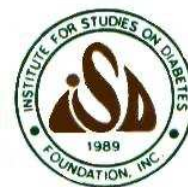


SCRIBBLINGS



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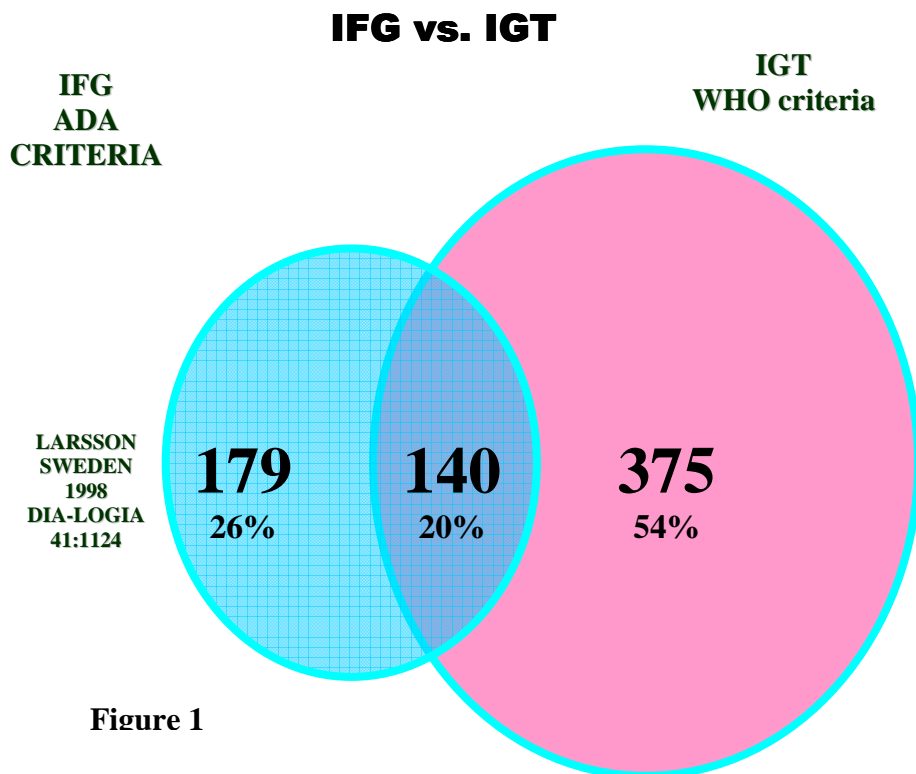
PREVENT DIABETES: PREVENT DISASTER

By: RICARDO E. FERNANDO, MD, FPCP, FPSEM

ISDFI Chairman and President

We are facing a world crisis today where there is an estimated 200-300M diabetics, with the number ever increasing. There are some 6-8M diabetics in the Philippines and there would be more than 20M direct blood relatives of diabetics: brothers, sisters, children, nephews, nieces, grandchildren, and many more “other” relatives – all potential diabetics in the future.^{1,2}

The fasting and the 2-hour glucose criteria diagnose different groups of subjects. The decoda study group simply recommended that both FBS and 2hour PGBS be done in screening for diabetics in Asian populations. The implication is – if 10 diabetics are caught with the FBS, there would be at least 20 more waiting for the 2hour PGBS.^{3,4}



ATTENTION:**ALL ISDFI ALUMNI**

Please advise us regarding your new addresses, telephone numbers and hospital / clinic affiliations.

We shall be glad to update you on the trends and developments in the Institute.

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Everyone receives excellent
and
humane diabetes care.

MISSION

Enable healthcare professionals
to deliver excellent
and
humane diabetes care

A STATEMENT OF PURPOSE

Current medical literature is full of advancing knowledge regarding diabetes mellitus. Such materials are readily accessible to physicians in developed countries but are hardly available to the practitioners in underdeveloped countries.

The Institute for Studies on Diabetes Foundation, Inc. (1989) now seeks to crystallize as much of the available information and as fast as they become reasonably accepted, pass the knowledge on to its students, friends and other interested parties in a language that will be acceptable to the academician and yet simple and sufficiently comprehensive.

To write a textbook on diabetes mellitus at this time would be short of folly considering how rapidly changes in concepts are becoming the rule. In fact progress in the understanding of the disease strongly demonstrates the truth in the saying that “the only permanent thing in this world is change.”

Thus SCRIBBLINGS would minimize the disadvantage of being a captive of time and give its readers a day to day bird’s eye-view of what is current in the rapidly changing world of diabetes mellitus.

SCRIBBLINGS would also give an opportunity for local work and effort to be recorded properly for the benefit of posterity. The world should not be given an excuse to call Filipino diabetes workers unproductive.

Finally, SCRIBBLINGS can act like a sounding board for all students of diabetes locally. It could ultimately serve the function of a forum on diabetes – where a collection of local thoughts and experience could critically studied and assessed by a discerning readership and made use of for the benefit of the country’s diabetics either in their original or modified form.

PREVENT DIABETES: PREVENT DISASTER - - - from page 1

Current estimates of prevalence of diabetes in this country are below what is real since:

- 1.) criteria being used have changed (are lower) today.
- 2.) there is no 2hour PGBS performed on subjects with "normal" FBS.
- 3.) screenings do not include 20 year olds and below. In the clinics there has been a remarkable increase of diabetes among children since 1960.
- 4.) no record on IFG, IGT, GDM other forms of diabetes.

There is very strong reason to believe that the basic pathologic mechanism underlying type 2 diabetes is oxidative stress. A normal oxygen atom has four pairs of electrons. The body's natural metabolism can rob the atom of an electron. It is now called a free radical which in turn tries to replace the lost electron

by raiding other molecules. This creates new free radicals and a chain reaction begins. The chain of electron theft leads to cell disintegration, opening the door to many body ills i.e. diabetes (β cell apoptosis), vascular inflammation (vascular wall damage).

There are many ligands causing oxidative stress: sedentary lifestyle, hyperglycemia, fatty acids, and clinical conditions like central obesity (adipocytokines = $TNF\alpha$, resistin, PAI-1, ANG II, leptin), hypertension (aldosterone, angiotensin II), dyslipidemia (high triglycerides and Sd LDL, low HDL), and diabetes (hyperglycemia, insulin resistance, endothelial dysfunction).

All these ligands stimulate the receptor for advanced glycosylation end- products (RAGE) which activates macrophage $NF\kappa B$ leading to the release of many inflammatory cytokines: IL-6, COX2, $TNF\alpha$, IL-1, ICAM, VCAM, ELAM, M-CSF and others. The result is generalized vascular inflammation of small and large vessels

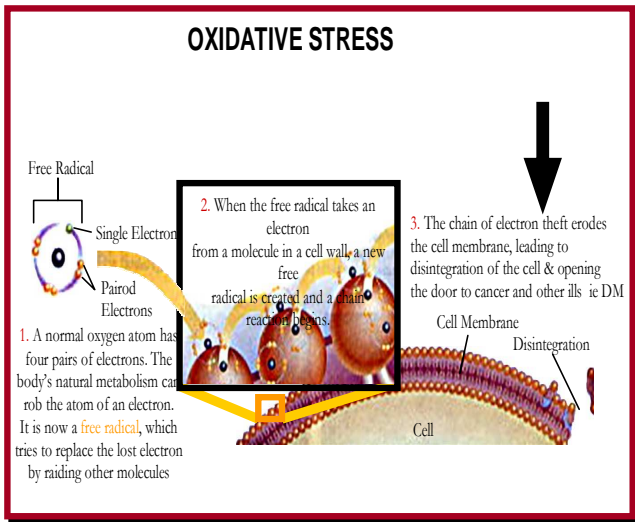


Figure 2

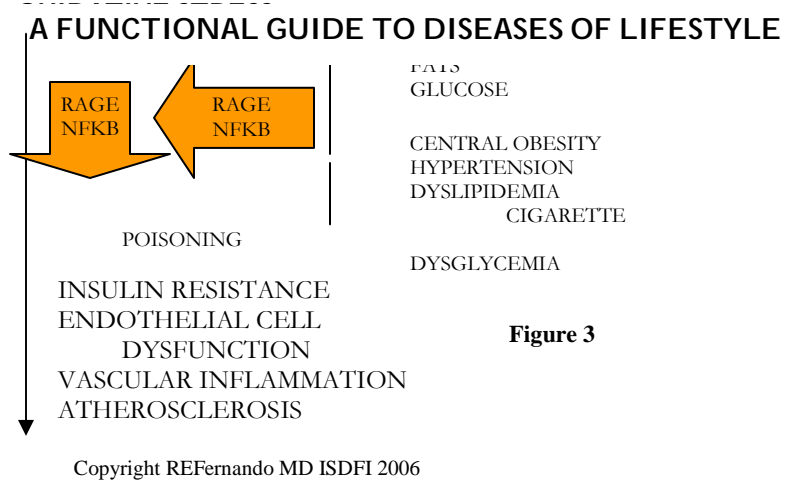


Figure 3

MULTIPLE LIGANDS IN OXIDATIVE STRESS

- Sedentary lifestyle, fatty acids, glucose
- Adipocytokines $TNF\alpha$
- Angiotensin II
- Aldosterone
- Lipoxidation (sdLDL RLP)
- Nicotine
- Hyperglycemia Amyloid B peptide
- Hyperinsulinemia
- AGEs lipoxidation/glycooxidation
- fast foods, processed foods, microwave
- S 100/Calgranulins
- Amphoterin
- Tansthyrectin
- other ligands proinflammatory

Oxi stress

Coronary angioplasty*****
RAGE → NFkB INFLAMMATION

Figure 4

The transcriptional factor $NF\kappa B$: a key role in the inflammatory events

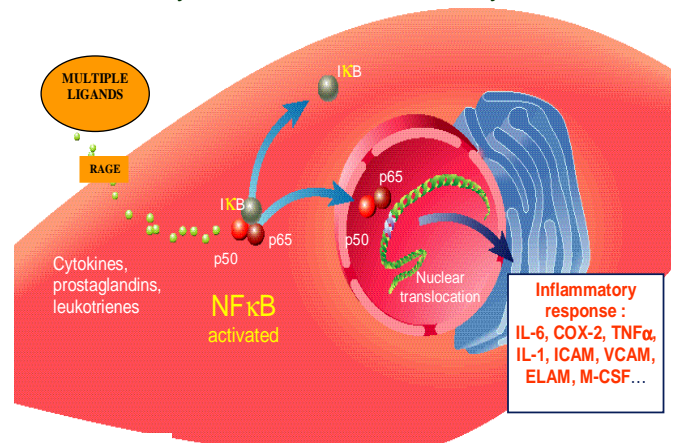


Figure 5

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PREVENT DIABETES: PREVENT DISASTER - - - from page 3

How then does diabetes begin? The beta cell is an endocrine organ. Endocrine hormones are released in a pulsatile manner, both during the fasting and post-prandial periods. The pulsatile insulin delivery provokes a larger insulin action compared to a constant non-pulsatile delivery.⁵ More than a century ago, it was observed that as fasting blood sugar rose in patients progressing from normal to diabetes, there was an increasing loss of early insulin response to an intravenous glucose challenge. This was observed even before glucose levels rose to those required for the diagnosis of impaired glucose tolerance. There was a reduction of glucose-induced insulin secretion with FBS 100 and complete loss at 115.⁶

Insulin is released from the beta cells in a biphasic manner – an early burst called “first phase” in the first 10 minutes, and a “second phase” that reaches a plateau in 2-3 hours, maintained until normoglycemia is restored. Loss of these phases of insulin secretion is the earliest sign of beta cell dysfunction.^{7,8}

Before diabetes develops, there is a decrease in amplitude and regularity of insulin response to glucose following lack of control of oscillations.¹² Blood sugar and insulin curves show effects of 1st and 2nd phases of insulin release on the normal post-challenge insulin curve. (see fig. 6 & 7)

Figure 2

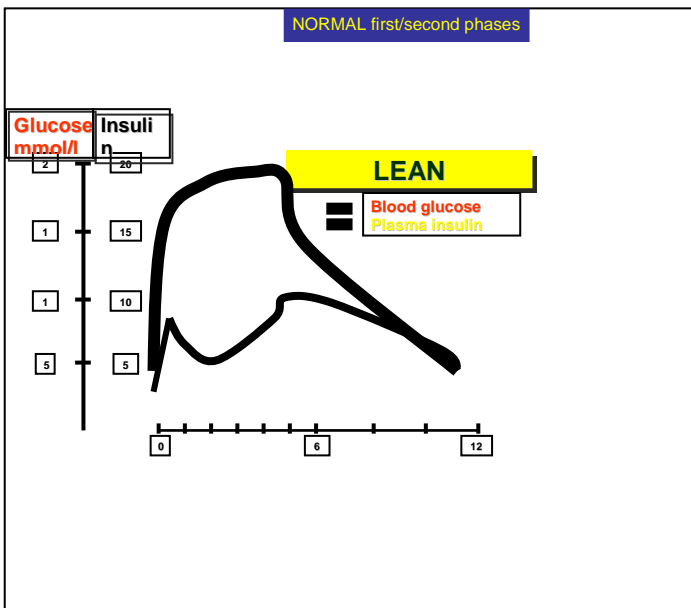


Figure 6

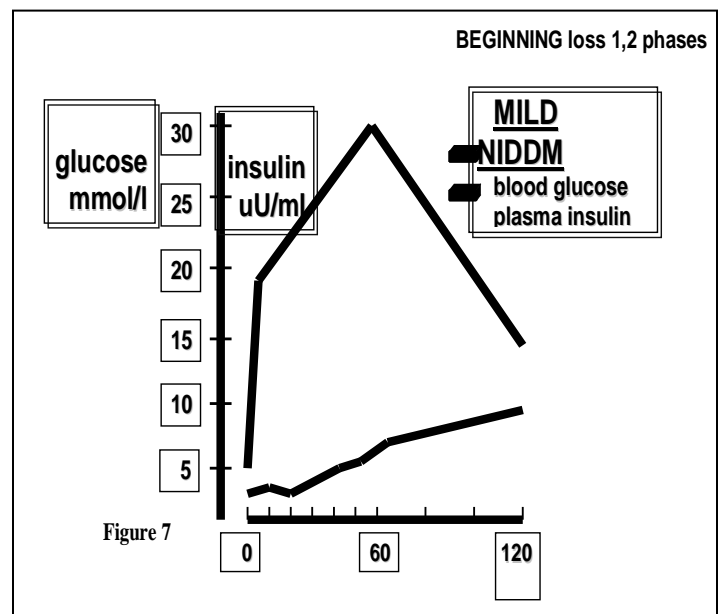


Figure 7

☛ *page 7*

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PREVENT DIABETES: PREVENT DISASTER - - - from page 5

The physiologic role of the early peak of insulin secretion is shown in figure 8 where emphasis is placed on the post-prandial blood sugar-limiting effect of 1st phase release. Note the notorious effect on the cardiovascular system recently recognized.^{9,10,11}

Defective function of the beta cells is now accepted to be a landmark of type 1 and type 2 diabetes.¹³ This functional impairment can be reversible. Reducing oxidative stress on the islet cell is a potential target of therapy.¹⁴

Treatment with diamicon has shown substantial improvement of high frequency insulin pulsatility, both acutely and after long term treatment. (see figure 9)^{5,15}

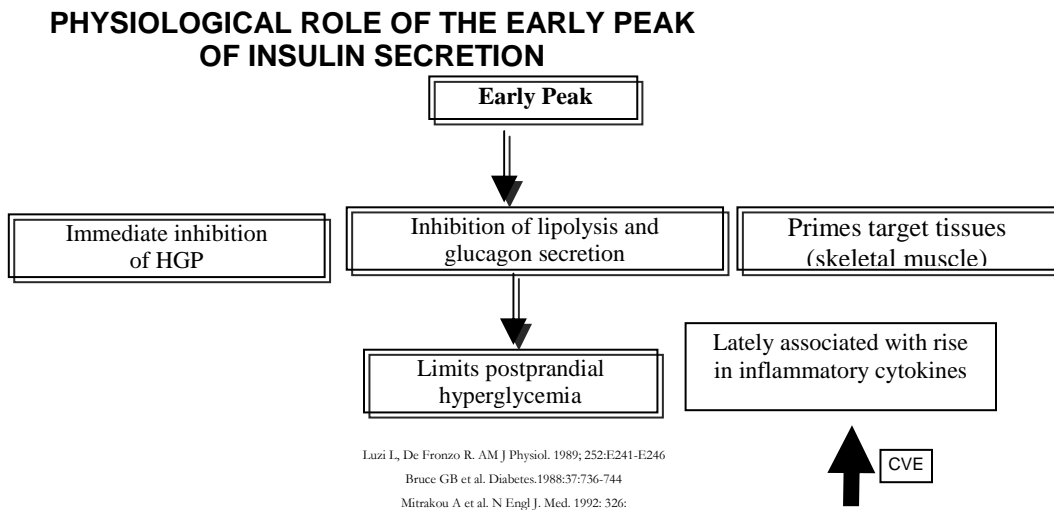
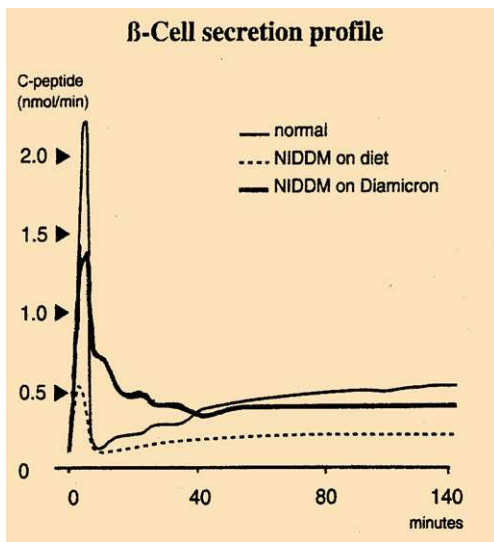


Figure 8

Restoration of Early Peak of Insulin Secretion



Diamicon MR restores the early peak of insulin secretion which is consistently reduced or absent in type 2 diabetes.

Matthews D. et al. - IDF Bull 1987 ; 32 (1) : 12-15

Figure 9

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PREVENT DIABETES: PREVENT DISASTER - - - from page 7

In non-diabetic people under normal conditions of life, venous blood glucose concentration is regulated between 3mM/DL (54mg/DL) and 6mM/DL (108mg/DL).¹⁶

The range of normal venous plasma glucose during the day travels between 3.5 mM/DL (63mg/DL) and 7.0 mM/DL (125mg/DL).¹⁷

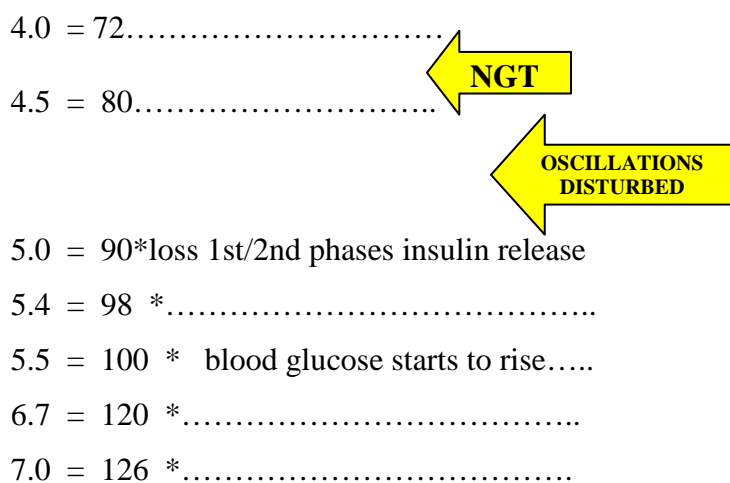
Progressive loss of first and second phases of insulin response occur at venous blood glucose levels between 5.0 – 5.4 well within the range considered as normal. There is increased risk of progression to clinical overt diabetes and cardiovascular events with FBS 5.5-6.1. Normal glycemia could be considered the blood glucose value which, when exceeded, is followed by a beta cell response aiming to bring blood glucose back to basal levels. Normal values may in some cases fall well below 5.5 or even below 5.0.^{18,19}

Glucose abnormalities after a myocardial infarction are not stress epiphenomena. They are due to decreased early phase beta cell secretion of insulin.²⁰

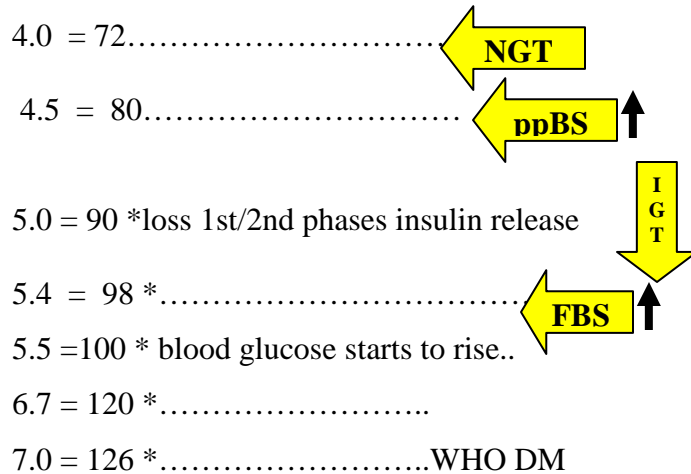
Not all “pre diabetics” are the same (FBS 100 vs. 110). Subjects with FBS 110 have greater risk of progression to frank diabetes with all its metabolic and cardiovascular risks. ADA screening has progressively been lowered to cut-off values from 140 to 125 to 110 and lately to 100.^{21,22,23}

There has been shown an increase in mortality risk of pre-diabetes IFG in Taiwan. IFG 110-125 is an independent risk factor and should be aggressively treated as a disease because its mortality risk for CVD and DM2 were significantly increased. 100-125 did not have the predictive power for later increase in CVD or diabetes mortality.²³

FASTING BLOOD SUGAR (VEIN)



FASTING BLOOD SUGAR (VEIN)



WHO SAID YOU CAN NOT PREVENT DIABETES? LIFESTYLE CHANGE DIAMICRON?? METFORMIN?? ACARBOSE?? TZD?? GLP 1 ag?? GIP at?? DPP4 at?? GIVEN EARLY ENOUGH??

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Figure 11

Figure 10

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PREVENT DIABETES: PREVENT DISASTER - - - from page 9

Increased beta cell apoptosis and impaired first and second phases of insulin secretion precede the development of IFG, which coincides with 50% defect in beta cell mass and onset of hepatic insulin resistance (diabetes 70%)²⁴

So when do you call diabetes DIABETES? Why the intense hesitancy to call it diabetes? Our concern comes from the real threat: diabetes is a heart disease, equivalent to a non-diabetic who has already had a myocardial infarction (equivalent to at least two risk factors); think of all the good people who have been lost to heart attacks and strokes with “essentially normal blood sugars” They could have been saved with perfect control of blood sugars, blood pressure, weight, and lipids.^{25,26,27}

Behind the hesitancy are socio-economic-insurance-political reasons, all of which would not like to increase the number of liabilities to uncontrollable limits! But the number of casualties resulting victimizes unknown numbers of hapless citizens who do not stand a chance in the face of the relentless onslaught of the disease and its complications.

There is no better time to fight diabetes than when it is not yet obvious!! And the young ones are the best targets together with the “still not diabetic relatives” of our current diabetic population.

A strong national awareness coupled with sincere (apolitical) prevention programs is the only obvious answer to our current dilemma. In fact, this attitude will contribute much to the local increase in the prevalence of diabetes and its complications!

It is worth referring to the following procedures frequently as early warning signs of impending trouble – tools in detecting the coming of tsunami!

- a. hsCRP / total cholesterol HDL ratio²⁸
- b. HOMA-IR²⁹

$$IR = \text{FG mM/L} \times \text{FI mU/L} \div 22.5$$

$$\text{FG} = \text{Fasting Glucose} \quad \text{FI} = \text{Fasting Insulin}$$
 2.1 – 2.7 = normal
 *The biggest opportunity for prevention lies between HOMA-IR 2.7 and 4.3. That is the time to strike hard with lifestyle change with or without pharmacotherapy! Seeking for evidence base? Convert READY, AIM, FIRE to READY – FIRE!
 4.3 – 5.2 = IGT
 8.3 – 9.5 = DM2
- c. Serial fasting blood glucose (drawn from a vein in a competent lab.)
- d. The OGTT has been called stupid by Dr. Dandonna in the last REF Lecture October 21, 2006 and may even be hazardous.

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Calendar of Activities July- September 2006

- | | |
|--------------------|----------------------------------------------------------------------------------------------------------|
| February | American Diabetes Association,
Advanced Post Graduate Course
New York, USA Prediabetes.
Morocco |
| June | American Diabetes Association
Yearly Meeting Washington DC,
USA |
| August 4-5 | PSD Advanced Workshop
Astoria Plaza |
| August 18-19 | UERMMMC-ISDFI Rizal
Diabetes Workshop Lopez Center |
| August 18-19 | UERMMMC-ISDFI Batangas
Foot Care Workshop Hote
l Pontefino, Pallocan West
Batangas City |
| September | European Association for Studies
on Diabetes Copenhagen,
Denmark |
| Sept. 29-30 | UERMMMC-ISDFI Dipolog
Diabetes Workshop Top Plaza
Hotel |

PREVENT DIABETES: PREVENT DISASTER - - - from page 11

- | | |
|---------------------------------------------------------|-------------------------------------------|
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THE DIABETOLOGIST

In a day when many people would like to claim they are diabetologists, we would like to reprint the following article printed in the 1992 scribblings as a reminder to our graduates. Then in 2003 diabetologia's 1st issue editor published a very interesting article on the diabetologists. This follows

THE DIABETOLOGIST – A NEW BREED OF SPECIALISTS**R.E. Fernando, M.D., FPCP, FPSEM**

Diabetologists are a new breed of doctors. "They are specialists in internal medicine, who possess a concentrated and on-going interest in diabetes mellitus. They continue to provide general medical care to their patients, but at the same time are abreast with the most up-to-date solutions to the problems of the diabetics. They give instructions to diabetics and their relatives as well as guidance to doctors, nurses, and other paramedical personnel".

Who then can be called a diabetologist?

Firstly, a specialist should have the educational and practical background that would give him confidence in what he would like to do. Good training is a very important factor in the success of his endeavors.

Yet a few bad apples do come from highly reputable training institutions and a few good apples may come surprisingly from rotten baskets. Certificates and diplomas do not offer absolute guarantees of competence.

Secondly, a specialist is expected to deal mostly with patients afflicted by a particular disease during

his day-to-day practice. If an internist elects to concentrate on a particular disease line for his life work – like diabetes – it should not be too presumptuous for him to call himself a student of diabetes – a diabetologist. I still remember that during my earlier days in practice, when I said I was going into diabetology, eyebrows were raised and the establishment started spreading the word around that there was no such specialty as diabetology. At that time, my shingle bore the inscriptions: Internal Medicine – Diabetes.

Thirdly, in the practice of a specialty, at least 60% of one's patient load should belong to that specialty. I have always felt that this should be one of the major criteria in confirming a specialist. Otherwise nobody can be blamed for calling that practitioner a generalist. So who is the doctor who has confined his clientele largely to diabetics?

Fourthly, no institution, association or society can presume that it is the only one that can infallibly pass judgment on the adequacy and competence of a specialist. In a developing country like ours, good apples and bad apples do get mixed up in the same basket. We really have very few pure specialty societies. Some societies are subjects of silent ridicule because of the nature of their memberships. The fact of the matter is, many of our so-

called specialists of note today did not take any local specialty board exams in the past, but were merely passive and happy beneficiaries of that vague innovation called “grandfather's clause” during the organization of their specialties. It is interesting to note how many of them are so pre-occupied today in making it unreasonably difficult for the younger ones to enter the specialty. I know a number of well-trained specialists who have not joined their specialty societies, some for socio-political reasons.

Anyway the country does not have any diabetes specialty board. The Philippine Diabetes Association is not a specialty society; it is a service organization made up of a heterogenous group of doctors, nurses, dietitians, and laymen. None of our current societies can claim monopoly over diabetes. It can be as much a claim of the endocrinologist as the internist or the pediatrician or the family physician – all of whom are presumed to be specialists.

Fifth, because of the nature of his practice, aside from a reasonable command of molecular biology/biochemistry/pharmacology, the diabetologist must know enough of eye/nerve/kidney, brain/heart/feet, and other systems, and infections, and surgery, and pregnancy – if he is to take care of his patients adequately.

Finally, the fact of experience is that each one has to establish his own credibility not only among his peers but also among his patients over so many trying years of practice. Young ones who would call themselves diabetologists should say so with their tongues in their cheeks hoping that time and honest hard work will vindicate their claim to the specialty. While the older ones who many times suffer from insecurity or hopeless egotism should honestly examine their own positions lest they suddenly find themselves in remarkably embarrassing situations,

and not try to bully their way into professional prominence. Take note that the first followers of Jesus Christ did not call themselves Christians – they were called Christians. The proper distinguishing tag should come after the product has proven itself.

The Institute for Studies on Diabetes does not manufacture diabetologists. It only hopefully catalyzes the metamorphosis of a dedicated internist into a diabetologist. The brunt of the total effort the proof still is on the shoulders of him who would be called a diabetologist.

The Diabetologist from the point of view of a Journalist - - - from page 16

C. Clinical Science – Angiology, Cardiology, Clinical pharmacology, Dermatology, Economics of health care, Endocrinology and Metabolism, Gastroenterology, Infectiology, Nephrology, Pediatrics, Preventive Medicine, Psychology, Transplantation.

The clinical investigator is an endangered species (Wyngaarden 1979).

Such experts are not burdened and limited in their efforts by clinical constraints. They study metabolic and other derangements as they occur in a diabetic organism in molecular detail and they have their own jargon, which occasionally can be hard to follow for the clinician. Their invaluable work, however, brings understanding and insights in detail and contributes about 50% of published articles.

Indeed, diabetes refers to a group of complex disease whose study requires institutions to provide close interaction of clinical and basic sciences, as well as expert training to diabetologists of all three groups. However, not only diabetologists need to be highly qualified, but the readers of Diabetologia are also confronted with the same demand. They are expected to have a keen interest in diabetes as well as in a broad spectrum of scientific disciplines.

To better meet the needs of patients suffering from diabetes and to entice the readers of Diabetologia so that physician diabetologists, clinical investigators and basic scientists alike eagerly await the journal's next monthly issue and fully read it, the influx of high quality manuscripts should, however, be increased even further.

Werner K. Waldhausl
Editor in Chief, Diabetologia. 2003

The Diabetologist from the point of view of a Journalist

I am overwhelmed by the clinical and scientific demands put on a diabetologist and identify three subgroups: the physician diabetologist, the clinical diabetology scientist and the basic scientist interested in diabetes.

The physician diabetologist in charge of patient care has to command clinical skills going far beyond the still too common attitude of glucose-centrism, which just focuses on treating elevated blood glucose concentrations and abnormal HbA1c. To serve his patients well, the modern physician diabetologist has to be more of an internist than just a blood glucose-centered diabetologist. He has to care not only for good metabolic control but also for maintenance of normal blood pressure, kidney function, vascular patency, endothelial and gastrointestinal function, and among others sexual health. In addition, he has to help prevent the progression of the disease in the patient's diabetic heart and diabetic foot. Against this background clinical diabetology has to be recognized as a demanding job whereby the physician is required to be knowledgeable in a considerable number of sub-specialties of Internal Medicine. He has to be thoroughly trained to be able to serve the patient properly and to co-ordinate any necessary support by specialists of all sorts. The

dimension of this task has not been fully perceived by many clinical practitioners involved in diabetes care.

The diabetologist scientist is confronted with similarly formidable expectations. He has to be knowledgeable both in Internal Medicine or Pediatrics and in Clinical Pharmacology, which includes study design and complex methodologies borrowing from many sub-specialties depending on the hypotheses tested. This can become a difficult task when the diabetologist scientist turns to studies of more complex cardiological, neurological or ophthalmological problems as they occur in the course of diabetes. Clearly, the diabetologist has to be a good physician but also an excellent clinical investigator. Such experts are in high demand in clinical science, but they are few in number and for many years have been regarded as an endangered species. They require utmost protection and support in any clinical and academic environment. Their training should be a major obligation for units of clinical diabetology, which could become a major provider of highly qualified clinical investigators.

The third group of diabetologists is the basic scientist interested in fundamental diabetes research. He can be found in a multitude of basic science areas.

A. Defined by subheadings - Epidemiology, clinical trials and Diabetes care, Etiology and Pathophysiology, Metabolism, Immunology, Islet of Langerhans, Diabetes Associated Complications, Genetics, Methodology.

B. Basic Science - Animal experimentation, Biochemistry, Blood Clotting, Cytology, Electrophysiology, Embryology, Molecular biology. Oxidative stress. Pharmacology, Physiologiacl Chemistry, Stable isotope technique, Virology. Xenotransplantation.