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LETTER TO THE EDITOR

Reply to AM Zivkovic and JB German

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Dear Sir:

In their letter, Zivkovic and German argue that the metabolic syndrome should be viewed from the perspective of systems biology. This view could aid in the understanding of individual variation in the risk-factor expression of the syndrome. Systems biologists attempt to understand how complex biological systems function in light of multiple interconnected pathways (1). It represents an integrative or synthetic approach to biological phenomena. Zivkovic and German contend that the metabolic syndrome is an example par excellence of a biological system gone astray. I am sympathetic to the systems biology approach to the metabolic syndrome. It may hold considerable promise for a better understanding of the syndrome.

As Zivkovic and German point out, some investigators, such as Reaven (2), have set forward the hypothesis that a single underlying factor—insulin resistance—dominates the causation of the syndrome. Although this is a powerful and useful hypothesis, it does not adequately account for variable expression of the risk factors associated with the syndrome. I contend that ≥3 levels of causation must be considered to account for the great variation in manifestations of the syndrome (3). First, most persons with the metabolic syndrome are either overweight or obese. A nutrient energy overload, manifest by obesity, places a strain on metabolic processes and sets the stage for development of the syndrome. However, obesity alone is not sufficient. Because many obese persons do not have the syndrome, metabolic susceptibility must also be a factor. One form of susceptibility is systemic and is characterized by a generalized metabolic dysfunction; in my view, this dysfunction is what many investigators call insulin resistance, although the overall derangement may involve pathways other than insulin signaling pathways. There also can be risk-factor specific dysregulation that modifies the responses in each risk factor. It seems to me that this model of the pathogenesis of the metabolic syndrome better accounts for individual variability than does the insulin-resistance model.

One question that is repeatedly asked about the metabolic syndrome is whether its whole is more than its parts. Presumably, the question being asked is whether the syndrome confers a greater risk of cardiovascular disease (CVD) than does its component risk factors. Zivkovic and German contend that a major message of systems approaches is that the whole is always greater than its parts. This thought is contained in the concept of *emergence*, which implies that new entities, such as living systems, emerge out of complex combinations of simple units (4). It is on this concept that Zivokvic and German seemingly base their conclusion that the metabolic syndrome embodies more risk than would be embodied by the sum of its risk components.

One argument supporting the view that the CVD risk accompanying the metabolic syndrome is greater than its component parts is the observation that risk factors are multiplicative, ie, their combined effect on risk is greater than the sum of the risk of individual risk factors. Presumably, risk factors are synergistic in their actions on the arterial wall. The multiplicative nature of CVD risk factors is well established in epidemiology and presumably is an example

of "systems biology at work."

Even if the risk associated with the metabolic syndrome were to equate to the sum of the component risk factors, the issue remains whether all of the risk components can actually be identified. Because atherogenesis is a chronic condition, it is difficult to define the relative contributions of each of the components of the syndrome. Two of the metabolic risk factors, elevated blood pressure and reduced HDL-cholesterol concentrations, are most strongly associated with atherosclerotic CVD events in epidemiologic studies, but these risk factors are not necessarily the only causes of clinical disease in patients with the syndrome. Because of colinearity with the other factors, predictive power does not always equate to causality. The contributions of elevated triacylglycerol-rich lipoproteins, a prothrombotic state, a proinflammatory state, and insulin resistance tend to be hidden behind blood pressure and HDL cholesterol, although considerable evidence exists that these 2 factors increase the risk of atherosclerotic CVD events.

Finally, the metabolic syndrome is progressive, ie, its risk factors tend to worsen with advancing age. For this reason, risk is compounded over time. Long-term risk rises progressively so that lifetime risk exceeds that which would be extrapolated from short-term risk projections.

On the whole, I essentially agree with Zivkovic and German that both the pathogenesis and accompanying risk of the metabolic syndrome should be viewed as a problem of systems biology. I encourage them to continue to explore this concept because it has implications beyond the metabolic syndrome, ie, to the entire field of risk prediction for disease.

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REFERENCES

1. Ideker T, Galitski T, Hood L. A new approach to decoding life: systems biology. Annu Rev Genomics Hum Genet 2001;2:343-72.
2. Reaven GM. The metabolic syndrome: is this diagnosis necessary? Am J Clin Nutr 2006;83:1237-47.
3. Grundy SM. Does a diagnosis of metabolic syndrome have value in clinical practice? Am J Clin Nutr 2006;83:1248-51.
4. Emmeche C, Køppe S, Stjernfelt F. Explaining emergence: towards an ontology of levels. J Gen Philosophy Sci 1997;28:83-119.

Articles by Grundy, S. M