and SAH after blood sample incubation over a period of 0, 2, 6, and 24 h at room temperature or at 4 °C. In the Primavette, Hcy obtained by HPLC decreased only slightly (−4.8%) after 6-h incubation at room temperature and returned to the baseline value after 24 h. At 4 °C a significant decrease of Hcy (6.9%) after 24-h incubation was found (P = 0.003). Applying FPIA for the determination of Hcy, no significant changes of Hcy compared with the baseline values were found. However, the comparison between baseline Hcy determined by FPIA and HPLC revealed that Hcy values obtained by FPIA were significantly higher (median difference 11%) than values obtained by HPLC (P < 0.001). In EDTA and acidic citrate plasma we observed no significant difference between Hcy obtained by FPIA and HPLC. The positive bias seen with Primavette tubes was likely due to interferences with the FPIA method by its proprietary components, which are kept secret by the manufacturer.

In acidic citrate samples Hcy increased slowly at room temperature, reaching the level of significance after 6 h (FPIA) and 24 h (HPLC), respectively. At 4 °C Hcy was stable over a 24-h period. In EDTA tubes a strong increase of Hcy was observed that was markedly decreased at 4 °C. In the Primavette, SAM was stable at room temperature and at 4 °C. At room temperature SAM decreased in EDTA and to a smaller extent in acidic citrate tubes. This decrease was clearly decelerated at 4 °C. At room temperature SAH increased in all 3 collection tubes and reached the highest values in the Primavette after 24 h. The increase was attenuated at 4 °C.

In Primavette and acidic citrate samples we observed 7- and 3-fold increases of plasma SAH after 24-h incubation at room temperature, whereas Hcy was stable and increased by 20%, respectively (geometric means). In EDTA samples SAH and Hcy increased 1.8-fold. Interestingly, the increase of SAH after 24 h correlated negatively with the increase of Hcy after 24 h in Primavette and acidic citrate samples (r = −0.647; P = 0.002) but not in EDTA samples (r = 0.067). Hcy is generated in erythrocytes from its precursor SAH by catalysis of SAH hydrolase. Therefore, the inhibition of SAH hydrolase activity causes an increase of SAH and no or low increase of Hcy. In contrast, in EDTA samples the increase of SAH is low because SAH is metabolized to Hcy. Furthermore, a leakage of SAH from erythrocytes into the plasma might occur because cellular SAH concentrations are approximately 10-fold higher than in plasma (4). In blood samples Hcy can be stabilized by the addition of an SAH hydrolase inhibitor (5).

In conclusion, our results indicate that the stabilizing effect of Primavette and acidic citrate on Hcy is due to the inhibition of SAH hydrolase activity. The inhibition of SAH hydrolase is more efficient in Primavette than in acidic citrate tubes. However, in Primavette samples Hcy obtained by FPIA was approximately 11% higher than Hcy obtained by HPLC.

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anistically to suggest some kind of disease entity. Second, the term and concept retain utility simply for want of a fuller description of the underlying pathology. Third, the concept is self-sustaining, in that the existing body of research attracts further research and comment. Fourth, industry promotes the syndrome in symposia and review articles, alongside related concepts such as the “cardio-metabolic syndrome” and “cardio-metabolic risk”.

But perhaps most interestingly, the metabolic syndrome thrives because the notion of a distinct pathophysiological entity indulges the intuitive essentialism and predilections for simplification and category formation that inhere in human cognition as evolutionary legacies (3). To Homo sapiens, a unified syndrome has gut appeal and even mystique—as exemplified by the allure of the phrase “syndrome X” (4). A closely connected nosologic issue that reflects similar inclinations is the tendency to dichotomize continuous variables into crude categories of disease and health.

It is possible, however, that no consensus will ever be achieved on a definition for the metabolic syndrome as a diagnostic category, and that no disease entity will be conclusively delimited. This lack of resolution, in a different sense, is also a matter of our evolutionary legacy. The systems that transact the business of cells and regulate human physiology evolved not with rational foresight, but through bricolage, the selective but ramshackle accretion of countless innovations of contingent origin (5). Consequently the regulatory systems of higher organisms are highly complex, interconnected, and multifarious; riven with redundancies and lacunae; and resistant to systematization.

This form of complexity is the fundamental reason why it is so difficult to define the metabolic syndrome, either as disease entity or diagnostic category. It is also why the metabolic syndrome cannot be adequately described on any single level, such as that of genetics, molecular biology, intercellular signaling, or physiological subsystems. And hence too, the number of pathophysiologic factors implicated in the metabolic syndrome, such as hepatic, hemodynamic, endothelial, and inflammatory elements, continues to grow.

Human cognition is serial and weighted toward simplicity; cell and organismal physiology is parallel and complex. The error in our conceptualization of the metabolic syndrome lies in overintegration, for in this setting it is to be expected that a spectrum or range of pathology should exist rather than a single cardinal disease pathway. Perhaps at the top level it is therefore preferable to envisage not a metabolic syndrome, but a cardiovascular, renal, and metabolic pathophysiologic matrix (CRM matrix), within which a range of related benign and disease states may develop.

The characteristic range of disease states that emerge within this matrix might be described as CRM spectrum disorders. The insulin resistance syndrome of Reaven might prove to be one such disorder; alternatively, several distinct metabolic syndromes, or defined axes of variation within a pathologic continuum, might be characterized. That is a matter for research. But as research proceeds, its correct task might be framed not as one of unification, but of taxonomy, whose goal is to elaborate the nature and relationships of the full range of CRM spectrum disorders and identify appropriate interventions for each.

Such an approach might also impact on the assessment of risk. One might, for instance, conceive of a CRM risk profile with an associated scoring system.

The concepts of a CRM matrix and CRM spectrum disorders run counter to the instinct to overintegrate, but allow instead for a family of disorders or range of pathology to be comprehended within a single analytic perspective. These concepts also provide a more realistic framework for ongoing research. As population genetics and molecular physiology advance and a more meticulous parsing of disease states becomes possible, and as computer-based prediction models grow in sophistication, medicine will need to move beyond the era of the all-encompassing syndrome and adopt a more systematic approach that better reflects the nature of biological systems and their evolutionary history.

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Effect of Corticosteroid Therapy on Low-Molecular–Weight Protein Markers of Kidney Function

To the Editor:
Serum cystatin C, β2-microglobulin, and β-trace protein are endogenous markers of glomerular filtration rate (GFR). Cystatin C, in particular, is a promising alternative to creatinine for the detection of incipient renal failure. However, corticosteroids affect the extrarenal metabolism of cystatin C, which limits the use of cystatin C as a marker of GFR in a variety of clinical settings. Low-molecular–weight (LMW) β-trace protein might be a useful alternative in this respect. The present study set