la même manière en diabétologie. Contrairement aux procédures standard de résolution des problèmes, les découvertes inattendues de ce type ont souvent créé des changements de modèle6.

L’histoire naturelle du diabète comporte une période prodromique plus ou moins silencieuse, suivie par une détérioration progressive de la tolérance au glucose qui aboutit à un diabète patent, voire sévère. Jusqu’à présent, malgré tous les progrès accomplis dans la recherche et le traitement du diabète, nous avons pris conscience de l’étendue de nos lacunes dans la compréhension de base de cette maladie, qu’elle soit de type 1 ou 2. Les traitements peuvent ainsi être considérés comme seulement compensateurs, dans la mesure où ils ne visent qu’à corrigir l’hyperglycémie (liée à une résistance à l’insuline ou à une perte progressive de la fonction des cellules β). Ces 25 dernières années, nous avons découvert qu’une intervention multifactorielle jouait un rôle essentiel dans la prévention des complications cardio-
vasculaires et rénales, nous apprennent ainsi que cette ma-
ladie ne concerne pas seulement le glucose. Un traitement
antihypertenseur et hypolipémiant peut parfois s’avérer plus
important que l’abaissement de la glycémie, en particulier
parce que celui-ci peut être difficile à mettre en œuvre effica-
cement. En outre, nous intensifions désormais les soins des
patients ayant des complications précoces, par exemple une
microalbuminurie et ses altérations associées. Jusqu’à la pu-
blication des résultats de deux études majeures sur le dia-
bète — l’Étude sur le contrôle et les complications du diabè-
etype 1, l’étude DCCT,7, program-
mée par le diabétologue Oscar Crofford (né en 1930) à l’Uni-
versité Vanderbilt, et l’Étude britannique prospective sur le dia-
bète (United Kingdom Prospective Diabetes Study, UKPDS),
programmée par Robert Turner (1938-1999) à Oxford, res-
pectivement en 1994 et en 1998 — il n’avait pas été claire-
ment établi que le contrôle glycémique était réellement im-
portant. Les sceptiques affirmaient toujours qu’ils avaient ob-
servé des patients dont le contrôle glycémique à long terme
était médicocre, et qui ne présentaient que des complications
diabétiques limitées au stade terminal (sans se rendre compte
de l’importance des autres facteurs, par exemple l’effet pro-
tecteur d’une pression artérielle basse).

Chez les patients atteints de diabète de type 1, l’étude DCCT
a mis en évidence les effets à long terme du contrôle glycé-
mique sur les complications diabétiques. Les résultats an-
noncés avant leur publication, dont la présentation reste vi-
vante à mon esprit lors du congrès de l’Association améri-
caine du diabète (American Diabetes Association) à Las
Vegas en juin 1993, concordaient avec ceux de la méta-ana-
lyse publiée le mois précédent par Wang et al. dans la revue
The Lancet. Le souvenez de l’annonce, 5 ans plus tard, des
données de l’étude UKPDS, lors du congrès de l’Associa-
tion européenne pour l’étude du diabète (European Asso-
ciation for the Study of Diabetes, EASD) qui s’est déroulé à
Barcelone, n’est pas moins vivace.

La question de l’impact de la glycémie sur le diabète de
type 2 est devenue cruciale après la présentation au début
des années 1970 des données du Programme américain sur
le diabète d’un groupe d’universités (University Group Dia-
betes Program, UGDP), qui ont suggéré que le contrôle glycé-
mique par des sulfamides hypoglycémiants pouvait même
être nocif. En 1976, Robert Turner s’est rendu au débat du
congrès de la Fédération internationale du diabète (Inter-
tional Diabetes Federation) à New Delhi, et a programmé
l’étude UKPDS peu de temps après. Les investigateurs d’Ox-
ford gardaient toujours un petit morceau de papier sur lequel
Turner griffonnait les grandes lignes de l’étude UKPDS (le
« Musée UKPDS »).

Certains d’entre nous avaient partiellement anticipé les ré-
sultats de l’étude UKPDS, dans mon cas parce que j’écrivais
un éditorial sur la réduction de la pression artérielle pour le
British Medical Journal, et que je me souviens bien de la prise
de conscience générale des rédacteurs reconnaissant tous
l’importance probable du contrôle glycémique dans la pré-
vention de la maladie microvasculaire. Nous n’étions pas
aussi assurés de sa relation avec la maladie macrovasculaire,
mais un suivi de 10 ans publié dans le New England Journal
of Medicine a démontré l’effet pérenne positif de l’étude
UKPDS. Il est rapidement apparu que l’abaissement de la
pression artérielle jouait également un rôle essentiel (l’hyper-
tension et l’hyperglycémie ne faisant pas « bon ménage »).

L’association d’un contrôle glycémique et d’une diminution
optimale de la pression artérielle est apparue comme une
stratégie centrale, contribuant à retarder la progression de l’in-
suffisance rénale terminale (IRT). Ces résultats ont été confir-
més ultérieurement par Hans-Henrik Parving du Steno Dia-
betes Center au Danemark10, et Ed Lewis de l’Université
Vanderbilt en utilisant un inhibiteur de l’enzyme de conver-
sion de l’angiotensine (IEC)11. D’autres confirmations sont ve-
nues de l’étude MDRD (Modification of Diet in Renal Disease,
Modification of the alimentation dans l’insuffisance rénale),
publiée en 1994, dont les principaux résultats montrent un
effet protecteur de la diminution de la pression artérielle, plu-
tôt que d’un régime hypoprotéiné.

L’étude de très grande échelle ADVANCE (Action in Diabet-
es and Vascular Disease: PreterAx and DiamicroN MR Con-
rolled Evaluation, Action sur le diabète et les maladies vasculaires :
evaluation contrôlée de Preterax et de Diamicron à libéra-
tion modifiée), publiée en 200712, a constitué une sorte de
poursuite de l’étude UKPDS dans la mesure où elle a inclus
des patients dont le diagnostic avait été posé quelque 8 ans
auparavant, contrairement aux patients de l’étude UKPDS
atteints de diabète nouvellement diagnostiqué. L’étude
ADVANCE a confirmé le bénéfice d’associer le contrôle de la
glycémie et celui de la pression artérielle. Elle n’a établi au-
cune limite inférieure aux valeurs des deux paramètres per-
mettant d’apporter ce bénéfice, en contradiction nette avec
les études ACCORD (Action to Control CardioVascular Risk
in Diabetes, Action pour le contrôle des risques cardio-vas-
culaires dans le diabète) et VADT (Veterans Administration
Diabetes Trial, Étude sur le diabète du ministère des anciens
combattants). Cela est probablement dû aux effets plus spé-
cifiques de l’association péridorfl / indapamide et de la gla-
zoïde à libération modifiée par rapport à ceux, respectivement,
de la metformine et de la rosiglitazone, qui ont été utilisées
dans les deux autres études. Dans une étude intéressante,
mais controversée, menée par Curie et al. publiée dans la
revue The Lancet en 201013, les durées de survie les plus
longues ont été associées à des valeurs intermédiaires de
l’HbA1c, d’environ 7,5 %, tandis que les valeurs élevées et fa-
bles ont été associées à des survies plus courtes. Cepen-
dant, différentes stratégies thérapeutiques ont été utilisées
dans cette étude de cohorte rétrospective, contrairement aux
conditions contrôlées de l’étude ADVANCE, qui n’avait éta-
blie aucune limite. L’administration du médicament une fois
par jour au cours de l’étude ADVANCE a également été extrêmement importante pour l’observance du traitement (« Les médicaments ne sont pas actifs si les patients ne les prennent pas », pour citer l’ancien chef du service fédéral de la santé publique C. Everett Koop [1916-]).

L’arsenal thérapeutique contre le diabète de type 2 a été complété depuis une décennie par une nouvelle classe d’agents sensibilisants à l’insuline, les thiazolidinediones. L’une de celles-ci, la troglitazone, a rapidement été retirée à cause d’une toxicité hépatique sévère, mais au moins deux médicaments sont restés commercialisés, la rosiglitazone et la pioglitazone. Néanmoins, des doutes persistent quant à leur sécurité d’emploi cardio-vasculaire et à leurs autres effets indésirables (œdème, prise de poids).

L’insuline est assurément la pierre angulaire du traitement du diabète de type 1, mais elle est également de plus en plus souvent utilisée dans le diabète de type 2, en particulier depuis que les données de l’étude UKPDS ont souligné l’importance d’un contrôle glycémique optimal, obtenu par convention, par de fréquentes injections ou l’utilisation d’une pompe à insuline permettant d’obtenir au mieux ces résultats (l’insuline inhalée s’étant avérée un échec majeur et extrêmement coûteux, à classer avec les concepts d’inhibition de l’al-dose réductase et d’inhibition de la formation de produits finaux de glycosylation avancée dans la prévention des complications). Les analogues de l’insuline, les insulines d’action rapide et les insulines d’action intermédiaire (par exemple l’insuline NPH [neutral protamine Hagedorn]) sont désormais largement utilisés. Les analogues de longue durée d’action, l’insuline détiémurée et l’insuline glargine, sont également très employés, en particulier en Europe. Il n’est pas toujours facile d’obtenir un meilleur contrôle glycémique que celui obtenu avec l’insuline NPH, sans parler des différences observées dans les complications à long terme. Néanmoins, les patients apprécient les nouveaux analogues et leurs courbes glyémiques sur 24 heures sont généralement plus lisses et plus stables.


Le rôle prédictif important de la microalbuminurie a été montré à la fois dans le diabète de type 1 et de type 2, respectivement en 1982 et en 1984. Elle constitue depuis un marqueur de risque majeur dans de nombreux essais cliniques, notamment l’étude PREMIER (PREterax in albuminuria) et l’étude ADVANCE. Bien que le blocage du système rénine-angiotensine ait été une caractéristique importante dans la plupart des études, il apparaît clairement que l’abaissement de la pression artérielle est en soi un élément fondamental. L’intervention de Giuseppe Remuzzi (1949-) à Bergame a été déterminante pour démontrer la contribution des IEC en cas de néphropathie débutante, qu’elle soit d’origine diabétique ou non16. L’étude ADVANCE a démontré le bénéfice de l’association périndopril / indapamide à tous les stades de l’insuffisance rénale chronique. L’amélioration du contrôle glycémique avec le glidiazide à libération modifiée a exercé un impact positif similaire sur la microalbuminurie. Comme l’expose en détail John Chalmers dans ce numéro de Medicographia, l’effet combiné de l’abaissement de la pression artérielle et du contrôle glycémique est même plus probant encore, et devrait permettre de réduire encore davantage la charge toujours croissante des complications vasculaires dans le diabète de type 2. Cet objectif reste le principal défi à relever au cours du siècle à venir.

Je ne terminerai pas cet éditorial sans insister sur la complication la plus grave et la plus coûteuse du diabète, c’est-à-dire l’insuffisance rénale terminale (IRT). Environ 2 millions de personnes à travers le monde sont dialysés, principalement aux États-Unis, au Japon et en Allemagne, et le gouvernement américain dépense 24 milliards de dollars par an pour ce traitement. La majorité des bénéficiaires sont diabétiques, principalement de type 2. Aux États-Unis, la dialyse est gratuite dans le cadre du programme Medicare ESRD. Un meilleur contrôle de la glycémie et de la pression artérielle est une stratégie essentielle pour la réduction de ces chiffres alarmants.
Between the time of Aretaeus of Cappadocia’s accurate clinical description of diabetes almost 2000 years ago and the introduction of insulin around 90 years ago, knowledge of the disease and its treatment had advanced little. Type 2 diabetes is a combination of insulin resistance, partly related to lifestyle and obesity, and progressive loss of β-cell function. It has reached almost epidemic proportions in the West and Asia. Treatment is often ineffective, e.g., 15% of US diabetics have an HbA1c of 10% or more. In Danish diabetics, the mean HbA1c is 8.0%, well above the 7% target proposed by the American Diabetes Association. Diagnosis, although simple, tends to be delayed, compounded by an often long clinically silent phase. The bulk of the world’s insulin is now injected by type 2 diabetic patients, after failure of diet and oral antidiabetic drugs. New drugs, such as glitazones and incretin modulators, are increasingly being used in the US, but long-term end point trials are not yet available. Intensive multifactorial intervention focused on lowering blood pressure and lipid and glucose levels is the key strategy in microalbuminuric patients. Landmark studies include the United Kingdom Prospective Diabetes Study (UKPDS) and Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE), together with A Diabetes Outcome Progression Trial (ADOPT) and the Steno 2 study on sulfonylureas. Education and new therapeutic strategies have greatly improved clinical management, but, interestingly, some of the great steps forward in diabetes care and treatment have been surprisingly serendipitous.

We owe the first description of a disease resembling type 1 diabetes, in the second century AD, to Aretaeus of Cappadocia. His writings contain a description that is accurate and clinical: “diabetes is an awful disease melting the body and limbs of the patient into urine. Life is short and painful and sooner rather than later the patient will expire.” Needless to say, he had no way of treating the patients he saw. Hippocrates never mentioned diabetes.

Pre-Aretaeus there are hints of diabetes in certain hieroglyphs and in accounts from India, where ants were drawn to sweet urine (almost a biological test for diabetes). In the past, type 2 diabetes was a disease of the rich, who were often obese from overeating. Nowadays, it has become more common among the poor and less educated. It is highly prevalent in certain populations, such as the Nauru Islanders, many of whom became obese and diabetic on the income from their phosphate de-
Diabetes was first described by Aretaeus of Cappadocia (2nd century AD). Diabetes was first described by Étienne Lancereaux (1829-1910). He classified diabetes into diabète maigre (“lean diabetes”) and diabète gras (“fat diabetes”), equivalent to diabetes types 1 and 2. Increased affluence and decreased physical activity have since created a near-epidemic of type 2 diabetes, which began mainly in the postwar US, but spread worldwide to China, India, and Japan, and to many countries in the Middle and Far East (but not among their guest workers). Treatment often remains ineffective, eg, 15% of US diabetics have an HbA1c of 10% or more. In Danish diabetics, the mean HbA1c is 8.0%, well above the 7% target proposed by the American Diabetes Association. The discovery of insulin and beyond Since the 1920s, we have had insulin to treat diabetic ketoacidosis and type 1 diabetes, but there are still regions in the world where not only insulin, but even proper diagnosis remain a luxury. Patients are still dying undiagnosed.

The bulk of the world’s insulin is injected by type 2 diabetics whose endogenous insulin production we now recognize as deteriorating over time due to a natural history of β-cell failure, as in type 1 diabetes. The sheer number of diabetics partly accounts for the enormous and increasing use of insulin, but most are also highly insulin resistant, requiring much more than the 40 units of insulin produced per 24 hours by healthy individuals. A dose of 200 units is not uncommon. It is axiomatic that the discovery of insulin for human use in Toronto in the early 1920s is the greatest event in the history of diabetology. The first patient, 14-year-old Leonard Thompson (1908-1935), was a typical type 1 diabetic. His before-and after-treatment pictures—from ketotic emaciation to outward normality—went around the world. In his case, there was no time for a proper clinical trial, but it was hardly needed. The treatment was a revolution, instantly transforming a death sentence into a manageable, if lifelong, disease.1

But how did insulin come to be produced worldwide, in particular in Europe, and especially Denmark? Shortly after receiving a Nobel Prize in 1920 for his studies of capillary systems, In obese patients with or without type 2 diabetes, C-peptide levels are often high due to a compensatory increase in insulin production, which decreases over time. No strict guidelines are available, and C-peptide and insulin assays are difficult to use in diagnosis as the results are not well standardized. For an illustration of the main facts concerning diabetes and its treatment, see Table I.

### Table I. Twelve key points about diabetes.

1. Diabetes was first described by Aretaeus of Cappadocia (2nd century AD).
2. Since World War II, diabetes has reached epidemic proportions due to obesity and unhealthy lifestyles.
3. Glycemic control remains poor in many patients.
4. Glycemic control is still difficult despite the many drugs available for type 2 diabetes.
5. Once-daily tablets improve compliance.
6. Multifactorial intervention is crucial, especially in patients with microalbuminuria.
7. Patient education is primordial.
8. Insulin is mandatory in type 1 diabetes, but is often also required by type 2 patients.
9. Sulfonylureas and metformin are still the most important oral drugs in type 2 diabetes. Newer drugs need further evaluation.
10. Some populations have a high prevalence of diabetes (eg, Pima Indians and Nauru Islanders).
11. The optimization of glycemic control during (and before) pregnancy has been a major success story.
12. Antihypertensive treatment effectively delays the onset of end-stage renal disease.

### SELECTED ABBREVIATIONS AND ACRONYMS

- **ADDITION**: Anglo-Danish-Dutch study of Intensive Treatment In peOple with screeN detected diabetes in primary care
- **ADOPT**: A Diabetes Outcome Progression Trial
- **ADVANCE**: Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation
- **DCCT**: Diabetes Control and Complications Trial
- **DIGAMI**: Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction
- **EASD**: European Association for the Study of Diabetes
- **PREMIER**: PREterax in albuMinuria rEgResion
- **PROACTIVE**: PROspective pioglitAzone Clinical Trial In macro-Vascular Events
- **UGDP**: University Group Diabetes Program
- **UKPDS**: United Kingdom Prospective Diabetes Study
the Danish zoophysicist August Krogh (1874-1949) embarked on an obligatory lecture tour of the world’s important university hospitals, which included Toronto’s. There he agreed with Frederick Banting’s departmental head, John Macleod (1876-1935), to take care of insulin production in Denmark (and possibly Europe) on a nonprofit basis. As far as we know, no contract or patent was ever involved: it was a true gentlemen’s agreement. Behind the agreement lay a personal motive: Krogh’s wife Marie suffered from diabetes (although not of an aggressive type; her death in 1943 was due to breast cancer).

On his return home in 1923, Krogh promptly founded a laboratory, the Nordisk Insulinlaboratorium, and also a foundation, the Nordisk Insulinfond, which became an active sponsor of research. From the start, he was partnered by Hans Christian Hagedorn (1888–1971), a cofounder of the Steno Diabetes Center. Porcine insulin is close in chemical structure to human insulin, and being a major pork producer Denmark was well positioned to manufacture insulin from porcine pancreases. Heparin production in Denmark today shares a similar link; it is produced from porcine intestine by Leo Pharma, a company that was also briefly involved in insulin production at an early stage.

After early disagreements with the reputedly fiery Hagedorn, two remarkable brothers, Thorvald and Harald Petersen, left the Nordisk Insulinlaboratorium in 1924 to set up a rival production company, Novo, a year later. The rivalry continued for 65 years until the two companies merged to form Novo Nordisk, launching the world’s first prefilled insulin syringe the same year, following the introduction 4 years earlier of the NovoPen.

Porcine insulin is now rarely used in Europe and insulin production is based on gene technology. Rapid-acting insulin soon became available along with long-acting insulins, such as insulin glargine (Lantus®) and insulin detemir (Levemir®). Despite the popularity of the latter, it is difficult to demonstrate that these provide better glycemic control than that obtained with neutral protamine Hagedorn (NPH) insulin (eg, Insulatard®).

Leif Sestoft developed the insulin pen idea while working at Hvidovre Hospital in the Copenhagen suburbs. A 2007 analysis found no major difference in renal outcome, measured by glomerular filtration rate, between pen and pump insulin delivery, although continuous infusion achieved superior glycemic control. The pen was a major breakthrough for treating both types of diabetes. Reliable and user-friendly, it is now used by most insulin-requiring diabetics in many countries. Although it is likely that improved long-term glycemic control using pen injection will result in fewer complications, this has so far been difficult to document. Perhaps the single most successful application has been in the facilitation and marked improvement of glycemic control in diabetic pregnancy. Despite the dramatic developments in insulin analogs and delivery systems, the basic principles of treatment remain the same, as do its problems: exogenous insulin does not travel via the portal vein to the liver as does pancreatic insulin, nor are the doses of exogenous insulin accurately titrated to blood glucose concentration. Complete normalization of glycaemia, as measured by HbA1c, thus remains elusive. Even the status of HbA1c as a marker has been called into question, on the basis of its sometimes less-than-linear relationship with estimated average glucose and random glucose levels.

**Pharmacological treatment with oral antidiabetic drugs**

Until the 1950s, insulin was the only pharmacological treatment of diabetes types 1 and 2, and it was serendipity that was responsible for the next paradigm shift in antidiabetic therapy. Marcel Janbon, an infectious disease physician experimenting with a new sulfonamide to treat the numerous cases of typhoid fever in wartime Montpellier (this was 1942), spoke to physiologist colleague Auguste Loubatières (1912–1977) about his findings. Janbon reported posttreatment convulsions, prolonged coma, and severe falls in blood glucose in some of his patients to Loubatières, who had been conducting diabetes research in dogs during the previous decade. Although in 1946, after several more years’ work, Loubatières concluded in his doctoral thesis that sulfonamide was an insulin secretagogue acting directly on the pancreas, it was not until a decade later in Germany that the first sulfonylureas were developed for use in diabetes. They have since been widely used in trials such as the United Kingdom Prospective Diabetes Study (UKPDS)—including in its 10-year follow-up, the Action in Diabetes and Vascular disease: Preterax and DiamicroN MR Controlled Evaluation (ADVANCE), and the Steno 2 study. In the latter two trials, gliclazide proved effective and devoid of cardiovascular side effects. Once-daily dosing with the modified release preparation greatly improves compliance.

In Europe, and subsequently in the US after a lag of several decades, the biguanide metformin was introduced as an insulin sensitizer and became widely used in combination with a sulfonylurea. Sulfonylureas lower HbA1c, often by 1.5% to 2%, and even more so when combined with metformin. Newer drugs, such as glitazones, which are not extensively used in Europe due to doubts about late effects and weight gain, cause a fall of between 0.5% and 1%.

One study of particular interest where sulfonylureas are concerned, A Diabetes Outcome Progression Trial (ADOPT), compared three oral therapies in newly diagnosed type 2 diabetics: rosiglitazone, metformin, and glibenclamide. Baseline characteristics were similar in the three groups, each comprising around 1450 patients with blinded follow-up over 4-5 years.

**Type 2 Diabetes and the liver**

It is well established that HbA1c is a better measure of glycemic control than either fasting plasma glucose or random glucose levels. The concentration of glycemic control in diabetic pregnancy. Despite the dramatic developments in insulin analogs and delivery systems, the basic principles of treatment remain the same, as do its problems: exogenous insulin does not travel via the portal vein to the liver as does pancreatic insulin, nor are the doses of exogenous insulin accurately titrated to blood glucose concentration. Complete normalization of glycaemia, as measured by HbA1c, thus remains elusive. Even the status of HbA1c as a marker has been called into question, on the basis of its sometimes less-than-linear relationship with estimated average glucose and random glucose levels.

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All-cause mortality was similar with all three therapies. Cardiovascular risk was lowest with glibenclamide, but hypoglycemia was most commonly seen with this drug (0.6% of episodes were considered serious).

β-Cell function remained the same after 5 years, which is remarkable. Hospitalization and fractures were rarest with glibenclamide, and, in addition, less anemia was observed. With rosiglitazone, the rate of monotherapy failure was lowest, but weight gain and edema were more frequent. Metformin was associated with more frequent gastrointestinal events.

Cost was factored into choice of treatment by the authors. Despite their initial bias in favor of rosiglitazone (the study drug in this comparison), it is not difficult to see why their data confirm the European preference for the familiar treatment stalwarts of sulfonylurea, metformin, and insulin.

Table IIA lists the major clinical trials in recent decades along with their key messages, while Table IIB shows conceptual innovations that have reshaped our day-to-day management of diabetes. Many of these trials were conducted in response to, or as an extension of, a trial that had gone before (Figure 1), at the same time as they attempted to resolve one of the keenly debated issues of day, beginning with the debate between Edward Tolstoi and Elliott Joslin (1869-1962) on whether lax or strict glycemic control is better. This debate, along with several others, can now be laid to rest (Table III).

### A. CLINICAL TRIALS

<table>
<thead>
<tr>
<th>Trial</th>
<th>Advance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes Control and Complications Trial (DCCT)</td>
<td>Landmark study in type 1 diabetes</td>
</tr>
<tr>
<td>United Kingdom Prospective Diabetes Study (UKPDS)</td>
<td>Landmark study in type 2 diabetes</td>
</tr>
<tr>
<td>PREterax in albuMinuria rEgRession (PREMIER)</td>
<td>Benefit in patients with abnormal albuminuria</td>
</tr>
<tr>
<td>Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE)</td>
<td>Landmark study in type 2 diabetes</td>
</tr>
<tr>
<td>Insulin pen vs pump studies (Cochrane analysis)</td>
<td>Similar results</td>
</tr>
<tr>
<td>A Diabetes Outcome Progression Trial (ADOPT) and PROSpective pioglitAzone Clinical Trial In macroVascular Events (PROACTIVE)</td>
<td>Studies with glitazones</td>
</tr>
<tr>
<td>Diabetes mellitus, Insulin Glucose infusion in Acute Myocardial Infarction (DIGAMI) study</td>
<td>Uncertain result</td>
</tr>
<tr>
<td>Steno 2 study</td>
<td>Multifactorial intervention beneficial in microalbuminuric type 2 diabetes</td>
</tr>
<tr>
<td>Anglo-Danish-Dutch study of Intensive Treatment In peOple with screeN detected diabetes in primary care (ADDITION)</td>
<td>Multifactorial intervention is not beneficial in newly diagnosed type 2 diabetes (results presented at the 2010 EASD meeting)</td>
</tr>
</tbody>
</table>

### B. CLINICAL CONCEPTS

- Self-care, home blood-glucose monitoring
- Diabetes nurses and dieticians
- Metabolic syndrome
- Microalbuminuria as a marker of high risk
- Cost was factored into choice of treatment by the authors. Despite their initial bias in favor of rosiglitazone (the study drug in this comparison), it is not difficult to see why their data confirm the European preference for the familiar treatment stalwarts of sulfonylurea, metformin, and insulin.

Table IIA and IIB. Advances in clinical trials and concepts of diabetes.

Abbreviation: EASD, European Association for the Study of Diabetes.

All-cause mortality was similar with all three therapies. Cardiovascular risk was lowest with glibenclamide, but hypoglycemia was most commonly seen with this drug (0.6% of episodes were considered serious). β-Cell function remained the same after 5 years, which is remarkable. Hospitalization and fractures were rarest with glibenclamide, and, in addition, less anemia was observed. With rosiglitazone, the rate of monotherapy failure was lowest, but weight gain and edema were more frequent. Metformin was associated with more frequent gastrointestinal events.

Biomarkers for predicting complications

In 1984, we showed that microalbuminuria predicted not only renal disease, but also early mor-

Figure 1. Major trials and conceptual developments in type 2 diabetes from the 1940s to 2010. Abbreviations: ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; BG, blood glucose; BP, blood pressure; IDF, International Diabetes Federation; NEJM, New England Journal of Medicine; SU, sulfonylurea; UGDP, University Group Diabetes Program; UKPDS, United Kingdom Prospective Diabetes Study.
Microalbuminuria, an excellent marker of complications, was the basic instrument used in the Steno 2 study launched in 1992. Renal biopsy is very rarely required for diagnosing diabetic nephropathy, the only indication being atypical onset of sudden proteinuria. Steno 2 allocated type 2 patients with microalbuminuria to intensified combined intervention (glycemic control using gliclazide, lipid lowering, and blood pressure lowering) or conventional multifactorial treatment. The effect on mortality and end-stage renal disease after 8 years was dramatic. As a result, this treatment has become standard for microalbuminuric patients and even for some normoalbuminuric patients (mainly those with poor control and other risk factors). The Anglo-Danish-Dutch study of Intensive Treatment In peOple with screeN detected diabetes in primary care (ADDITION) used the same multifactorial strategy, but in newly diagnosed patients. In contrast, the results presented at the European Association for the Study of Diabetes (EASD) meeting in Stockholm in September 2010 were negative.

Table III. Much debated issues, past and present, concerning diabetes and the kidney.

<table>
<thead>
<tr>
<th>Issue</th>
<th>Author’s assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Role of genetic analysis in risk assessment, diagnosis, and treatment</td>
<td>As yet undocumented</td>
</tr>
<tr>
<td>Need for high blood pressure to maintain renal perfusion</td>
<td>Historically interesting, but a misunderstanding</td>
</tr>
<tr>
<td>Role of renal biopsy in diagnosing non-diabetic nephropathy in type 1 and 2 diabetics (regardless of presence/absence of retinopathy)</td>
<td>Renal biopsy very rarely required</td>
</tr>
<tr>
<td>Role of low-protein diet in delaying progression of diabetic nephropathy, also during ACE inhibitor and ARB therapy</td>
<td>A low-protein diet does not delay the fall in glomerular filtration rate during ACE inhibitor/ARB therapy</td>
</tr>
<tr>
<td>ARBs as the first-line choice in type 2 diabetes and microalbuminuria/light albuminuria</td>
<td>Either ACE inhibitor or ARB therapy can be used</td>
</tr>
<tr>
<td>Role of the pill in predisposition to future nephropathy</td>
<td>Unconfirmed in major US studies</td>
</tr>
</tbody>
</table>

Figure 2. The three proponents of microalbuminuria.
From left: Giancarlo Viberti, Hans-Henrik Parving, and Carl Erik Mogensen. [Eli Friedman, 1984].

Figure 3. Ten partly or totally serendipitous discoveries in diabetes (outer circle) that radically improved diabetes care (inner circle).

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

albuminuria to intensified combined intervention (glycemic control using gliclazide, lipid lowering, and blood pressure lowering) or conventional multifactorial treatment. The effect on mortality and end-stage renal disease after 8 years was dramatic. As a result, this treatment has become standard for microalbuminuric patients and even for some normoalbuminuric patients (mainly those with poor control and other risk factors). The Anglo-Danish-Dutch study of Intensive Treatment In peOple with screeN detected diabetes in primary care (ADDITION) used the same multifactorial strategy, but in newly diagnosed patients. In contrast, the results presented at the European Association for the Study of Diabetes (EASD) meeting in Stockholm in September 2010 were negative.
What new prospects are on the horizon?

Although difficult to document in properly designed trials, our daily experience tells us that self-monitoring and the introduction of classes in which patients learn from specialists, nurses, and dieticians have transformed the clinical management of diabetes. It is interesting to note that the advances described in the editorial and in this paper have often been serendipitous (Figure 3, page 13), although it is no accident that most have emerged from well-established centers populated by prepared minds (discoveries rarely come out of the blue). Some have even created paradigm shifts.7 There is no reason to believe that this pattern is likely to change. Of the prospects listed in Table IV, a number are of “Holy Grail” status, unabashedly so: it is only by keeping them in our minds that we will recognize them when they present themselves in the most unexpected of guises.

Table IV. Possible future developments in diabetes.

<table>
<thead>
<tr>
<th>Possible Future Developments</th>
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</thead>
<tbody>
<tr>
<td>A viral infection specifically targeting β cells is found to precede type 1 diabetes, paving the way to vaccine-based prevention</td>
</tr>
<tr>
<td>Islet cell and pancreas transplantation (already performed in a limited number of patients) becomes more widely available</td>
</tr>
<tr>
<td>A long-term glucose sensor is developed for titrating insulin dosage in an automated closed-loop system</td>
</tr>
<tr>
<td>A blood pressure-lowering agent is developed to prevent or regress retinopathy and nephropathy from diagnosis</td>
</tr>
<tr>
<td>Stem cell therapy is developed to replace native β cells and produce insulin in a close-dependent physiological manner</td>
</tr>
<tr>
<td>An effective genetic marker is identified and preventive trials conducted</td>
</tr>
<tr>
<td>An effective pharmacological weight-loss strategy is developed</td>
</tr>
</tbody>
</table>

Keywords: glycated hemoglobin; paradigm shift; serendipity; microalbuminuria; multifactorial intervention; ACE inhibition; sulfonylurea; insulin; metformin
Changes in human behavior and lifestyle associated with globalization have resulted in a dramatic increase in the prevalence and incidence of type 2 diabetes globally. Until recently, there was a strong emphasis on genetic susceptibility, and on environmental and behavioral factors such as a sedentary lifestyle, overly rich nutrition, and obesity (particularly central adiposity). More recently, focus has shifted to the potential contribution of the maternal environment and the impact of in-utero influences, ie, the role of epigenetics. This may be an important factor in the very high prevalences of type 2 diabetes now being seen in nations such as India and China, two countries that numerically bear the main brunt of the epidemic. Type 2 diabetes is appearing increasingly in children and adolescents, and the frequency of diagnosis of pediatric type 2 diabetes is outstripping that of type 1 diabetes in some countries already. The prevention of diabetes and control of its micro- and macrovascular complications will require a major integrated approach directed at societal and individual behavioral change if we are to see significant reduction in the huge premature morbidity and mortality it causes. Diabetes is looming as one of the greatest threats to public health in the 21st century. This is an impelling rationale for strengthening efforts for its prevention and control.

The United Nations General Assembly voted unanimously to pass Resolution 61/225 declaring diabetes an international public health issue. For the first time, governments acknowledged that a noninfectious disease could pose as serious a threat to world health as infectious diseases such as HIV/AIDS, tuberculosis, or malaria. This United Nations resolution recognized that tackling diabetes is likely to be one of the most important challenges for the global public health community in the 21st century.”

If anyone had predicted 30 years ago that diabetes mellitus would be one of the biggest public health problems facing the human race in 2010, they would not have been taken seriously. Yet, in 1977, when we published the prevalence of diabetes in the Pacific island nation of Nauru,1 the writing was on the wall. Elsewhere, our studies of the secular rises in type 2 diabetes in the Indian Ocean island nation of Mauritius2,3 were a barometer that provided further predictions of the global epidemic.4

In an earlier review article on the global epidemiology of diabetes published in Medicographia in 1987,5 I pointed out that the mounting problems of chronic noncommunicable disease, and in particular diabetes, raised the important challenge of noncommunicable disease prevention, a 21st-century parallel to the prevention of infectious disease at the turn of the 19th century. Prevention of diabetes is a major challenge that faces nearly every nation and it is now being recognized by the international community. In December 2006, against the background of an escalating diabetes epidemic, the United Nations General Assembly voted unanimously to pass
Resolution 61/225 declaring diabetes an international public health issue. For the first time, governments acknowledged that a noninfectious disease could pose as serious a threat to world health as infectious diseases such as HIV/AIDS, tuberculosis, or malaria. This United Nations resolution recognized that tackling diabetes is likely to be one of the most important challenges for the global public health community in the 21st century.

The most recent global predictions by the Baker IDI Heart and Diabetes Institute for the International Diabetes Federation (IDF) suggest that currently there are 285 million people with diabetes worldwide. This is set to escalate to 438 million by 2030, a 54% increase. Figure 1 shows these data from the 2009 IDF Diabetes Atlas with the expected increases in the next 20 years to 2030 by geographic region and the global total. Many of these cases of diabetes will remain undiagnosed, and indeed untreated, particularly in developing nations (Figure 1).

Just to give a perspective, type 2 diabetes has reached epidemic proportions in many developing nations and some Middle-Eastern nations, as well as in disadvantaged minorities in developed countries, eg, Australian Aboriginals and Torres Strait Islanders; Native-, African-, and Mexican-Americans in the USA; and also in Asian Indians and Chinese.

Table I illustrates the dramatic rises in diabetes prevalence in several Asian nations compared to the prevalence in the USA. The increases in Asia are much greater. Compared with a 1.5-fold increase in the USA from 1978-2000, South Korea experienced a dramatic 5.1-fold increase between 1971 and 2001.

We, and others, have reviewed the epidemiology of type 2 diabetes in great detail elsewhere. Rather than provide a repeat of these earlier papers, this review focuses on more recent studies which underline the dramatic escalation in the number of cases of diabetes in both developed and developing nations.

**Figure 1.** Global projections for the diabetes epidemic: 2010-2030 (millions). In each box, the top figure represents the number of people with diabetes in that region (millions) in 2010; the middle figure is the projected number of people with diabetes (millions) in 2030; and the bottom figure is the percentage change from 2010 to 2030. Modified from reference 6: International Diabetes Federation. IDF Diabetes Atlas. 4th ed. Brussels, Belgium: International Diabetes Federation; 2009:21-27. © 2009, International Diabetes Federation.

**Table I**

<table>
<thead>
<tr>
<th>Region</th>
<th>2010 (millions)</th>
<th>2030 (millions)</th>
<th>Increase (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>World</td>
<td>285</td>
<td>438</td>
<td>54%</td>
</tr>
<tr>
<td>Asia</td>
<td>12.1</td>
<td>101.0</td>
<td>72%</td>
</tr>
<tr>
<td>55.2</td>
<td>20%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26.6</td>
<td>94%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.4</td>
<td>53.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42%</td>
<td>65%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.0</td>
<td>29.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>76.7</td>
<td>112.8</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>55.2</td>
<td>112.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>37.4</td>
<td>112.8</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>112.8</td>
<td></td>
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</tr>
<tr>
<td>18.0</td>
<td>29.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20%</td>
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</tr>
<tr>
<td>76.7</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

**SELECTED ABBREVIATIONS AND ACRONYMS**

- **AUSDIAB** AUStalian DIABetes and obesity study
- **AUSDRISK** AUStalian type 2 Diabetes RISK assessment tool
- **FINDRISK** FINnish Diabetes RISK score
- **FPG** fasting plasma glucose
- **IDF** International Diabetes Federation
- **IFG** impaired fasting glucose
- **IGT** impaired glucose tolerance
- **OGTT** oral glucose tolerance test
One of the most recent and largest studies of diabetes in a white population is the Australian DIABetes and obesity study (AUSDIAB). In 2000, AUSDIAB studied 11,247 adults and provided the first national Australian data on the prevalence and incidence of diabetes. In comparisons of AUSDIAB with the only previous Australian population–based study to include an oral glucose tolerance test (OGTT) (in Busselton, Western Australia), we were able to show that there was a rapidly rising prevalence of diabetes in Australia, with a more than doubling of the age-specific prevalence of diabetes from 1981 to 2000 (Figure 2). In 2005, there was a follow-up study that found that the age-standardized annual incidence of diabetes for men and women was 0.8% (95% CI, 0.6 to 0.9) and 0.7% (95% CI, 0.5 to 0.8), respectively. The annual incidence was 0.2% (95% CI, 0.2 to 0.3), 2.6% (95% CI, 1.8 to 3.4), and 3.5% (95% CI, 2.9 to 4.2) in those with normoglycemia, impaired glucose tolerance (IGT), and impaired fasting glucose (IFG), respectively, at baseline. In those with IFG, the incidence was significantly higher in women (4.0% vs 2.0%), while in those with IGT, it was significantly higher in men (4.4% vs 2.9%). In age- and sex-adjusted models, glycated hemoglobin (HbA1c) was a predictor of diabetes in the whole population, in those with normoglycemia and in those with IGT or IFG at baseline. The incidence of diabetes was 10-20 times greater in those with IGT or IFG than in those with normoglycemia at baseline. The AUSDIAB data reflect, in general, the status of diabetes in developed nations with a predominantly white population. What is also noteworthy is the more pronounced earlier age of onset of type 2 diabetes in the AUSDIAB cohort.

Much more dramatic and reflective of the rise and rise of diabetes are the data emerging from Asian nations as they experience the influence of modernization and industrialization, and their economies begin to blossom. The “epicenter” for the diabetes epidemic is in Asia, with India and China having the highest number of cases of type 2 diabetes. As was mentioned earlier, if our 1975 study in the Pacific island of Nauru was one of the first warnings of the potential global epidemic, our subsequent studies in the Indian Ocean nation of Mauritius, another barometer of the potential escalation, have provided further data. Its multiethnic population of some 1.3 million inhabitants predominantly comprises Asian Indians, Creoles (mainly African), and Chinese. This distribution of ethnic groups in Mauritius reflects approximately two-thirds of the world population, providing a microcosm of the global picture.

Our serial studies in Mauritius apart from demonstrating a high prevalence and incidence of diabetes have demonstrated a notable secular prevalence increase from 12.8% in 1987, to 15.2% in 1992, and 17.9% in 1998. Our latest study, in 2006, shows a further increase in prevalence to 23.4% (unpublished data). Consequently, the results from this small island population have suggested that modernization could have a very serious impact on diabetes rates in both India and China, in terms of the impact on both health as well as on the national economy. Indeed, this has turned out to be the case. This, evidence that the prevalence of type 2 diabetes doubled in Singaporean Chinese between 1984 and 1992, and the high prevalence of diabetes in Taiwan have provided alarming indicators of the size of a potential future epidemic in the People’s Republic of China.

### Table I. The multiplicative increase in diabetes prevalence in selected Asian nations compared with the United States of America.

<table>
<thead>
<tr>
<th>Country</th>
<th>Survey period</th>
<th>Increase in prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>1978-2000</td>
<td>1.5-fold</td>
</tr>
<tr>
<td>Taiwan</td>
<td>1985-1995</td>
<td>1.6-fold</td>
</tr>
<tr>
<td>Singapore</td>
<td>1985-1992</td>
<td>2.1-fold</td>
</tr>
<tr>
<td>China</td>
<td>1986-2000</td>
<td>3.4-fold</td>
</tr>
<tr>
<td>India</td>
<td>1979-2000</td>
<td>4.0-fold</td>
</tr>
<tr>
<td>Korea</td>
<td>1971-2001</td>
<td>5.1-fold</td>
</tr>
</tbody>
</table>

From a very low prevalence of diabetes in 1980 in Shanghai where the prevalence of type 2 diabetes was less than 1%, the prevalence has risen markedly to 6.9%. In addition, a report from Qingdao showed a dramatic secular increase in prevalence, eg, between 2001/2002 and 2006, the urban prevalence in men aged 35 to 75 years increased from 11.3% to 19.2%. At the time, it was suggested that China had the second highest number of people with diabetes in the world after India.

However, a more recent report with results from a 2007/2008 national study among Chinese adults has put China well in front. A nationally representative sample of 46,239 adults, 20 years of age and over, was selected from 14 provinces and municipalities. Previously diagnosed diabetes was determined
on the basis of self-report. The rest of the participants underwent an OGTT. The age-standardized prevalence of all diabetes was 9.7% (men, 10.6%; women, 8.8%) and for prediabetes it was 15.5% (men, 16.1%; women, 14.9%). Extrapolated nationally, the authors point out that this reflects 92.4 million adults with diabetes and 148.2 million adults with prediabetes. The prevalence of diabetes was higher among urban residents than among rural residents (11.4% vs 8.2%). The results indicate that diabetes has become a major public health problem in China and that strategies aimed at the prevention and treatment of diabetes are needed. This is likely to be a significant understatement of the profound impact this will have on their health system, especially as modernization and industrialization gather pace.

A similar large secular increase in diabetes has occurred in India and, indeed, other Asian nations.1,11-14 India once led the world with the largest number of diabetic subjects. It earned the dubious distinction of being the world’s “capital” for diabetes, a title that now more appropriately belongs to China! In an urban national study reported in 2001, the age standardized prevalence of type 2 diabetes was 12.1%. The highest rates were seen in the southern part of India with 13.5% in Chennai and 16.6% in Hyderabad.21 A more recent study showed a dramatic secular increase in diabetes from 13.9% in 2000 to 18.6% in 2006,22 a rise of 34% in a relatively short period.

Other “hot spots” for diabetes include the Gulf region in the Middle East, another area where the epidemic is taking hold.10 A survey conducted in Qatar among Qatari nationals above 20 years of age showed that the prevalence of diabetes was high at 16.7%.23 Diagnosed diabetes constituted 10.7%, while newly diagnosed cases accounted for 5.9%. IGT was diagnosed in 12.5% and IFG occurred in 1.3%. Interestingly, prevalence can vary depending on population within a country. A 1999/2000 study in the United Arab Emirates covered both the local community and expatriate workers.24 The crude prevalence of diabetes was 20%. It was higher, at 25%, in citizens from the United Arab Emirates than in expatriates (with a prevalence of 13%-19%, depending on their original country of origin). The authors stated that prompt action would be needed in order to avert a major public health crisis. In Oman, another Gulf nation, the prevalence of diabetes by fasting plasma glucose ≥7 mmol/L in the capital, Muscat, was 17.7% compared to 10.5% in rural areas.25 The prevalence of self-reported diabetes was 4.3%. Similarly, a high prevalence of diabetes has been noted in other countries in that region, including Saudi Arabia and Kuwait.10

Type 2 diabetes in children—the emerging threat
There is now a major emerging global phenomenon that reveals a new perspective of the global diabetes epidemic. This is the younger age of onset being seen in type 2 diabetes, which was formerly considered a disease of adults.4 However, in recent years, type 2 diabetes is appearing at a younger age, not only in the young adult population, but also in adolescents and, occasionally, in children.1,26 As might be expected, the majority of the cases are being seen in ethnic groups already shown to be at high risk of type 2 diabetes such as the Pima Indians.27 Until now, type 1 diabetes has been the major form seen in children, but it seems likely that type 2 diabetes is set to become the predominant form within the next 10 years in many ethnic groups and potentially also in white children. Type 2 diabetes has already been reported in children from Japan and other Asian nations, the USA, the Pacific Islands, Hong Kong, Australia, and the United Kingdom.9 In Japan, type 2 diabetes is already more common in children than type 1 diabetes. Type 2 diabetes accounts for 80 percent of cases of diabetes in childhood in that country.28 This is certainly an emerging public health problem of significant proportions as the fall in the age of onset of type 2 diabetes is an important factor influencing the future burden of the disease. Onset in childhood heralds many years of disease and an accumulation of the full range of both micro- and macrovascular complications, particularly as compliance to hypoglycemic medications is often an issue.27

The risk determinants for type 2 diabetes in children and adolescents are similar to those seen in adults, with obesity almost always being present.22 In-utero exposure to hyperglycemia now appears to be an additional risk factor to having a family history of diabetes,30 and suggests that better management of diabetes in pregnancy and prevention of gestational diabetes may reduce the risk of diabetes developing in the offspring.

The crucial need for screening and prevention
Type 2 diabetes is common and serious, but often asymptomatic in the early stages, which sometimes last up to five years or more. Interventions are available that reduce morbidity and mortality, as well as the risk of developing diabetes,31,32 a compelling argument for screening the population for those at highest risk.

Screening programs should begin with simple tools that are effective in identifying those at highest risk, but which can be used by the general public.33 Those found to be at high risk should undergo further screening and diagnostic blood glucose testing to accurately characterize their glucose tolerance status, and these people should commence a lifestyle intervention program (relevant whether they have diabetes or are at risk of it in the future). Nevertheless, it should be recognized that absolute evidence for the benefit of screening is not yet available.

The cost-effectiveness of screening strategies is the subject of current interest. A very recent study from the USA34 used a mathematical model (the Archimedes model) to estimate the cost-effectiveness of several screening strategies.
### The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK)

1. **Your age group**
   - Under 35 years: 0 points
   - 35 – 44 years: 2 points
   - 45 – 54 years: 4 points
   - 55 – 64 years: 6 points
   - 65 years or over: 8 points

2. **Your gender**
   - Female: 0 points
   - Male: 3 points

3. **Your ethnicity/country of birth:**
   3a. Are you of Aboriginal, Torres Strait Islander, Pacific Islander, or Maori descent?
   - No: 0 points
   - Yes: 2 points

3b. Where were you born?
   - Australia: 0 points
   - Asia (including the Indian subcontinent), Middle East, North Africa, Southern Europe: 2 points
   - Other: 0 points

4. **Have either of your parents, or any of your brothers or sisters been diagnosed with diabetes (type 1 or type 2)?**
   - No: 0 points
   - Yes: 3 points

5. **Have you ever been found to have high blood glucose (sugar) (for example, in a health examination, during an illness, or during pregnancy)?**
   - No: 0 points
   - Yes: 6 points

6. **Are you currently taking medication for high blood pressure?**
   - No: 0 points
   - Yes: 2 points

7. **Do you currently smoke cigarettes or any other tobacco products on a daily basis?**
   - No: 0 points
   - Yes: 2 points

8. **How often do you eat vegetables or fruit?**
   - Everyday: 0 points
   - Not everyday: 1 point

9. **On average, would you say you do at least 2.5 hours of physical activity (for example, walking, cycling, or swimming) per week (for example, 30 minutes a day on 5 or more days a week)?**
   - Yes: 0 points
   - No: 6 points

10. **Your waist measurement taken below the ribs (usually at the level of the navel, and while standing)**
    - Waist measurement (cm)

For those of Asian or Aboriginal or Torres Strait Islander descent:
   - **Men**
     - Less than 90 cm: 0 points
     - 90 – 100 cm: 4 points
     - More than 100 cm: 7 points
   - **Women**
     - Less than 80 cm: 0 points
     - 80 – 90 cm: 4 points
     - More than 90 cm: 7 points

For all others:
   - **Men**
     - Less than 102 cm: 0 points
     - 102 – 110 cm: 4 points
     - More than 110 cm: 7 points
   - **Women**
     - Less than 88 cm: 0 points
     - 88 – 100 cm: 4 points
     - More than 100 cm: 7 points

Add up your points

Your risk of developing type 2 diabetes within 5 years:

- **5 or less:** Low risk
  - Approximately one person in every 100 will develop diabetes.
- **6 – 14:** Intermediate risk
  - For scores of 6–8, approximately one person in every 50 will develop diabetes.
  - For scores of 9–14, approximately one person in every 20 will develop diabetes.
- **15 or more:** High risk
  - For scores of 15–19, approximately one person in every seven will develop diabetes.
  - For scores of 20 and above, approximately one person in every three will develop diabetes.

If you scored 6–14 points in the AUSDRISK you may be at increased risk of type 2 diabetes.

Discuss your score and your individual risk with your doctor. Improving your lifestyle may help reduce your risk of developing type 2 diabetes.

If you scored 15 points or more in the AUSDRISK you may have undiagnosed type 2 diabetes or be at high risk of developing the disease.

See your doctor about having a fasting blood glucose test. Act now to prevent type 2 diabetes.

The overall score may overestimate the risk of diabetes in those aged less than 25 years.
The Australian Type 2 Diabetes Risk Assessment Tool was originally developed by the Baker IDI and Diabetes Institute on behalf of the Australian, State and Territory Governments as part of the COAG initiative to reduce the risk of type 2 diabetes.

Table II. The Australian type 2 Diabetes RISK assessment tool (AUSDRISK).
The authors used person-specific data from a representative sample of the US population to create a simulated population of 325,000 people aged 30 years without diabetes. They found that compared with no screening, all simulated screening strategies reduced the incidence of myocardial infarction (3-9 events prevented per 1000 people screened) and diabetes-related microvascular complications (3-9 events prevented per 1000 people). They concluded that in the USA population, screening for type 2 diabetes is cost effective when started between the ages of 30 years and 45 years, with screening repeated every 3-5 years.

Taking into account the continuing discussions about the effectiveness of screening for undiagnosed type 2 diabetes and identifying those at high risk of developing diabetes in the near future, the following broad approach is recommended: 1. Use of a preliminary screening tool such as FINDRISK (Finnish Diabetes RISK score)35 or AUSDRISK (Australian type 2 Diabetes RISK assessment tool)36 (Table II, page 19). These can be done by the general public as well as by health-care professionals. 2. All those identified as being at high risk should enter a lifestyle intervention program and have blood glucose testing. 3. Fasting plasma glucose (FPG) is the initial blood glucose screening test for those at high risk, according to the preliminary screening tool. 4. On the basis of FPG (see below), the following steps should be taken:

- FPG < 5.5 mmol/L – no further blood testing needed
- FPG 5.5-6.9 mmol/L – proceed to OGTT
- FPG ≥ 7.0 mmol/L – repeat FPG to confirm the clinical diagnosis.

The most dramatic increases in type 2 diabetes have occurred in populations where there have been major changes in lifestyle.4,8-10 This entails adverse changes in diet and reductions in physical activity levels, with consequent increases in the prevalence of overweight people and obesity, particularly when excess adiposity is centrally distributed.4

When looking for an opportunity to prevent type 2 diabetes, risk factors should be viewed in terms of being either modifiable, eg, sedentary behavior, or nonmodifiable, eg, genetic, age, or gender (Table III).

<table>
<thead>
<tr>
<th>Modifiable risk factors</th>
<th>Nonmodifiable risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overweight (obesity)</td>
<td>Ethnicity (African-American, Native American, Asian-American, or Pacific Islander)</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td></td>
</tr>
<tr>
<td>Previously identified glucose intolerance (IGT and/or IFG)</td>
<td>Family history of type 2 diabetes</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Gender</td>
</tr>
<tr>
<td>Dietary factors</td>
<td>History of gestational diabetes</td>
</tr>
<tr>
<td>Intrauterine environment</td>
<td>Polycystic ovary syndrome</td>
</tr>
<tr>
<td>Smoking</td>
<td>Inflammation</td>
</tr>
</tbody>
</table>

An important new area becoming the focus of more attention is the intrauterine environment. The intrauterine environment influences the risk of developing type 2 diabetes.37 Offspring from diabetic pregnancies are often large and heavy at birth, develop obesity in childhood, and are at high risk of developing type 2 diabetes at an early age.38 Quite independently of this, there is increasing interest in the influence of epigenetic scenarios of in-utero exposure to risk factors, eg, poor maternal nutrition, which increases the risk of diabetes, obesity, and cardiovascular disease in adult life.33 This emphasizes the need for a “whole-of-life” approach to the prevention of type 2 diabetes and its complications.

Conclusion

Diabetes is a chronic disease that through its complications can seriously impact the quality of life of individuals and their families through premature illness and death. Because diabetes now affects much of the workforce, it has a major effect on both individual health and national productivity. The socioeconomic consequences of diabetes are likely to significantly impact the economies of many developing nations in addition to their devastating impact on the economies of developed nations, such as the USA, UK, and Australia. With diabetes being one of the greatest threats to public health in the 21st century, the rationale for strengthening efforts to prevent and control this menacing chronic disease is surely impelling.

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La pandémie galopante du diabète de type 2 : un besoin critique de prévention et d’amélioration de sa détection

L’augmentation dramatique de la prévalence et de l’incidence du diabète de type 2 est due globalement aux changements comportementaux et de style de vie ainsi qu’à la mondialisation. Une grande importance a été accordée jusqu’à maintenant à la susceptibilité génétique et aux facteurs environnementaux et comportementaux comme la sédentarité, un régime alimentaire trop riche et l’obésité (en particulier l’obésité abdominale). Plus récemment, l’attention s’est portée sur la contribution éventuelle de l’environnement maternel et sur l’impact de conditions particulières telles que l’obésité intra-utérine.

En conclusion, la prévention est le meilleur moyen d’éviter les complications du diabète de type 2. Le traitement est nécessaire pour contrôler les complications et améliorer la qualité de vie des patients. Les mesures de prévention incluent une alimentation équilibrée, une activité physique régulière, un poids de santé et la prévention du tabagisme.

Keywords: diabetes mellitus; type 2; epidemic; global; screening; prevention.
Many decades ago, type 2 diabetes was already known to be associated with damaging complications. Although the symptoms of hyperglycemia could be prevented, there was continuing debate about how best to avoid the damaging long-term effects. Early observational data suggested that optimizing metabolic control could be advantageous, but findings from the Universities Group Diabetes Program (UGDP) trials suggested that the solution might not be straightforward. Was good control improving outcome or increasing dangers to the patient? A series of subsequent trials have thrown light on the question—suggesting that the answer depends on the selection of patients for different regimens. Taking care in the clinical appraisal of a patient allows the selection of optimum therapy, which the synthesis of trials suggests will reduce both microvascular and macrovascular disease. It is now apparent that early treatment of both glycemia and hypertension is beneficial, and the trials of lipid lowering suggest that the risk of cardiovascular disease can be significantly reduced. All the trial data suggest that hyperglycemia is a risk for cardiovascular disease and should be lowered if possible. The target for glycemia is for a glycated hemoglobin (HbA1c) level lower than 7.5%, and this may be nearer 6.5% if achieved slowly and without dangerous hypoglycemia. Early intervention is clearly beneficial. Late intervention to strict targets requires a careful incremental approach.

Background

Estimates from current epidemiology suggest that the number of those with type 2 diabetes will increase to 285 million people by the year 2010, and to more than 400 million by 2030. The problem is not confined to country, race, or geographical location, and so an unprecedented challenge is one of provision of appropriate health care. Many decades ago, type 2 diabetes was already known to be associated with damaging complications. Although the symptoms of hyperglycemia could be prevented, there was a continuing debate about how best to avoid the damaging long-term effects. Early observational data suggested that optimizing metabolic control could be advantageous, but until the Universities Group Diabetes Program (UGDP) trial no systematic trial evidence had been published. The UGDP results were not clear, however, and so, in the following decades, a variety of trials were undertaken. Astonishingly, not a single one of these trials was without controversy over its design, results, or interpretation. Nevertheless, the synthesis of the knowledge adduced from them all allows us a clear vision of the advantages...
and disadvantages of the pursuit of normoglycemia. Our understanding has been evolutionary—though perhaps a physician from 1985 transported a quarter of a century ahead in time would feel that there had been a revolution in attitudes and therapeutics.

**Trials of glycemic control**

**UGDP**

Throughout the 1950s and 1960s, there had been a growing awareness that diabetes complications—both of microvascular and macrovascular origin—were presenting the greatest challenge to the quality of life and longevity of type 2 diabetes patients. Clinical acumen and observation had demonstrated that patients with glycosuria and very high blood glucose levels had a poor quality of life, but some physicians thought that moderate glycosuria might be advantageous in terms of weight loss—a view now resurgent with the development of sodium-glucose cotransporter 2 (SGLT-2) inhibitors.

UGDP was the first trial to attempt to optimize glycemia using a controlled trial approach. Launched in 1960, this placebo-controlled, multicenter clinical trial aimed to determine which, if any, of the treatments for type 2 diabetes was efficacious. Although the differences seen in cumulative total mortality were not statistically significant, a subgroup analysis suggested that cardiac deaths occurred more frequently in the tobutamid group. The investigators terminated this limb of the study. However, the randomization was significantly skewed at baseline—there was 30% more electrocardiographic abnormality, 40% more angina, and 90% more hypercholesterolemia in the tobutamide group. Randomization had failed to deliver equipoise in the outcome.

**UKPDS**

The United Kingdom Prospective Diabetes Study (UKPDS) was established to definitively answer the glycemic control controversy as well as to attempt to answer important questions about the class of agents used to achieve control. UKPDS was one of very few trials that recruited newly diagnosed type 2 diabetes patients (5012 in total)—an important point, as it transpired, since only UKPDS had the capacity to answer the question of the suitability of early treatment before the onset of serious complications. Despite this criterion, it was nevertheless apparent that many had early signs of trouble ahead—background retinopathy and ECG abnormalities, in particular. The evolution of complications was meticulously recorded—the trial lasted a median of 10 years, with some patients having been followed for 20 years at closeout.

UKPDS had stringent aims for euglycemia on monotherapy, but allowed fasting glucose to rise to 15 mmol/L before adding additional agents. Because one of the aims was to address the question of which monotherapy should be used, glycemia rose progressively throughout the trial. In contrast with later trials, the aim was to persist with monotherapy for as long as possible rather than to achieve a predominant glycemic target. At closeout, the results showed that intensive glucose control was efficacious in reducing many complications. Metformin, used only in the overweight, reduced diabetes-related deaths (risk reduction [RR], 0.58; \( P = 0.017 \)) and myocardial infarction (RR, 0.61; \( P = 0.01 \)) compared with conventional treatment. This is the prime evidence base for the use of metformin. It has been criticized as being based on a UKPDS subset of low statistical power, but one should note that the effect demonstrated in small numbers increases our certainty that this is clinically, as well as statistically, useful. In the main study of sulfonylurea or insulin use, there were clear reductions in relative risk in the intensively treated group: a 12% risk reduction for any diabetes related end point \( (P=0.029) \); a 25% risk reduction for microvascular end points \( (P=0.0099) \); a 21% risk reduction for retinopathy at twelve years \( (P=0.015) \); and a 33% risk reduction for albuminuria at twelve years \( (P=0.000054) \). The 16% risk reduction for myocardial infarction had borderline significance \( (P=0.052) \).

The study compared intensive versus conventional treatment for blood glucose control and achieved a glycated hemoglobin (HbA1c) level of 7% in the intensive groups of the study population compared with 7.9% in the conventional group (Figure 1). Nevertheless, questions remained—especially the question of how low an HbA1c level one should aim for in glycemic control. Would more aggressive glucose control decrease macrovascular or microvascular disease further?

**Figure 1. Diagram of the glycemic control achieved in UKPDS, ADVANCE, and ACCORD showing differences in duration, duration of diabetes at recruitment, and glycemic control achieved.**

Grey lines show the control groups. Other groups are shown in color: UKPDS: green = glibenclamide, cyan = chlorpropamide, yellow = insulin; ACCORD: red = intensive control group; ADVANCE: blue = intensive control group.

**Abbreviations:** ACCORD, Action to Control CardiOvascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and diabeticSepN MR Controlled Evaluation; HbA1c, glycated hemoglobin; UKPDS, United Kingdom Prospective Diabetes Study.
**PROACTIVE**

In 2005, PROACTIVE (PROspective pioglitAzone Clinical Trial In macroVascular Events) reported its results. PROACTIVE was a prospective, randomized controlled trial of 5238 patients with type 2 diabetes who had evidence of macrovascular disease. The median follow-up was just under 3 years. Patients were assigned to pioglitazone or placebo taken in addition to their glucose-lowering drugs and other medications. The primary end point was a composite of cardiovascular disease, including surgical intervention in the coronary or leg arteries and amputation above the ankle. The outcome of this was not significant (P=0.095). However, the main secondary end point—the composite of all-cause mortality, nonfatal myocardial infarction, and stroke—was, with a significant, favorable response to pioglitazone (P=0.027).

The trial was marred by the problem of the selection of a primary combined outcome that involved not only the onset of new pathology, but also surgical interventions relating to pathology. Surgical interventions are not emerging pathology—they are a response to emerging pathology and, as such, have many constraints on their timing. A decision about when an amputation is undertaken is as much a clinical decision as it is an emergent complication of diabetes. By contrast, the timing of a myocardial infarction is a direct measure of an underlying pathology. A multiplicity of outcomes increases the event count, but can do so at the expense of specificity. Nevertheless, the secondary analyses in PROACTIVE were highly significant—a risk reduction of 28% for myocardial infarction (P=0.045) and 47% for fatal and nonfatal stroke (P=0.009).

**RECORD**

In a remarkable coup-de-théâtre, Nissen et al10 produced a meta-analysis that seemed to demonstrate that rosiglitazone might have an adverse effect on cardiovascular outcome. This meta-analysis has been criticized,11 especially on the grounds that it was not based on a comprehensive search of all the studies that might yield evidence of rosiglitazone’s cardiovascular effects and that the studies were combined on the basis of a lack of statistical heterogeneity, despite variability in study design and outcome assessment. Then, in 2009, the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes (RECORD) trial reported.12 This trial featured 4447 patients with type 2 diabetes on metformin or sulfonylurea monotherapy with a mean HbA1c of 7.9%. They were randomly assigned to take additional rosiglitazone or a combination of metformin and sulfonylurea. In a 5.5 year follow-up, there was no difference in the primary outcome. There was an increase in heart failure causing admission to hospital or death in the rosiglitazone group (hazard ratio [HR], 2.10; 95% confidence interval [CI], 1.35 to 3.27), and upper and distal lower limb fracture rates increased, mainly in women. So, although rosiglitazone lowers glycemias, it seems that there is a significant increase in complications.

**ACCORD**

In 2008, three cardiovascular disease trials reported at the American Diabetes Association. These were ADVANCE (Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation), ACCORD (Action to Control CardioVascular Risk in Diabetes), and VADT (Veterans Affairs Diabetes Trial). ACCORD13 produced a startling headline result that mortality was worse in the group that was intensively treated to lower HbA1c toward 6%. At one year, stable median HbA1c levels of 6.4% and 7.5% were achieved in the intensive-therapy group and the standard-therapy group, respectively. During follow-up, the primary outcome (a composite of nonfatal myocardial infarction, stroke, or cardiovascular death) occurred in 352 patients in the intensive-therapy group, compared with 371 in the standard-therapy group (HR, 0.90; 95% CI, 0.78 to 1.04; P=0.16). However, 257 patients in the intensive-therapy group died, compared with 203 patients in the standard-therapy group (HR, 1.22; 95% CI, 1.01 to 1.46; P=0.04).13 This finding brought the main result from UKPDS into question again. Is intensive glucose lowering harmful? Here, however, the significant differences between ACCORD and UKPDS should be noted.

UKPDS recruited “healthy” new-onset type 2 diabetes patients (serious disease of any kind was a contraindication). In ACCORD, those recruited had been diagnosed a median of 10 years previously and were selected for preexisting cardiovascular disease or specific risk factors. Sudden changes in glycaemia in such patients may not be advisable. In this trial, the reports show that the majority of the glucose-lowering effect had already been achieved within the first 4 months, by which time median HbA1c was 6.6%. Although there was no explicit evidence that hypoglycemia was the precipitating cause of death, it remains the number one suspect for the increased death rate. Hypoglycemia rates were three times higher in the intensively treated group (death precludes con-

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**SELECTED ABBREVIATIONS AND ACRONYMS**

- **ACCORD**: Action to Control CardioVascular Risk in Diabetes
- **ADVANCE**: Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation
- **DCCT**: Diabetes Control and Complications Trial
- **HbA1c**: glycated hemoglobin
- **PROACTIVE**: PROspective pioglitAzone Clinical Trial In macroVascular Events
- **RECORD**: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of glycemia in Diabetes
- **UGDP**: Universities Group Diabetes Program
- **UKPDS**: United Kingdom Prospective Diabetes Study
- **UKPDS-PTM**: United Kingdom Prospective Diabetes Study Post-Trial Monitoring
- **VADT**: Veterans Affairs Diabetes Trial

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**References**

temporaneous measurement of blood glucose). Many of the patients were receiving rosiglitazone (91% in the intensive arm and 57% in the standard therapy arm). The excess mortality was not simply cardiovascular; hypoglycemia can cause falls or nocturnal aspiration that leads to pneumonia. In the elderly, any significant medical event may be seriously life-threatening.

**ADVANCE**

ADVANCE\(^{14}\) is the largest trial of cardiovascular disease in type 2 diabetes to date, recruiting 11,140 patients with type 2 diabetes randomized to standard or intensive glucose control with the aim of using gliclazide (modified release) plus other drugs, as required, to achieve an HbA\(_1c\) value of 6.5% or less. After a median of 5 years’ follow-up, mean HbA\(_1c\) in the intensive-control group was 6.5% compared to 7.3% in the standard-control group. In the intensive-control group, there was a reduced incidence in the combined end point of major macrovascular and microvascular events (HR, 0.90; 95% CI, 0.82 to 0.98; \(P=0.01\)), as well as that of major microvascular events (9.4% vs 10.9%; HR, 0.86; 95% CI, 0.77 to 0.97; \(P=0.01\)), primarily because of a reduction in the incidence of nephropathy (HR, 0.79; 95% CI, 0.66 to 0.93; \(P=0.006\)). However, the type of glucose control had no significant effect on major macrovascular events (HR with intensive control, 0.94; 95% CI, 0.84 to 1.06; \(P=0.32\)), death from cardiovascular causes (HR with intensive control, 0.88; 95% CI, 0.74 to 1.04; \(P=0.12\)), or death from any cause (HR with intensive control, 0.93; 95% CI, 0.83 to 1.06; \(P=0.28\)), although the 12% decrease in cardiovascular death is worth noting given the significant 35% increase in ACCORD.

**VADT**

This trial\(^{15}\) randomized 1791 predominantly male military veterans (mean age, 60.4 years) to intensive or standard glucose control, achieving about a 1.5% HbA\(_1c\) difference over a median duration of 5.6 years. There was no significant difference between the two groups in any component of the primary outcome or in the rate of death from any cause—a finding unremarkable in that the trial was essentially underpowered (both in terms of numbers of subjects and duration). There was, however, a lessening of progression of albuminuria (\(P=0.01\)).

**UKPDS Post-Trial Monitoring**

UKPDS monitored its patients for outcome after the study for a median of ten years—with biochemical indices for five of these. The study, published as UKPDS-PTM (UKPDS Post-Trial Monitoring),\(^{16}\) examined whether the effects of being in the intensively controlled group would dissipate with time. After the trial, everyone was given advice about intensive control. The 3277 patients remaining in the trial were asked to attend annual UKPDS clinics for 5 years, but no attempts were made to maintain their previously assigned therapies. Annual questionnaires were used to survey patients who were unable to attend the clinics, and all patients in years 6 to 10 were assessed using questionnaires. In the years that followed their inclusion in the trial, no glycemic differences were strived for, nor seen. The null hypothesis was that with no differences in treatment, the differences in outcome would be lost. But far from there being a diminution of the glycemic trial effect over the ten years, the lower incidence of pathological effects was maintained, and with the advent of more events the statistical probabilities of error declined. In the sulfonylurea-insulin group, relative reductions in risk persisted at 10 years for any diabetes-related end point (9%, \(P=0.04\)) and microvascular disease (24%, \(P=0.001\)), and risk reductions for myocardial infarction (15%, \(P=0.01\)) and death from any cause (13%, \(P=0.007\)) emerged over time as more events occurred (Table I).\(^{16}\) In the metformin group, significant risk reductions persisted for any diabetes-related end point (21%, \(P=0.01\)), myocardial infarction (33%, \(P=0.005\)), and death from any cause (27%, \(P=0.002\)). So, despite there being no glycemic differences, a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause were observed during the 10 years of posttrial follow-up.

### Evolution or revolution?

It has taken many years for a clear picture to emerge from the glycemic trials, and our understanding has evolved. Nevertheless, looking back on what we knew in 1997 and what we know now, the change in knowledge is a revolution. How do all the trials lock together into one cohesive pattern? The lessons learnt are summarized in Table II (page 26). Interestingly, it turns out that UKPDS\(^2\) and UKPDS-PTM\(^{16}\) hold the important core of what we need to know; the other trials color in the details. UKPDS established beyond any reasonable doubt that outcomes in those whose blood pressure and glycemic control were near normal were better, and it provided the major evidence base for the use of metformin.\(^{17}\) It laid to rest the old canard that it was somehow the “diabetes” causing the problems—perhaps by insulin resistance or some other arcane

**Table I. Relative risk reduction with sulfonylurea/insulin after 10 years’ follow-up in UKPDS.**

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Any diabetes-related end point</td>
<td>12</td>
<td>0.029</td>
<td>9</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>25</td>
<td>0.0099</td>
<td>24</td>
<td>0.001</td>
</tr>
<tr>
<td>MI</td>
<td>16</td>
<td>0.052</td>
<td>15</td>
<td>0.014</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6</td>
<td>0.44</td>
<td>13</td>
<td>0.007</td>
</tr>
</tbody>
</table>
process. UKPDS-PTM\textsuperscript{16} went further. It established that the first ten years of treatment were crucial to outcome—that there was a glycemic legacy effect. There has been no suggestion from the authors that this was a “metabolic memory” effect—a term used by the Diabetes Control and Complications Trial (DCCT). The effects are most likely to be simply related to atherosclerosis. Higher blood glucose over ten years leads to more vascular damage, and the effect is permanent.

ACCORD taught us all a sharp lesson. Taking high-risk patients and imposing very tight glycemic control led to the perverse outcome of greater mortality in the intensive group. This shows that we need to use clinical care in those in whom hypoglycemia (the major suspect for the adverse outcome) may pose a problem. These patients were identified as general groups in the trial by the presence of preexisting high HbA\textsubscript{1c}, or by having been diagnosed at a younger age. Extra caution is needed in those in whom established pathology can be detected. The effects shown in the ADVANCE trial,\textsuperscript{18} whose duration of diabetes was similar to that of ACCORD (8 years), were mainly attributable to a 21% relative reduction in nephropathy, but unlike the ACCORD trial, there was no indication that achieving the target of 6.5% gradually over four years had any detrimental cardiovascular effects nor did it cause increased mortality. How can one explain the differences between these outcomes? ADVANCE used gliclazide (mainly gliclazide modified release) and metformin to lower glycemia in the intensive control group, which contrasts with ACCORD where rosiglitazone was used extensively (in both arms), as was insulin and sulfonylurea in combination. In ACCORD, glycemic targets

<table>
<thead>
<tr>
<th>Lesson</th>
<th>Trial</th>
<th>Outcome</th>
<th>Detail</th>
<th>Therapy</th>
<th>Intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hyperglycemia is a treatable and reducible risk</td>
<td>UKPDS\textsuperscript{7}</td>
<td>Better glycemic control improves outcome (microvascular- and diabetes-related end points)</td>
<td>HbA\textsubscript{1c} 7.0% (6.2%–8.2%) in the intensive group compared with 7.9% (6.9%–8.8%)</td>
<td>Sulfonylurea</td>
<td>From diagnosis or insulin</td>
</tr>
<tr>
<td>2 Metformin is an effective first-line treatment</td>
<td>UKPDS\textsuperscript{17}</td>
<td>Better glycemic control improves outcome (microvascular and macrovascular)</td>
<td>7.4% in the metformin group compared with 8.0% in the conventional group. Effects shown in diabetes-related end points, all-cause mortality, and MI</td>
<td>Metformin</td>
<td>In the overweight (\textgt;120% ideal body weight)</td>
</tr>
<tr>
<td>3 Treatment needs to focus on early glycemic control</td>
<td>UKPDS-PTM\textsuperscript{16}</td>
<td>Early glycemic control has a legacy effect</td>
<td>Effects in the first ten years persist despite no later difference in control</td>
<td>Sulfonylurea, insulin, and metformin</td>
<td>In newly diagnosed patients studied for a median of 20 years</td>
</tr>
<tr>
<td>4 Aggressive treatment in those with established pathology is counterproductive</td>
<td>ACCORD\textsuperscript{13}</td>
<td>Trial closed after 3.5 years because of a 25% increase in all-cause mortality in the intensive-control group</td>
<td>HbA\textsubscript{1c} 6.4% and 7.5% in intensive and control groups, respectively</td>
<td>In the intensive group: insulin, 77% rosiglitazone, \texttextless;92% sulfonylurea*, 78% metformin, 95%</td>
<td>Median duration of type 2 diabetes 10 years, and who had either established cardiovascular disease or additional cardiovascular risk factors</td>
</tr>
<tr>
<td>5 Progressive incremental therapy towards target late in diabetes reduces complications</td>
<td>ADVANCE\textsuperscript{18}</td>
<td>Relative risk reduction, 14%; 95% CI, 3% to 25%; \textit{P}=0.015</td>
<td>HbA\textsubscript{1c} 7.3% and 6.5% at the end of the trial</td>
<td>Mainly gliclazide modified release (91%) and metformin (74%)</td>
<td>Median duration of diabetes 8 years</td>
</tr>
</tbody>
</table>

\* Excluding gliclazide

\textbf{Table II. Lessons learnt from trials of glycemia in diabetes.}

\textit{Abbreviations:} ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation; HbA\textsubscript{1c}, glycated hemoglobin; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study; UKPDS-PTM, United Kingdom Prospective Diabetes Study Post-Trial Monitoring.
It was aggressively pursued and control of glycemia over time did not deteriorate (Figure 2). By contrast, in ADVANCE, the target HbA1c of below 6.5% was achieved progressively over a period of 4 years—a much slower rate than that of the ACCORD patients, and the totality of the updated mean difference was much less. So, the differences between the two trials were a marked difference in the rate of achievement of target glycemia, a very high hypoglycemia rate in ACCORD (nearly 4 times greater than the rate in ADVANCE), and a clear difference in the choice of agents for the two trials. ACCORD suggests that intensive glycemic control achieved fast and late in diabetes using multiple agents might not be wise. ADVANCE suggests that the achievement of such targets over a period of several years should not be contraindicated and that there may be gains to be achieved in the prevention of renal disease. ACCORD teaches us that very sudden changes in glycemia in the elderly may do more harm than good, while ADVANCE suggests real benefits from this approach.

What about hypoglycemia? Here, I think we are closer to real answers. ACCORD had a very high rate of hypoglycemia, and there are many rational reasons to suppose this to be dangerous in the elderly. So, we need to take new stock of this as a real life-threatening risk as well as a threat to quality of life. Hypoglycemia in the elderly threatens events related to falls, aspiration pneumonia, accidents, forgetfulness, and other significant risks.

The trials reported here have focused on glycemic control, but type 2 diabetes cannot simply be treated as a disease of abnormal glucose. The trial data are strongly indicative that lipids and blood pressure should be treated in parallel, and they are more rational reasons to suppose this to be dangerous in the elderly. So, we need to take new stock of this as a real life-threatening risk as well as a threat to quality of life. Hypoglycemia in the elderly threatens events related to falls, aspiration pneumonia, accidents, forgetfulness, and other significant risks.

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**Conclusions**

All the trial data suggest that hyperglycemia is a risk for cardiovascular disease and should be lowered if possible. The targets for glycemia are an HbA1c lower than 7.5%, and this may be nearer 6.5% if achieved slowly and without dangerous hypoglycemia. Early intervention is clearly beneficial. Late intervention to strict targets requires a careful incremental approach.

**References**

8. Stratton IM, Adler AI, Neil HA, et al. Association of glycaemia with macrovascular...


Keywords: trials; type 2 diabetes; cardiovascular disease; gliclazide; insulin; rosiglitazone; pioglitazone; ADVANCE; ACCORD; UGDP; UKPDS; PROACTIVE; RECORD; VADT; Steno 2

ÉTUDES CLÉS MARQUANTES DANS LA PRISE EN CHARGE CLINIQUE DU DIABÈTE DE TYPE 2 : UNE ÉVOLUTION OU UNE RÉVOLUTION ?

Depuis des dizaines d’années, il est reconnu que le diabète de type 2 s’associe à des complications importantes. Bien que l’on puisse prévenir les symptômes de l’hyperglycémie, le débat sur la meilleure façon d’éviter ses effets délétères à long terme perdure. Les premières données observationnelles suggèrent que l’optimisation du contrôle métabolique pourrait être bénéfique, mais les résultats des études UGPD (Universities Group Diabetes Program) montrent que la solution n’est peut-être pas si simple. Un contrôle optimal améliore-t-il l’évolution ou augmente-t-il le risque pour le patient ? Une série d’études ultérieures a éclairci la question, suggérant que la réponse dépend de la sélection des patients selon les différents schémas d’études. D’après les résultats de ces études, la prise en compte du profil clinique du patient permet de choisir un traitement optimal qui réduira à la fois la maladie micro- et macrovasculaire. Il est maintenant évident qu’un traitement précoce de la glycémie et de l’hypertension est bénéfique, et les études sur la baisse des lipides démontrent que le risque cardio-vasculaire peut être réduit de façon significative. Toutes les données des études suggèrent que l’hyperglycémie représente un risque de maladie cardio-vasculaire et qu’elle doit être abaissee si possible. L’hémoglobine glyquée (HbA1c) doit être inférieure à 7,5 %, et elle pourrait même s’approcher de 6,5 % si la baisse est progressive et sans hypoglycémie dangereuse. Un traitement précoce est à l’évidence bénéfique. Une intervention tardive pour obtenir les valeurs recommandées nécessite une démarche progressive préventionneuse.
Evidence implicates hyperglycemia-derived oxygen free radicals as mediators of diabetic complications. However, intervention studies with classic antioxidants, such as vitamin E, have failed to demonstrate any beneficial effect. Recent studies demonstrate that a single hyperglycemia-induced process of superoxide overproduction by the mitochondrial electron-transport chain seems to be the first and key event in the activation of all the other pathways involved in the pathogenesis of diabetic complications. These include increased polyol pathway flux, advanced glycation end product formation, and hexosamine pathway flux, and activation of protein kinase C. These processes result in acute endothelial dysfunction in diabetic blood vessels that, convincingly, also contributes to the development of diabetic complications. While waiting for more focused tools, we will have to use other options, particularly the oral hypoglycemic agent gliclazide, which reduces glycemia while exerting an antioxidant effect.

In the last few decades the occurrence of type 2 diabetes mellitus has rapidly increased internationally, and it has been estimated that the number of diabetic patients will more than double within 15 years. As type 2 diabetes is mainly characterized by the development of increased cardiovascular disease (CVD) morbidity and mortality, it has been suggested that diabetes could be considered a CVD. However, diabetes is also characterized by dramatic microangiopathic complications, such as retinopathy, nephropathy, and neuropathy.

Recent evidence suggests that glucose overload may damage cells through oxidative stress. This is currently the basis of the “unifying hypothesis,” in which hyperglycemia-induced oxidative stress may account for the pathogenesis of all diabetic complications.

The central role of oxidative stress in the pathogenesis of diabetic complications

It has been suggested that four key biochemical changes induced by hyperglycemia—(i) increased flux through the polyol pathway (in which glucose is reduced to sorbitol, lowering levels of both reduced nicotinamide adenine dinucleotide phosphate [NADPH] and reduced glutathione); (ii) increased formation of advanced glycation end products (AGEs); (iii) activation of protein kinase C (PKC) (with effects ranging from vascular occlusion to expression of proinflammatory genes); and (iv) in-
creased shunting of excess glucose through the hexosamine pathway (mediating increased transcription of genes for inflammatory cytokines)—are all activated by a common mechanism: overproduction of superoxide radicals.\(^3\)

Excess plasma glucose drives excess production of electron donors (mainly NADH/H\(^+\)) from the tricarboxylic acid cycle; in turn, this surfeit results in the transfer of single electrons rather than the usual electron pairs) to oxygen, producing superoxide radicals and other reactive oxygen species (instead of the usual product, H\(_2\)O). The superoxide anion itself inhibits the key glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, and consequently, glucose and glyceraldehyde intermediates spill into the polyol and hexosamine pathways, as well as additional pathways that culminate in PKC activation and intracellular AGE formation (Figure 1).

However, superoxide overproduction is also accompanied by increased nitric oxide (NO) generation, due to the uncoupled state of endothelial nitric oxide synthase (eNOS) and inducible nitric oxide synthase (iNOS),\(^3\) a phenomenon favoring the formation of the strong oxidant peroxynitrite, which in turn damages DNA.\(^2\) DNA damage is an obligatory stimulus for the activation of the nuclear enzyme poly(adenosine diphosphate (ADP)-ribose) polymerase (PARP).\(^4\) PARP activation in turn depletes the intracellular concentration of its substrate NAD\(^+\), slowing the rate of glycolysis, electron transport, and adenine triphosphate formation, and producing ADP-ribosylation of the glyceraldehyde-3-phosphate dehydrogenase.\(^4\) These processes result in endothelial dysfunction (Figure 2).

These pathways have been confirmed by at least one study on the perfusion for 2 hours of isolated rat hearts with solutions of 11.1 mmol/L glucose, 33.3 mmol/L glucose, or 33.1 mmol/L glucose plus glutathione. In the hearts perfused with high glucose concentrations, coronary perfusion pressure increased significantly; there was a 40% increase in NO levels and an upregulation of iNOS, but a 300% increase in the production of superoxide species; nitrotyrosine and cardiac cell apoptosis also increased significantly.\(^5\) All these effects were substantially prevented by glutathione, which effectively removes reactive oxygen species, including peroxynitrite.\(^5\)

However, more recently, evidence from in vitro studies suggests that marked fluctuations in glucose levels, as seen in diabetic patients, have consequences that are even more deleterious than those of continuous high glucose levels, and that oxidative stress is convincingly involved. For example, in

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**Figure 1.** Potential mechanism by which hyperglycemia-induced mitochondrial superoxide overproduction activates four pathways of hyperglycemic damage.

Excess superoxide partially inhibits the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), thereby diverting upstream metabolites from glycolysis into pathways of glucose overutilization. This results in increased flux of dihydroxyacetone phosphate (DHAP) to diacylglycerol (DAG), an activator of protein kinase C (PKC), and of triose phosphates to methylglyoxal, the main intracellular advanced glycation end product (AGE) precursor. Increased flux of fructose-6-phosphate to uridine diphosphate-N-acetylglucosamine (UDP-GlcNAc) increases modification of proteins by O-linked N-acetylglucosamine (GlcNAc) and increased glucose flux through the polyol pathway consumes nicotinamide dinucleotide phosphate (NADPH) and depletes glutathione.

**Abbreviations:** AGE, advanced glycation end product; DAG, diacylglycerol; DHAP, dihydroxyacetone phosphate; GAPDH, glyceraldehyde-3-phosphate dehydrogenase; GFAT, glutamine:fructose-6-phosphate aminotransferase; Glu, glutamate; Gln, glutamine; NAD(P), nicotinamide dinucleotide (phosphate); P, phosphate; PKC, protein kinase C; UDP-GlcNAc, uridine diphosphate-N-acetylglucosamine.
cultures of human umbilical vein endothelial cells, levels of nitrotyrosine (a marker of oxidative stress), intercellular adhesion molecule 1 (ICAM-1), vascular cellular adhesion molecule 1, E-selectin, interleukin 6 (IL-6), and 8-hydroxydeoxyguanosine (a marker of oxidative damage of DNA) all increased after incubation in a medium containing 20 mmol glucose compared with incubation in a 5 mmol glucose medium, but alternating the two media caused even greater increases. In addition, intermittent hyperglycemic conditions increased rates of cellular apoptosis, and stimulated the expression of caspase 3 (a proapoptotic protein), but decreased Bcl2 (an antiapoptotic protein). These effects were abolished by adding superoxide dismutase (SOD), which scavenges free radicals, or inhibitors of the mitochondrial electron-transport chain, suggesting that overproduction of free radicals in the mitochondria mediates the apoptotic effects of increased glucose concentrations and fluctuations.

Oxidative stress in diabetes: in vivo evidence

The response-to-injury hypothesis of atherosclerosis states that the initial damage affects the arterial endothelium, in terms of endothelial dysfunction. Notably, today’s evidence confirms that endothelial dysfunction, associated with oxidative stress, predicts CVD. Indeed, studies show that high glucose concentrations induce endothelial dysfunction in diabetic as well as normal subjects. The role of free radical generation in producing hyperglycemia-dependent endothelial dysfunction is also suggested by studies showing that the acute effects of hyperglycemia are counterbalanced by antioxidants.

Numerous studies have also noted the effect of hyperglycemia-induced oxidative stress on inflammation. A study in which insulin secretion was blocked, and subjects were maintained at plasma glucose levels of 15 mmol/L for 5 hours, found that levels of IL-6, tumor necrosis factor α (TNF-α), and the proinflammatory cytokine IL-18 rose significantly and returned to baseline within 3 hours in the control group. However, patients with impaired glucose tolerance had significantly higher TNF-α and IL-6 levels at baseline, and cytokine levels reached substantially higher peaks and stayed elevated for considerably longer than in the control subjects. All changes in plasma cytokine levels were abolished by infusion of the antioxidant glutathione, consistent with the hypothesis that hyperglycemia, especially in the form of spikes, is linked to immune activation via an oxidative mechanism. Another study matching diabetic patients and healthy controls found increases in circulating ICAM-1 in both groups during an oral glucose tolerance test (OGTT); these increases were also abolished by glutathione. Glutathione administered without a glucose load decreased circulating ICAM-1 levels in the diabetic group, but not in the control group, again suggesting that hyperglycemia increases ICAM-1 levels via an oxidative mechanism.

More direct evidence for the central role of oxidative stress is derived from clinical studies that measured markers. For example, among 20 diabetic patients, either a low-carbohydrate or a high-carbohydrate meal increased levels of plasma glucose, insulin, triglycerides, and malondialdehyde (a marker for lipid peroxidation), and decreased nonesterified fatty acids and the total radical-trapping antioxidant parameter (TRAP), a global measure of antioxidant capacity in the plasma. However, the high-carbohydrate meal (designed to produce higher postprandial glucose levels) increased glucose and malondialdehyde more, decreased TRAP significantly more, and rendered low-density lipoprotein more susceptible to oxidation than the low-carbohydrate meal. The decrease in TRAP highlights the fact that oxidative stress may also ensue from the failure of normal antioxidant defenses: the same group found that during the OGTT, TRAP was reduced from baseline in both well-controlled, nonsmoking diabetic subjects and healthy age-matched subjects, as were levels of protein-bound thiol (-SH) groups, vitamins C and E, and uric acid.

As aforementioned, a superoxide anion combines with NO to produce a peroxynitrite ion; this species is capable of peroxidizing lipoproteins and damaging DNA, which then activates the nuclear enzyme poly(ADP-ribose) polymerase, depleting intracellular NAD+ and (among other effects) causing acute endothelial dysfunction. In one study involving 12 healthy subjects, infusion of L-arginine (to supply NO) reversed hyperglycemia-induced increases in systolic and diastolic blood pressure, heart rate, plasma catecholamine levels, ADP-induced platelet aggregation, and blood viscosity. However, infusing N⁴-monomethyl-L-arginine, which inhibits the synthesis of endogenous NO, produced effects that were very similar to those produced by hyperglycemia. Thus, decreased NO availability may be one mechanism by which hyperglycemia induces hemodynamic and rheological changes in blood. It has been shown, however, that unlike normal con-
controls, patients with diabetes have significantly elevated fasting nitrotyrosine levels, as well as postprandial increases after eating a standard mixed meal; the effect was significantly normalized by insulin aspart (which targets postprandial glucose), but not by regular insulin.17

Finally, consistent with the recent emerging role of glucose fluctuations, a new study confirms that in type 2 diabetes, diurnal glucose fluctuations are the most powerful predictors of oxidative stress generation.18

**New perspectives: oxidative stress and hyperglycemia-induced “metabolic memory”**

Large randomized studies have established that early intensive glycemic control reduces the risk of diabetic complications, both micro- and macrovascular.19 Moreover, epidemiological and prospective data support the idea that early metabolic control has a long-term influence on clinical outcomes.19 This phenomenon has recently been defined as “metabolic memory.”9 Potential mechanisms for propagating this “memory” are the nonenzymatic glycation of cellular proteins and lipids and an excess of cellular reactive oxygen and nitrogen species, in particular those that originated at the level of glycated mitochondrial proteins, perhaps acting in concert with one another to maintain stress signaling.9

**Experimental evidence supporting the concept of “metabolic memory” and its possible link with oxidative stress**

Several years ago, there were preliminary reports of the possibility that “hyperglycemic memory” for hyperproduction of fibronectin and collagen in endothelial cells persists after glucose normalization.20 Using the same design, ie, 14 days in high concentration glucose followed by 7 days of culture in normal concentration glucose, it has been shown that the overproduction of free radicals in endothelial cells persists after normalization of glucose concentration, and this is accompanied by a prolongation of the induction of PKC-β, NAD(P)H oxidase, Bax, collagen, and fibronectin, in addition to 3-nitrotyrosine.21 This suggests that oxidative stress may be involved in the “metabolic memory” effect.

The effect of reinstatement of good glucose control on hyperglycemia-induced increased oxidative stress and nitrative stress has also been previously evaluated in the retina of rats maintained with poor glucose control before initiation of good control.22 In diabetic rats, 2 or 6 months of poor control (glycated hemoglobin [HbA1c] >11.0%) was followed by 7 months of good control (HbA1c = 5%) soon, or 6 months, after induction of diabetes, and were sacrificed after 13 months.24 For rats in which good control was initiated soon after the induction of diabetes, oxidative stress and NO remained elevated in both urine and renal cortex.25 These data suggest that hyperglycemia-induced oxidative stress and NO, as well as activation of apoptosis and NFκB, can be prevented if good glycemic control is initiated very early, but are not easily reversed if poor control is maintained for longer durations. Therefore, these findings suggest the persistence of hyperglycemia-induced damage in such organs, even after glycemia normalization.

However, if excess reactive species are central to the development of hyperglycemia-related diabetic complications, could this excess explain the persistence of the risk of complications even when hyperglycemia is reduced or normalized?

The above reported studies suggest that long-lasting effects of hyperglycemia result in increased oxidative stress, while inhibiting oxidative stress has preliminarily been shown to reverse these effects.11 Mitochondrial overproduction of superoxide in hyperglycemia has been suggested as the “unifying hypothesis” for the development of diabetic complications.5 Therefore, it is reasonable to assume that mitochondria are also important players in propagating “metabolic memory.” Chronic hyperglycemia is thought to alter mitochondrial function through glycation of mitochondrial proteins.25 Levels of methylglyoxal, a highly-reactive alpha-dicarbonil byproduct of glycolysis, increase in diabetes.26 Methylglyoxal readily reacts with arginine, lysine, and sulfhydryl groups of proteins,26 in addition to nucleic acids,26 inducing the formation of a variety of structurally identified AGEs in both target cells and plasma.26 Methylglyoxal has an inhibitory effect on mitochondrial
respiration and methylglyoxal-induced modifications are targeted to specific mitochondrial proteins. These premises are important because a recent study has described, for the first time, a direct relationship between formation of intracellular AGEs on mitochondrial proteins and the decline in mitochondrial function and excess formation of reactive species. Mitochondrial respiratory chain proteins that underwent glycation were prone to produce more superoxide, independent of the level of hyperglycemia. The glycation of mitochondrial proteins may be a contributing explanation for the phenomenon of “metabolic memory.” The glycation of mitochondrial proteins that overproduce free radicals, independent of actual glycation, can also lead to a catastrophic cycle of mitochondrial DNA damage, as well as functional decline, cellular injury, further oxygen radical generation, and the continued activation of pathways involved in the pathogenesis of diabetic complications. Furthermore, mitochondrial proteins become damaged or posttranslationally modified as a consequence of a major change in a cell’s redox status. This may affect mitochondrially destined proteins that are imported into the mitochondrial outer membrane, inner membrane, or matrix space via specific import machinery transport components.

In other words, it may be postulated that the cascade of events in “metabolic memory” is the same as that proposed by Brownlee; the source of superoxide is still the mitochondria, but, in addition, the production of reactive species is unrelated to the presence of hyperglycemia; it depends on the level of glycation of mitochondrial proteins.

How could oxidative stress be reduced with pharmacological intervention?
Antioxidant therapy may be of great value in diabetic patients. However, the classic antioxidants, like vitamins E and C, do not seem to be helpful. New insights into the mechanisms leading to the generation of oxidative stress in diabetes are now available. Presumably, these findings will lead to the discovery and evaluation of new antioxidant molecules, such as superoxide dismutase (SOD) and catalase mimetics, that may hopefully inhibit the mechanism leading to diabetic complications at an early stage. While waiting for these specific new compounds, it is reasonable to suggest that substances already available, such as statins, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, should be used for their effectiveness as “causal and preventive” antioxidants (for an up-to-date review, see reference 28).

The availability of compounds that simultaneously decrease hyperglycemia, restore insulin secretion, and inhibit oxidative stress produced by high glucose is an interesting therapeutic prospect for the prevention of vascular complications of diabetes. Gliclazide, an oral hypoglycemic agent that belongs to the sulfonylurea class, has been demonstrated to be effective and safe in numerous clinical trials and in clinical practice. Several studies have demonstrated, both in vitro and in vivo, that gliclazide shows antioxidant potential, independent of its hyperglycemia-lowering effect. Gliclazide is a general free radical scavenger in vitro—in contrast with glibenclamide, which fails to produce any effect below a concentration of 25 µg/mL (gliclazide induced strong concentration-dependent inhibition of free radical generation at therapeutic concentrations). Jennings et al confirmed these effects of gliclazide on oxidative stress in clinical conditions. They found that gliclazide-treated type 2 patients with retinopathy had a highly significant and sustained decrease in peroxidized lipids and an increase in erythrocyte SOD activity. Interestingly, glucose control did not differ between therapeutic groups, which supports the hypothesis that the effect results from the molecule gliclazide itself, rather than from a general improvement in metabolic control.

The antioxidative property of gliclazide convincingly impacts the vascular system in diabetes. Fava et al studied both the antioxidative potential of gliclazide in vivo and its effect on vascular reactivity. In this experiment, blood glucose control remained unchanged from baseline and similar in both groups, as patients were already being treated, which excludes any glucose-related “bias effect.” Thirty type 2 diabetic patients received glibenclamide or gliclazide in a 12-week, randomized, observer-blinded, parallel study. Blood pressure responses to an intravenous bolus of L-arginine were measured pre- and posttreatment. Gliclazide, but not glibenclamide, significantly reduced systolic and diastolic blood pressure in response to intravenous L-arginine. This provided the first demonstration that gliclazide significantly enhances NO-mediated vasodilatation and thus improves vascular reactivity in type 2 diabetic patients.

Finally, and this could be of great relevance, in order to avoid the development of diabetic complications, it has been shown that gliclazide can block the “metabolic memory” effect. In my opinion, all these effects may contribute to explaining why gliclazide prevented nephropathy in the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE).

Conclusions
Our understanding of the molecular pathways activated inside the cell by hyperglycemia is growing, and evidence about the involvement of oxidative stress in the development of diabetic complications is becoming abundant, making the “unifying hypothesis” more persuasive every day. Against this background, the finding of unexpected protective effects of drugs intended for different uses or different pathologies has given us an intriguing opportunity to elucidate their underlying mechanisms, to tune up these “weapons” to be more and more effective, and to confirm the hypothesis formulated. These goals are becoming increasingly important due to the massive spread in diabetic pathology that is expected to occur in the coming years.
Il existe des preuves de l’implication des radicaux libres oxygénés dérivés de l’hyperglycémie comme médiateurs des complications diabétiques. Cependant, des études d’intervention impliquant des antioxydants classiques, comme la vitamine E, n’ont montré aucun effet bénéfique. Des études récentes démontrent qu’un seul processus de surproduction de superoxyde par la chaîne de transport de l’électron mitochondrial induite par une hyperglycémie semble être le premier événement clé dans l’activation de toutes les autres voies impliquées dans la pathogénèse des complications diabétiques. Ces complications s’assortissent d’une augmentation de la voie des polyols, de la formation des produits de fin de glycation avancée, et de la voie des hexosamines et d’une activation de la protéine kinase C. Ces processus conduisent à une dysfonction endothéliale aiguë dans les vaisseaux sanguins diabétiques, qui contribue certainement aussi au développement des complications diabétiques. En attendant des outils plus ciblés, nous devrons utiliser d’autres options, en particulier le gliclazide, hypoglycémiant oral qui diminue la glycémie tout en exerçant un effet antioxydant.
The idea that type 2 diabetes (T2DM) is mainly due to insulin resistance stems from the 1930s, but became dominating from the 1980s. However, evidence since the 1960s indicates that insulin response to glucose is markedly diminished from the earliest signs of glucose intolerance. Insulin pump treatment induces near-normoglycemia in T2DM with doses similar to type 1 diabetes, indicating that hyperglycemia is caused by lack of insulin, insulin resistance acting as an amplifier. Insulin secretion is genetically controlled. T2DM risk gene polymorphisms hint toward mechanisms of reduced insulin secretion in diabetes-prone subjects, in whom insulin response decreases as the number of diabetic alleles increases. I hypothesize that the genetic background of the \( \beta \) cell determines its adaptation capacity to increased insulin demand imposed by augmented caloric intake and insulin resistance; failure to adapt eventually leads to T2DM. Therefore, I regard the "prediabetic" \( \beta \) cell as a normal cell with limited adaptability, diabetes risk being entirely context-dependent (nutritional load and insulin sensitivity). Once hyperglycemia is established, \( \beta \) cells are exposed to continuous nutrient stimulation, with consequent oxidative and endoplasmic reticulum (ER) stresses. The result is increasing functional deficiencies and \( \beta \)-cell apoptosis, hence reduced \( \beta \)-cell mass. Some of its mechanisms are discussed. An intriguing as yet unanswered question is whether the mechanisms of \( \beta \)-cell deficit in the diabetic environment operate before hyperglycemia in overfed, insulin-resistant subjects. Therapeutic agents preventing \( \beta \)-cell oxidative and ER stress could stop the progression and perhaps initiation of T2DM.

Medicographia. 2011;33:35-41 (see French abstract on page 41)
that diabetes may be the result of insulin resistance is not new. Indeed, the presence of obesity in the vast majority of patients with type 2 diabetes (T2DM) makes it a reasonable assumption that some degree of insulin resistance must exist in this disorder.

The striking advancements over the past three decades in the field of insulin action, including the detailed understanding of the molecular biology of the insulin receptor and its signaling pathways as well as of the regulation of glucose transporters, have naturally further attracted the attention of investigators to insulin resistance as a main pathophysiological factor in type 2 diabetes, sometimes presented as the sole factor. Thus, as recently as 2000, the Journal of Clinical Investigation stressed this by publishing a “Perspective” series entitled On diabetes: insulin resistance. Yet, many investigators demonstrated as soon as insulin immunoassays became available in the early 1960s that the insulin response to a glucose challenge is markedly reduced in type 2 diabetics, including in normoglycemic subjects with glucose intolerance (IGT) only. The adoption of dogmatic, monolithic views by many investigators of both “camps” did not facilitate the development of open-minded approaches to analyze the etiology of diabetes in its full physiological context, notwithstanding some balanced views pointing to the fact that the biology of type 2 diabetes is not simple, and that pure β-cell deficit or exclusive insulin resistance are rare events since in fact these two factors are interlinked, as would be expected from any closed-loop feedback regulatory system.

**Insulin resistance, plasma insulin levels, and β-cell function**

The variability of the insulin response to glucose as well as that of the sensitivity to insulin is remarkably large in the normal population. In the obese, while insulin sensitivity is reduced and insulin response is augmented, variation is as wide, with considerable overlap with the levels of lean subjects. Thus, there exist substantial numbers of subjects with either a markedly low insulin response or a low sensitivity to insulin who nevertheless retain normal glucose tolerance. Indeed, at least 2/3 of obese subjects never develop IGT or type 2 diabetes; yet they are insulin resistant and hyperinsulinemic. In type 2 diabetic patients, except in its very severe forms, both fasting and postprandial plasma insulin levels are normal or higher than normal. This observation provides the rationale for insulin resistance in diabetes: if blood glucose remains high despite substantial levels of insulin, hormone action must be defective. This is a static view of a highly dynamic regulatory system, confusing cause and effect: what are “substantial” levels of insulin, ie, what degree of hyperinsulinemia is adequate for a given degree of hyperglycemia? Glucose vs insulin dose-response curves have been constructed from acute experiments (eg, see reference 16); however, lacking data on long-term experimentally induced hyperglycemia in normal subjects, how can we determine whether a given plasma insulin value in a chronically hyperglycemic diabetic is higher or lower than normally expected?

![Figure 1. Fasting plasma insulin levels in 15 type 2 diabetic patients prior to and following 6-month treatment with the sulfonylurea gliclazide.](image)

**Figure 1.** Fasting plasma insulin levels in 15 type 2 diabetic patients prior to and following 6-month treatment with the sulfonylurea gliclazide. Data calculated from reference 17. Abbreviation: T2DM, type 2 diabetes mellitus.

Two examples strikingly demonstrate how lack of consideration for physiological regulation leads to erroneous conclusion. The first relates to fasting insulin concentration. Many investigators, including our group, find that the fasting plasma insulin level in type 2 diabetic patients is higher than normal; however, fasting glucose also is higher: does it contribute to the fasting hyperinsulinemia of the patient? In 15 mildly obese type 2 diabetics treated with the sulfonylurea gliclazide for 6 months we found that, in parallel with the normalization of blood glucose, the initially high fasting plasma insulin levels fell to the range found in weight-matched normoglycemic controls despite the use of the β-cell stimulator gliclazide; this is illustrated in Figure 1. Thus, fasting insulin is also under the control of ambient blood glucose concentration. The second example relates to the bell-shaped insulin curve often used to describe changes in β-cell function during the fall of glucose tolerance from normal to IGT and T2DM. This is an artefact due to the use of 120-minute plasma insulin values in the
oral glucose tolerance test (OGTT); patients with IGT having higher glucose levels throughout the test generate a strong signal for amplifying the secretion of insulin at a time when blood glucose is still high enough to stimulate the β-cell, resulting in a typical late insulin peak. In fact, if earlier (eg, 30 min) time points are chosen, the insulin response to OGTT shows a linear fall from normal via IGT to T2DM.18-20 In short, providing the plasma insulin data are interpreted with full reference to the physiology of regulated insulin secretion, it becomes clear that β-cell responsiveness to glucose is lower than normal in IGT, and even less so in T2DM.

The above discussion does not mean that I negate the existence of insulin resistance in type 2 diabetic patients; the scientific literature is replete with data convincingly showing that insulin resistance is part of the pathogenesis of T2DM. Nevertheless, I remain convinced that T2DM is a disorder of insulin deficit, the input of insulin resistance to its pathogenesis increasing with the severity of obesity. To my mind, the best demonstration of the above was achieved in mildly obese type 2 diabetic patients treated with continuous subcutaneous insulin infusion (CSII). In pilot studies in 23 white patients, we could achieve fasting and postprandial normoglycemia with a mean daily insulin dose around 0.6 units per kg body weight.17,21 Similar results were obtained in a larger group of Chinese patients.22 The amounts of insulin administered through CSII in these studies were not strikingly higher than the doses routinely used in insulin pump–treated type 1 diabetic patients (Table I). Thus, a similar degree of insulin deficit seems to exist in both types of diabetes, which leads me to conclude that insulin resistance in T2DM is not the main factor inducing hyperglycemia.

### β-Cell function during the development of type 2 diabetes

The earliest modifications of the insulin response to glucose that can be detected as glucose tolerance starts deviating from normal are the early or first-phase insulin response, and the physiological oscillations of secretion.5,6,8,23,24 The latter requires numerous blood samplings, and therefore has not gained popularity among clinicians and investigators. In contrast, early insulin response to glucose can be measured during oral or IV glucose tolerance tests; however, glucose clamps allow the most detailed definition of the kinetics of the plasma insulin response to glucose. The first-phase response is markedly reduced in subjects with IGT, and further diminishes as fasting hyperglycemia appears. At these stages of the disease, the later or second-phase insulin response to glucose is normal, but with the progression of the severity of diabetes also this phase collapses. These changes are schematically illustrated in Figure 2.

Low first-phase insulin response is found also in some subjects with normal glucose tolerance.5,6 Several studies over the past few years have demonstrated that a low insulin response is a predictor of future glucose intolerance and T2DM, both in lean and obese subjects belonging to various ethnic groups.15-21 In our study, lean and physically active Swedish subjects with normal glucose tolerance were followed for a mean period of 25 years; the only initial parameter that was significantly correlated to later glucose intolerance was first-phase insulin response corrected for insulin sensitivity (disposition index).25 These results are summarized in Table II (page 38).

What is the genetic/molecular basis of the low insulin response in nondiabetic subjects? Extensive studies over 4 decades in family members related or unrelated to diabetic patients, in-
cluing in monozygotic twin pairs, have shown that several aspects of the insulin response to glucose in man are under strong genetic control. However, it is only now that we are gaining some insight into the possible cellular mechanisms that may be responsible for the decrease of β-cell function in subjects at risk of developing diabetes. Indeed, the numerous whole genome association studies that have been performed over the past decade have identified allelic variants of several genes, mostly involved in β-cell development, function and survival, that collectively participate in the risk of diabetes development. As the number of risk alleles that a subject carries increases, several aspects of β-cell function deteriorate; most pertinently, the insulin response to oral or IV glucose decreases in proportion to the number of risk alleles.

By which cellular mechanisms these risk alleles impair insulin secretion is not known. However, recent findings from Gloyn et al suggest that, at least regarding the highest-risk gene, transcription factor 7–like 2 (TCF7L2), the association of insulin granules with the voltage-gated calcium channels in the β-cell may be disturbed, thus reducing the efficiency of the insulin exocytotic machinery. It stands to reason that within a short space of time, the mechanisms of low insulin response to glucose, which is a strong risk factor for T2DM, will be fully clarified at the molecular level.

Progression of diabetes and deterioration of β-cell function: decrease in cell function or cell mass?

It has been the experience of most clinicians that as the duration of diabetes increases so does the severity of the disease. This old observation has received its scientific approval through the United Kingdom Prospective Diabetes Study (UKPDS): whatever the treatment modality chosen, the level of HbA1c increases with time (for a review, see reference 35). However, it is also the experience of most clinicians that, whatever the treatment modality chosen, induction of strict normoglycemia throughout the day over a period of years in type 2 diabetes is nearly impossible; therefore, it is not clear whether T2DM is an inherently progressive disorder due to the nature of its pathogenesis, or whether progression is secondary to the unregulated metabolic state which reflects our inability to provide adequate treatment (the latter is my belief, entirely unproven). Whether primary or secondary, the progression of diabetes is paralleled by the progressive decline of β-cell function, as measured by the plasma insulin response to glucose (see Figure 2 also). Plasma insulin may decrease either because β-cell function, ie, the function of individual β cells, is reduced, or because the number of β cells declines, ie, β-cell mass is reduced.

♦ Is β-cell mass reduced in type 2 diabetes?

There is consensus that some degree of β-cell mass reduction does occur at some stage in T2DM, but there is also considerable disagreement as to the extent of the reduction and its significance for diabetes development. Presently the dominating view, most strongly advocated by the Butler group in Los Angeles, is that β-cell mass is markedly reduced already at the stage of IGT, a further deficit being apparent in overt diabetes even if treated only by diet. By contrast, studies in Europe and find considerably less reduction in β-cell mass. It has to be stressed that real β-cell mass was calculated only by Rahier et al, while Butler et al measured β-cell area, which reflects β-cell mass less adequately. Perhaps more importantly, the Rahier laboratory in Brussels points to the extraordinarily wide range of β-cell masses both in the diabetic and nondiabetic groups, with the existence of major overlap between the hyperglycemic and normoglycemic subjects. These observations make it difficult to ascribe a definitive role to reduced β-cell mass in the genesis of hyperglycemia. Obviously, it may be argued that the hyperglycemia of the patient should have driven β-cell mass to increase substantially as a compensatory mechanism, which is not observed.

To gain some insight into the dynamics of β-cell mass changes during the development of diabetes, we utilized an animal model of nutrition-dependent type 2 diabetes, the gerbil Psammomys obesus. These animals have an inborn insulin resistance, but retain normal glucose tolerance under caloric restriction; when given a diet with circa 40% higher calories and low fiber content, they rapidly become hyperglycemic. Figure 3 shows that as the animals develop hyperglycemia, they rapidly lose pancreatic insulin stores, since the β cells are forced to secrete all their insulin granules in the face of the unrelenting hyperglycemic stimulation. Nevertheless, β-cell mass remains normal for a considerable period; it even increases slightly due to increased β-cell proliferation induced by the high glucose levels. β-Cell mass collapses only after prolonged diabetes, with severe worsening of the hyperglycemia (so-called end-stage diabetes). Thus in this model, possibly in analogy with European type 2 diabetic patients, from a pathophysiological viewpoint significant β-cell mass reduction occurs only in long-standing and advanced T2DM. In earlier stages, the β-cell deficiency seems to be more of a functional nature. I therefore prefer to use the term “function-

### Table II. Prediction of the 2-hour blood glucose concentration during OGTT in 269 healthy lean subjects after a mean of 25 years. The data relate to the initial test values. The P value denotes the relation between the initial (ΔI/ΔG)/HOMA-IR and the 2-hour blood glucose level of OGTT performed 25 years later.

<table>
<thead>
<tr>
<th></th>
<th>P value</th>
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<tbody>
<tr>
<td>Fasting plasma glucose</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma insulin</td>
<td>NS</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>NS</td>
</tr>
<tr>
<td>(ΔI/ΔG)/HOMA-IR</td>
<td>P=0.004</td>
</tr>
</tbody>
</table>

**Abbreviations:** (ΔI/ΔG)/HOMA-IR: glucose-induced insulin response measured at 5 minutes of a glucose clamp, corrected for HOMA-IR; HOMA-IR, homeostasis model assessment of insulin resistance; NS, nonsignificant; OGTT, oral glucose tolerance test.

al β-cell mass” to denote a globally insufficient insulin delivery situation, until we gain access to in vivo imaging techniques to allow in situ β-cell mass determination in our patients.

Why do β cells die in a diabetic environment?

Extensive work over the past decade has shown that mimicking the diabetic environment in vitro, ie, exposure to high concentrations of glucose and fatty acids over extended periods, causes death of β cells by apoptosis (for a review, see reference 40). Both oxidative stress and endoplasmic reticulum (ER) stress in the β cell, induced by the high nutrient exposure, contribute to initiating programmed cell death. Our laboratory has been interested in β-cell ER stress over the past few years. In β-cells exposed continuously, ie, in a non-cyclic manner, to high glucose levels proinsulin biosynthesis is under continuous stimulation; this puts the ER system under high pressure, since proinsulin has to be correctly folded and exported to the Golgi apparatus for processing and further maturation in insulin granules. The ER responds to the increase in proinsulin mRNA translation and chaperone-guided proinsulin folding by what is named the unfolded protein response (UPR), which is an adaptive feedback response aimed at reducing the workload by partially blocking the translation of mRNAs and degrading them, and augmenting chaperones to prevent misfolding of newly formed proteins as well as removing misfolded proteins from the ER. If the load on the ER persists despite these measures, then the UPR activates several mechanisms that end in apoptosis, leading to the removal of the deficient cell (for a short-but-comprehensive overview, see reference 41). We have shown that exposure to chronic high glucose levels activates the inositol-requiring enzyme 1α (IRE-1α) arm of the UPR both in β-cell lines and in Psammomys obesus islets.42 Furthermore, fatty acids (palmitate) and glucose exhibited a high degree of synergism in activating IRE-1α. This eventually leads to activation of c-jun N-terminal kinase (JNK) and increase in β-cell apoptosis; by using specific JNK inhibitors we could demonstrate that JNK is indeed responsible for initiating the caspase cascade and β-cell death.42 Importantly, the effect of glucose on the IRE-1α cascade is mammalian target of rapamycin (mTOR)-dependen-ent, since it could be inhibited by reducing the activity of mTOR complex 1 (mTORC-1) with rapamycin, thus rescuing β cells from glucolipotoxicity-induced death.42 This unfortunately does not mean that rapamycin can be used as a therapeutic agent against type 2 diabetes. To our dismay, when we administered rapamycin to diabetic Psammomys obesus, the animals developed even higher hyperglycemia together with extreme lipemia and massive β-cell apoptosis.43 Thus, the in vivo situation is more complex than that observed under well-controlled in vitro experiments. Intensive efforts are ongoing in numerous laboratories to design means for counteracting ER stress (as well as oxidative stress) in β cells; these may eventually lead to the generation of new classes of antidiabetic drugs aimed at prolonging the life of the β cell, thus prevent-ing the seemingly ineluctable progression of type 2 diabetes.

Conclusions

Is T2DM a disease of insulin deficiency or insulin resistance? Obviously both. Nevertheless, I am comforted in my nearly 50-year-old belief in the primacy of insulin deficiency for the pathogenesis of T2DM by the consensus that has emerged in the last decade over the fact that hyperglycemia is not possible in the absence of β-cell deficiency. Compared to the near-total lack of insulin of the type 1 diabetic, the β-cell deficiency of the type 2 diabetic patient is modest, and therefore would not be sufficient to lead to the full diabetic state in such a high proportion of subjects without additional environmental factors. This is a classic gene-environment interaction. It is a fascinating idea that, had the whole genome as-sociation studies been performed immediately after World War II in the undernourished populations of Europe and Asia, none of the polymorphic genes being hotly investigated today would have been found to be associated with type 2 diabetes. Indeed, these polymorphic alleles seem to render the β cell somewhat less efficient, ie, place it at the lower end of normal variation in terms of its functional adaptability and
resistance to stress; nevertheless, these \( \beta \) cells are normal until faced with unreasonable demands. I think too much emphasis is put on insulin resistance; I believe that the greatly augmented caloric intake, ie, the greatly increased nutrient flux in the \( \beta \) cell, is the real problem, insulin resistance acting as a potent amplifier. The consequence of this thought is that the risk for an individual to develop T2DM would be inversely correlated with the magnitude of adaptability of his \( \beta \) cells and directly correlated with the degree of caloric intake/insulin resistance to which he would be exposed. Thus, the "stronger" the \( \beta \) cell, the greater the degree of obesity that can be tolerated while maintaining normal glucose tolerance.

There are cases of lean, insulin-sensitive T2DM, as there are cases of diabetes with severe insulin resistance and extreme hyperinsulinemia. However, these are rare. For the majority of type 2 diabetics, to prevent hyperglycemia and its consequences either food intake has to be reduced drastically, or the \( \beta \) cell enforced to cope with the increased workload. Neither seems easy. Almost all research today on the \( \beta \) cell in connection with T2DM deals with the cells' reaction to various stresses, ie, the glucolipotoxicity situation. That this is most relevant to the fate of the \( \beta \) cell in the diabetic environment, and therefore to diabetes progression, is clear. A legitimate question does arise, however: Are the various mechanisms of \( \beta \)-cell stress discussed above (and in the literature) responsible also for the initiation of hyperglycemia? In other words, is \( \beta \)-cell stress a secondary reaction to diabetes (glucolipotoxicity), almost a complication of the disease, or is it the etiopathogenic event that leads to the gradual impairment of glucose homeostasis until glucose intolerance and diabetes appear? This is an important question that awaits its solution through future research.

References
11. Kulkarni RN, Bruning JC, Winnay JN, Postic C, Magnuson MA, Kahn CR. β-Cell stress discussed above (and in the literature) responsible also for the initiation of hyperglycemia? In other words, is β-cell stress a secondary reaction to diabetes (glucolipotoxicity), almost a complication of the disease, or is it the etiopathogenic event that leads to the gradual impairment of glucose homeostasis until glucose intolerance and diabetes appear? This is an important question that awaits its solution through future research.

Keywords: insulin secretion; first-phase response; low insulin response; insulin resistance; IGT; type 2 diabetes; beta-cell function; beta-cell mass; ER stress

Dysfonction des cellules β versus résistance à l’insuline dans le diabète de type 2 : l’éternelle question de l’œuf et de la poule

L’idée de la résistance à l’insuline comme cause principale du diabète de type 2 (DT2) naquit dans les années 1930 pour s’imposer dans les années 1980. Il existe cependant des preuves depuis les années 1960 selon lesquelles la réponse insulinique au glucose diminue franchement dès les premiers signes d’intolérance au glucose. Le traitement par pompe à insuline rétablit une glycémie proche de la normale dans la DT2 avec des doses identiques à celles utilisées dans le diabète de type 1, montrant que l’hyperglycémie est due au manque d’insuline, la résistance à l’insuline agissant comme amplificateur. La sécrétion d’insuline est génétiquement contrôlée. Le polymorphisme du gène à risque de DT2 laisse supposer des mécanismes impliquant une diminution de la sécrétion d’insuline chez les sujets prédisposés au diabète. La réponse de ces sujets diminue tandis que le nombre d’allèles diabétiques augmente. Je pense que le contexte génétique des cellules β détermine leurs capacités à s’adapter à une demande accrue d’insuline imposée par la stimulation de la prise calorique et de la résistance à l’insuline ; c’est un échec d’adaptation qui conduit au DT2. Je considère donc la cellule β « prédiabétique » comme une cellule normale ayant une adaptabilité limitée, le risque diabétique étant complètement dépendant du contexte (charge nutritionnelle et sensibilité à l’insuline). Lorsque l’hyperglycémie est établie, les cellules β sont exposées à une stimulation nutritive continue, avec le stress oxydatif et du reticulum endoplasmique (RE) qui s’en suivent. Le résultat consiste en une augmentation des déficiences fonctionnelles et de l’apoptose des cellules β, aboutissant à une réduction de la masse de celles-ci. Certains de ces mécanismes sont contestés. Une question fascinante, mais qui reste encore en suspens, est de savoir si les mécanismes du déficit β-cellulaire dans un contexte diabétique interviennent avant l’apparition de l’hyperglycémie chez les sujets suralimentés insulinorésistants. Des traitements empêchant le stress oxydatif des cellules β et du RE pourraient arrêter la progression et peut-être la survenue du DT2.
A global guideline presents a huge and unique challenge. Many national guidelines address one group of people with diabetes in the context of one health-care system, with one level of national and health-care resources. This is not true in the global context where, although every health-care system seems to be short of resources, the funding and expertise available for health care vary widely between countries and even between localities.”

How evidence-based medicine has shaped international guidelines over the past 25 years

by S. Colagiuri and R. Colagiuri, Australia

Diabetes has reached epidemic proportions throughout the world. There is overwhelming evidence that the diabetes burden can be reduced through prevention and improving overall diabetes management. Despite the available evidence, strategies have not been widely incorporated into clinical practice, and the care received by many people with diabetes is less than optimal worldwide. Evidence-based diabetes guidelines are an essential tool for redressing this situation. The evidence-based guideline movement has evolved over many years in response to the explosion of medical knowledge, a perceived need to protect against the potential for biases in the consensus approach, and the ever-increasing need to optimize the cost-effectiveness of treatment interventions. Evidence-based medicine is designed to complement and integrate clinical experience. The International Diabetes Federation is leading a worldwide movement to make diabetes care more consistent, more systematic, and more accountable through engagement of the international diabetes community in the development and implementation of guidelines. There has been much progress over the past 25 years. Evidence-based medicine is now firmly entrenched as an essential component of health-care services and delivery. Evolution and refinement of the guideline development process continues with moves towards simplifying and reducing the human and financial cost of preparing guidelines without compromising integrity. In addition, the focus has shifted from guideline development to addressing the, as yet, unresolved challenge of guideline implementation.

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The World Health Organization (WHO) proposes that 80% of all diabetes is preventable, and there is overwhelming evidence that diabetes complications can be prevented or delayed by processes and practices of care aimed at: improving overall diabetes management; correcting blood glucose, blood pressure, and lipid abnormalities; avoiding smoking and excessive food intake; increasing physical activity; and controlling body weight. The cost-effectiveness of interventions to improve diabetes care has been well established by many international studies. Despite the available evidence, prevention strategies have not been widely incorporated into clinical practice, and the care received by many people with diabetes is less than optimal worldwide.

The reasons for this disappointing situation are unclear, but are likely to be multifactorial and may include lack of practitioner awareness of the evidence, deficiencies in undergraduate and continuing medical education, and/or a mismatch between provider education and workplace culture and constraints, eg, insufficient material and human resources to implement the evidence. Whatever the reason, given the extent of the evidence that the morbidity and premature mortality associated with diabetes are reduced when care is closely aligned with guidelines, the globally endemic wide variations in the clinical care of diabetes are unacceptable.

Evidence-based diabetes guidelines are an essential tool for redressing this situation. Their recommendations synthesize the evidence to identify which clinical practices and processes of diabetes care lead to better outcomes. They provide practitioners and consumers with objective information about which interventions are likely to work best for most people with diabetes in most situations, and provide a solid foundation for clinical policy and protocols. Similarly, guideline recommendations establish standards and benchmarks that can assist funders and policy makers to allocate resources judiciously and assess the need for services and workforce development to achieve desired standards of care and, ultimately, improved health outcomes.

**Background**

Early consensus guidelines and position statements based on expert knowledge and clinical wisdom were a vital step in setting standards and benchmarks for promulgating and evaluating “best practice” and raising the profile and quality of diabetes care worldwide. As the next logical step, the evidence-based guideline movement evolved over many years in response to: (i) the explosion of medical knowledge enabled by technological advances; (ii) the associated proliferation of medical evidence in the form of journal reports; (iii) a perceived need to protect against the potential for biases in the consensus approach; and (iv) the ever-increasing need to optimize the cost-effectiveness of treatment interventions.

The role of clinical management guidelines is to synthesize and summarize research evidence into easily accessible information on the effects and possible consequences of available treatment options for use by clinicians and consumers. Field and Lohr defined evidence-based guidelines as: “...systematically generated statements which are designed to assist health care clinicians and consumers to make informed decisions about appropriate treatment in specific circumstances.”

Since then, guideline development has evolved into a highly sophisticated, technical, and resource-intensive model of research. Today, guideline methodology has its own body of evidence with each of several national research authorities around the world publishing their own requirements and grading criteria. In tandem with the evolution of guideline development methodology, a variety of clinical management guidelines across almost all common disease areas has proliferated in a global attempt to promote evidence-based clinical practice, reduce unacceptable variations in treatments, and minimize potential treatment harm.

Evidence-based medicine aims to apply the best available evidence to medical decision-making. Evidence-based guidelines, which formulate recommendations based on evidence, influence policy and regulations, and are an essential starting point for improving clinical care. However, their application in evidence-based individual decision-making by the healthcare provider for the benefit of an individual patient needs to take into account the many other factors that influence treatment choices, including relevance to the individual and the patient’s expectations and values, cost, and cost-effectiveness. Evidence-based medicine should complement and integrate clinical experience.

The methodology for preparing evidence-based guidelines is well established and includes identifying specific research questions around important clinical issues. These questions are the focus of the subsequent systematic reviews and synthesis of the medical literature that generate the evidence for formulating clinically relevant recommendations to guide patient care. Several national research authorities set out strict criteria for developing guidelines, and the development process is rigorous, objective, replicable, and transparent. Nonetheless, it should be recognized that guideline methodology has some inherent limitations. The heavy reliance on ran-
Evidence-based medicine and international diabetes guidelines – Colagiuri and Colagiuri

The International Diabetes Federation (IDF)

The International Diabetes Federation (IDF) is an umbrella international non-governmental organization (NGO) of over 200 national diabetes associations in over 160 countries and has been leading the global diabetes community since 1950. IDF’s mission is to promote diabetes care, prevention, and a cure worldwide. The IDF led the “Unite for Diabetes” campaign, which secured a UN resolution on diabetes in December 2006. The resolution encourages UN member states to develop national policies for the prevention, treatment, and care of diabetes in line with the sustainable development of their health-care systems, taking into account internationally agreed development goals, including the Millennium Development Goals.

There is now extensive evidence on the optimal management of diabetes, offering the opportunity of improving the immediate and long-term quality of life of people with diabetes. Unfortunately, such optimal management is not reaching many, perhaps the majority, of the people who could benefit. Reasons include the size and complexity of the evidence base, and the complexity of diabetes care itself.

Guidelines are one part of a process that seeks to address these problems. Many guidelines have appeared internationally, nationally, and more locally in recent years, but most of these have not used the rigorous new guideline methodologies for identification and analysis of the evidence. The IDF is leading a worldwide movement to make diabetes care more consistent, more systematic, and more accountable through engagement of the international diabetes community in the development and implementation of guidelines. The IDF Clinical Guidelines Taskforce focuses on developing evidence-based guidelines and clinical care recommendations which are globally and locally relevant.

A global guideline presents a huge and unique challenge. Many national guidelines address one group of people with diabetes in the context of one health-care system, with one level of national and health-care resources. This is not true in the global context where, although every health-care system seems to be short of resources, the funding and expertise available for health care vary widely between countries and even between localities.

Levels of diabetes care

All people with diabetes should have access to cost-effective evidence-based care. It is recognized that in many parts of the world the implementation of particular standards of care is limited by lack of resources. The IDF has developed a practical approach to promote the implementation of cost-effective evidence-based care in settings between which resources vary widely. The approach that has been adopted is based on acknowledging and making recommendations in relation to three levels of care:

- **Standard care**
  Standard care is evidence-based care which is cost-effective in most nations with a well-developed health-service base, and with health-care funding systems consuming a significant part of national wealth. Standard care should be available to all people with diabetes and the aim of any health-care system should be to achieve this level of care. However, in recognition of the considerable variations in resources throughout the world, other levels of care are described which acknowledge low and high resource situations.

- **Minimal care**
  Minimal care is the lowest level of care which anyone with diabetes should receive. It acknowledges that standard medical resources and fully trained health professionals are often unavailable in poorly funded health-care systems. Nevertheless, this level of care aims to achieve with limited resources (medications, personnel, technologies, and procedures) a high proportion of what can be achieved by standard care. Only low-cost or highly cost-effective interventions are included at this level.

- **Comprehensive care**
  Comprehensive care includes the most up-to-date and complete range of health technologies that can be offered to people with diabetes, with the aim of achieving the best possible outcomes. However, the evidence-base supporting the use of some of these expensive or new technologies is relatively weak.

Approaches to guideline development

Developing guidelines is a time-consuming and costly process that is beyond the resources of many health-care systems. As the science of evidence-based medicine continues to evolve, there is now increasing questioning of the need for and the relevance of the traditional full guideline development process. In 2003, the IDF addressed this in its Guide for Guidelines which proposed two basic approaches to developing an evidence-based guideline:

- **Full-process guideline**
- **Derived guideline**
The full-process guideline involves a full and systematic development of the clinical questions to be addressed, and develops recommendations supported by complete and formal evidence searching and review, using primary sources.

The derived guideline similarly develops clinical questions, but then seeks out and adapts previously developed full-process guidelines, updating the evidence base and seeking supporting evidence to develop recommendations for local circumstances. Preparing a derived guideline, a relatively simple process, can be done without a complex management structure or considerable resources and time, without compromising the end result.

While the move to review the need for full-process guidelines is welcome, this should not imply a return to consensus statements prepared by a small group with a limited and often uncritical review of the literature.

**Complexity of decision-making in clinical management**

Diabetes care is complex and involves a range of interventions – education, lifestyle modification (diet, physical activity), medications for diabetes complications prevention and treatment (eg, cardiovascular and renal disease), and ongoing monitoring and review (including self-monitoring blood glucose [SMBG], clinical [blood pressure and weight], and pathological [glycated hemoglobin, lipids, etc]). While multifactorial intervention has been shown to reduce morbidity and premature mortality, demonstrating the efficacy of individual components of care has been more difficult (eg, education, SMBG). Clinical decision making requires more than just taking into account efficacy of a particular treatment, and this should be taken into account in formulating and interpreting guideline recommendations. Factors which influence the treatment used in a particular patient include not only the evidence of effect on glycemic control and diabetes outcomes, but also include contraindications, potential side effects, patient preference, local availability, prescribing restrictions, and the cost to the individual and health-care system. Ultimately, diabetes care decision-making is based on a balance between benefit and safety in the context of availability and cost. Fortunately, there is considerable high-quality evidence available to guide clinical diabetes care. However, there are limited data on clinical outcomes comparing different treatment schedules.

The United Kingdom Prospective Diabetes Study (UKPDS) reported similar improvements with sulfonylurea- and insulin-based treatment policies on microvascular complications and on any diabetes-related end point. Although metformin therapy was associated with improved cardiovascular outcomes in a subgroup of overweight individuals, it should be noted that this was against a backdrop of no improvement in microvascular outcomes and no significant reduction in glycated hemoglobin.

Most of the data relating to pharmaceutical interventions are based on efficacy in improving blood glucose, which is generally similar between agents depending on whether it is used as first-, second-, or third-line therapy. Therefore, individual treatment choices are ultimately more often based on other considerations. These include unwanted consequences, such as the risk of hypoglycemia and weight gain, which are inevitable with insulin, but which differ between other agents and between studies. The cost to the individual, the healthcare system, and society is an important consideration, and cheaper, well-established, and efficacious treatments (eg, metformin and sulfonylureas) continue to be widely used and recommended in guidelines globally.

**Guideline implementation**

The translation of guidelines into everyday practice remains a vexed problem with little clear direction about what works best across all circumstances. According to Grimshaw et al, failure to translate guidelines into everyday practice features among the commonest findings of health-service research.

Nonetheless, there is some evidence, although variable, on the effectiveness of certain strategies for improving the uptake of guidelines by health professionals in clinical practice. Many approaches have been used with varying success, but the most effective have been multidimensional and locally specific. The main targets of guideline implementation strategies are health-care professionals, health-care funders, and people with diabetes. However, other stakeholders, such as government and industry, have an important role in promoting and facilitating guideline implementation.

Successful guideline implementation requires more than its formulation and publication. Together, with its wide distribution among organizations worldwide, the IDF has been holding regional workshops to present its guidelines, explain their aims and evidence-based methodology, and analyze face-to-face with health-care organizations and providers the difficulties of successful implementation and possible strategies to solve such problems.

During these workshops the guidelines are presented, and attendees explain their approach to improving diabetes care and the problems identified for successful implementation and acceptance of care strategies. Small groups consider the pros and cons of the guideline, barriers to successful implementation, and possible strategies to overcome such barriers.

Greater attention and support is needed for guideline implementation. Indeed, guideline development is rarely indicated unless there are plans, developed at the same time, for implementation of the recommendations. This should be considered an integral part of the planning stage of guideline development. Guideline implementation requires participation of people with diabetes, official support from government and
health-financing entities, adequate distribution of a simplified version for daily use at primary health-care level, and training of providers/users. These strategies imply the appropriate allocation of human and economic resources.

There has been much progress over the past 25 years. Evidence-based medicine is now firmly entrenched as an essential component of health-care services and delivery. Evolution and refinement of the guideline development process continues with moves towards simplifying and reducing the human and financial cost of preparing guidelines without compromising integrity. Finally, the focus has shifted from guideline development to addressing the, as yet, unresolved challenge of guideline implementation.

References


Keywords: evidence-based medicine; diabetes; guidelines

Comment la médecine basée sur les preuves a façonné les recommandations internationales ces 25 dernières années

Le diabète devient une véritable épidémie dans le monde entier. Des preuves évidentes prouvent que le fardeau du diabète peut se réduire grâce à sa prévention et à l’amélioration de sa prise en charge globale. Malgré ces témoignages, la pratique clinique n’a pas intégré de stratégies globales et les soins reçus dans le monde entier par de nombreux diabétiques sont insuffisants. Les recommandations basées sur les preuves pour le diabète sont un outil fondamental pour redresser la situation : elles ont évolué depuis plusieurs années en réponse à l’explosion des connaissances médicales, à la nécessité de prévenir les biais possibles dans l’approche consensuelle et au besoin toujours croissant d’optimiser la rentabilité des traitements. La médecine basée sur les preuves a pour but de compléter et intégrer l’expérience clinique. La Fédération internationale du diabète conduit un mouvement mondial pour que la prise en charge du diabète soit plus cohérente, plus systématique et plus responsable par l’implication de la communauté diabétique internationale dans le développement et l’application des recommandations. De grands progrès ont été fait ces 25 dernières années. La médecine basée sur les preuves est maintenant solidement enracinée comme composante essentielle du service et de la délivrance des soins. Ces recommandations évoluent et s’affinent dans le sens d’une simplification et d’une réduction des coûts humains et financiers de leur préparation, sans compromettre leur intégrité. De plus, l’attention s’est déplacée du développement des recommandations au déni non encore résolu de leur application.
The reductions in cardiovascular events observed in the Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation (ADVANCE) trial through routine blood pressure lowering with perindopril/indapamide and intensive glucose control with a Diamicron MR-based regimen have provided added incentive to develop tools for more accurate assessment of cardiovascular risk in patients with type 2 diabetes. Models based on earlier studies, including the Framingham and United Kingdom Prospective Diabetes Study risk equations, were based on populations treated in a much earlier therapeutic environment, before the availability of many of today’s protective cardiovascular drugs. Accordingly, we have used the opportunity afforded by the ADVANCE population with type 2 diabetes, a population that is both contemporary and representative of the broad cross-section of people with type 2 diabetes worldwide, to develop a new, improved risk engine for predicting the risk of cardiovascular events. The predictive baseline characteristics used to estimate cardiovascular risk through the ADVANCE risk engine are age at diagnosis of diabetes, known duration of diabetes, sex, pulse pressure, treated hypertension, atrial fibrillation, retinopathy, HbA1c, urinary albumin/creatinine ratio, and non-high-density-lipoprotein cholesterol. This model provides a considerable improvement over the older risk equations in predicting the risk of cardiovascular events. The new ADVANCE risk engine will shortly be available, through a specific ADVANCE Web site, to assist physicians around the world in calibrating their patients’ risk profile and in optimizing their therapeutic management to alleviate the global burden of cardiovascular disease in patients with type 2 diabetes.

Medicographia. 2011;33:47-51 (see French abstract on page 51)
Indeed, many patients with diabetes live long lives with quite good health, while others are cut down prematurely! It is clearly of vital interest to these patients, their families, and their physicians to have an accurate assessment of the risk of serious complications of diabetes so that appropriate plans for prevention may be formulated. Since cardiovascular disease constitutes the major burden of ill health in type 2 diabetes, there is an urgent need for tools that help the physician to advise the patient about the risks of serious cardiovascular events, such as heart attacks and strokes, so that together they can plan and implement the lifestyle and therapeutic measures needed to reduce this risk and prevent these complications.

The need for accurate prediction of cardiovascular risk is much greater now that the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) has clearly demonstrated the benefits of both routine blood pressure lowering with the fixed combination of perindopril and indapamide and more intensive glucose control with a DiamicroN MR-based regimen, irrespective of baseline blood pressure or baseline glycated hemoglobin (HbA1c).

Many studies have highlighted the importance of key individual risk factors, such as the level of HbA1c, and presence or absence of albuminuria, in determining the level of risk in the individual patient. However, modern guidelines increasingly emphasize the importance of estimating the individual’s global cardiovascular risk as a more appropriate basis for risk factor management. Global cardiovascular risk is a quantitative estimate of an individual’s chances of experiencing a cardiovascular event within a given time period. This estimate depends on the combination and intensity of all risk factors rather than on the presence of any single risk factor. In this paper, we examine the performance of a variety of existing “clinical prediction models,” also referred to as “absolute risk equations,” in estimating cardiovascular risk, and we present preliminary information describing the new “ADVANCE risk engine,” based on a contemporary and representative population of individuals with type 2 diabetes around the world.

**Figure 1.** 4-year predicted rates of major cardiovascular events in ADVANCE by the Framingham and UKPDS equations.

<table>
<thead>
<tr>
<th>Events</th>
<th>Model equation</th>
<th>E:O ratio &amp; 95% CI</th>
<th>O (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CVD</strong></td>
<td>Framingham - Anderson</td>
<td>2.70 (2.46-2.95)</td>
<td>6.1%</td>
</tr>
<tr>
<td></td>
<td>Framingham - D’Agostino</td>
<td>3.02 (2.76-3.31)</td>
<td>6.1%</td>
</tr>
<tr>
<td><strong>CHD</strong></td>
<td>Framingham - Anderson</td>
<td>2.46 (2.17-2.79)</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>Framingham - D’Agostino</td>
<td>3.89 (3.43-4.41)</td>
<td>3.2%</td>
</tr>
<tr>
<td></td>
<td>UKPDS</td>
<td>2.98 (2.62-3.38)</td>
<td>3.2%</td>
</tr>
<tr>
<td><strong>Cerebrovascular</strong></td>
<td>Framingham - Anderson</td>
<td>0.96 (0.84-1.10)</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td>Framingham - D’Agostino</td>
<td>1.25 (1.09-1.43)</td>
<td>2.8%</td>
</tr>
<tr>
<td></td>
<td>UKPDS</td>
<td>1.99 (1.74-2.28)</td>
<td>2.8%</td>
</tr>
</tbody>
</table>

**Abbreviations:** ADVANCE, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation; CHD, coronary heart disease; CVD, cardiovascular disease; UKPDS, United Kingdom Prospective Diabetes Study.


**Selected abbreviations and acronyms**

| ADVANCE Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation |
| CVD cardiovascular disease |
| HbA1c glycated hemoglobin |
| UKPDS United Kingdom Prospective Diabetes Study |
D’Agostino,6 and UKPDS equations.7,8 This overestimation control arm).9 arm and the standard care group of the blood pressure–lowering signed to the placebo group in the blood pressure–lowering vascular events.7,8

In order to assess the performance of a risk equation in a contemporary population, it is necessary to test and quantify how well a particular model, derived from a distinct and specific population, predicts risk in another quite different and independent modern population. The main criteria used to describe the performance of the model being tested are termed “calibration” and “discrimination.” We illustrate this below, in assessing the performance of the older Framingham and UKPDS equations in the contemporary ADVANCE cohort.5,8

“Calibration” quantifies how close the predictions are to the actual outcome. For instance, a 5-year estimated probability of cardiovascular disease of 20% for a patient means that, in a given group of patients with similar characteristics, 20% will experience a cardiovascular event within a 5-year period. Figure 1 shows that, in the cohort of ADVANCE patients who had no known history of cardiovascular disease at enrolment in the trial, the 4-year risk of cardiovascular events was largely overestimated by the Framingham-Anderson,5 Framingham-D’Agostino,6 and UKPDS equations.7,8 This overestimation was observed in men and women, whites and non-whites, and in the double-placebo cohort of ADVANCE (ie, those assigned to the placebo group in the blood pressure-lowering arm and the standard care group of the blood pressure-control arm).9

“Discrimination” describes the performance of a model in distinguishing between patients who go on to develop a cardiovascular event and those who remain event free. Discrimination using the Framingham and UKPDS equations in predicting CVD events in the ADVANCE patients was modest to acceptable for coronary heart disease and for total CVD, but poor for stroke.9

Recalibration is a method for improving an equation’s predictive capacity. It usually consists of adjusting the equation by replacing the average value of the risk factors and event rates in the equation (derived from the original population) by those in the test population. When applied to the Framingham and UKPDS equations, this approach substantially attenuated the overestimation of risk for the ADVANCE patients. However, discrimination was not improved, indicating the need for a new equation with improved discriminatory capability for people with diabetes, particularly those receiving many contemporary cardiovascular risk-reducing therapies.9

### Development of the new ADVANCE risk engine for predicting risk and improving cardiovascular event prevention in type 2 diabetes

In developing a new model for risk prediction, it is important to address the limitations of the existing models. The inclusion in ADVANCE of participants from many countries has provided the opportunity to account for the substantial variation in the care of diabetes and cardiovascular disease around the world, whereas existing models have been derived from homogenous populations from the UK and the USA. The generalizability of the ADVANCE cohort to current contemporary populations of patients with type 2 diabetes around the world is shown in Table I, which compares the characteristics of patients participating in ADVANCE with those of individuals with type 2 diabetes at community level in a number of countries.10-13 The ADVANCE model also aims to predict total cardiovascular risk and therefore to capture the interrelation between components of cardiovascular disease, such as coronary heart disease and stroke, unlike other models, such as the UKPDS equations, that focus specifically and separately on these components. Moreover, the complexity of the relationship between chronic hyperglycemia and cardiovascular risk has not been as well addressed in existing models. In the ADVANCE model, further improvements have been achieved through the integration of risk factors to capture exposure to chronic hyperglycemia both before and after the clinical diagnosis of diabetes.

### Table I. Baseline characteristics for the ADVANCE participants and other cross-sectional studies.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>ADVANCE2</th>
<th>Berthold et al11</th>
<th>AUSDIAB12</th>
<th>DEPAC13</th>
<th>ENTRED10</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>66</td>
<td>65</td>
<td>64</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.5</td>
<td>7.3</td>
<td>7.3</td>
<td>7.7</td>
<td>7.2</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28</td>
<td>29</td>
<td>30</td>
<td>31</td>
<td>28</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>145</td>
<td>143</td>
<td>144</td>
<td>141</td>
<td>140</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>7</td>
<td>7</td>
<td>8</td>
<td>10</td>
<td>11</td>
</tr>
<tr>
<td>Macrovascular disease (%)</td>
<td>32</td>
<td>34</td>
<td>29</td>
<td>&gt;31</td>
<td>&gt;21</td>
</tr>
</tbody>
</table>

that emerged as independent predictors and were chosen for inclusion in the ADVANCE risk engine are shown in Table II.\textsuperscript{14} Age at diagnosis of diabetes and known duration of diabetes were preferred to age at baseline, in order to improve the applicability of the ADVANCE equation to other populations. Although cognitive function has been confirmed as an independent predictor of CVD in ADVANCE,\textsuperscript{12} this characteristic was not considered for inclusion in the model, given the difficulties in assessing cognitive function in a standardized way around the world. Surprisingly, smoking status was not a significant predictor when tested alone or together with other risk factors in the ADVANCE population, possibly reflecting the small proportion of current smokers in that cohort.

The capacity to predict the risk of events was tested against the actual recording of events that occurred during the post-randomization period of follow-up within the ADVANCE population. The calibration of the ADVANCE model was excellent and the discrimination acceptable with an area under the curve (AUC) of 0.7. Validation of the ADVANCE model in an external, independent population of people with type 2 diabetes is currently proceeding. To facilitate the uptake of the ADVANCE model in clinical practice, a risk scoring table is being developed. This will assign scores for various levels of each of the ten final risk factors selected, in each individual patient. Other tools from this model are also planned, including an online calculator.

**Conclusions**

The ADVANCE trial has provided a major impetus for development of accurate tools to predict the risk of cardiovascular events in individuals with type 2 diabetes. The routine administration of the fixed combination of perindopril and indapamide reduced all-cause mortality by 14%, cardiovascular mortality by 18%, major vascular events by 9%, and coronary and renal events by 14% and 21%, respectively.\textsuperscript{7} Additionally, more intensive glucose control using a gliclazide MR–based regimen reduced the risk of major macro- or microvascular events by 10%, of major cardiovascular events by 14%, and of new or worsening nephropathy by 20%. Given these potential benefits, it is incumbent on physicians responsible for the care of patients with type 2 diabetes to ensure that they prescribe such treatments for all patients at high risk of experiencing cardiovascular events. In turn, this places a premium on developing the capacity to predict the risk of cardiovascular events much more accurately than was previously possible.

It is in this context that the new ADVANCE risk engine presents a new and valuable tool. In an effort to overcome some of the limitations of the existing models for estimating cardiovascular risk in people with diabetes, the new model is founded on some of the unique features of the ADVANCE cohort. The ADVANCE model is based on parameters that are easily assessable and widely available in routine clinical care. When tested, the performance of this new model was highly acceptable. Inclusion of participants from developing countries in the ADVANCE cohort highlights the potential of the ADVANCE risk engine for assisting cardiovascular risk stratification efforts in many settings around the world.

We are currently actively working to develop a specific ADVANCE risk engine Web site that will assist physicians all around the world to determine the risk of cardiovascular disease in their own individual patients with type 2 diabetes, and we invite all physicians to use this tool as soon as it becomes available.

**References**


**Keywords:** perindopril/indapamide; Preterax; Diamicron MR; type 2 diabetes; blood pressure lowering; intensive glucose control; cardiovascular risk; risk prediction; calibration; discrimination

**FACTEURS PRÉdictifs D’éVAluation du Risque Cardio-vasculaire : les leçons d’ADVANCE**

La diminution des événements cardio-vasculaires observés dans l’étude ADVANCE (Action in Diabetes and Vascular disease : PreterAx and Diamicron MR Controlled Evaluation) grâce à l’abaissement de la pression artérielle par le recours systématique à l’association périndopril-indapamide et au contrôle intensif de la glycémie par Diamicron LM a encouragé le développement de nouveaux moyens pour évaluer plus précisément le risque cardio-vasculaire des diabétiques de type 2. Les modèles basés sur des études anciennes, comme les équations de prévision du risque des études de Framingham et de l’UKPDS (United Kingdom Prospective Diabetes Study), concernent des populations traitées dans un environnement thérapeutique bien antérieur à la mise sur le marché des nombreux agents actuels assurant une protection cardio-vasculaire. C’est pourquoi nous avons saisi l’opportunité offerte par la population diabétique de type 2 de l’étude ADVANCE, une population à la fois contemporaine et représentative des diabétiques de type 2 dans le monde, pour développer un nouveau moteur de recherche permettant de prévoir le risque d’événements cardio-vasculaires. Les données prévisionnelles initiales utilisées pour estimer le risque cardio-vasculaire grâce au moteur de recherche de l’étude ADVANCE ont été basées sur l’âge au moment du diagnostic du diabète, la durée connue du diabète, le sexe, la pression pulsée, la présence ou non d’une hypertension traitée, d’une fibrillation auriculaire ou d’une rétinopathie, le taux d’HbA1c, le rapport albumine/créatinine urinaire et le cholestérol non HDL. Ce modèle permet une amélioration considérable des anciennes équations de prévision du risque d’événements cardio-vasculaires. Le nouveau moteur de recherche de l’étude ADVANCE sera bientôt disponible sur un site Internet dédié à ADVANCE, pour aider les médecins du monde entier à ajuster le profil de risque de leurs patients et à optimiser leur prise en charge thérapeutique pour alléger la charge globale de la pathologie cardio-vasculaire des diabétiques de type 2.
Will you use HbA$_{1c}$ to screen for type 2 diabetes?

In June 2009, the American Diabetes Association proposed that glycated hemoglobin (HbA$_{1c}$) assay should be the new standard diagnostic test for diabetes. HbA$_{1c}$ has definite advantages as a screening tool because unlike traditional tests, it reflects average blood glucose level over several months rather than at a particular point in time. It is more convenient and more reproducible than fasting blood glucose, but also more expensive. Our authors share their views on HbA$_{1c}$.

1. L. Czupryniak, Poland
2. S. Duran-Garcia, Spain
3. H. Gawish, Egypt
4. L. Ji, China
5. S. R. Joshi, India
6. E. Mannucci, Italy
7. J. F. Raposo, Portugal
8. O. Smirnova, Russia
9. B. L. Wajchenberg, Brazil
Will you use HbA1c to screen for type 2 diabetes?
It has recently been published that “it is reasonable to consider an HbA1c range of 5.7% to 6.4% as identifying individuals with high risk for future diabetes and to whom the term prediabetes may be applied if desired.” Glycated hemoglobin (HbA1c) is a widely used marker of chronic glycemia and plays a critical role in the management of patients with diabetes. Prior expert committees have not recommended the use of the HbA1c test for the diagnosis of diabetes, due to a lack of standardization of the assay. More recently an international committee, after an extensive review of both established and emerging epidemiological evidence, recommended the use of the HbA1c test to diagnose type 2 diabetes, with a threshold of ≥6.5%. The diagnostic test should be performed using a method certified by the NGSP (National Glycohemoglobin Standardization Program). Point-of-care HbA1c assays are not sufficiently accurate at this time to use for diagnostic purposes. There is an inherent logic to using a chronic marker of dysglycemia rather than an acute one, particularly since HbA1c has several advantages to fasting plasma glucose (FPG), including greater convenience (since fasting is not required), evidence to suggest greater preanalytical stability, and less day-to-day perturbations during periods of stress and illness.1,2

In Spain, as in other European countries, the cost is similar to the determination of baseline glycemia on two different days, with greater convenience for the patient. In patients with abnormal FPG, the need for glucose overloads could be avoided, with the ensuing savings in analytical costs and time invested by patients. Both the Spanish Endocrinology and Nutrition Society (SEEN) and the Spanish Diabetes Society (SED) have recently expressed support for the recommendations of the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF).3 One debatable point is the impression held by many clinicians that the correlation between HbA1c and mean daily glycemias is not entirely linear in some patients. But this does not seem to be preventing us from using HbA1c as a reliable diagnostic tool in the general population. In order to overcome a potential lack of protection in subjects with undiagnosed diabetes, the Endocrine Society has suggested that intensive cardiovascular protection therapy should be initiated in all subjects with an HbA1c between 5.7% and 6.5%, and this recommendation has also been fully accepted by the SEEN and the SED. The documents published recap situations in which HbA1c must not be used as a diagnostic tool or in the assessment of glycemic control (severe ferropenias, hemolytic anemias, thalassemias or other hemoglobinopathies, hereditary spherocytosis, cancer, kidney failure, liver failure, or advanced age). Both societies clearly specify that HbA1c must not be used as a diagnostic tool in type 1 diabetes mellitus, in gestational diabetes,4,5 or in pediatric patients.

The application of this test in the diagnosis of type 2 diabetes, as well as in situations of type 2 prediabetes, may have major repercussions in habitual clinical practice on the pass-on costs in the health system and on the early prevention of the development of vascular complications. It must not be forgotten that, in any case, the goal is to diagnose this condition as early on as possible, which may be easier with the availability of this diagnostic tool.

References
Glycated hemoglobin (HbA1c) value and its cutoff level have always been the subject of debates. A target goal of HbA1c ≤7% was recommended by the American Diabetes Association (ADA), while both the American College of Endocrinology (ACE) and the American Association of Clinical Endocrinology (AACE) adopted a lower target of HbA1c ≤6.5% in 2001. Although HbA1c had been proved to be significantly linked to the risk of diabetes complications, until recently it was not accepted for use in the diagnosis of diabetes. In June 2009, the ADA raised the prospect of making HbA1c essential for the diagnosis of diabetes. A threshold HbA1c of 6.5% or above being diagnostic of diabetes, and levels between 5.7% and 6.4% identifying patients at high risk of developing diabetes and its complications. The ADA’s last report succeeded in starting a debate among professionals internationally.

The effect of ethnicity on HbA1c is going to be of great concern with the shift toward HbA1c-based diagnosis for diabetes. This might necessitate having different HbA1c cutoff values for the diagnosis of diabetes in different populations. An assessment of the impact of ethnicity on HbA1c that compares data and epidemiological studies is expected in the future.

Worldwide debate is mainly based on the cutoff points for diagnosis, which need more evidence to be substantiated. An HbA1c of 6.5% has been unequivocally linked to microvascular complications such as diabetic retinopathy and peripheral neuropathy. It has also been linked to macrovascular complications, increased cardiovascular risk, and carotid intimal thickening with its cerebrovascular insults. This is why it is widely believed that a cutoff HbA1c value of 6.5% for diagnosis is going to underestimate the problem. Diabetologists are willing to intervene early, at least with lifestyle modification and metformin, which are supported by adequate evidence, but an HbA1c cutoff value of 6.5% is going to have the reverse effect.

For developing countries like Egypt, where there is no national program for screening sponsored by the government, other difficulties might come up. The issue of cost is crucial in applying ADA recommendations. The cost of HbA1c testing is around 7 times that of plasma glucose testing in Egypt. HbA1c testing is not routinely available in all laboratories, especially in rural areas. The issues of standardization, quality control, and reproducibility in different labs will be of great concern.

Illnesses interfering with HbA1c assay are of the utmost importance, even if the new methods of estimation take them into account. A high prevalence of all types of anemia, including hemoglobinopathies, is present in Egypt. This will add another barrier to the widespread acceptance of ADA recommendations not only in Egypt, but also in other Mediterranean countries.

The advantages of using HbA1c percentage as a diagnostic test for diabetes, as the ADA mention, are its reproducibility and convenience, as fasting is not required. But the disadvantages outweigh these advantages, especially in developing countries.

In conclusion, the utility of HbA1c as a marker for metabolic control cannot easily be extended to validate its use for the diagnosis of diabetes. A consensus with clear answers to all questions raised should be reached before HbA1c becomes widely accepted as a reliable diagnostic tool.
The increasing prevalence of diabetes across the world has become a major public health issue of global concern. Early diagnosis and treatment of diabetes is key for reducing the risk of diabetic complications. For a long time, researchers have been looking for easier and more accurate ways of diagnosing diabetes.

In 2009, after reviewing the evidence on the role of glycated hemoglobin (HbA1c) in diagnosing diabetes, an international expert committee jointly organized by the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), and the International Diabetes Federation (IDF) recommended the use of HbA1c as a diagnostic tool for diabetes, with HbA1c ≥6.5% as the diagnosis cutoff.

Following this announcement, the ADA officially recommended HbA1c as the preferred parameter for diagnosing diabetes, recommending an HbA1c ≥6.5% as the cutoff for this purpose and classifying 5.7% ≤HbA1c ≤6.4% as a high risk category for diabetes as well as cardiovascular diseases. The advantage of HbA1c for the diagnosis of diabetes over the current gold standard based on glucose measurement is well elaborated in the statement of the international expert committee.

In China, two issues need to be addressed before HbA1c can be recommended as the diagnostic tool for diabetes. Firstly, the HbA1c threshold associated with diabetic complications (in particular diabetic retinopathy) needs to be evaluated to rule out the possibility that the HbA1c cutoff for diagnosing diabetes might be race specific, since a Japanese study shows that the HbA1c risk threshold for significant increased retinal degeneration is 5.7%, which is quite different from the ADA recommended threshold.

Secondly, great effort needs to be taken to standardize the HbA1c testing method. According to a recent survey, there was great variability when measuring the same blood sample among different clinical labs. In addition, the HbA1c assay needs to gain popularity in China since HbA1c has not been widely used in the clinical management of diabetes in the past.

To address these issues, studies are now being undertaken to look for the HbA1c cutoff for diagnosing diabetes and to examine the relationship between HbA1c level and risk of retinopathy in the general Chinese population. A grant program, the China HbA1c Education Program, was launched to educate health-care providers and patients on how to use HbA1c in the daily management of diabetes. Another important part of this program is to educate laboratory technicians to use standard assays of HbA1c in order to provide a high-quality service in diabetes care.

Obviously, there are some major reasons in opting for HbA1c: objectivity in reflecting chronic hyperglycemia; high replicability; much greater relevance to cardiovascular events in diabetics; and greater convenience, as there is no need to take into account the time of blood sampling and food intake.

In China, two issues need to be addressed before HbA1c can be recommended as the diagnostic tool for diabetes. Firstly, the HbA1c threshold associated with diabetic complications (in particular diabetic retinopathy) needs to be evaluated to rule out the possibility that the HbA1c cutoff for diagnosing diabetes might be race specific, since a Japanese study shows that the HbA1c risk threshold for significant increased retinal degeneration is 5.7%, which is quite different from the ADA recommended threshold.

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HbA1c assay method or will preclude HbA1c testing. Any con-
fore, the advantages of HbA1c testing compared with glucose
type 2 diabetes are the same as the diagnostic tests; there-
tive differences in the relationship between glucose levels and
are more prevalent. HbA1c levels appear to increase with age,
of these conditions, particularly in populations in which they
There are, however, limitations to the use of HbA1c for screen-
ing. In some parts of the world, the costs of providing for its
assay preclude routine use. In addition, there are patient con-
ditions, such as HbS, HbC, HbF, and HbE, that interfere with
some HbA1c assay methods that either will require a specific
HbA1c assay method or will preclude HbA1c testing. Any con-
dition that changes red cell turnover, such as hemolytic ane-
mia, chronic malaria, major blood loss, or blood transfusion,
will lead to spurious HbA1c results. Clinicians must be aware
of these conditions, particularly in populations in which they
are more prevalent. HbA1c levels appear to increase with age,
but the extent of the change, whether it relates to factors oth-
er than glucose metabolism, and the effect of the age-relat-
ed increases on the development of complications are not
sufficiently clear to adopt age-specific values in a screening
scheme. Similarly, racial disparities in HbA1c, based on puta-
tive differences in the relationship between glucose levels and
HbA1c, have been suggested; however, here too, their etiol-
ogy and significance are unclear, and it is premature to estab-
lish race-specific diagnostic values. Finally, there are rare clin-
cical settings, such as rapidly evolving type 2 diabetes, where
the HbA1c level will not have had time to “catch up” with the
acute elevations in glucose levels; however, in these very rare
cases, diabetes should be diagnosable with typical symp-
toms and casual glucose levels $>$200 mg/dL (11.1 mmol/L),
despite a nondiagnostic HbA1c level. The above section high-
lights the false positive and false negatives of HbA1c that are
relevant to clinicians.

Based on a detailed review, an international Expert Commit-
tee has concluded that the best current evidence supports the
following recommendations:

- Individuals with an HbA1c level <6% but >6.5% are likely to
  be at the highest risk for progression to diabetes, but this range
  should not be considered an absolute threshold at which
  preventative measures are initiated.
- The classification of subdiabetic hyperglycemia, such as
  prediabetes, is problematic because it suggests that all indi-
  viduals so classified will develop diabetes and that individuals
  who do not meet these glycemia-driven criteria (regardless
  of other risk factor values) are unlikely to develop diabetes—
  neither of which is the case. Moreover, the categorical clas-
  sification of individuals as high risk (eg, impaired fasting gly-
  cemia [IFG] or impaired glucose tolerance [IGT]) or low risk,
  based on any measure of glycemia, is less than ideal because
  the risk for progression to diabetes appears to be a continu-
  um. Glucose-related terms describing subdiabetic hypergly-
  cemia will be phased out of use as clinical diagnostic states,
  as HbA1c measurements replace glucose measurements for
  the diagnosis of diabetes.
- When assessing risk, implementing prevention strategies,
or initiating a population-based prevention program, other di-
  abetes risk factors should be taken into account. In addition,
  the HbA1c level at which to begin preventive measures should
  reflect the resources available, the size of the population af-
  fected, and the anticipated degree of success of the interven-
  tion. Further analyses of cost-benefit should guide the selec-
  tion of high-risk groups targeted for intervention within specific
  populations.
- In developed economies where methodologies are well
  standardized, HbA1c may be used as a diagnostic add-on tool.
  But in developing countries where both liberal use as well as
  standardization of methodology is poor, it is a premature step.
  Also, there is still a role for glucose tolerance curves in mod-
  ern metabolic medicine in several areas of epidemiology as
  well as clinical practice.

Reference

1. International Expert Committee. International expert committee report on the role
An International Expert Committee, which included members designated by American, European, and International Diabetes Associations, proposed to include glycated hemoglobin (HbA1c) among the diagnostic criteria for diabetes, with a threshold of 6.5%. HbA1c is a more stable parameter than blood glucose, allowing a reliable assessment of carbohydrate metabolism without the need for repeated measurements that are required for the diagnosis of diabetes based on glyceric levels. The greater stability of this parameter may explain the results of epidemiological studies showing that HbA1c is a better predictor of the microvascular complications of diabetes and cardiovascular disease than either fasting glucose or postload/postprandial glucose. Furthermore, both fasting and postload glucose contribute to HbA1c.

Individual patients can show an isolated increase in postload glucose with normal fasting glycemia and vice-versa. Any screening strategy based on fasting glucose only will inevitably miss some diabetic patients with isolated postload hyperglycemia. The use of HbA1c can overcome this problem. A further advantage of HbA1c over blood glucose as a screening tool for diabetes is that it does not need to be measured in a fasting state—which can be difficult to ascertain.

On the other hand, the use of HbA1c as a screening and diagnostic tool has some disadvantages, which should be recognized. The correct measurement of this parameter requires high pressure liquid chromatography (HPLC) apparatus, which is not always available in peripheral laboratories. Values of HbA1c obtained with different methods can be very misleading. Furthermore, the standardization of HbA1c methods is far from complete. The use of the so-called Diabetes Control and Complications Trial (DCCT)-aligned standards attenuates the problem without completely eliminating it; in fact, a certain interlaboratory variability persists even among DCCT-aligned laboratories. It should also be considered that several conditions can lead to an increase or decrease in HbA1c levels independent of glucose metabolism; these include several forms of anemia, hemoglobinopathies, malaria, alcohol abuse, splenectomy, etc. Therefore, the results of measurements of HbA1c should always be carefully interpreted by clinicians. We should be aware that, particularly in older patients, the use of HbA1c could lead to an overestimation of the prevalence of diabetes. A further problem is the cost of determining HbA1c, which is higher than that for determining blood glucose; this aspect is a relevant limitation for HbA1c-based screening programs in underdeveloped countries, some of which have a high prevalence and incidence of diabetes.

Any clinical decision should be based on a careful evaluation of advantages and disadvantages. Although the standardization of laboratory procedures and costs are relevant issues, the benefits of using HbA1c in the screening of diabetes largely outweigh the disadvantages. In particular, the possibility of identifying cases of diabetes characterized by postload hyperglycemia with normal (or near-to-normal) fasting glucose, without the need to perform an oral glucose tolerance test is a major advantage, together with the possibility of diagnosing diabetics without the need to repeat the test, and of using blood samples drawn under nonfasting conditions for screening. At the same time, clinicians should be aware that values of HbA1c should not be used for diagnosis without critical consideration of the clinical conditions that could interfere with results.

References
Not yet. In contrast to type 1 diabetes, type 2 diabetes mellitus (T2DM) has been a difficult disease to diagnose throughout time. In fact, apart from their common definition as hyperglycemic conditions, their etiologies are significantly different.

But T2DM itself can be a heterogeneous disease, clinically varying from abnormal postprandial hyperglycemia to fasting hyperglycemia, or in some instances, both. Even from an investigational point of view, no consensus has been attained. In the last few decades, numerous techniques (clamps, glucose/insulin ratios, mathematical models) have been presented that only reveal details of this regulation, and genetic research is still far from identifying a common factor (if there is one).

Considering these facts, the pertinent questions are why is it important to diagnose T2DM and why is earlier better? Here, we have consensus. We know that diabetes should be diagnosed to prevent micro- and macrovascular disease, causes of morbidity and mortality. We know now that our therapeutic armamentarium is capable of changing the natural history of T2DM. We also know that macrovascular disease starts during the early stages of this condition.

T2DM has a high prevalence. In Portugal, recent data point to 11.7% of the population (aged between 20 and 79 years) as having diabetes, 43% of whom are unaware of the diagnosis. The diagnosis in these cases was obtained via fasting hyperglycemia, an abnormal 2-hour oral glucose tolerance test (OGTT) value, or both. Are these good screening tools? Are they easy to use and inexpensive, with good specificity and sensitivity? For years, we have used OGTT as the gold standard for the diagnosis of T2DM. Because of the different costs involved with this test, we later evolved to using the fasting glycemia criterion, lowering the reference value from 7.77 mmol/L (140 mg/dL) to 7 mmol/L (126 mg/dL) to increase sensitivity. Several studies then demonstrated that while there is certainly a considerable overlap in the populations diagnosed by these two different criteria, there are still significant proportions diagnosed by each one. What does this mean? Probably that they detect the previously referred to T2DM heterogeneity.

In 2009, the American Diabetes Association (ADA) adopted a new criterion. Representing a “physiological” average of glycemic fluctuations, glycated hemoglobin (HbA1c) is certainly a tempting candidate for a good screening tool. What has to be demonstrated before its acceptance for widespread use?

We have to consider methodological arguments: there is still no international consensus in the use of standards or units for HbA1c, and regional differences in the normal distribution of HbA1c are not known. The cost of an HbA1c test is significantly higher than the cost of measuring glycemia. The recent appearance of point-of-care HbA1c determination using different methodologies (and different correlations to the high pressure liquid chromatography [HPLC] standard) has created more interest in this new diabetes diagnostic criterion.

Apart from the methodological questions, there are others still waiting to be answered: Is the choice of an HbA1c value of 6.5% the best one for all? What is the overlap of T2DM diagnosis using HbA1c with the previously used criteria? Which populations (if there are any) are at greater risk of developing complications: a population with fasting hyperglycemia, with postprandial hyperglycemia, or with elevated HbA1c? Is glycemic variability, considered by some to be an indicator of increased cardiovascular risk, expressed by HbA1c?

In my opinion, and having discussed all these arguments, I consider the ADA’s current recommendation of continuing to use previous criteria and of using the new HbA1c one for the diagnosis of diabetes to be at least prudent and will give us time to answer all these questions. After decades of apparent stagnation, diabetes has been in a state of constant turmoil in the last few years, in different fields. A period of judicious reflection should follow.
Over the past few decades, the diagnosis of diabetes mellitus (DM) has been based on plasma glucose levels, either fasting or 2 hours after a 75-gram oral glucose load. While developing the new diagnostic criteria in 1997, the first Expert Committee on the Diagnosis and Classification of Diabetes Mellitus considered the results of studies that examined the association between fasting plasma glucose (FPG) levels and retinopathy development. Three epidemiologic studies identified the glycemic level below which there was minimal prevalence of retinopathy and above which the prevalence of retinopathy increased in a linear progression. The values of FPG, 2-hour plasma glucose after a 75-gram oral glucose load, and glycated hemoglobin (HbA1c) were the same for each population. Their study findings allowed the establishment of the diagnostic criteria that are currently recommended by the World Health Organization (WHO).

There are many cases of diabetes that are still not diagnosed in a timely manner. The need for active screening and early detection of DM is highlighted by the fact that about half of patients already have at least one diabetes-related complication at the time of diagnosis.

In January 2010, the American Diabetes Association (ADA) first recommended the use of an HbA1c test to diagnose diabetes, with a threshold of ≥6.5% for identifying diabetes, and a range of 5.7% to 6.4% for prediabetes screening. Before this date, the International Expert Committee, after a review of epidemiological studies, had already proposed using an HbA1c test for diagnosing diabetes, but this suggestion had been rejected, partly due to the absence of standardization of the assay. Today, HbA1c assays are highly standardized, therefore their results can be uniformly applied.

The diagnostic test should be performed using a method certified by the National Glycohemoglobin Standardization Program (NGSP) and standardized in accordance with the Diabetes Control and Complications Trial (DCCT) reference assay. The measurement of HbA1c, as the diagnostic criterion of diabetes has some advantages, since it is more convenient (as fasting is not required), more stable, less variable, and less affected by temporal factors, such as stress and coexisting diseases.

The relationship between HbA1c values and mean glucose levels has been unequivocally established. However, it should be remembered that HbA1c level as an indicator of glycemic control has several limitations, as it can increase in nondiabetic patients with end-stage renal failure receiving hemodialysis treatment, in patients with iron deficiency anemia, dyslipidemia, or cirrhosis, as well as in pregnant women. The diagnostic value of HbA1c can be limited in conditions associated with decreased erythrocyte lifetime (e.g., in hemolytic anemia) or in hemoglobinopathies. This should be kept in mind in cases where the results of HbA1c do not correspond to the clinical situation in a particular patient.

The new ADA recommendation to use HbA1c assays for the screening of diabetes and prediabetes is an important step forward in the diagnosis of the disease. Indeed, the determination of HbA1c should be considered more objective and reliable than that of FPG and even that of the oral glucose tolerance test (OGTT), as HbA1c reflects the state of carbohydrate metabolism over a long-term period. Random plasma glucose measurement requires confirmation with an additional OGTT examination. Moreover, HbA1c measurement does not require any special preparation or additional time, whereas the OGTT and simple FPG test require a carbohydrate diet in the days preceding the test, starvation before the test, as well as prolonged examination time.

I suppose the HbA1c test would be preferable for screening in high-risk populations. However, to verify the diagnosis of DM in asymptomatic patients, as well as prediabetes in the case of elevated HbA1c, it will also be necessary to repeat this test or perform an OGTT.

The significant arguments against the routine use of this assay for these purposes in our country today are the higher cost of the analysis and the absence of the corresponding standardized methods and equipment. I suppose that another obstacle is doctors’ inertia of thinking, especially general practitioners and physicians. On the other hand, in large medical centers, it is not only possible, but entirely feasible to use this assay for screening the limited number of subjects at high risk of DM with obesity and vascular diseases.
According to what has been suggested by experts in the area of diabetes and now by the American Diabetes Association (ADA), which considers glycated hemoglobin (HbA1c) an appropriate diagnostic test, the main factors in support of using HbA1c as a screening and diagnostic test are: HbA1c does not require patients to fast; it is a marker of chronic glycemia, reflecting average plasma glucose levels over 2 to 3 months; less day-to-day perturbations during periods of stress and illness; methods for its measurement are standardized and reliable; and errors caused by nonglycemic factors, such as hemoglobinopathies, are infrequent. The cutoff point suggested was 6.5%, as at this level the prevalence of diabetic retinopathy begins to rise above that of nondiabetic patients.

A disadvantage of the measurement of HbA1c for screening and diagnosis of diabetes is an incomplete correlation between HbA1c and average plasma glucose in “high glycators,” who have a higher HbA1c than that predicted with actual mean glucose level, while “low glycators” exhibit opposite characteristics. A quarter of the population exhibits one or other extreme glycator profiles, so the use of HbA1c levels as absolute “goals” for diagnosis and treatment is “inappropriate if not coupled with glucose measurements.”

The existing glycemic criteria for diagnosing diabetes—fasting plasma glucose (FPG) ≥126 mg/dL, and random plasma glucose or 2-h post–oral glucose tolerance test (OGTT) plasma glucose ≥200 mg/dL—were originally established based on an expert committee’s evaluation of levels of glycemia associated with diabetic retinopathy, continue to be accepted as criteria for the diagnosis of diabetes. Since, as indicated, the concordance between HbA1c and glucose-based tests is not complete, particularly considering that HbA1c, FPG, and 2-h post–OGTT measure different physiological processes, it has been suggested that an HbA1c from 6.5% to 6.9% or higher, be considered a screening test requiring confirmation by the diagnosis of diabetes using direct measures of glucose.

In the Hoorn study in 2753 subjects aged 45 to 65 years, the correlations between HbA1c, and FPG and 2-h post–OGTT glucose were 0.45 and 0.33, respectively, so that no more than one-quarter of the variance in HbA1c could be explained by glycemia. In this study, HbA1c >6.5% was quite specific. Its sensitivity being low, the current OGTT criteria failed to identify a high proportion of individuals with HbA1c >6.5%. Similar findings were observed in other studies.

Regarding the high-risk categories of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), it was suggested that an HbA1c of 6.0% to 6.4% would identify patients at high risk for diabetes (ie, progressing to >6.5%), so in a sense, these patients would represent a group equivalent to those classified as having IFG/IGT. However, this does not imply that populations at lower HbA1c levels are not at risk but, rather, they are at lower risk, since the risk for diabetes appears to be a continuum. It can be argued that is also the case with HbA1c, and any cutoff values chosen are somewhat arbitrary.

Using two cutoff values, rather than one, for HbA1c, gives high sensitivity for screening plus optimal specificity for diabetes diagnosis: HbA1c ⩾5.5% and <7.0% predicts the absence and presence of type 2 diabetes, while with an HbA1c of 6.5%–6.9%, diabetes is highly probable.

References
The results of the Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE) in June 2008 highlighted the role of Diamicron MR (gliclazide modified release) as a cornerstone treatment in the clinical management of type 2 diabetes. This agent has been available since 2000 in a 30-mg strength, allowing 24-h coverage with a once-daily dosage. In ADVANCE, Diamicron MR was used in the intensified glucose-lowering strategy and showed distinctive therapeutic benefits in terms of glycemic control, HbA1c reduction (down to 6.5%), and clinical end points, with a 21% reduction in diabetic nephropathy, a 7% reduction in total mortality, and a 12% reduction in cardiovascular mortality. Last but not least, these benefits were associated with an excellent safety profile with respect to risk of hypoglycemia and absence of weight gain. Importantly, these results were achieved using a specific, simple, and pragmatic algorithm, which led to the optimization of Diamicron MR dosage before the addition of other therapy. At the end of the study, most patients were on the maximum dosage of 120 mg (ie, 4 tablets) per day. Today, a new scored-tablet formulation of Diamicron MR is available, Diamicron MR 60 mg, ensuring improved efficacy through greater ease of use and better patient compliance. Moreover, Diamicron MR 60 mg compares favorably with other oral antidiabetic drugs, thanks to its specific antioxidant properties, giving Diamicron MR 60 mg a unique profile.

With the ever-growing pandemic of type 2 diabetes throughout the world, the burden of vascular complications is expected to rise inexorably. It is thus of the utmost importance to find therapeutic strategies that are able to stabilize, if not prevent, these types of debilitating complications. The last century was witness to staggering discoveries that completely revolutionized the clinical management of type 2 diabetes, beginning with the discovery of insulin in 1921, up to 2000, with the latest discoveries of new pharmacological targets. In parallel, the improvement in pathophysiological knowledge highlighting the role of inflammation and oxidative stress in the pathogenesis of type 2 diabetes, together with epidemiological studies, paved the way for and validated new therapeutic strategies that stress the need to treat patients as early as possible. The United Kingdom Prospective Diabetes Study (UKPDS) in newly diagnosed patients with type 2 diabetes was the first landmark trial to demonstrate the benefit of tight glycemic control in microvascular complications and, to a lesser extent, in a subgroup of 342 over-

Crowning four decades of evidence-based benefits and advances in diabetes: Diamicron MR 60 mg by S. Laroche, France
weight patients, in macrovascular complications.1,2 At the time, "proof of concept" was based on oral therapies, such as sulfonylureas (chlorpropamide and tolbutamide) and metformin, but also on the early use of insulin.

It was not until 2000 that a glycated hemoglobin (HbA1c) target was carefully evaluated in a series of large morbidity-mortality trials, Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation (ADVANCE)3 and Action to Control Cardiovascular Risk in Diabetes (ACCORD),4 whose results were released at the same time at the American Diabetes Association (ADA) congress in San Francisco in June 2008. The discrepancy in results regarding total and cardiovascular (CV) mortality led to numerous debates, which ended with the publication of the COllaborators on TRIals Of Lowering glucose (CONTROL) meta-analysis,5 a meta-analysis of the five megatrials on clinical outcomes advocating a "gentle" strategy like ADVANCE’s, with an individualized approach according to patient profile.

It is nowadays clear that apart from aiming to reach target HbA1c, the achievement of glycemic control is a far from simple matter. Care and consideration must be taken in choosing a therapeutic strategy with the best benefit-to-risk ratio, the greatest convenience for patients, and the best evidence for clinicians of both short- and long-term clinical benefits.

**From discovery to clinical research**

The story of the discoveries of oral antidiabetic drugs in the past is absolutely amazing, as many of them were not the result of a systematic, step-by-step approach, but rather often a matter of chance. This was indeed the case for the biguanides and sulfonamides, which were first developed as anti-infectious agents in the 1940s. In the 1950s, the first generation of another important class of antidiabetic agents, the sulfonylureas, which includes tolbutamide and chlorpropamide, was brought to market. Thanks to the promise shown by the first generation, the next generation of sulfonylureas, which includes glipizide, glibenclamide, glimepiride, and gliclazide (DiamicroN), was developed.

The modified-release formulation of DiamicroN (DiamicroN MR) was first launched as a 30 mg tablet in the year 2000. It had clear advantages in terms of pharmacokinetic and pharmacodynamic properties, improving bioavailability, enabling once-daily dosage (up to 120 mg per day), and providing less variability and better tolerability, especially with regard to hypoglycemia. Several advantages of this new formulation were subsequently demonstrated, notably regarding the safety profile by direct comparison with other second-generation sulfonylureas like glimepiride (GUIDE [GlUcose control In type 2 diabetes: Diamicro modified release versus glimEpiride] study),6 in which there were twice as few hypoglycemic episodes with Diamicro MR. In recent years, focus has shifted toward ever better performance with the search for a formulation that combines optimal efficacy and compliance.

Nevertheless, the best demonstration of efficacy still remains the gold standard “clinical outcomes” criteria, namely vascular complications, and this was the reason for the design of the ADVANCE study, the largest study ever performed in type 2 diabetes. ADVANCE started in 2000 and its results were disclosed in Diabetologia at the prestigious ADA congress in 2008.

**ADVANCE: the integration of evidence-based medicine into clinical management**

**Study design**

The ADVANCE study was an investigator-initiated international trial whose design can be found in previous publications.7 In summary, ADVANCE was a combined 2×2 factorial study comparing active BP lowering with Preterax (a fixed combination of perindopril/indapamide) versus placebo, and comparing intensive glucose control with Diamicro MR (gliclazide modified release) versus conventional treatment, on major vascular outcomes in diabetes. The trial was conducted in 215 centers and 20 countries. Patients eligible for recruitment were at least 55 years of age, and had a history of microvascular and macrovascular disease or at least one CV risk factor. Patients were randomly assigned to either standard blood pressure control or reinforced blood pressure control with Preterax and to either intensive glucose-lowering therapy with an HbA1c target of 6.5% or lower, or standard glucose control. The principal treatment in the intensive glucose-lowering regimen was Diamicro MR (30 to 120 mg daily, ie, 1 to 4 tablets daily). Patients in each study group were
followed up for a median of 5 years. The primary end points of ADVANCE were a composite of major macrovascular events (nonfatal stroke, nonfatal myocardial infarction, or CV death) and a composite of major microvascular events (new or worsening nephropathy or diabetic eye disease), considered together or separately. Moreover, the two treatment strategies were assessed separately as well as together (in those patients receiving both intensive regimens), so as to determine their joint effect.

**Results**

**Main results of the glucose-lowering arm**

Of the 12,877 patients from Europe, Canada, Asia, and Australia registered for the study, 11,140 were randomized. Hence, the ADVANCE population was highly representative of the population of patients with diabetes worldwide, and also highly representative of daily clinical practice, patients having a mean age of 66 years and having had diabetes for about 8 years. The two treatment groups had similar blood glucose parameters at baseline, including mean HbA1c (7.5%), and fasting plasma glucose (FPG) (8.5 mmol/L). In both groups, 32% of patients had a history of macrovascular disease and 10% had microvascular disease. CV risk factors, including mean blood pressure, serum cholesterol and triglycerides, body mass index, and cigarette smoking, were comparable in the two groups. At the end of follow-up, the mean HbA1c achieved was 6.5% in the intensive group and 7.3% in the conventional group. In the intensive blood glucose-lowering strategy based on Diamicron MR, the target of 6.5% was reached after 36 months and was maintained until the end of the study. At the end of the study, over 80% of the patients had achieved an HbA1c ≤7%, while 65% had reached an HbA1c target below 6.5%. In contrast, standard glucose lowering reduced mean HbA1c to 7.3% after 6 months and HbA1c remained stable thereafter (Figure 1). A new analysis presented at the International Diabetes Federation (IDF) 2009 in Montreal showed that the efficacy of Diamicron MR on HbA1c was remarkably consistent across a wide variety of subgroups, defined according to their characteristics at baseline, and in particular regardless of baseline HbA1c, body mass index (BMI), duration of disease or age, and also previous treatments and treatment regimen (P<0.0001) (Figures 2, Figures 3 and 4 page 66). The strongest predictor of reduction in HbA1c during follow-up was baseline HbA1c. It is also interesting to note that an increase in diabetes duration also independently correlated with a fall in HbA1c (patients with the longest diabetes duration having the most sustained efficacy on HbA1c) (Figure 3).

The intensive glucose-lowering strategy based on Diamicron MR achieved its primary end point, a significant 10% relative risk reduction (RRR) in the composite of macro- and microvascular complications, compared with standard control (18% versus 20%, respectively; P=0.01), and this effect appeared to be driven by a 14% decrease in microvascular events (9.4% versus 10.9%; P=0.01), and particularly by a
21% significant reduction in renal events (new or worsening nephropathy) \((P=0.006)\), together with a 30% decrease in macroalbuminuria \((P<0.001)\).²

New results presented at the European Association for the Study of Diabetes (EASD) 2010 congress showed that not only was Diamicron MR able to prevent progression to diabetic nephropathy, but that it was also able to regress macroalbuminuria and microalbuminuria to normoalbuminuria—the albuminuria of 62% of patients with baseline albuminuria in the intensively treated group regressed by at least one stage, with the majority achieving normoalbuminuria.⁹

Importantly, in contrast to the ACCORD results, where a significant 22% increase in total mortality was seen,⁴ there was not only no increase in total mortality in ADVANCE, but a 7% reduction (although this was not significant). The reduction in CV mortality (12% decrease, \(P=0.12\)) was even more pronounced. Lastly, it should be noted that the effects of study treatment on vascular outcomes were consistent across subgroups of age, sex, baseline blood pressure, baseline HbA₁c, previous vascular disease, or concomitant CV medications.

**Results from the interaction analysis**

The factorial design of ADVANCE also allowed the assessment of the interaction of the two active treatment strategies (Preterax and Diamicron MR) at the end of the follow-up period of the blood pressure-lowering arm of the study (4.3 years). The effects of the two treatments were independent and fully additive, amplifying the benefits of each treatment taken separately, with a significant 24% reduction in CV mortality, a 33% reduction in renal disease, and an 18% reduction in all-cause mortality.¹⁰ It is important to stress that the benefits in terms of diabetic nephropathy are relevant in light of the strong relationship between CV events and indices of renal impairment.¹¹

**Safety analysis**

In the intensive glucose control group, there was no weight gain, even in the obese. Severe hypoglycemia was quite uncommon, although more frequent than in the standard control group (Table I). Compared with ACCORD, there was 6 times less severe hypoglycemia even though median HbA₁c was identical (6.4%) and, furthermore, the 3.5 kg gain in ACCORD puts the weight neutrality observed in ADVANCE into perspective.⁸

**What did ADVANCE tell us?**

The intensive glucose control strategies used in ADVANCE and ACCORD differed substantially both regarding HbA₁c target and how this target was achieved.³⁴ In ADVANCE, opti-
mized titration of Diamicron MR up to the maximum dose was implemented before the addition of any other oral antidiabetic, which resulted in progressive rather than aggressive glucose control as seen in ACCORD. Even though the publication of several post hoc analyses of ACCORD tried to analyze the association between increased mortality, especially CV mortality, and multiple parameters, such as severe hypoglycemia and HbA1c, at baseline and during follow-up, it is clear today that the treatment strategy in ADVANCE appears to be safe, whereas we still don’t understand the exact underlying cause of excess mortality in ACCORD.

Shortly after the publications of the ADVANCE and ACCORD results, a series of meta-analyses were undertaken to assess and to give a broader perspective of the effect of intensive glucose lowering on macrovascular outcomes by combining the data of several large morbidity-mortality trials (UKPDS, ADVANCE, ACCORD, the Veterans Affairs Diabetes Trial [VADT], and the PROspective pioglitAzone Clinical Trial In macroVascular Events [PROACTIVE] study). By far, the most interesting of these meta-analyses is the CONTROL meta-analysis, as it was performed in collaboration with the investigators of each megatrial and analyzed with source data. CONTROL found very consistent results in terms of CV event risk reduction (10% decrease), in particular a decrease in nonfatal myocardial infarction (17% reduction) with no significant effect on stroke or total mortality, although there was heterogeneity between the different trials both in terms of populations studied and therapeutic strategies. A favorable decreasing trend in terms of CV event mortality and morbidity and the best efficacy-to-benefit ratio was found in ADVANCE.

In addition to randomized clinical trials (RCTs) like ADVANCE and ACCORD, observational studies are of interest as they provide physicians with a picture of daily practice and are also an important source of additional information when their results are viewed in the context of large RCTs. Several national studies have been published showing a reduction in the risk of vascular complications and death in different subsets of patients, with a trend toward a superior beneficial effect with Diamicron MR.

Recent retrospective studies with very large cohorts found very consistent findings with ADVANCE, when comparing Diamicron MR with other sulfonylureas (glibenclamide and glimepiride). In particular, one nationwide study in more than 70,000 patients with type 2 diabetes that compared different glucose-lowering therapeutic strategies on the risk of overall and CV mortality. The results are particularly interesting as they show that in patients treated solely with Diamicron MR, there was a significant 67% risk reduction in total mortality and a 71% risk reduction in CV mortality, in comparison with glibenclamide. Another national registry, from Denmark, was presented during the last European Society of Cardiology (ESC) congress in Barcelona in 2009. It included more than 8000 Danish type 2 diabetics with a past history of myocardial infarction. All the patients included were treated with oral antidiabetic drugs in monotherapy. Of the oral antidiabetic drugs, Diamicron MR was the only sulfonylurea with a positive trend toward reduction in total mortality, whereas glimepiride and glibenclamide were associated with a significant increase in mortality.

**What next with ADVANCE?**

**ADVANCE-ON**

Even though no significant difference in reduction in macrovascular events and mortality could be observed between the intensive and standard blood glucose-lowering treatment groups, a reduction in microvascular events in the intensive blood glucose-lowering group taking Diamicron MR became obvious from the 5th year of treatment onward. The patients in ADVANCE may require much longer follow-up to demonstrate clear benefits in CV outcomes, given that the UKPDS long-term follow-up took 16 to 20 years to demonstrate a clearcut significant difference in death and myocardial infarction.

Moreover, it is important to consider the lower-than-anticipated rate of events in ADVANCE (less than 3% per year) resulting from the improvement in the multifactorial management of patients with diabetes. This was associated with the lower than anticipated difference in HbA1c between the intensive and conventional glucose-lowering arms, which may have further limited the possibility of demonstrating a significant effect on macrovascular events. The long-term follow-up of ADVANCE (ADVANCE-ON) has been designed to observe the posttrial effect of intensive glucose lowering with Diamicron MR over a 5-year period, in ADVANCE patients worldwide. The two primary outcomes are death from any cause and major CV events. The expected results should confirm the beneficial effects of an intensive glucose-lowering strategy in the long term.

**ADVANCE risk engine**

Providing tools to help clinicians achieve optimal management of their patients with diabetes is fundamental. In the past, the development of risk engines for CV risk estimation were based on two important trials: Framingham (CV risk in patients with an impaired lipid profile) and UKPDS (newly diagnosed diabetic patients). However, clinical management of type 2 diabetes has profoundly changed over the last few decades, owing to results of landmark studies (UKPDS, Steno 2) that shed light on the importance of multifactorial treatment that targets all CV risk factors. As a result, the UKPDS and Framingham risk engines are no longer adequate for the modern management of type 2 diabetes.

Accordingly, a new risk engine has been developed, the ADVANCE risk engine, based on the large and contemporary ADVANCE cohort of patients with type 2 diabetes receiving appropriate therapeutic strategies for optimal clinical man-
When the ADVANCE mathematical model is applied to the Framingham and UKPDS cohorts, the predictive risk of CV events was found to be overestimated, showing the real need for a new tool to adequately predict risk in the modern clinical management of patients with type 2 diabetes. It is anticipated that this new model will provide a reliable and valuable tool for alleviating the ever growing burden of CV complications in diabetes.

What makes Diamicron MR 60 mg different from other drugs?

- **Unique structure and formulation**
  Patient compliance is of the utmost importance in the clinical management of diabetes. The once-daily formulation of Diamicron MR was one of the reasons justifying its choice in ADVANCE. Diamicron MR is the first oral hypoglycemic agent with an innovative formulation based on a hypromellose-based polymer that expands in the gastrointestinal tract to form a gel that progressively releases gliclazide over 24 hours, enabling once-daily administration before breakfast (a factor in improved patient compliance). The release of Diamicron MR 60 mg matches a circadian profile.

At the end of follow-up in ADVANCE, 70% of patients in the intensive glucose-lowering group were receiving the maximal, optimized dose of Diamicron MR of 120 mg/day, ie, 4 tablets daily, thanks to the progressive and constant titration used in the study (Figure 5).

In accordance with the ADVANCE results, a new formulation was developed: Diamicron MR 60 mg. Diamicron MR 60 mg is the first ever scored modified-release tablet in diabetology. The formulation boasts a unique hydrophilic modified-release matrix. This innovative matrix stores gliclazide inside millions of microunits, allowing the tablet to be scored. This in turn enables the number of tablets to be taken daily to be halved, for both better compliance and better flexibility. This new formulation has been available internationally since 2009.

- **Unique insulin secretion profile**
  Several studies using a variety of methods have convincingly demonstrated that the loss of the first phase of insulin secretion is one of the earliest demonstrable abnormalities in type 2 diabetes. Restoring this early peak results in improved postprandial glucose control and lower second-phase postprandial insulin levels. Diamicron MR’s pharmacokinetic profile favors this restoration and improves β-cell function, restoring glucose-stimulated insulin secretion to a near-normal profile, ie, enhancing the first peak of insulin secretion and normalizing the late secretion phase. This has been confirmed by clamp experiments in type 2 diabetic patients as well as in isolated perfused pancreas.

The molecular mechanism of action of sulfonylureas has been progressively uncovered over the last two decades. Studies with cloned pancreatic-type sulfonylurea receptors have enabled the precise characterization of the receptor interaction profiles of the different sulfonylurea receptor isoforms in smooth muscle cells. Diamicron binds with high affinity and high selectivity to the SUR-1 receptor and demonstrates rapidly reversible binding, in contrast to the virtually irreversible binding of glibenclamide and glimepiride under the same conditions.

- **β-Cell specificity and antioxidant properties**
  There is growing evidence that β-cell dysfunction is crucial for the development and the progression of type 2 diabetes. Both quantitative and qualitative defects have been reported in the progression of the disease, raising new demands on therapeutic approaches focused on the long-term maintenance of β-cell mass and function.

Thus, the characteristics of the insulin secretion profile induced by Diamicron MR, which are close to those of the physiological profile, provide certain explanations for the lower hypoglycemia risk and weight neutrality reported in ADVANCE.
of pancreatic cell lines clearly demonstrate specific protection with HbA1c management of type 2 diabetes. In ADVANCE, the target of sustained glycemic control is a very important goal in the future. With regard to the sulfonylurea group, which characterizes its chemical structure, thanks to the aminoazabicyclo-octyl ring grafted onto the sulfonylurea group, which characterizes its chemical structure. With regard to the β-cell, in vitro experiments on human pancreatic cell lines clearly demonstrate specific protection of β-cell mass and function compared with glibenclamide and gliclazide, under hyperglycemic conditions.34-36 In the last publication by Del Guerra et al,35 isolated human islet cells exposed to intermittent high glucose concentrations demonstrated decreased responsiveness to acute glucose challenge as well as deleterious effects on β-cell mass. In this experiment, gliclazide, but not glibenclamide, increased Pdx-1 (pancreatic and duodenal homeobox 1) and Ki-67 expression, markers of β-cell differentiation and regeneration both at a gene and protein level, in addition to significantly increasing insulin release. This finding confirms and extends previous results on the prevention of β-cell apoptosis under the same experimental conditions.34

Sustained glycemic control is a very important goal in the management of type 2 diabetes. In ADVANCE, the target of HbA1c ≤6.5% was achieved with intensive Diamicron MR-based therapy, and this effect was obtained progressively over 36 months and remained stable thereafter, delaying the use of insulin by up to 44 months after randomization.37 This has also been documented in previous studies comparing Diamicron with other sulfonylureas, including one with glibenclamide.38 This study investigated the time interval before the initiation of insulin therapy, and found a significantly longer interval before the initiation of insulin with Diamicron (mean 14.5 years) than with glibenclamide (mean 8 years), along with better blood glucose control, as shown by HbA1c values (6.8% vs 7.4%, respectively; P<0.0001). These benefits might be explained by the direct protective effect of Diamicron MR on pancreatic β-cell function.

Last but not least, the beneficial effect of Diamicron MR shown in ADVANCE regarding micro- and macrovascular end points may be partially explained by the free radical-scavenging properties of Diamicron MR. In a previous study, Diamicron MR was shown to have beneficial effects on the progression of atherosclerosis, which was assessed by the measurement of the average carotid intima-media thickness. The outcome with Diamicron MR was better than that with glibenclamide in patients with type 2 diabetes.39 The antiatherogenic effect of Diamicron MR could be due to its antioxidant properties, which restore endothelial function, reduce platelet reactivity, and exert an anti-inflammatory effect.40-45

From international guidelines to daily practice

The past two years have seen an incredible amount of data come from megatrials such as ADVANCE and ACCORD, and it has taken time to take on board the new lessons arising from these apparently discrepant results. Now the “hot debate” phase is over, it is the time for implementation, and the new guidelines from the ADA, EASD, and IDF will undoubtedly help clinicians to realize these lessons in their daily clinical practice.

The ADVANCE intensive glucose-lowering strategy based on Diamicron MR proved to be the most pragmatic and most practical, as well as being the strategy with the best benefit-to-risk ratio, for ensuring efficient and long-term sustained lowering of HbA1c down to 6.5% in a representative population of patients with type 2 diabetes. Not only was glycemic control achieved, but Diamicron MR–based therapy was also proven to protect patients from vascular complications, especially nephropathy (with a 21% decrease), and even to regress albuminuria to normoalbuminuria (in 62% of patients with albuminuria at baseline).

New guidelines are now focusing on the need to tailor clinical management to the different phenotypes in the wide and heterogeneous population of patients with type 2 diabetes. Subgroup analysis in the ADVANCE population showed very consistent results with Diamicron MR, whatever the patient profile at baseline, together with an excellent safety profile.

Conclusion

Only a stepwise approach with a safe, proven, and effective strategy will enable the medical community to curb the growing diabetes pandemic worldwide. Diamicron MR 60 mg offers a unique solution with the best combination of efficacy, safety, and weight neutrality, while offering patients an innovative formulation to help compliance. This therapeutic strategy constitutes a key step in a multifactorial approach ensuring maximum benefit and safety for all type 2 diabetic patients. ■

References

Diamicron MR 60 mg


Keywords: diabetes; intensive glucose lowering; diabetic complications; vascular complications; nephropathy; treatment; clinical management; clinical trial; ADVANCE; gliclazide MR
DIAMICRON LM 60 : LE COURONNEMENT DE 40 ANS DE BÉNÉFICES DÉMONTRÉS ET D’AVANÇÉES DANS LE DIABÈTE

Les résultats de l’étude ADVANCE (Action in Diabetes and Vascular disease : PreterAx and Diamicron MR Controlled Evaluation) en juin 2008 ont souligné le rôle fondamental de Diamicron MR (gliclazide à libération modifiée [LM]) dans la prise en charge clinique du diabète de type 2. Ce médicament, disponible depuis 2000 sous forme de comprimés à 30 mg, permet une prise quotidienne couvrant les 24 h. Dans l’étude ADVANCE, Diamicron LM a été utilisé dans une stratégie intensive de réduction de la glycémie et a démontré de façon convaincante son bénéfice thérapeutique à la fois sur le contrôle glycémique, en abaissant l’HbA1c jusqu’à 6,5 % et sur des critères cliniques, en diminuant de 21 % la néphropathie diabétique, de 7 % la mortalité totale et de 12 % la mortalité cardio-vasculaire. Il faut en outre souligner que ces bénéfices s’associent à une excellente tolérance, tant en ce qui concerne le risque d’hypoglycémie que l’absence de prise de poids. Il est important de noter que ces résultats ont été obtenus en utilisant un algorithme spécifique, simple et pragmatique, permettant l’optimisation de la posologie de Diamicron LM avant d’y ajouter un autre traitement. À la fin de l’étude, la plupart des patients prenaient la dose maximale de 120 mg par jour, soit 4 comprimés par jour. Aujourd’hui, une nouvelle présentation sécable de Diamicron LM est disponible, Diamicron LM 60 mg, assurant ainsi une meilleure efficacité grâce à une meilleure commodité d’emploi et une meilleure observance. De plus, Diamicron LM 60 mg soutient favorablement la comparaison avec d’autres antidiabétiques oraux, au vu de ses propriétés antioxydantes particulières, conférant à Diamicron LM 60 mg un profil original.
Over the past 25 years, evidence-based medicine has entered the diabetes world, and we now have the results of a large number of clinical trials to help influence clinical practice as well as guideline recommendations. The 1993 publication of the main results of the DCCT [Diabetes Control and Complications Trial] proved convincingly for the first time that improved glycemic control could prevent the long-term microvascular complications of diabetes.

What are the most important breakthroughs of the last 25 years in the field of diabetes?

Interview with L. A. Leiter, Canada

Diabetes mellitus, the most rapidly evolving pathology in the world, is associated with staggering costs and burdens due to diabetic complications that lead to consequent morbidity and mortality. Fortunately, over the past twenty-five years, diabetes has been a field characterized by major breakthroughs in several areas, including its pathophysiology, diagnosis, prevention, and clinical management. Over this time period, we have also benefited from the results of a large number of well-conducted randomized clinical trials, which have provided important evidence of the optimal management of diabetes, both to help improve glycemic control as well as to prevent the potentially devastating long-term complications of diabetes. These trials have served to inform evidence-based diabetes clinical practice guidelines that have been introduced in most jurisdictions around the world. Finally, we have also had a large number of new therapies and technologies introduced, which have also helped to revolutionize the management of diabetes.

WHAT ARE THE MOST IMPORTANT BREAKTHROUGHS OF THE PAST 25 YEARS...

...in the field of diabetes pathophysiology?

First of all, over the past 25 years, the “glucose hypothesis” has finally been proven. Based on clinical trial evidence in both type 1 and type 2 diabetes (Diabetes Control and Complications Trial [DCCT]), United Kingdom Prospective Diabetes Study [UKPDS], Action in Diabetes and Vascular disease: PreterAx and DiamicroN MR Controlled Evaluation [ADVANCE], etc) on the value of glucose reduction in the prevention of the complications of diabetes, especially microvascular ones, there is no doubt that hyperglycemia plays a direct role in the pathophysiology of diabetic complications. At the same time, a number of putative mediators have been proposed, including increased levels of sorbitol and increased advanced glycation end products. Work from Michael Brownlee et al has resulted in a so-called “unifying hypothesis.” It has been shown that glucose-induced activation of protein kinase C isoforms, increased glucose flux through the aldose reductase pathway, and increased formation of glucose-derived advanced glycation end products all lead to increased reactive oxygen species. There has also been much interest in insulin resistance as a pathogenetic abnormality. There remains controversy with regard to the exact pathophysiology of metabolic syndrome and whether it, by
itself, imparts additional risk above and beyond that of its component risk factors. There is no doubt, however, that there is clustering of abnormalities in glucose intolerance, dyslipidemia, and hypertension and that these are commonly associated with increases in insulin resistance, increases in visceral fat, and a proinflammatory state. Meta-analyses have suggested that the presence of metabolic syndrome is associated with about a 1.5- to 2-fold increase in cardiovascular risk above and beyond that imparted by traditional risk factors. There is also a better understanding that increases in visceral fat may be associated with these various metabolic abnormalities, leading to increased risk for cardiovascular (CV) disease, although some recent data suggest that it might actually be increases in hepatic fat rather than visceral fat that are the key pathogenetic abnormality.

One of the many key contributions of UKPDS was the clear description of the progressive nature of type 2 diabetes as a result of progressive β-cell failure. It now appears that this is multifactorial in origin and results from glucose toxicity, lipotoxicity, deposition of amyloid, as well as other factors. There has also been increasing evidence on the importance of glucose toxicity in contributing to both β-cell failure as well as insulin resistance. The improvement in β-cell function and insulin resistance associated with the new sodium-dependent glucose cotransporter 2 (SGLT-2) inhibitors has helped to confirm this hypothesis in humans.

Over the past 25 years, we have also accrued a huge body of evidence on the role of the incretin system in the pathophysiology of not just type 2 diabetes, but perhaps also its complications. Patients with type 2 diabetes have decreased levels of the two major incretin hormones, glucagon-like peptide 1 (GLP-1) and gastric inhibitory poly-peptide (GIP), leading not just to decreased insulin secretion, but also increased levels of glucagon.

**...in the field of diabetes diagnosis and prevention?**

The criteria for diabetes and earlier states of glucose abnormalities have evolved. We now do not just have impaired glucose tolerance (IGT), reflective of a postprandial glucose abnormality, but also impaired fasting glucose (IFG), reflective of borderline high fasting glycemia. Although they have been collectively termed prediabetes, there has been opposition to this term, and thus alternate terms are being discussed. Nonetheless, there is no doubt that there is much greater awareness that glucose tolerance should not be considered a dichotomous variable and that intermediate states of glucose intolerance, or “dysglycemia,” can be associated with increased risk for cardiovascular disease as well as diabetes. This has led to a series of diabetes prevention studies. Evidence from three large randomized controlled trials, the Chinese Da Qing Study, the US Diabetes Prevention Program, and the Finnish Diabetes Prevention Study, have provided compelling evidence that intensive lifestyle intervention can prevent or delay the development of diabetes in individuals with IGT. In addition, we now have data that anti-hyperglycemic agents, including metformin, acarbose, rosiglitazone, and pioglitazone, can also reduce progression of IGT to diabetes mellitus. The most recent of the diabetes prevention trials, the Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study, was the first diabetes prevention trial to be designed and powered to find out whether the prevention of diabetes is also associated with a reduction in CV disease risk. Although valsartan exerted a modest 14% reduction in the development of new diabetes, neither valsartan nor nateglinide had any impact on CV events.

**...in the field of diabetes clinical management?**

The increased use of self-monitoring of blood glucose (SMBG) has allowed us to improve glycemc control while minimizing risk for hypoglycemia in our insulin-treated patients. At the same time, it has recently been questioned whether the use of SMBG actually improves glycemc control in non-insulin-treated patients. Many of these studi-
ies have not adequately assessed this question, as patients
were not necessarily provided with adequate information as to
what to do with the results of their testing. Nonetheless, these
studies have certainly raised awareness that the use of SMBG
by itself may not necessarily improve glycemic control. Rather,
it is a tool to provide information that can be utilized by a prop-
erly educated patient in collaboration with a diabetes health-
care team to improve glycemic control.

Another major advance has been the routine use of glycated
hemoglobin (HbA1c) to monitor glucose control in patients
with diabetes. There is no doubt that the routine use of this
test has revolutionized diabetes care in that it has provided
both clinicians and patients with a proper estimate of over-
all glycemic control.

...in the field of diabetes clinical trials?

Over the past 25 years, evidence-based medicine has
entered the diabetes world, and we now have the
results of a large number of clinical trials to help in-
fluence clinical practice as well as guideline recommenda-
tions. The 1993 publication of the main results of the DCCT
proved convincingly for the first time that improved glycemic
control could prevent the long-term microvascular complica-
tions of diabetes. In the original trial period, however, there
was no reduction in macrovascular events. With passive fol-
low-up of patients for an additional ten years, it becomes
evident that intensive insulin therapy was also associated with
a 42% reduced risk for the primary CV composite end point
and a 57% reduced risk for the typical major adverse clinical
event (MACE) composite of nonfatal myocardial infarction,
stroke, or CV death. This long-term influence of early good
glycemic control on clinical outcomes has been termed “meta-
bulic memory” or “glycemic legacy.” More recent results from
three large trials designed to look at the effects of intensive
glycemic control on the macrovascular complications of dia-
betes, the Action to Control CardioVascular Risk in Diabetes
(ACCORD), ADVANCE, and the Veterans Affairs Diabetes
Trial (VADT), confirmed the benefit of good glycemic control
on microvascular complications, but did not show significant
benefit in any of these studies individually on macrovascular
events. When the results of these studies were meta-anal-
alyzed, however, an overall 15% reduced risk of myocardial in-
farction was observed. Furthermore, these study results prob-
able minimized the potential benefits of improved glycemia
as the difference in HbA1c between the intensive and stand-
ard therapies was only about 1%. The results of the extend-
ed follow-up of UKPDS, which demonstrated a significant
reduction in risk for myocardial infarction and for total mortal-
ity that was not observed at the end of the initial intervention,
were not only consistent with glycemic legacy, but also demon-
strated that the reduction in CV events with improved glycemia
may take longer than that observed with reduction in low-den-
sity lipoprotein cholesterol (LDL-C) or blood pressure lower-
ing. Although an increase in mortality was observed in the
ACCORD study, which has led some individuals to back away
from striving for good glycemic control, the ADVANCE study,
guiding gliclazide-based therapy, did not have a similar increase
in mortality, despite the achievement of relatively similar HbA1c
levels. The most recent analyses from ACCORD would sug-
gest that the increased mortality was not, as initially suggest-
ed by some observers, a result of HbA1c targets that were too
low, achieved too quickly, or a consequence of hypoglycemia,
but rather a result of “unsuccessful” intensive therapy.

...in the field of diabetes complications?

One of the major paradigm shifts in diabetes care over
the past 25 years has been a shift away from the
“glucocentric” approach to the prevention of diabetes
complications. The dramatic benefit of lipid lowering with statins
to reduce macrovascular risk has been demonstrated in pa-
tients without known coronary artery disease (CAD), in studies
like the Collaborative AtoRvastatin Diabetes Study (CARDS),
and in those with known CAD, in studies like the Treating to
New Targets (TNT) study. Nonetheless, there have been more,
recent attempts at further reducing the high residual risk ob-
served in diabetes by using combinations of lipid-lowering
drugs. In the ACCORD Lipid trial, no additional benefit was
observed with the routine addition of fenofibrate to simvas-
tatin in about 5500 patients with type 2 diabetes (although
there was potential benefit in the subgroup of patients with
high triglyceride and low high-density-lipoprotein cholesterol
[HDLC] levels). Studies investigating combinations of statins
with various other HDL-C–raising therapies, including niacin
and cholesteryl ester transfer protein inhibitors, are ongoing.

A large number of blood pressure–lowering trials, including
the Hypertension Optimal Treatment (HOT) trial and UKPDS,
have demonstrated the value of intensive blood pressure low-
ering in diabetes. Furthermore, in the ADVANCE trial, a
combination of perindopril and indapamide was associated with
a significant reduced risk of complications in a group of pa-
tients whose blood pressure averaged 135/77 mm Hg ver-
sus the standard treatment group, in whom the average blood
pressure was 140/77 mm Hg. In contrast, in the ACCORD
Blood Pressure trial, using a combination of various antihyper-
tensives, no additional overall benefit was observed when a
systolic blood pressure of 120 mm Hg versus 140 mm Hg was
aimed for, although a 41% reduced risk for stroke was ob-
served. The results with the angiotensin-converting enzyme
(ACE) inhibitors ramipril and perindopril in the Heart Outcomes
Prevention Evaluation (HOPE) and ADVANCE trials, respec-
tively, and with the angiotensin receptor blocker (ARB) telmis-
artan in the ONgoing Telmisartan Alone and in combination
with Ramipril Global Endpoint Trial (ONTARGET) study, have
also demonstrated the vascular protective benefits of these
drugs, even in patients with diabetes without hypertension.
The Steno 2 trial highlighted the importance of a multifactorial
approach to cardiovascular risk reduction with a 50%-60% reduced risk for both micro- and macrovascular complications over the initial 8 years of follow-up and a 46% reduced risk of mortality after an additional 5 years of follow-up.

The risk of kidney complications was also dramatically reduced. The glycemic control and blood pressure–lowering trials mentioned above were all associated with renal benefits as well. Furthermore, a large number of trials, employing primarily ACE inhibitors in type 1, and ARBs in type 2, diabetes, have shown reductions in proteinuria and progression of renal disease. Although the ONTARGET trial did not show a benefit in adding an ARB to an ACE inhibitor on renal or cardiovascular end points, the ongoing ALiskiren Trial In Type 2 diabetes Using carDio-renal Endpoints (ALTITUDE) will address the potential additional benefit of adding the direct renin inhibitor aliskiren to an ACE inhibitor or ARB on cardiorenal end points.

Finally, the treatment of diabetic retinopathy has also dramatically altered over the past 25 years. Both strict glycemic and blood pressure control have been shown to prevent the onset and progression of retinopathy. Laser photocoagulation has been demonstrated to benefit both severe nonproliferative and proliferative retinopathy as well as clinically significant macular edema, while surgical vitrectomy has been shown to result in better visual recovery in patients with advanced proliferative retinopathy. More recently, intraocular injections of pharmacologic interventions, including anti–vascular endothelial growth factor (anti-VEGF) agents and steroids, have also shown promise for the treatment of macular edema and retinal neovascularization.

...in the field of diabetes clinical management?

Multiple new medications have become available for the treatment of type 2 diabetes. While metformin and the sulfonylureas continue to be widely utilized, new classes of antihyperglycemic agents that have been launched over the past 25 years include alpha glucosidase inhibitors (acarbose), thiazolidinediones (rosiglitazone, pioglitazone), dipeptidyl peptidase 4 (DPP-4) inhibitors (sitagliptin, vildagliptin, saxagliptin), and GLP-1 analogues (exenatide, li- raglutide). There has also been a move towards early combination therapy of antihyperglycemic agents. The greater number of available medications has provided the clinician with more therapeutic choices and more opportunities to individualize therapy. At the same time, we are still lacking the clinical trials to guide us on how best to utilize these medications, in terms of which drugs to use and in what therapeutic order.

Another major advance has been the availability of newer insulin analogues. The rapidly acting analogues (aspart, lispro, glulisine) are associated with greater convenience for our patients as well as better postprandial control and reduced risk of hypoglycemia. Similarly, the long-acting insulin analogues (detemir, glargine) are also associated with a reduced risk for hypoglycemia as well as less day-to-day glycemic variability. Insulin pens have made it easier for our patients to use insulin.

There has been increasing use of insulin pumps, primarily in the treatment of type 1 diabetes, as well as of the somewhat-less-complex patch pumps. Pump therapy is associated with better glycemic control for patients with increased HbA1c levels, reduced frequency of hypoglycemia, less glycemic variability, and a general improvement in quality of life. The more recent availability of real-time continuous glucose monitors has further improved our ability to properly assess and minimize glycemic excursions. As a result, there is increasing optimism that the integration of continuous glucose monitors into insulin pumps will result in the availability of the long-awaited “closed-loop” insulin pump in the not too distant future.

A major change in the way that we have managed diabetes over the last 25 years has been the emergence of clinical practice guidelines. Guidelines from various organizations from around the world have suggested treatment targets, algorithms, and other treatment recommendations to help improve outcomes in patients with diabetes. Unfortunately, there remains ongoing evidence of a significant treatment gap, with many of our patients not reaching treatment targets. Renewed efforts at knowledge translation must be employed in order to get more patients to goal and subsequently improve clinical outcomes.

Keywords: diabetes mellitus; breakthroughs; pathophysiology; diagnosis; prevention; clinical management; clinical practice guidelines
Quels sont les avancées les plus importantes dans le domaine du diabète ces 25 dernières années ?

Le diabète, la pathologie évoluant le plus rapidement dans le monde, impose des coûts et des fardeaux exorbitants dus aux complications diabétiques responsables d’une morbidité et d’une mortalité importantes. Heureusement, ces 25 dernières années, le diabète a bénéficié d’avancées majeures dans plusieurs domaines, y compris sa physiopathologie, son diagnostic, sa prévention et sa prise en charge clinique. Au cours de cette période, les résultats de nombreuses études cliniques randomisées, bien conduites, ont confirmé qu’une prise en charge optimale du diabète améliore le contrôle glycémique et prévient les complications à long terme potentiellement dévastatrices du diabète. Ces études ont permis l’élaboration de recommandations pratiques cliniques sur le diabète, reprises par la plupart des instances mondiales. Enfin, l’apparition de nombreux nouveaux traitements et technologies a aussi permis de révolutionner la prise en charge du diabète.
The Mediterranean Group for the Study of Diabetes (MGSD) was set up in 1985, on the initiative of Professor Molinatti from Turin, Italy, as a specific center of excellence in diabetes, grouping together well-recognized experts from Mediterranean countries to meet the unrequited needs of all health professionals in the Mediterranean area involved in the delivery of diabetes care. The MGSD, a member of the International Diabetes Federation since 1995, is a nonprofit, nonpolitical association of diabetologists from Mediterranean countries. The specific aim of the MGSD is to act as a bridge between both sides of Mediterranean basin by promoting an exchange of information and knowledge on diabetes research and care delivery, with special emphasis on epidemiology, education, and clinical therapy. While the countries involved share a common geographical basin, they have very different ethnic origins, languages, and dietary habits, offering a unique opportunity for comparison in the field of diabetes worldwide. Since its establishment, the MGSD has grown and become an association that attracts the medical community in the field of diabetes from the north and south banks of the Mediterranean Basin. Within this domain, the MGSD facilitates the exchange of diabetic knowledge and expertise in scientific research, in practical aspects of patient care, and in patient education.

Medicographia. 2011;33:77-82 (see French abstract on page 82)

The role of scientific societies in the sharing of expertise

The Mediterranean Group for the Study of Diabetes (MGSD) and the study on gestational diabetes in the Mediterranean region

by M. Marre, France

In the Mediterranean Basin, epidemiologic evidence shows increases in both the incidence of diabetes and its complications. Thus, the disease, especially type 2 diabetes mellitus (T2DM), is evolving as a major health problem in this area. The prevalence of T2DM varies widely, while that of type 1 diabetes mellitus varies from 0.01% to 0.85% in the various countries. There appears to be a relationship between T2DM prevalence and population density of the country and degree of urbanization.

The organization of specific scientific societies throughout the world into local networks of expertise is a very important development for multidisciplinary research groups, maintaining connections among specialists and promoting the sharing of experience and funding resources. Diabetes is no longer an epidemic that can be ignored: the disease is a widespread problem, increasing rapidly in every part of the world. We must unite to prevent diabetes, to improve diabetes care for the millions affected, and, ultimately, to find cost-effective ways of tackling one of the largest health problems we now face. The Mediterranean Group for the Study of Diabetes (MGSD) was set up to bring the medical community face to face with these issues and challenges.

Epidemiology of diabetes in the Mediterranean Basin

The Mediterranean area represents a unique regional example of interplay between varying ethnic and socio-economic groups. The region can be regarded as a single unit with a large number of common ethnic and cultural features, but it is heterogeneous in terms of socio-economic and demographic factors. Thus, most of
the Northern Mediterranean countries (European coast) share the features of other industrialized countries, while most of the Southern Mediterranean (African coast) belongs to the developing world. The Mediterranean islands and Eastern Mediterranean countries (Asian coast) share a mixture of these features. In the Mediterranean Basin, epidemiologic evidence shows increases in both the incidence of diabetes and its complications. Thus, the disease, especially type 2 diabetes mellitus (T2DM), is evolving as a major health problem in this area. The prevalence of T2DM varies widely, while that of type 1 diabetes mellitus varies from 0.01% to 0.85% in the various countries. There appears to be a relationship between T2DM prevalence and population density of the country and degree of urbanization.1

Type 1 diabetes

In the Mediterranean and neighboring areas, the incidence rates of type 1 diabetes in children under the age of 15 years show wide variations. In Italy, the incidence of type 1 diabetes in children aged 0-14 years is 6-11.7 (per 100 000 per year), while in Sardinia the incidence is 34.4, one of the highest in Europe.2 In general, the highest incidence is among subjects aged 10-14 years and the lowest in children aged 0-5 years, for both genders. However, an earlier peak incidence in children aged 5-9 years is a common feature of insular Italian areas, but not of Northern Italy. In France, Levy-Marchal showed that the annual diabetes incidence rates for 1988 and 1995 were 7.17 and 9.28 per 100 000, respectively; this study included 2 million subjects under 20 years of age.3 Similar results have been reported in Spain (8-10.9 per 100 000 per year), and in Croatia and Slovenia (7.2 and 7.6 per 100 000 per year, respectively).4 The incidence in the Mediterranean countries is different from the incidence in Northern Europe; indeed, in Finland, Tuomilehto et al reported that for children under 14 years, the annual incidence rate in 2000 was 45 per 100 000.4 In contrast with other European countries, the incidence of the disease in the Mediterranean area does not follow any geographical pattern. Probably differences in environmental factors (diet, toxins, and viral infections), genetic susceptibility, or both are important for such a wide variation. As in other areas of the world, variation in incidence appears to be related to ethnicity, demonstrating the importance of the differential genetic susceptibility in different populations. Indeed Sardinians, who together with Finns have the highest incidence of type 1 diabetes in the world, have a high frequency of HLA haplotypes implicated in type 1 diabetes susceptibility and paucity of protective alleles when compared with other white populations.1 Moreover, the interactions between different genes and environmental factors may be important, as suggested by some studies performed in Israel. In contrast, studies in Sardinian migrants showed that the high incidence of type 1 diabetes is more a consequence of their genetic background than of environmental influences.5 This does not mean that environmental factors are not relevant in the etiology of type 1 diabetes, but rather that environmental triggers may have a major impact on genetically predisposed subjects. Worldwide a female excess is found in low-incidence populations, while the reverse is true in several high-incidence populations. In the Mediterranean countries, the male to female ratio is close to 1:1.

Type 2 diabetes

T2DM is the major component of the worldwide diabetes epidemic. King et al6 reported that the prevalence of diabetes in adults aged 20 years and over was 7.5% in 1995, 7.8% in 2000, and will be 10% in 2025, in Italy. In Spain, a similar thing is happening; the prevalence of diabetes will rise from 7.2% in 1995 to 9.5% in 2025. In contrast, the same authors reported that in France and Croatia, there will only be a mod-
erate increase in the prevalence of diabetes in the adult population: from 2.1% in 1995 and 2000 to 2.6% in 2025 in France, and from 4.4% to 5.1% in Croatia. In these countries, as in all the developed world, the majority of people with diabetes are aged 65 years. Moreover, several studies have found significantly higher prevalence rates in urban environments than in rural ones, within the same country. Comparisons of migrant populations living in rural and urban settings in the same country also show an excess of diabetes in urban communities. This aspect is actually not only very interesting, but highly relevant since we are witnessing an important migratory flow from developing countries to Europe. Since both the prevalence of T2DM and the mean age of patients are increasing in most European countries, there has been a consequent increase in the prevalence of cardiovascular and microvascular complications. Recent intervention trials have shown that improved glycemic control and aggressive treatment of hypertension can reduce the risk of macrovascular and microvascular complications.

The Mediterranean Diet

The relation between health and the Mediterranean Diet, defined as the “food pattern typical of some Mediterranean regions in the early 1960s, such as Crete, parts of the rest of Greece, and Southern Italy,” was initially evaluated cross-sectionally in the Seven Countries Study, where the morbidity from coronary heart disease was significantly less in Crete and Greece compared with Finland and the USA, and this was attributed to the dietary pattern and the resulting low serum levels of cholesterol and triglycerides.

A finger prick test. Recent intervention trials have shown that improved glycemic control and aggressive treatment of hypertension can reduce the risk of macrovascular and microvascular complications.
The follow-up of the various cohorts of the Seven Countries Study showed a relationship between mortality and various dietary parameters of the baseline examination. This relation has been further investigated in various epidemiological studies. In a population-based prospective study with 22,043 adult participants in Greece with a median follow-up of 44 months, better adherence to the Mediterranean Diet pattern (judged by a 2 unit increment in a scoring system on a 10-point scale) was associated with a reduction in overall mortality (hazard ratio [HR], 0.75). The reduction in mortality was also evident for both death due to coronary heart disease (adjusted HR, 0.67) and death due to cancer (adjusted HR, 0.76). Again, no associations between mortality and individual components of the Mediterranean Diet Score were documented, suggesting that the combination of components rather than a particular component is important for the reduction of mortality.

The effects of various important dietary components in the Mediterranean Diet in mortality in diabetic patients have not been extensively investigated. In a recent publication, the 10-year all-cause mortality of 1000 diabetic patients was related independently to saturated fat and egg consumption. There is no association between egg intake and mortality in the nondiabetic population, as has been shown in a special analysis of the above-mentioned Health Professionals Follow-up Study (HPFS). However, an association was found in this study in diabetic men, but not diabetic women. The effects of the Mediterranean Diet in diabetics warrant further research.

The beneficial effects on health of the Mediterranean Diet have been tested in various intervention studies. It is difficult to conduct such studies since the complexity of dietary modifications makes it impossible to develop a double-blind intervention to analyze its effect on health.

The Mediterranean Group for the Study of Diabetes – MGSD

Two other considerations also inspired the founders of the MGSD: (i) the underrepresentation of the Mediterranean Basin in the major international diabetology associations, whether on a research or clinical basis; and (ii) linguistic specificity, French still being a lingua franca for many of the region’s specialists. So, the official languages of the association are English and French.

The missions of the MGSD have been defined in its constitutional text (12th July, 1985) as attempting to respond to the need for information and training in diabetology on both sides of the Mediterranean. The ultimate aim is that of ensuring equitable and optimal standards of diabetes care. The association is nonpolitical and runs on a nonprofit basis.

The aims of the MGSD

1. To promote, through congresses held every two years and by other suitable means, information and studies in the field of assistance to diabetic patients, with particular regard to self-management, prevention of complications, and social and legislative problems.
2. To coordinate and standardize research in the epidemiology of diabetes in Mediterranean countries.
3. To promote studies regarding patient education, upgrading these according to the needs of each country.

The MGSD in action

- Communication

The main MGSD meeting, held every 2 years, provides an excellent forum for the discussion of original papers relating to specific issues in diabetes by means of either oral or poster presentations. Members mingle, meet, and talk, applaud the winners of the Hippocrates and Averroes prizes awarded for the two best abstracts, and conduct MGSD official business, the election of the board and the appointment of the president.

The last meeting, following those held in Rome, Athens, Nice, Madrid, Tunis, Rome, Marrakech, Lisbon, Nice, and Istanbul, was held in Malta in April 2009. Our next congress will take place in Gammarth in Tunisia from April 28 to May 1, 2011.

To round off these activities, the MGSD also boasts an information and communication organ, me.di@.news, which was initially available in paper form only, but which became digital in November 2002. A Web presence is obviously a mark of modernity, but also, and above all, it is a rapid and reliable method of communicating with the entire MGSD membership: in addition to me.di@.news, the MGSD offers
abstracts, full-text articles, and slide presentations on specific topics on its Web site www.mgsd.org. The MGSD has also produced the Diabetes Pocket Manual. This was first published in 2000, and later updated in 2003. A new version will be published in 2011.

◆ Training
As years went by and experience was gained, it appeared to successive presidents that the Group’s main mission was to provide quality information to health professionals in charge of diabetic patients and training to the youngest doctors in this field. Thus, in addition to the 2-yearly conference, fellowships are also offered to assist the organization of postgraduate courses within teams of international repute.

Although this was sufficient justification in itself for setting up the MGSD, the founders felt duty bound to develop their aims and working practices along similarly original lines. It soon became apparent that on top of conventional meetings that bring health professionals together and keep them abreast of the latest key developments in the specialty, there was little point, given the absence of adequate training and resources, in trying to set up topic-based study groups (eg, on the Mediterranean Diet, diabetes and migration) to produce clinical or epidemiologic studies.

For this reason, and thanks to the unflagging commitment of its successive presidents—Profs Molinatti (Italy), Alivisatos (Greece), Serrano Rios (Spain), Crepaldi (Italy), Drouin (France), Kadiri (Morocco), Charbonnel (France), and Duran-Garcia (Spain)—the MGSD sought to establish training programs empowering those entering the specialty with the requisite technical skills to conduct wide-ranging national studies.

◆ Research
The relative high prevalence of T2DM should be reflected in a similarly elevated prevalence of gestational diabetes mellitus (GDM), since pregnancy uncovers any underlying insulin resistance. Maltese population data serve to illustrate this observation. The Maltese population has repeatedly been shown to have a marked increased prevalence of insulin resistance, which exhibits itself via an overall higher prevalence of diabetes mellitus and impaired glucose tolerance (IGT), mainly of the non-insulin-dependent variety. This higher prevalence of insulin resistance is reflected by a relatively high prevalence of GDM. Epidemiological studies have shown that the prevalence of GDM in the pregnant Maltese population is approximately 5.9%. There is a further 0.3% of the population who suffer from a preexisting form of diabetes. The nonpregnant Maltese population in the reproductive age group has been shown to have an overall diabetes mellitus/impaired glucose tolerance prevalence of 2.2%, which contrasts significantly with the overall 6.2% figure reported for the pregnant population.

The MGSD has initiated an original study, “Gestational diabetes in the Mediterranean region: prevalence, risk population, pregnancy outcome, and nutritional contributors,” with the following objectives:

◆ Primary objectives:
- to serve as a pilot study assessing the prevalence of GDM in the Mediterranean region.
- to identify the biological profile and risk factors of pregnant Mediterranean women with GDM

◆ Secondary objectives:
- to relate the obstetric outcome to the carbohydrate metabolic profile.
- to investigate the rate of reversal of GDM to normal
- to assess the influence of nutritional dietary practices on the development of GDM in Mediterranean women.

This study involves more than 10 countries. Results are due in 2011 and should lead to a number of international communications and publications.

All in all, with some 525 members on its books and backed by a committed board and chairman, the MGSD, which has been a member of the International Diabetes Federation since 1995, has more than fulfilled its founders’ purpose in focusing on specifically Mediterranean issues in diabetes and the delivery of diabetes care. For its part too, Servier has been committed to providing financial and logistic support to the project since its inception. Each MGSD member is invited to inject his or her own input into supporting, expanding, and advertising the activities of not just “another” group, but a group which was set up to cater for the specific needs of a region, one most members call “home.”

The Mediterranean Group for the Study of Diabetes has initiated an original study, “Gestational diabetes in the Mediterranean region: prevalence, risk population, pregnancy outcome, and nutritional contributors,” which involves more than 10 Mediterranean countries. The results, which are due in 2011, will appear in a number of international publications.
RÔLE DES SOCIÉTÉS SCIENTIFIQUES DANS LE PARTAGE DE L’EXPERTISE : LE MGSD (MEDITERRANEAN GROUP FOR THE STUDY OF DIABETES) ET L’ÉTUDE SUR LE DIABÈTE GESTATIONNEL DANS LA RÉGION MÉDITERRANÉENNE


Keywords: Mediterranean Group for the Study of Diabetes; International Diabetes Federation; patient care; patient education; diabetes research; epidemiology; clinical therapy

References
Type 2 diabetes (T2D) is among the most striking examples of the challenges that medicine will face over the coming decade. First, as a highly multigenic disease in which medical research has failed to identify a unique abnormality behind causative β-cell defects, designing efficient therapies will require original strategies that are much more complex by far than the classic identification of a cause and its pharmacologic targeting for a definitive cure. Second, the worldwide epidemic of T2D and geographical variations in its incidence cannot be explained on a genetic basis. What will need to be understood is the interaction between a complex genetic background and environmental factors that have dramatically changed over the last sixty years. We still lack relevant animal models for T2D, and these are crucial for designing new therapeutic strategies to overcome the disease process. We need to delineate the true part of chronic inflammation, as it could pave the way for a new window for therapeutic prevention of the disease. We are all waiting for techniques to quantify β-cell mass in vivo to better understand the natural history of the disease and to open the way for drugs that will restore physiological β-cell mass. Although a defect in β-cell function has now been unequivocally identified as the central cause of T2D development, currently available therapies that restore early β-cell defects, namely the loss of the first-phase insulin response, only do so on a short-term basis. This may be the most complex challenge we have in front of us.

Medicographia. 2011;33:83-89 (see French abstract on page 89)
first- and second-phase response are characteristic of type 2 diabetes. The IGIS symposia, as major T2D publications have also done, have put β-cell dysfunction and the islet of Langerhans back under the scope in T2D pathophysiology. Indeed, the 1980s and 1990s were times when T2D was regarded as purely a disease of insulin resistance. A striking change has been brought about in the past decade; even the staunchest proponents of insulin resistance agree that T2D does not develop unless β cells fail. More importantly, many leading research groups that in the past exclusively worked on insulin action are now including β cells and the islets of Langerhans in the picture.

**Genetic background of type 2 diabetes**

The completion of the human genome sequence in 2001 is a landmark accomplishment in genomics and genetics. Set as a major goal in the late 1980s, it discovered an unprecedented amount of biological information, opening the way for new research strategies, new understanding of diseases, and “breakthrough” technological developments. Moreover, the availability in 2010 of genome sequences from different individuals is paving the way in the molecular understanding of human diversity, a key feature of survival in all species, but also of disease susceptibility. Identification of well over 100 single nucleotide polymorphisms (SNPs), differing by single base changes that span the whole genome, is providing us with a unique set of genetic tools. Variations in the genome underlie phenotypic variations in monogenic diseases as well as susceptibility to or protection from a vast array of complex polygenic disorders. High throughput techniques now allow the routine assessment of up to 500,000 SNPs in large populations.

Genome-wide association studies have confirmed the involvement of T2D susceptibility genes that have previously been identified using the candidate gene approach. They have also come up with a set of new gene variants, most of which impact on β-cell function. The risk attached to each individual gene is low. It is multigene association that drives genetic risk. The gene variant with the highest relative risk (~1.4-1.5, i.e., a 40%-50% risk increase) in T2D is transcription factor 7-like 2 (TCF7L2). Although initially an unexpected finding, TCF7L2 has now been implicated in key functions that control insulin secretion and glucose metabolism. It controls the secretion of incretins, in particular glucagon-like peptide 1 (GLP-1). Insulin secretion in subjects with the at-risk genotype is reduced in response to IV glucose and arginine, and not only oral glucose, suggesting a direct role on β cells.

Unequivocal evidence for common variants involved in T2D targets. The gene variant with the highest relative risk (~1.4-1.5, i.e., a 40%-50% risk increase) in T2D is transcription factor 7-like 2 (TCF7L2). Although initially an unexpected finding, TCF7L2 has now been implicated in key functions that control insulin secretion and glucose metabolism. It controls the secretion of incretins, in particular glucagon-like peptide 1 (GLP-1). Insulin secretion in subjects with the at-risk genotype is reduced in response to IV glucose and arginine, and not only oral glucose, suggesting a direct role on β cells.

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### Table I. List of IGIS (International Group on Insulin Secretion) symposia in the last decade.

6. Type 1 and type 2 diabetes: less apart than apparent? Diabetes. 2005;54(suppl 2).
8. Animal models of islet dysfunction. Diabetes Obes Metab. 2007;9(suppl 2).

### Selected abbreviations and acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI</td>
<td>body mass index</td>
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<tr>
<td>ER</td>
<td>endoplasmic reticulum</td>
</tr>
<tr>
<td>GLUT-1</td>
<td>glucose transporter 1</td>
</tr>
<tr>
<td>IGIS</td>
<td>International Group on Insulin Secretion</td>
</tr>
<tr>
<td>IRS-1</td>
<td>insulin receptor substrate 1</td>
</tr>
<tr>
<td>mtDNA</td>
<td>mitochondrial deoxyribonucleic acid</td>
</tr>
<tr>
<td>PPARG</td>
<td>peroxisome proliferator-activated receptor gamma [gene]</td>
</tr>
<tr>
<td>ROS</td>
<td>reactive oxygen species</td>
</tr>
<tr>
<td>SNP</td>
<td>single nucleotide polymorphism</td>
</tr>
<tr>
<td>T2D</td>
<td>type 2 diabetes</td>
</tr>
<tr>
<td>TCF7L2</td>
<td>transcription factor 7–like 2 [gene]</td>
</tr>
<tr>
<td>TLR</td>
<td>Toll-like receptor</td>
</tr>
<tr>
<td>UCP-2</td>
<td>mitochondrial uncoupling protein 2</td>
</tr>
</tbody>
</table>

**IGIS after a decade of β-cell research: where do we stand today? — Boitard**
Table II. Genes/loci for which variants have been consistently associated with type 2 diabetes. Genes 1-17 are loci associated with type 2 diabetes, while genes 18-26 are loci associated with type 2 diabetes and fasted blood glucose.

<table>
<thead>
<tr>
<th>Gene</th>
<th>Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 ADAMTS9</td>
<td>ADAM metalloproteinase with thrombospondin type 1 motif, 9</td>
</tr>
<tr>
<td>2 CDC123-CAMK1D</td>
<td>Cell division cycle 123 homolog (S. cerevisiae) and calcium/calmodulin-dependent protein kinase 1D</td>
</tr>
<tr>
<td>3 CDKAL1</td>
<td>CDK5 regulatory subunit associated protein 1-β like 1</td>
</tr>
<tr>
<td>4 HNF-1β</td>
<td>Hepatocyte nuclear factor 1β</td>
</tr>
<tr>
<td>5 CDKN2A/2B</td>
<td>Cyclin-dependent kinase inhibitor 2A and 2B</td>
</tr>
<tr>
<td>6 IRS1</td>
<td>Insulin receptor substrate 1</td>
</tr>
<tr>
<td>7 KCNJ11</td>
<td>Potassium inwardly rectifying channel subfamily J, member 11</td>
</tr>
<tr>
<td>8 FTO</td>
<td>Fat mass and obesity associated</td>
</tr>
<tr>
<td>9 HHFEX</td>
<td>Hematopoietically expressed homeobox</td>
</tr>
<tr>
<td>10 IGF2BP2</td>
<td>IGF-2 mRNA binding protein 2</td>
</tr>
<tr>
<td>11 JAZF1</td>
<td>Juxtaposed with another zinc finger gene 1</td>
</tr>
<tr>
<td>12 KCNQ1</td>
<td>Potassium voltage-gated channel, KQT-like subfamily, member 1</td>
</tr>
<tr>
<td>13 NOTCH2</td>
<td>Notch homolog 2</td>
</tr>
<tr>
<td>14 PPARG</td>
<td>Peroxisome proliferator-activated receptor gamma</td>
</tr>
<tr>
<td>15 THADA</td>
<td>Thyroid adenoma associated</td>
</tr>
<tr>
<td>16 TSPAN8-LGR5</td>
<td>Tetraspanin 8 and Leucine-rich repeat-containing G protein coupled receptor 5</td>
</tr>
<tr>
<td>17 WFS1</td>
<td>Wolfram syndrome 1 (wolframin)</td>
</tr>
<tr>
<td>18 SLC30A8</td>
<td>Solute carrier family 30 (zinc transporter), member 8</td>
</tr>
<tr>
<td>19 GCKR</td>
<td>Glucokinase regulator</td>
</tr>
<tr>
<td>20 GCK</td>
<td>Glucokinase</td>
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<tr>
<td>21 MTNR1B</td>
<td>Melatonin receptor 1B</td>
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<tr>
<td>22 ADCY5</td>
<td>Adenylate cyclase 5</td>
</tr>
<tr>
<td>23 PROX1</td>
<td>Proopio protein homeobox 1</td>
</tr>
<tr>
<td>24 DGKB-TMEM195</td>
<td>Diacylglycerol kinase beta and transmembrane protein 195</td>
</tr>
<tr>
<td>25 TCF7L2</td>
<td>Transcription factor 7-like 2</td>
</tr>
<tr>
<td>26 ADRAR2A</td>
<td>Adrenergic alpha-2A receptor</td>
</tr>
</tbody>
</table>

**Pathophysiology of type 2 diabetes**

Disruption of the adaptation of insulin secretion to insulin requirements, especially in response to insulin resistance, as seen in physically inactive obese individuals, leads to T2D.

**Animal models of type 2 diabetes**

This type of multigenic background points to T2D being associated with multiple defects. The genes involved also point toward β-cell defects as being central to T2D development. Monogenic diabetes syndromes, such as maturity onset diabetes of the young, are mostly related with gene mutations that impact β-cell function. In mice, glucose intolerance or diabetes have been reported in multiple models in which the knock-out of key genes in β-cell function, action of insulin on peripheral tissues, control of fat mass, or key biological functions has occurred. With few exceptions, however, the underlying genetic background in which genes are rendered defective has seldom been considered, although it possibly underlies the β-cell defects that lead to diabetes as a failed response to insulin resistance. For example, the db mutation and insulin receptor silencing lead to very different phenotypes depending on the genetic background into which it is introduced. In common mouse strains, diabetes has been elicited with a highly unphysiological high-fat diet. In these models, differential risk is seen as being dependent on the underlying
genetic background. However, although many animal models of T2D have now been described,12,13 none of them seems to closely mimic human disease. The Psammo-Mys (sand rat) is especially interesting since it clearly identifies the failing interaction between a genome and the environment, as is likely to be the case in human T2D. The sand rat has an essentially vegetarian diet in its natural habitat. Once fed laboratory chow, it becomes insulin resistant and hyperglycemic and eventually is struck by β-cell apoptosis that is irreversible if its diet is not reversed.14

**The inflammatory component**

An important component that links nutrients, increase in visceral adipocyte mass, and insulin resistance is inflammation.15 There is epidemiological evidence that markers of inflammation are predictive of T2D.16 The integration of metabolism and innate immunity through nutrient-sensing pathways, which are shared by pathogen-sensing pathways, trace the role of inflammation in insulin resistance, especially in obesity. Nutrients, ie, free fatty acids, glucose, and amino acids, signal through receptors and pathways that are shared by pathogens and/or cytokines. Macrophages and adipocytes also share many functions. Preadipocytes can transdifferentiate into macrophages. Both macrophages and adipocytes secrete cytokines. Nutrients can directly activate macrophages and adipocytes through common receptors, such as Toll-like receptors (TLRs), which have been shown to sense broad classes of molecular structures common to groups of pathogens. TLRs are central to innate immunity and inflammation. TLR4, a receptor of lipopolysaccharides, and TLR2, a receptor for pathogen lipoproteins, are activated by free fatty acids.17,18 TLR4 knockout mice are protected from fat-induced insulin and insulin resistance. TLR5, a receptor for bacterial flagellin, has been shown to control metabolic pathways through sensing gut microbiota. TLR5 knockout mice exhibit hyperglycemia and develop the hallmark features of metabolic syndrome, including hyperlipidemia, hypertension, insulin resistance, and increased adiposity. TLR signaling pathways have also been linked to atherosclerosis in mice.19

Infiltration of visceral adipose tissue by macrophages, and subsequently lymphocytes, is seen in obesity.15,20,21 The flood of free fatty acids and cytokines (eg, tumor necrosis factor α) linked to obesity and the metabolic stress driven by nutrient overload directly impact the action of insulin on the liver. In addition to the production of cytokines and to the overproduction of reactive oxygen species (ROS), many inflammatory signaling pathways that inhibit insulin-receptor signaling are directly triggered by nutrients, such as circulating lipids. The role of endoplasmic reticulum (ER) stress, the consequence of the accumulation of unfolded proteins in the ER, has also been underscored in these processes. Activation of kinases, such as Jun n-terminal kinase (JNK), inhibitor of nuclear factor κB kinase subunit β (IKK-β), extracellular-signal regulated kinase (ERK), ribosomal protein S6 kinase (S6K), mammalian target of rapamycin (mTOR), protein kinase C, and glycogen synthase kinase 3β, through inflammation leads to serine phosphorylation of insulin receptor substrate 1 (IRS-1), reducing both tyrosine phosphorylation of IRS-1 in response to insulin, the ability of IRS-1 to associate with the insulin receptor, and downstream signaling by insulin. The activation of macrophages, via the sensing of fatty acids by TLR4 leading to the production of proinflammatory cytokines and activation of TLRs expressed by adipocytes, can result in nuclear factor κB–driven proinflammatory responses.

**β-Cell mass in type 2 diabetes**

While a defect in β-cell function is now considered central to the T2D process, whether it is related to a decrease in β-cell mass or not remains an open issue. The lack of in vivo techniques to quantify β-cell mass has hampered its study in patients with various stages of T2D development. Currently, all studies rely on immunocytochemical techniques to quantify β-cell mass, in most cases on autopsy material. The strongest reductions reported in some publications remain largely above the minimal threshold that allows accurate insulin secretion and glycemic control, as shown by studies following partial pancreatectomy.22 Most studies have shown at least a moderate reduction in β-cell volume and/or β-cell mass in T2D patients compared with normal controls. One study has shown a reduction of up to 63% in β-cell volume in obese T2D patients compared with nondiabetic obese subjects, and a 41% reduction in nonobese T2D patients, but it did not assess β-cell mass. A 40% reduction was observed in impaired fasting glucose patients. The frequency of β-cell apoptosis increased 10-fold in lean T2D patients and 3-fold in obese T2D patients in the same study.23 A study that assessed β-cell mass found that it was reduced by 41% and 38% in T2D patients with a BMI <25 and 26-40, respectively, compared with nondiabetic controls. One of the most striking features in this study, as in previous studies, is the marked intersubject variability within each group, in the controls as well as the T2D patients, and, as a consequence, the large overlap between the nondiabetic and T2D groups. Pancreatic insulin concentrations were 30% lower in T2D patients than in controls. β-Cell mass did not correlate with age at diagnosis, but it did decrease with duration of clinical diabetes (24% and 54% reduction in subjects with <5 and >15 years of overt diabetes, respectively).24 The decrease with diabetes duration was postulated to be a consequence, rather than a cause, of T2D. Again, the small difference in β-cell mass observed in the T2D patients within 5 years of diabetes onset was capable of causing diabetes in the absence of β-cell dysfunction.

**β-Cell defects in type 2 diabetes**

As reduction in β-cell mass does not directly explain defective insulin secretion, a major focus of ongoing research is the clarification of mechanisms of β-cell failure in T2D.25 Early mechanisms of β-cell failure leading to T2D do not necessarily correspond with mechanisms of progressive silencing of β cells
and reduction of β-cell mass seen throughout the development of the disease once diagnosed. T2D subjects show early alteration of plasma insulin levels, with both quantitative and qualitative changes. Qualitative changes include impaired acute insulin response to glucose, attenuation of pulsatile insulin concentration, and exaggerated proinsulin-to-insulin ratio. These abnormalities have tentatively been attributed to a loss of the first-phase insulin response to glucose and of the oscillations during the second phase of insulin secretion. Defects in proinsulin processing at the β-cell and islet levels have been witnessed. However, the mechanisms of the defects of stimulus-secretion coupling in the β-cells of T2D subjects still remain unidentified.26

The highly multigenic form of T2D points to β cells as the driving force in diabetes. Multiple functional pathways are involved, including pathways controlling β-cell development, growth, survival, and response to glucose, but also those controlling the response to a wide variety of secretagogues, each of which imprints a subphenotype that by itself does not drive β-cell failure. It is their association that explains the progressive demise of β cells through interactions with a suboptimal environment. In most individuals, β cells adapt to high metabolic demand and maintain normoglycemia at the price of increased insulin secretion and hyperinsulinemia. This implies increased β-cell function and increased β-cell mass. A β-cell mass increase is indeed seen with increasing BMI in both nondiabetic subjects and T2D subjects in studies that quantified β-cell mass.23,24 It is postulated that, in genetically susceptible individuals, defective adaptation of β cells beyond a threshold that is likely to vary between individuals leads to the development of impaired tolerance to glucose and T2D. Early factors that are often present before the onset of T2D, including hyperlipidemia and low-grade inflammation, contribute to the initiation of impaired glucose tolerance, in addition to chronic overstimulation of insulin secretion.

Pancreatic β cells exposed to increased metabolic demand display modified gene expression profiles and altered function, survival, and growth that are likely to contribute to the slow deterioration of functional β-cell mass that is characteristic of T2D. In vitro data obtained by exposing islets to high glucose concentrations show an adaptive response, including increased glucose sensitivity, which seems detrimental in the long term (glucotoxicity). Similar observations have been made by exposing islets to high free fatty acid concentrations (lipotoxicity). Pancreases obtained from T2D patients show altered gene expression that affects multiple β-cell pathways.27 While glucose-stimulated insulin secretion by T2D islets is profoundly altered, secretion stimulated by arginine and by sulfonlyureas is partially conserved. These defects are accompanied by reduced mRNA expression of glucose transporter 1 (GLUT-1), GLUT-2, and glucokinase, and by diminished glucose oxidation. In addition, 5’ adenosine monophosphate–activated protein kinase (AMPK) activation is reduced. The expression of insulin decreases, while that of pancreatic duodenal homeobox 1 (PDX-1) and forkhead box protein O1 (FOXO-1) increases. Nitrotyrosine and 8-hydroxy-2-deoxyguanosine concentrations point to oxidative stress within the islets. These modifications may be at least partially reversible, a key issue in T2D.25 The physiological role of cytokines, some of them produced by β cells, such as interleukin 1, remains elusive. Overexposure of the islets or local overproduction of these cytokines leads to oxidative stress.26 The low levels of radical scavengers characteristic of β cells is one factor that may explain the high sensitivity of β cells to oxidative stress.

Furthermore, many models have shown that markers of ER stress correlate with β-cell failure in experimental models. In humans, this occurs in patients who carry mutations of the insulin gene that impact proinsulin processing throughout the insulin secretion process.29 Again, ER stress is an adaptive response of cells exposed to an accumulation of misfolded proteins, also known as the “unfolded-protein response.” It leads to an increase in the transcription of genes that activate genes that are crucial for secretory functions, cause transcriptional arrest of most proteins, and induce genes that restore the proper folding of proteins. In the long term and when overloaded, it leads to cell apoptosis.

In many regards, the pathological β-cell failure seen in T2D is an age-related process. Many aspects of β-cell physiology that directly impact aging have been underscored. The relationship between the progressive failure of β cells and mitochondria in T2D cannot be ignored. Apart from the many reports citing the role of mitochondrial mutations or defects that lead to β-cell failure and diabetes,26,27 a 50% decrease in mitochondrial DNA (mtDNA) copy-number in skeletal muscle and peripheral blood cells of T2D patients has been observed.

The diabetic state is generally characterized by accelerated tissue aging, which is perhaps related to mitochondrial dysfunction. Among modifications that may be related to “mitochondrial aging” in the form of point mutations in mtDNA, there is an age-related increase in the production of ROS, with a concurrent weakening of the defense mechanisms against these free radicals. This deleterious process is amplified in β cells due to their low level of natural enzymatic defenses, ie, reactive oxygen species scavengers (catalase and superoxide dismutase). ROS may play a role in the impairment of glucose-induced insulin secretion seen both in aging and in T2D. The direct study of diabetic islets from T2D patients shows parallel events: reduced insulin response to glucose, low adenosine triphosphate (ATP) levels, a low ATP/ADP (adenosine diphosphate) ratio, impaired hyperpolarization of the mitochondrial membrane, and increased expression of mitochondrial uncoupling protein 2 (UCP-2), complex I, and complex V of the respiratory chain. Morphology shows higher mitochondrial density volume, despite normal numbers of mitochondria in T2D islets.30
**Perspectives**

The human genome sequence provides an unprecedented catalogue of markers and genes to fill the gap between disease phenotypes/subphenotypes or identification of the loci associated with diabetes and the characterization of genes involved. We can now foresee the integration of gene products into metabolic networks with the global perspective of comprehensively viewing cell and organ function on a genome-wide basis. This will require combining genetic approaches with technologies to characterize gene and protein expression. New advances will be required to apply gene expression to large scale studies and allow computational integration of the data generated. The perspectives of genomics have been examined from the point of view of medical genetics. Other avenues will open the field of pharmacogenetics to diabetes. Dramatic examples of pharmacogenetics’ power to predict the action of drugs and their adverse effects have long been reported. Availability of the genome sequence will allow the systematic search for gene variants that influence the effects of drugs. The forthcoming challenge is to design therapies that can correct the highly multigenic state attributed to the T2D β cell. Some of the currently available therapies re-store functional features primarily affected in the early stages of T2D development, for instance, the loss of first-phase insulin release, but they only do so on a short-term basis.

**References**


**Keywords:** diabetes; insulin; β cell; insulinresistance; genome
IGIS après 10 ans de recherche sur la cellule bêta : où en sommes-nous aujourd’hui ?

Le diabète de type 2 (DT2) est l’exemple le plus frappant des défis auxquels la médecine aura à faire face dans les 10 prochaines années. Tout d’abord, s’agissant d’une pathologie fortement multigénique pour laquelle la recherche médicale n’a pas réussi à identifier une anomalie unique responsable des défaillances de la cellule bêta, la conception de thérapeutiques efficaces nécessitera des stratégies originales de loin beaucoup plus complexes que l’identification classique d’une cause et de sa cible pharmacologique pour un traitement définitif. D’autre part, l’épidémie mondiale de DT2 et les variations géographiques de son incidence ne peuvent pas s’expliquer sur une base génétique. Ce que nous devons parvenir à comprendre, c’est l’interaction entre un substratum génétique complexe et des facteurs environnementaux qui ont spectaculairement changé ces 60 dernières années. Nous manquons toujours de modèles animaux pertinents de DT2, déterminants pour l’élaboration de nouveaux traitements permettant de maîtriser les processus pathologiques. Nous devons déterminer la part réelle de l’inflammation chronique, ce qui pourrait ouvrir de nouvelles perspectives de prévention thérapeutique de la maladie. Nous attendons tous l’arrivée de techniques permettant de quantifier la masse cellulaire bêta in vivo afin de mieux comprendre l’histoire naturelle de la maladie et d’ouvrir la voie à des médicaments qui restaureront la masse cellulaire bêta physiologique. Bien qu’une anomalie bêta-cellulaire ait été identifiée sans équivoque comme la cause centrale du développement du DT2, les traitements actuellement disponibles qui restaurent les anomalies bêta cellulaires à un stade précoce, à savoir la perte de la réponse insulinique initiale, ne le font qu’à court terme. Voici peut-être le défi le plus complexe qui se présente à nous.
A TOUCH OF FRANCE

Under this heading, each issue of Medicographia features two cultural articles. The first one touches on the history of medicine, based around a great figure from French history, while the second one addresses broader aspects of France’s heritage, such as history, art, literature, and the description of museum collections.

Light, optics, and color: the Impressionist eye
A triple revolution in the artist’s gaze
C. Régnier, France

Claude Monet,
becoming one with nature
I. Spaak, France

The Impressionist eye?
Detail from Claude Monet’s Impression, Sunrise (1872)
Oil on canvas. Musée Marmottan, Paris.
© Giraudon/Bridgeman Giraudon.

Claude Monet,
Poppies at Argenteuil [Les Coquelicots à Argenteuil] (1873). Oil on canvas (50×65.3 cm). Musée d’Orsay, Paris, France. © Service presse RMN/ Hervé Lewandowski.
Light, optics, and color: the Impressionist eye

A triple revolution in the artist’s gaze

by C. Régnier, France

Impressionism can be regarded as the child of the century of Science," wrote Academician René Huyghe in the catalogue for the Centenary of Impressionism exhibition held in the Grand Palais, Paris, in 1974. The Impressionists had arrived on the scene “officially” a century earlier, in 1874, in tandem with a remarkable expansion in scientific and medical disciplines: optics, ocular physiology, clinical ophthalmology, retinal microscopy, photography, and colorimetry. The Impressionists were alert to some of these developments, but they painted above all from instinct or, if we go by Jean Renoir’s memoir, Renoir, my father, using a more specific part of their anatomy. Their attitude to science was ambivalent: they were adamant about opposing its claim to dictate their art, whether by its laws or by the unassailable logic of reasoning based on observation of the real world. And yet, in their signature subject matters—the representation of nature and 19th century bourgeois society—the Impressionists espoused a form of pictorial realism not so distant from the new laws being uncovered in optics, colorimetry, and ocular physiology. This disconcerted an audience unused to confronting the complexities of optical analysis: optics informs us that shadows are blue, whereas common sense tells us they are gray. The Impressionists banished subjectivity from their gaze, and with it any romantic view of the world, incurring indirect reproach for doing so.

Medicographia. 2011;33:92-100 (see French abstract on page 100)
the time: its mission was to capture fleeting impressions and moving colors rather than transcribe stable images. French painters had previously been held in check by an academic training that focused on the technicalities of line while downplaying issues of color, which was viewed simply as an accident of light. Yet color was central to scientific and philosophical debates during this period.1,2

From the Salon des Refusés to the salon of the Impressionists and their friends

The Company held its first exhibition in the former studio of the photographer Nadar (1820-1910) from April 15 to May 15, 1874. Bringing together 29 artists, it comprised 165 photographs, drawings, engravings, watercolors, and canvases. Monet exhibited twelve works, Pissarro five, Renoir six, Degas ten, and Sisley five. Despite opposition from Degas, Paul Cézanne (1839-1906) was allowed to exhibit three. Degas invited his protégés, headed by Morisot and Rouart, while Monet brought Eugène Boudin (1824-1898) and Pissarro introduced Édouard Béliard (1832-1912).

However, to their chagrin, their “master” Jean-Baptiste Corot (1796-1875) declined his invitation. “He remains the greatest,” wrote Degas in 1883, “he anticipated everything.” Monet added, “There’s only one master, Corot. We’re nothing in comparison, nothing.” Manet stayed away too, preferring to compete in official salons, as did Johan Jongkind (1819-1891). The exhibition drew only 3500 visitors compared to the 400,000 for the Salon des Refusés. Just fifteen paintings were sold. But press coverage was considerable, with eleven articles appearing under some well-known bylines between April 16 and May 7.3 Critics wrestled with names for the new school of painting. On April 25, writing in the satirical daily Le Charivari about the painting Monet had simply called Impression, Louis Leroy rebaptized it Impression, Sunrise and proceeded to lay on the irony: “Since I was impressed, there had to be some impression in it.” On April 29, the conservative La Presse referred to “the disciples of Monsieur Manet, pioneers of the painting of the future, the most determined and official of the School of Impression’s representatives.” The moderate, republican Le Siècle was more specific: “Once they’ve captured the impression, they say their role is finished…. Anyone wishing to characterize and explain them in a word would have to coin the term impressionists. They are impressionists in that they do not transcribe a landscape, but the sensation produced by the landscape.” On May 1, L’Artiste proposed: “If this little group were to set themselves up as a school, it should be called ‘The School of the Eyes’.” On May 7, Paris-Journal’s Ernest Chesneau came up with “The Outdoor School.” As for the artists themselves, who preferred the name “Independents,” they turned Le Charivari’s put-down on its head and proudly proclaimed themselves “Impressionists.”4

At their third exhibition in April 1877, the eighteen exhibitors founded the arts journal L’Impressionniste. Although only four issues ever appeared, all in 1877, the title made the name official. Indeed, the third exhibition only brought together impressionist painters who referred to themselves as such. Around ten of the original artists from the 1874 exhibition dropped out,
Impressionists shared a number of attitudes and working techniques:

- As rebels against the Academy, determined to steep themselves in contemporary reality and represent what they saw in ways that their audience could directly enjoy without special training, they refused to paint historical, mythological, or sentimental subjects;
- Their analysis of light led them to load their palettes with pure colors only and apply the law of complementary colors; black was banished;
- Realizing that complementary colors mutually intensify their luminosity when adjacent, but extinguish one another to gray-black when mixed, they applied pure colors in little brushstrokes;
- Shunning studios, they often painted outdoors to better capture the light;
- They relegated human figures to the distance, concentrating on light and atmosphere; and
- They replaced dark shadowing in faces and light-colored clothing with cold tints, such as greens and blues, that generated a play of colors independent of the object’s shape.

Edmond de Goncourt (1822-1896) identified their main influence as Japanese. Félix Bracquemond (1833-1914), an exhibitor at the 1874 Salon, had begun copying the works of Hokusai (1760-1849) as early as 1856, anticipating the “Japonism” that was to captivate many other Impressionists.\(^4\),\(^5\) The Impressionists dazzled their early supporters with their work with light, the novelty of their gaze, and their juxtaposition of colors, all of which ran parallel—indeed interwove—with some of the scientific developments of the time, specifically in optics, colorimetry, ocular physiology, and the anthropology of vision.
Photography: a revolution for painters

The discovery of photography (etymologically, drawing with light) transformed the artists’ world, relieving them of the obligation to represent reality in a plethora of detail. The deconstruction of movement over time in series of still photographs (chronophotography) by Eadweard Muybridge (1830-1904) and Étienne-Jules Marey (1830-1904) revealed what the eye was unable to analyze alone. “What the eye has no time to grasp,” wrote Marey, “the camera translates... in the minutest detail.”

Manet and Degas worked from photographs. Frédéric Bazille (1841-1870) used a daguerreotype to produce his *Naked young man lying on the grass* (1870). All were unfazed by the contempt of Charles Baudelaire (1821-1867), who in 1859 wrote:

If photography is allowed to supplement art in some of its functions, it will soon have supplanted or corrupted it altogether, thanks to the stupidity of the multitude which is its natural ally. It is time for it to return to its true duty, which is to be the servant of the sciences and arts—but the very humble servant, like printing or shorthand, which have neither created nor supplemented literature.

By relaxing the traditional approach to composition, with its formal opposition between subject and background, some Impressionist paintings resemble snapshots that capture a moment of time in the moving light of a landscape (or in people’s daily lives). In the ways they framed their subject matter and played with focus and space, the Impressionists took over a number of techniques from photography, while also showing that photography was not the only technique able to capture a fleeting gaze. The artist’s eye was often compared to an imperfect camera that the brain corrected or amplified. The engineer-historian Auguste Laugel (1830-1914) wrote:

Imagine a camera with a misaligned objective, defective lens, and a plate sensitive only in scattered areas. The photographer would be ill-prepared for taking a good picture. Yet all these faults and more we find in the human eye.

The development of photography was punctuated by successive improvements in optical technique, notably objectives, shutters, and lenses. It also grew in parallel with striking advances in the exploration of the eye, notably the development of the ophthalmoscope.

The ophthalmoscope, chromatoscope, and Parinaud’s scale

In 1850, Hermann von Helmholtz (1821-1894), a professor of physiology and pathology in Königsberg, told his father:

I’ve invented something that will be extraordinarily useful in ophthalmology... a combination of lenses that illuminate the dark retina through the pupil without using blinding light, yet at the same time display the retina in all its detail... The transparent parts of the eye act as a magnifying glass, enlarging the retina twenty-fold.
Polish-born Xavier Galezowski (1832-1907) was responsible for developing retinal chromatoscopy. His doctoral thesis, submitted in 1865, was entitled *Ophthalmoscopy of changes in the optic nerve and the cerebral diseases on which they depend.* In 1868, he published *Retinal chromatoscopy in ocular diagnostics preceded by a study on the physical and physiological laws of colors,* containing six plates showing a 44-shade color scale, four character scales to measure visual acuity (blood, blue, red, yellow), and a scale to measure astigmatism. Galezowski based ocular diagnostics on the study of color vision. Galezowski's student Henri Parinaud (1844-1905) became a leading French ophthalmologist during the Impressionist era. With clinical interests spanning neurology and ophthalmology, Parinaud was close to the renowned neurologist Jean-Martin Charcot (1825-1893), joining him at the Salpêtrière Hospital. His eponymous scale analyzing visual acuity (blood, blue, red, yellow), and a scale to measure astigmatism into a routine procedure.

**Painters of light and color**

What set the Impressionist school apart was their visual realism and enthusiastic deconstruction of light. In rebellion against time-honored chiaroscuro, Manet painted light-on-light. *The luncheon on the grass* marked the arrival of "light painting." Most Impressionists painted in the open air; it was Manet who introduced Pissarro to outdoor painting. With the notable exception of Degas, it became their studio.

By painting in daylight, the Impressionists captured the ways in which landscape changes according to the time of day, climate, and season. In the 1890s, Monet tracked this perpetual variation in his serial studies of haystacks, poplars, and cathedrals. Sisley adopted a similar approach: "I always begin a picture with the sky because it determines the representation of matter, objects, time of day, and sunlight." In the summer of 1869, Renoir worked with Monet on the technique of fragmenting color in light, first in views of the waterside café *La Grenouillère* in Chatou, a western suburb of Paris, and then on the banks of the Seine at Argenteuil. They painted leaves light green, and dabbed them with yellow sunlight. Renoir added touches of violet shade. The effect was to recreate the colors of the light spectrum.

**Vision, artists’ eyes, and science**

Issues of vision, optics, and the health of artists’ eyes abounded in late 19th century literature. Physiologists, clinicians, and enlightened amateurs made learned attempts to explain the origin of art in terms of experimental method and scientific analysis. In his *Optics and the arts*, Laugel set vision above the other senses: "The eye makes us masters of everything and gives us a kind of hold over the world. It is our unrivalled instrument of knowledge...transporting us across space to the remotest worlds and allowing us to imagine infinity." Vision was the supreme sensory perception and its corollary in art was painting.

Helmholtz initiated the incursion of physiology and optics into the critical theory of painting, thanks to his interest in every component of vision: its physics (the emission and propagation of light), physiology (neuronal transmission of sensation), and psychology (perception). With Scottish physicist James Clerk Maxwell (1831-1879), he defined the three attributes of color: hue (red, etc), saturation (intense vs dull), and lightness (light vs dark). With Ernst Wilhelm von Brücke (1819-1892), a pioneer in the physiology of sensation and a major influence on Sigmund Freud, he published studies on the scientific principles behind the fine arts, in particular on the relationship between optics and painting.

Helmholtz and von Brücke recognized that the laws of physics were inadequate for representing objects colored by natural light. They warned artists not to make the mistake of trying to represent objects as we see them. Instead they lauded the changing role of light in the beauty of a painting: "A little more poetry and a little less strong sunlight would be highly desirable in our modern landscapes." Explaining that air reflects blue light better than red light, but that red light comes into its own as the day advances, they advised painters not to hesitate in using violet, purple, or lilac colors (as Impressionists were often criticized for using). Von Brücke and Helmholtz recognized that the use of these colors "does not go well with the other colors in the landscape and readily destroys their harmony." They also considered the spectator retina ill-prepared to accept jarring juxtapositions of colors. They concluded their attempt to bring science and art closer together with a defense and celebration of artistic genius.
What should a work of art, in the most elevated sense of the term, aim at? It should capture and excite our attention, and awaken a wealth of associated ideas and feelings lying dormant within our souls….Only this appears to account for the power of art to move the human soul, which so often exceeds that of reality.12

Theories and disputes over color vision
The second half of the 19th century saw a huge increase in contributions to the theory of color vision. Between 1875 and 1879, close on 30% of papers on the physiology of optics were devoted to color vision, over double the proportion in 1870.

For French artists, the most popular and best-studied theoretician of color was Michel Eugène Chevreul (1786-1889), a national institution whose funeral at the grand old age of 102 was celebrated with all the pomp that the Third Republic could muster. Trained as an organic chemist, Chevreul was appointed director of the dye works at the Gobelins Manufactory in 1824, where he remained for half a century. The staff there complained about being unable to achieve a satisfactory effect with certain dyes. Chevreul discovered that although these dyes were chemically unstable, the real difficulty arose when using certain colors next to each other. In 1839, he published The principles of harmony and contrast of colours13 showing that colors are defined by the color of the objects around them. For any color to exist, it has to refer to its complementary color, which the eye tends to summon up more or less automatically. When presented with two (or more) colors, the eye makes an “optical mix” and creates a new color. Chevreul’s laws helped colorists to eliminate unwanted contrast effects. Using Newton’s corpuscular theory of light, he also produced a complete catalogue of color complementarity in a circular chromatic diagram that measured the effects of mutual proximity.14
Chevreul considered light the retinal "impression" of deconstructed radiation reflected by external objects. Helmholtz, on the other hand, viewed color as a sensation produced via sensory organs, believing that it resided neither in the object nor in the light that it reflected, but in the subject’s visual apparatus. “Impressionists” and “sensationists” were locked in dispute.15

Eugène Delacroix (1798-1863) and the Impressionists knew about Chevreul. For example, rather than use green, they knew that applying blue next to yellow would induce the eye and brain to generate the color green. Georges Seurat (1859-1891) put theory into practice by painting outdoor scenes using minute dots of pure color (Pointillism), placing greens next to reds in a way that the eye combines into yellow, for example. The Impressionists were also familiar with the contrast between warm and cold colors. In Waterloo Bridge (1903), painted from his room in the Savoy Hotel, Monet set blue and orange next to one another, much like Renoir in Two sisters (On the terrace) (1881), in which he sets four complementary colors side by side. In 1879, the American Ogden Nicholas Rood (1831-1902) published his color wheel and three-constant color theory (purity, luminosity, and hue) that influenced the Neo-Impressionists and Pointillists, such as Seurat. “If we had to synthesize the various science-based methods employed in modern art,” wrote Pissarro, “we could say that they are based on Chevreul’s theory of colors, Maxwell’s experi-ments, and the measurements by N.O. Roods.” Pissarro, along with Seurat and Signac, were termed “scientific Impressionists.” In 1888, in France, Charles Henry (1859-1926) followed Roods with his own version of a color wheel based on wavelengths and the effects on recipient psychology. He in-

Auguste Renoir (1841-1919). Les Deux Soeurs (Sur la Terrasse) [Two Sisters (On the Terrace)]. Oil on canvas (100.5×81 cm). The Art Institute of Chicago, Ill, USA. © The Art Institute of Chicago/Corbis.
spired both Seurat and Paul Signac (1863-1935). Other artists rejected the idea that scientific theory influenced their work. Renoir told the art dealer Ambroise Vollard (1866-1939):

The truth is that in painting, as in the other arts, nothing you do, however small, can be encapsulated in a formula…. You think you know a lot when you’ve learned from the ‘scientists’ that it’s the contrast between yellow and blue that produces violet shade, but in fact, having learned that, you still know absolutely nothing. There’s something extra about painting that can’t be explained and that’s essential.”

In 1909, American artist Albert Henry Munsell (1858-1918) published his color system, which organized colors by hue, luminosity, and saturation (chroma). It became the most successful attempt at establishing a numerical color classification standard, and was adopted worldwide.

Impressionists’ ocular pathology

Painters’ ocular pathology became a hot topic in the late 19th century. In 1863, one of Helmholtz’s students, Richard Liebreich (1830-1917), published and illustrated one of the first atlases of retinal ophthalmoscopy. In 1870, he gave a lecture in London entitled, “Turner and Mulready: Visual defects in painting,” which was published to great effect. Visitors to London galleries and museums were reported as donning magnifying glasses and color filters to reproduce the visual defects suffered by Turner and Mulready. Degas, who himself had a form of color blindness and loss of visual acuity, confirmed Liebreich’s contention that any painter with a visual disorder was likely to reproduce its effects in his art. Detractors felt vindicated in their distaste for the Impressionists’ work. Playwright August Strindberg (1849-1912) described Sisley’s work as “colorless, anemic, in a word albino.”

Pissarro for his part chuckled: “We’re afflicted with the painters’ disease, color blindness, the disease of the painters who see everything in blue,” whereas poet Jules Laforgue (1860-1887) actually praised what he sensed as a physiological explanation for the Impressionists’ achievements, their “uncommon sensibility of eye.” By ignoring the collections of pictures in museums amassed through the centuries and their art school training, the Impressionists forged a new eye for themselves, sensitive only to luminous vibration. It saw naturally, and painted what it saw. To the three great illusions—line, perspective, and studio lighting—by which earlier technicians of painting had lived, the Impressionists responded with “vibration, contrast of color, and open air.” For Laforgue, there was no doubt: “The Impressionist eye is, in short, the most advanced in human evolution, the one which until now has grasped and rendered the most complicated combinations of nuances known.”

References

At a time when photography was challenging painting as the dominant means of reproducing reality, the advent of Impressionism provided a counterbalance to photography's objectivity. By expressing their individual perceptions of what they saw rather than trying to replicate it, Claude Monet (1840-1926), founder of the Impressionist movement, and his fellow painters—Bazille, Caillebotte, Cézanne, Degas, Morisot, Pissarro, Renoir, and Sisley—turned the subjective conception of nature into a pivotal art movement that still captivates today.

In the evening of his life, Claude Monet wrote to his friend Georges Clemenceau, “I've simply looked at what the universe has shown me, to bear witness with my brush.” When, on Monet's death in December 1926, Clemenceau discovered a dark pall draped over the painter’s casket, he exclaimed, “No! No black for Monet.” Looking around the room, his eyes lighted on an “old cretonne in the colors of periwinkles, forget-me-nots, and hydrangeas,” which he had spread over the Impressionist master’s coffin, in homage to his work and to his love of gardens. Monet has been reproached for representing everything in the same way, whether figures, stones, clouds, water, or wind. His iridescent subjects too have been criticized, along with his colored vibrations and the unreality of his touch. Yet it was Claude Monet who brought us out of the stuffy exhibition rooms and academies where painting was stagnating. He stripped away prejudice and convention, and gave us new ways of seeing. Showered with honors during his lifetime, yet lauded as a “classic of modernity” by later generations of Cubists and Surrealists, Monet was also praised years after his death by abstract painters moved by the almost monochrome waterscapes that engrossed him in his final years at Giverny. Reconciling deep attachment to the nature he revered and a free-spirited poetic world, Monet abolished the distance between artist and beholder, who together become one with nature.

Seven minutes. One session on a canvass in his Peupliers (Poplars) series (1890-1892) could not exceed seven minutes, Claude Monet explained to a young American woman artist. Because, in that time, the light slipped from the leaf he was observing to the next, a subtle change that triggered a new “impression.” And a painting that mixed diverse impressions would denature the authenticity of the vision.

Monet stressed the importance of freshness in the way of seeing a landscape. Seeking to explain Monet’s method of harmonizing touches of paint as a succession of scattered patches, an art critic wrote how his landscapes were arranged on the canvas like “that child's game where objects are reconstituted piece by piece.”

Considered as the “father” of the Impressionist movement, Claude Monet (1840-1926) had but one ambition: to capture the moment. He devoted his life to this, tirelessly depicting the nature he venerated, seeking absolute proximity. To the point of
imagining the creation of a garden at his property in Giverny that would no longer only be a source of inspiration, but a work of art in its own right, a kind of painting in three dimensions in which painter, nature, and beholder would be united.

By dint of unremitting work, and at the cost of never-ending dissatisfaction with the results, Monet created a masterly body of work. For sixty years, he painted: the Normandy beaches of his youth; the Forest at Fontainebleau, where he loved to set up his easel with his painter friends Renoir and Bazille; the open-air dance halls along the banks of the Seine; lunches in the garden of his house at Argenteuil; the Côte d’Azur in the sun; snow; Paris in festive mood; family life; and magnificent series of paintings—*Haystacks, Poplars, and Cathedrals*. He depicted the quintessence of a subject without betraying the play of light and shade.

"I grasped what painting could be"
Claude Monet was born in Paris on November 14, 1840, and spent most of his childhood and teenage years in Le Havre, where his parents set up in 1845. And it was in Le Havre that as a schoolboy he started to paint. Or rather draw. Apart from sketches of landscapes and boats, he won a modest reputation as a caricaturist, a talent he exploited at the expense of his fellow townspeople. A stationer/picture framer exhibited his caricatures alongside canvasses by Eugène Boudin, who would become a skilled painter of Normandy beaches and earn from Camille Corot the accolade, “king of the skies.” Monet remarked:

It’s true. I knew Boudin, who was fifteen years older than me, I believe, in Le Havre when I was doing my utmost to make a name for myself as a caricaturist. I was fifteen or so.

Imbued as he then was with the “academic principles of art,” Monet admitted that at first he disliked Boudin’s “open air” painting. Until the day, at Boudin’s urging, he joined him on a long walk along the coast. “You’re gifted,” Boudin told him. “Drop this other work, which you’ll tire of. Your drawings are excellent, but don’t stop there. Do like me, learn to draw well, to love the sea, the light, the blue sky.” Boudin’s insistence was determinant for the future Impressionist master.

I agreed to go and work outdoors with him. I bought a paint box and off we went to Rouelles (north-east of Le Havre)...
Boudin put up his easel and set to work. It was like a veil that
suddenly falls: I understood, I grasped what painting could be.
I owe it to Eugène Boudin that I became a painter.

Was it the revelation of nature or of instantaneity that marked
Monet forever? Thereafter he devoted his art to the first in-
stant, which conditions the way of seeing as if each time the
eye is seeing the scene for the first time. The American artist
Lilla Cabot Perry (1848-1933), Monet’s neighbor at Giverny
for ten years, said of him:

He would have wanted to be born blind and then, after sudden-
ly recovering his sight, to start painting while knowing nothing
of the objects placed before him. The first look at the subject
was, he maintained, always the truest.

**Painting as the bird sings**

Although Monet hated theories and lessons, he lavished ad-
vice on the young American:

> When you go out to paint, try to forget what objects you have
> before you—a tree, a house, a field, or whatever. Merely think,
> here is a little square of blue, here an oblong of pink, here a
> streak of yellow, and paint it just as it looks to you, the exact
> color and shape, until it gives your own naïve impression of
> the scene before you.

This original purity, Monet’s obsession, was coupled with a
fundamental need to throw open the doors of his studio so
he and his subjects could breathe fresh air. Wasn’t it him af-
fer all who set up his easel on a balcony of the Louvre to paint
a street scene (*Le quai du Louvre* [1867]), while his classmates
copied the great masters inside the mu-
seum? He wanted “to paint as the bird
sings,” turning his back on interpreta-
tions, idealizations, and other conventions
 taught in Parisian artists’ studios in the
1860s and 1870s. This stance, moreover,
 made him a hero for a handful of young
 artists resistant to the overly scholastic
 restrictions of academic teaching. From
1863, Monet studied at the Paris studio
of the Swiss painter Charles Gleyre, along
with Renoir, Sisley, and Bazille. But he
couldn’t stomach Gleyre’s bidding that
they respect the classical style rather than
paint reality. “I immediately urged them
to revolt,” Monet remembered. “Let’s leave,” I told them.
“The place lacks sincerity.” He headed for Chailly in the For-
est of Fontainebleau, a few kilometers from Barbizon, once
a source of inspiration to nonconformist landscape painters
like Corot, Rousseau, Millet, and Daubigny.

*Rouen Cathedral. The Portal and the Tour d’Albane in the
Sunlight [Le portail et la tour d’Albane, plein soleil] (1893-94).*
*Oil on canvas (82.2×63 cm). Musée d’Orsay, Paris, France.*
© Service presse RMN/Thierry Le Mage.
Monet took classes there and showed a pronounced liking for large perspectives (Le pavé de Chailly [1864]), undergrowth, centennial trees, clearings, and thickets. Inspired by Manet’s scandalous Le déjeuner sur l’herbe (see page 97) exhibited at the 1863 Salon des Refusés (Exhibition of the Rejected), he worked for months on a canvass intended for the salon of 1865. The salon was a sort of rite of passage, where painters sought official recognition and hoped to become known to art lovers and critics. Monet worked tirelessly on his immense composition (4.60 meters by over 6 meters) organized around a group of young women in pale dresses and their companions in morning coats or waistcoats, picnicking with cakes and fruit, glasses, plates, and bottles placed on a spotless tablecloth spread on the ground. But Monet never did complete the painting of life-size figures at an open-air luncheon bathed in the play of light filtering through the leaves, and instead turned for inspiration to a quite different scene.

“A story of energy and truth”

Monet’s portrait, Camille, of his 19-year-old model and future wife Camille Doncieux, depicts a typical Parisian figure of this period, shown from behind wearing a dazzling striped dress and jacket trimmed with fur. Painted indoors in four days, and later named Femme à la robe verte (The Woman in the Green Dress), the painting was praised to the skies by a young critic and close friend of Paul Cézanne—Emile Zola:

Tired of coming across no new talent, I noticed this young woman trailing her long dress...I don’t know him—Monet—yet it seems to me that I am one of his oldest friends. Because...
his picture tells a story of energy and truth. And yes, here's a character, here's a man in a crowd of eunuchs. Look at the dress. It's flowing and solid. It trails gently, it lives, it proclaims who this woman is.

With *Femme à la robe verte*, Monet took his first step on the path to fame and to relative financial ease.

I'm happier and happier. I have resolved to withdraw to the country. I work a lot, with greater determination than ever. My success at the Salon has helped me sell several paintings.

At his new home in Ville d’Avray (near Paris), Monet again started work on a huge composition—*Femmes au jardin (Women in the Garden)* ([1867])—where once more we see Camille Doncieux, soon to give birth to their son Jean on August 8, 1867. One art critic suggested that the four women portrayed are in fact four different versions of Camille.

During his to-ing and fro-ing between the Paris area and Normandy, Monet created his dazzling vision of a moment of happiness with his father, aunt, and a distant cousin in *Terrasse à Sainte-Adresse (Terrace at Sainte-Adresse)* ([1867]), fusing with virtuosity the combination of sea, figures, and gardens, all dear to the painter. Flags flutter in the wind, flowers glow in sunlight that flattens rather than sculpts forms, small craft sail on a choppy sea, azure waves draw the eye to outlines of ships steaming along the horizon.

“I’ve always hated theories”

Patches of color, the interplay of light and shade, and spontaneity all heralded the Impressionism that drew so many barbs in 1874 when Monet and his fellow painters organized their first independent exhibition. Yet these young rebels of painting were not the first to seek to recreate the most basic components of vision. Jean-Baptiste Corot (1796-1875), for example, had already exhorted artists not to lose the simplicity of guileless ways of seeing. Art critics then spoke of “childish scribbles” or of clumsy sketches that ran counter to the artistic conventions of the time. It was Monet’s *Impression, Sunrise* (see page 94) painted in 1873 at Le Havre that gave its name to this new school of painting, nicknamed “Impressionism” by its detractors. Influenced by the paintings of Turner discovered in London during his self-imposed exile during the Franco-Prussian War of 1870 and the siege of Paris, Monet never considered this canvas a finished work. And he regretted having been the source of the label “Impressionism.”

“I’ve always hated theories…My only quality is to have painted directly from nature by seeking to render my impressions of the most fleeting effects, and it grieves me to have been the cause of the name given to a group.

Guy de Maupassant accompanied the painter on several outdoor painting trips from 1885 and described the hours of walking in the open air searching for a country scene that Monet deemed right for painting. When Monet stopped, it was be-
cause he "saw." It was as if he was possessed by a vision, the pristine impression that he was tracking, recapturing, pursuing, deepening. "He was, in truth, no longer a painter, but a hunter," wrote Maupassant. Maupassant observed Monet weighed down with paintbrushes, easels, and paints:

He was followed by children carrying his canvasses, five or six on the same subject at different times of day with different effects. He took or returned the canvasses one by one depending on the changes in the sky. Before the subject, he watched the light and shade, and in a few brush strokes caught the sunbeam that falls, the cloud that passes. I saw him seize this way a glittering light on white cliffs and fix it with a run of shades of yellow that rendered strangely surprising the effect of this elusive and blinding dazzle.

One of his favorite motifs was a large panorama with nothing to impede the eye’s gaze. He avoided picturesque subjects and meaningful details, and when they do appear, they blend into the whole as if the painter feared defining them too clearly at the expense of general harmony. Figures too: the small boy seated on the ground, the young women walking away in *Le déjeuner* (around 1873-74), the woman with a parasol in *La promenade* (1875) and *Les Coquelicots à Argenteuil* (1873), and the people in the *Essais de figures en plein air* (1886). All these figures are treated “as landscapes,” explained Monet, who in the end removed them altogether from his paintings.

"An eye, but what an eye!"
The absence of contours, the doing away with contrasts is common to all the Impressionists. Through pure colors, dull paste, and no glaze, Monet above all sought a subtle harmony of the whole, where each detail blends to give the viewer the feeling not of a passive onlooker, but of a participant in the scene.

Cézanne bowed before the virtuosity of his contemporary: “An eye, but what an eye!” Monet himself conceded that he had exceptional visual acuity: “Perhaps in me originality is reduced to rendering the complexity of visual phenomena too fleeting to be captured by an ordinary eye.” He confessed though to permanent discontent and to the need to work ceaselessly. “It really is dreadfully difficult…It all proves that..."
you have to think of nothing but that, and by dint of thinking, you find it,” he wrote to his friend Bazille, and on July 25, 1890, to a journalist:

I’m wretched and sick and tired of painting. It’s assuredly a constant torture! Don’t expect to see anything new. The little that I have been able to do is destroyed, scraped off, or slashed. You don’t realize how terrible the weather has been for the last two months. It drives you mad when you’re trying to capture the weather, the atmosphere, the mood.

He boasted, exaggerating somewhat, that he never worked on paintings except at the site itself, and then only if the atmospheric conditions allowed. Yet in complete contradiction to his assertions of total spontaneity, one day he declared: “You aren’t an artist unless you carry the painting in your mind before executing it.” Those close to him knew how things really stood. Monet never hid from his art dealer Paul Durand-Ruel that he needed time to rework and perfect his creative outpourings. This was how he proceeded with his masterful paintings of water lilies in the ornamental lake created for him at Giverny, which he reworked in a studio constructed especially for the purpose.

“I’m becoming more and more of a homebody”

Almost all the subjects Monet painted between 1890 and 1898 were in the immediate vicinity of his house at Giverny, which he bought in 1890, seven years after moving there. Trips to London, Venice, and Norway renewed his inspiration, pushing to the extreme his obsession with light in the mists and fogs on the Thames and the pinkish glow of Venetian palaces. But the older he got, the harder he found it to leave his beloved garden. “I’m becoming more and more of a homebody, enjoying the beautiful things before my eyes.”

However, his eyesight was deteriorating, despite two cataract operations. “I work not without difficulty, because my eyesight is fading day by day,” he complained in 1920. But he worked furiously. “I am a slave to work, ever seeking the impossible. I have little time left and must devote all of it to painting.”

For the last thirty years of his life, Monet worked tirelessly on his series of Water Lilies. Originally a simple commission to decorate the walls of a dining room, these stretches of plants
and still waters became an obsession. As he grew old, Monet sought to render “the illusion of a whole without end, of a wave without horizon or shore.” He applied paint in thinner and thinner layers, reducing the water lilies to their essence in his last paintings, which are both profound and disquieting. Conceived especially for the Orangerie Museum in Paris, Monet gave eight compositions of large decorative panels to the state to celebrate the victory of 1918. He planned to install them close to the floor as he wanted to make visitors bend forward as they would to peer into a pond: a last act of humility demanded by the painter in homage to sublime nature.

Claude Monet – ne faire qu’un avec la nature

“Je n’ai fait que regarder ce que m’a montré l’Univers, pour en rendre témoignage par mon pinceau », écrit Claude Monet à son ami Georges Clemenceau au soir de sa vie. Né le 14 novembre 1840 à Paris, l’artiste s’éteint le 5 décembre 1926. « Non ! Pas de noir pour Monet ! » s’exclame l’homme politique en découvrant que l’on a recouvert la bière d’un drap foncé. Des yeux, il cherche dans la pièce et fait étendre sur le cercueil du maître impressionniste une « cretonne ancienne aux couleurs des pervenches, des myosotis et des hortensias » en hommage à son œuvre et à son amour pour les jardins. On a reproché au peintre de tout représenter de la même façon, qu’il s’agisse de figures, de pierres, de nuages, d’eau ou de vent. On a critiqué sa matière trop irisée, ses vibrations colorées, l’irréalité de sa touche. C’est pourtant Claude Monet qui nous a sorti des boudoirs, des chambres et des académies où végétait la peinture. Grâce à lui, l’œil est neuf, débarrassé d’un monde de préjugés et de conventions. Conciliant l’attachement profond à la nature qu’il vénérait et la suggestion d’un univers poétique autonome, il a aboli la distance entre le maître et le spectateur. C’est à lui que nous devons le grand bonheur de découvrir la véritable magie de la lumière dans un tableau, et cette formidable audace de s’autoriser à rêver.

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