Ann Natl Acad Med Sci (India), 42 (Suppl.) : 5-10, 2006
Edited by : J.S. Bajaj & K.K. Talwar

Editorial

Metabolic Syndrome
From Inert Facts to Informed Action

Emeritus Prof. J.S. Bajaj
M.D., F.R.C.P.(Lond.),F.R.C.P.(Ed.),F.A.M.S., D.M.(h.c. Karolinska)
Hon. D.Sc.(B.H.U.); D.Sc. (h.c. MGR Med. Univ.);D.Sc.(h.c. GND Univ.)
Hon. D.Sc. (Madras); Hon. D.Sc. (Punjabi Univ.), D.Sc. (h.c. Univ. Health Sc; Andhra)

Honorary President, International Diabetes Federation;
Chairman, Academic Council, National Academy of Medical Sciences.

With due apologies to Charles Dickens, the recently generated intense debate on the Metabolic Syndrome (MS), may well be captioned as "A Tale of Two Worlds". The debate is essentially centered around *Egomantics*, a somewhat catastrophic combination of semantics *and* superego. While my distinguished colleagues at the International Diabetes Federation (IDF) concede that MS is 'perhaps an etiologic mystery but far from a myth'(1), the leadership of the American Diabetes Association (ADA) and European Association for the Study of Diabetes (EASD) insist that 'the MS has been imprecisely defined, there is a lack of certainty regarding its pathogenesis, and there is considerable doubt regarding its value as a cardiovascular disease risk marker' (2). Nevertheless, they also grudgingly admit that 'the term MS has now taken hold in the medical literature. It has been defined and institutionalized, principally by the World Health Organization (WHO) (3) and the Third Report of the National Cholesterol Education Program's Adult Treatment Panel (NCEP-ATP III) (4) albeit with different definitions. In addition, other organizations have developed similar, but again not identical, definitions (5,6). The fact that a version of the MS has its own ICD-9 code (277.7) also suggests that it is well thought out'.

Responding (or perhaps reacting) to what they call *'shot across the bow of the MS'*, the gallant knight(s), presumably representing the viewpoint of International Diabetes Federation, state (1) : 'we recognize the importance of debate : however, the appearance of this initiative on behalf of two of the world's leading regional diabetes organizations raises questions of motive and timing. Are the criticisms part of a "turf protection" scenario or do they have a valid scientific basis?'. This logic reflects the assumption

that the view of the whole i.e. IDF must have a greater credence and credibility than that of its individual constituents i.e. ADA and EASD. Almost like the logic behind MS and its constituents!

Essentially, the scientific argument of the protagonists is based on the facts that : (i) MS represents a risk-factor clustering that increases the "global risk" for atherosclerotic cardiovascular disease (ACVD) (7,8); (ii) the constituent risk factors appear to be of metabolic origin; (iii) the seemingly apparent contradictions between different definitions of MS result from the 'healthy process of evolution' (9); (iv) regardless of the precise metabolic pathways involved, both central obesity and insulin resistance are common risk conditions underlying the MS (7); (v) for a condition such as the MS in which there is a clustering of risk factors, precise clinical criteria are difficult to propose; (vi) proposed thresholds of the risk factors by necessity are arbitrary, but in the ATP III and IDF clinical definitions, their use has the virtue of simplicity; (vii) as current thresholds employed for clinical diagnosis are based on contemporary recommendations of accepted expert panels, Kahn and colleagues (i.e. opponents) are stretching credibility with the claim that the current clinical definition of the MS is imprecise; (viii) as a general rule, the risk from MS for major ACVD events is approximately twice as high as for those without the syndrome (10). For type 2 diabetes, MS confers an approximate 5-fold greater risk (10); (ix) it cannot be overemphasized that MS is not an *absolute risk predictor.*

Finally, the protagonists tend to close the argument for their forceful defense of MS by stating : 'the ADA/EASD attempt to disregard the MS will only confuse health professionals at all levels. The utility of the syndrome as a public health initiative has been put at risk by a statement that has "come out of the blue" and does not reflect the *past intellectual and constructive contributions of some of the individual authors!*' What a pity that an academic and scientific debate is closed by questioning the past intellectual and constructive contributions of some of the opponents!

The last statement was provocative enough to invite a befitting retort from Richard Kahn, the first author of the ADA/ EASD joint statement. In his article 'The Metabolic Syndrome (Emperor) wears no clothes (11)', Kahn laments the fact that despite over 10,000 articles on the subject, there is much missing information. He raises the critical question : 'whether we know enough about this constellation of risk factors to warrant adopting a unique clinical construct that has value to either physicians and / or patients?' He sums up the basic issues in support of his line of argument : (i) there is no biological basis for the diagnostic algorithm ; (ii) with many revisions of the diagnostic algorithm, there is a lack of specific biological evidence that warrants the change and / or clarifies as to

how the new/revised definition enhances the sensitivity, specificity, and positive predictive value of the diagnosis; (iv) MS, as defined, is a relatively insensitive indicator of insulin resistance (12,13); (v) if the syndrome includes other 'prothrombotic and proinflammatory states' or factors, why are there no such criteria in the definition?, and finally (vi) since all of the syndrome variables have no upper cut-off limits, many individuals will be so diagnosed because they have overt diabetes, hypertension, or severe lipid abnormalities.

The proponents, in a recent publication (14), draw support from the scientific statement published by American Heart Association and National Heart, Lung, and Blood Institute, endorsing essentially the concept and definition of MS (15,16). In a follow-up of this statement, Grundy reinforces the proponent's arguments and states (17) : 'Five risk factors of metabolic origin (atherogenic dyslipidemia, elevated blood pressure, elevated glucose, a prothrombotic state, and a proinflammatory state) commonly cluster together. This aggregation is frequently observed in clinical practice, and it has been convincingly documented in prospective studies by cluster analyses. Risk factor clustering cannot be explained by chance occurrence alone. Thus, if the metabolic syndrome is defined as multiple risk factors that are metabolically interrelated, then the syndrome certainly exists.' The discerning readers will readily notice the inclusion of 'a prothrombotic state, and a proinflammatory state' amongst the cluster of risk factors while the proponents donot include these in the 'international consensus'.

In this cacophony of arguments and counterarguments, what seems to have been forgotten (especially by those who live near Stratford-upon-Avon) is the axiom : *'you cannot stage Hamlet without the Prince of Denmark'*. Both the proponents and opponents cite the 'seminal' work of Gerald Reaven who, in his Banting Lecture in 1988, provided the conceptual framework of clustering of metabolic risk factors, suggesting the term 'Syndrome X' (18). His peers honoured him by naming the syndrome as Reaven's Syndrome. When the scientific level of current debate was reduced to questioning the *past intellectual and constructive contributions* of some of the individual authors of ADA/EASD statement, the Oracle finally spoke. In a thought provoking article : 'The Metabolic Syndrome : is this diagnosis necessary' (19), Gerald Reaven has imparted poise and equanimity to the raging debate. In his masterly review, Reaven concludes : '(i) providers should avoid labeling patients with the term metabolic syndrome ; (ii) adults with any major CVD risk factor should be evaluated for the presence of other CVD risk factors; and (iii) all CVD risk factors should be individually and aggressively treated. If these goals are achieved, there is no longer a need for a diagnosis of metabolic syndrome, a controversy about the best definition of the

metabolic syndrome, or any confusion as to the clinical approach to patients who, although they are at greater risk of CVD, do not qualify for a diagnosis of metabolic syndrome.'

Such an approach finds a resounding echo in the recently published joint statement of American Diabetes Association and American Heart Association (20): 'Both the American Heart Association and the American Diabetes Association remain jointly committed to a reduction in heart disease, stroke, and new-onset diabetes. We strongly recommend that all providers assess patients for their global risk for CVD and diabetes. Despite many unresolved scientific issues, a number of *cardiometabolic risk factors* have been clearly shown to be closely related to diabetes and CVD : fasting / postprandial hyperglycemia, overweight/obesity, elevated systolic and diastolic blood pressure, and dyslipidemia. Although pharmacologic therapy is often indicated when overt disease is detected, in the early stages of these conditions, lifestyle modification with attention to weight loss and physical activity may well be sufficient.'

This clarion ***Call for Action*** is a pragmatic approach. While future research will continue to clarify MS-related issues, health care providers at all levels, from primary health care workers and primary care physicians to nurses, pharmacists, practitioners of Family Medicine, and finally upto and including specialists and tertiary care providers must join together to implement *'risk reduction'* approach. Health Policy Planners and Health Administrators must affect such changes not only in health policies but also in all related intersectoral policies such as agriculture, tobacco industry, information and broadcasting, and telecommunication to impart health-friendly orientation to all actions focused at 'risk reduction' and to educate communities regarding hazards of *coca-colonisation and McDonaldisation.*

If this debate results in the development and implementation of appropriate action plans as suggested above, and such plans *a priori* take into consideration the health needs and resources of each country, besides stimulating research efforts to provide the much needed information presently missing, it would have admirably served its purpose. It would certainly have the whole-hearted support of all of us, who have served the cause of primary diabetes care and of the delivery of preventive and promotive community health services to deprived population. Hopefully, such an appeal coming from one who has served and nurtured the International Diabetes Federation for nearly four decades, and has continuing admiration for the past and present leadership of both the IDF and ADA, may strike a sympathetic chord in those involved in this no holds-barred debate . Otherwise this appeal will remain, like that of exhortation by Reaven, a cry in the wilderness.

As Bertrand Russell in his ***Unpopular Essays*** states : *"for it is not enough to recognize that all our knowledge is, in a greater or lesser degree, uncertain and vague; it is necessary at the same time to learn to act upon the best hypothesis without dogmatically believing it".*

References :

1. Zimmet PZ, Alberti G (2005). The Metabolic Syndrome : Perhaps an Etiologic Mystery but Far From a Myth - Where Does the International Diabetes Federation Stand? *Medscape Diabetes & Endocrinology.* **7** (Posted 10/11/2005).
2. Kahn R, Buse J. Ferrannini E, Stern M (2005). The metabolic syndrome : time for a critical appraisal : joint statement from the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* **28** : 2289-2304.
3. World Health Organisation : Definition, Diagnosis, and Classification of Diabetes Mellitus and its Complications : Report of a WHO Consultation. Geneva, World Health Org., 1999.
4. Expert Panel on the Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (2001). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) *JAMA.* **285**: 2486-2497.
5. Balkau B, Charles MA, Drivsholm T, Borch-Hohnsen K, Wareham N, Yudkin JS, Morris R, Zavaroni I, Van Dam R, Feskins E, Gabriel R, Diet M, Nilsson P, Hedblad B, European Group For The Study Of Insulin Resistance (EGIR) (2002). Frequency of the WHO metabolic syndrome in European cohorts, and an alternative definition of an insulin resistance syndrome. *Diabetes Metab.* **28** :364-376.
6. Einhorn D, Reaven GM, Cobin RH, Ford E, Ganda OP, Handelsman Y, Hellman R, Jellinger PS, Kendall D, Krauss RM, Neufeld ND, Petak SM, Rodbard HW, Seibel JA, Smith DA, Wilson PW (2003). American College of Endocrinology position statement on the insulin resistance syndrome. *Endocr Pract.* **9** :237-252.
7. Lemieux I, Pascot A, Couillard C et. al. (2000). Hypertriglyceridemic waist : a marker of the atherogenic metabolic triad (hyperinsulinemia ; hyperapolipoprotein B; small, dense LDL) in men ? *Circulation.* **102**: 179-184.
8. Grundy SM, Brewer HB Jr, Cleeman JI, Smith SC Jr, Lenfant C (2004). National Heart, Lung, and Blood Institute; American Heart Association. Definition of metabolic syndrome: report of the National Heart, Lung, and Blood Institute/American Heart Association conference on scientific issues related to definition. *Arterioscler Thromb Vasc Biol.* **24** : e13-e18.
9. Bloomgarden ZT (2003). The Endocrine Society meeting : topics in insulin sensitivity and hypertension. *Diabetes Care.* **26** : 2679-2688.
10. Eckel RH, Grundy SM, Zimmet PZ (2005). The metabolic syndrome. *Lancet.* **365** : 1415-1428.
11. Kahn R (2006). The Metabolic Syndrome (Emperor) Wears No Clothes. *Diabetes Care.* **29** : 1693-1696.
12. Cheal KL, Abasi F, Lamendola C, McLaughlin T, Reaven GM, Ford ES (2004).

Relationship to insulin resistance of the Adult Treatment Panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes.* **53** :1195-1200.

13. McLaughlin T, Abbasi F, Cheal K, Chu J, Lamendola C, Reaven G (2003). Use of metabolic markers to identify overweight individuals who are insulin resistant. *Ann Intern Med.* **139** :802-809.
14. Zimmet P, Alberti G (2006). Diabetes and the metabolic syndrome : The IDF definition. *Diabetes Voice.* **51** : 11-14.
15. Grundy SM, Cleeman JI, Daniels SR, et. al. (2005) Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Circulation.* **112** : e285-e290.
16. Grundy SM, Cleeman JI, Daniels SR, et. al. (2005). Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. *Circulation.* **112** : 2735-2752.
17. Grundy SM (2006). Does the Metabolic Syndrome Exist? *Diabetes Care.* **29** :1689-1692.
18. Reaven GM (1988). Banting Lecture 1988. Role of insulin resistance in human disease. *Diabetes.* **37** : 1595-1607.
19. Reaven GM (2006). The metabolic syndrome : is this diagnosis necessary? *Am Jour of Clin Nutr.* **83** :1237-1247.
20. Eckel RH, Kahn R, Robertson RM, Rizza RA (2006). Preventing Cardiovascular Disease and Diabetes : A call to action from the American Diabetes Association and the American Heart Association. *Diabetes Care.* **29**:1697-1699.