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Thought barriers to understanding rheumatic diseases – Viewed anew

Romatolojik hastalıkları anlamada düşünce engelleri – Yeni bir gözden geçirme

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Dr. Yazici asked me to bring up to date views I expressed in 1994 about perceptions of disease causation and treatment that have impeded our understanding of rheumatic diseases. I am pleased to do so with the qualification that my views are intended to characterize general concepts not specific hypotheses, though they may apply to the latter.

Starting from the recognition that there is great clinical overlap among the rheumatic diseases, and that the affected organs within an individual patient may change dramatically over time, the three perceived barriers were:

- Expecting that a single cause would explain the diseases.
- Expecting that chronic rheumatic diseases could be effectively treated with the medical practice patterns used for acute diseases.
- Expecting that reductionist research strategies would reveal the precise causal abnormalities and appropriate therapies.

These perceptions were commonplace in 1994, derived from experience with infections and injuries. However, evidence was already at hand to indicate their inadequacy for chronic illnesses and to buttress the arguments presented in that paper.

Since 1994, extraordinary advances in biological and clinical research have further undermined the validity of the barriers. The emerging data reveal the striking variability in the biologic processes that could play a role in disease causation, and the inappropriateness of much of conventional treatment. The issue now is how we interpret the data and how we act upon it.

It is widely agreed that the pathogenesis of inflammatory rheumatic disease is immunological, specifically a consequence of autoimmunity. But the mechanism remains obscure. Autoimmunity is present in normal people though usually not as extensively as in persons with rheumatic disease. The cells of the immune system, particularly the T and B cells, have both stimulating and repressing capabilities on aspects of the immune response, and they secrete many cytokines that have stimulating and repressing effects on other cells and on inflammation. Inhibition of the TNF cytokine improves but does not cure rheumatoid arthritis.

Because of the familial tendency of rheumatic diseases, a genetic basis of rheumatic diseases has been presumed but a specific abnormality has not been found. Genome wide analyses have revealed only weak associations. Genetic abnormalities could underlie function of cells of the immune system but here too, though associations have been made, no clear immunocyte malfunction has been found. Indeed, research has revealed extraordinary variation in gene function and thereby cell function. For example, chromosome expression can be

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Bu yazı, 16-20 Ekim 2011 tarihlerinde Antalya'da düzenlenen XII. Ulusal Romatoloji Kongresi'nin açılış konuşmasının özeti olarak hazırlanmıştır. */ This article is a summary of the keynote address of the XIIth National Congress of Rheumatology held between October 15-18, 2011 in Antalya, Turkey.*

altered by methylation of DNA and acetylation of histone, and DNA and messenger RNA function can be changed by microRNAs. Protein synthesis can be further modified by prions which are self-replicating proteins that can breed true. These multiple ways to change gene function without altering the coding sequence of DNA fall in the emerging field of epigenetics.

The biological complexity of rheumatic diseases is evident in their large clinical variation: (1) differences in target organs and their change over time, (2) differences in severity, (3) variation in age of onset, (4) discrepancies between clinical and laboratory abnormalities, and (5) differences in responses to the same therapy. Further, biological reactions can be influenced by social, environmental and psychological conditions, and stress can induce secretion of pro-inflammatory and other cytokines. And this long list of variation does not include the possibility of healing processes that could modify or prevent the disease.

Given the large number of potentially relevant biological variables, understanding causation will require a form of biologic systems analysis that can incorporate many variables.

In the treatment realm, much has also changed since 1994, and not just in medications. Most important has been recognition that chronic diseases, including rheumatic diseases, require a new pattern of health care. That pattern is based on care by a team consisting of the physician, a patient who is educated in self-care, and a case manager. The focus is on continuity and coordination of care, with a registry of patients to facilitate monitoring over time, and use of community treatment services. Many versions of chronic care have been developed; in the US the most prominent are the Chronic Care Model of health care practice and the Medical Home based on primary care. Care by these systems has proved to be more effective and less costly than conventional care. For purposes of this discussion, such care allows a more natural pattern of disease to emerge, unaffected by the shortcomings of conventional care. Thereby, clinical and biological investigators will have a more true understanding of the diseases they are studying.

The issue before us now is how we make use of this abundant knowledge to understand rheumatic diseases better, to improve our patients' health, and to make our professional lives richer.