Thought Barriers to Understanding Rheumatic Diseases
Halsted R. Holman Revisited

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Abstract

Halsted R. Holman, in a 1994 Arthritis & Rheumatism editorial, discusses how “thought barriers” can make our understanding of rheumatic diseases more difficult. The medical teaching-practice has traditionally been centered on acute disease; however, most rheumatic diseases are chronic. There is also the prevailing notion of a single lesion for each disease, a concept stemming from infectious diseases. Related to this is an investigative strategy of reductionism. We commonly overlook interactive biological pathways, which make up many of our diseases. In this regard, Holman advises us that 1. abnormalities are not necessarily harmful; 2. in rheumatological diseases, not only are multivariate causes-pathways operative, but the same pathways can be influenced by separate influences; 3. in chronic disease, “the task of the physician is to manage the course of disease over time,” a scheme where the patient is at the center of achieving and monitoring progress; and 4. our current medical care system is mainly based on acute care, and needs to be adopted more to the needs of chronic care. In the current manuscript, three additional “thought barriers” are proposed: 1. our urge to lump diseases is too simplistic and hinders progress; 2. the same is true for our resistance in not including diseased control groups in genetic association studies; and 3. misuse of the controlled clinical trial. The popular inductive reasoning with the propensity to prove rather than to falsify one’s self might be the common denominator in many of the barriers discussed.

We perhaps all have special pieces of literature, scientific or otherwise, that we return to time and again for reflection, to relearn, or simply to enjoy again. To me, Halsted R. Holman’s article Thought Barriers to Understanding Rheumatic Diseases is just such an article. In preparing this manuscript, I searched the online Web of Knowledge for the number of publications that had cited this particular article. The relatively small number of citations I observed to Holman’s Thought Barriers to Understanding Rheumatic Diseases, I reasoned, was surely another “thought barrier.”

I will first briefly go through what I consider are the highlights of what Holman had to say and will then venture some additional thought barriers. The fundamental problem in our current research efforts is that “the prevailing conceptual base of our investigation is incommensurate with the rheumatic disease problems which we confront.” There are three important reasons for the inadequacy of our approach:

1. The whole of medical teaching-practice traditionally has been centered on acute diseases, which come and go abruptly. Most diseases rheumatologists have to deal with, on the other hand, are chronic.
2. There is the prevailing notion of the “single lesion,” mainly a concept derived from infectious diseases, that we like to see when we are looking for a cause.
3. Somewhat related to item 2 (author emphasis), an investigative strategy of reductionism is common. We tend to overlook interactive biological pathways, which make up many of our diseases.

After laying out these “thought barrier” concepts, Holman gives a vivid account of the time when antinuclear antibodies (ANA) were first discovered; lupus patients were treated for high ANA levels, resulting in undue harm. The editorial continues with how our concept of understanding and managing rheumatologic diseases has changed from treating the
laboratory abnormality to giving more emphasis to clinical severity. Furthermore, the diseases we have to deal with have many overlapping clinical and laboratory features, and all of these are somewhat related to our evolving understanding of autoimmunity and how much of that we should consider as normal. Holman then provides a list of important clinical attributes that “have to be taken into account if the biology of the disease is to be understood” (Table 1). It is to be noted that the clinical attributes listed in the table are very difficult to reconcile with a single cause, the single disease mechanism concept. The final text of the article offers three pieces of advice on how to overcome some of these thought barriers:

1. We should significantly alter our approach to biological understanding by a better realization that a. “abnormalities are not always harmful and correction is not always beneficial” and b. in diseases, we have to take care of not only multivariate causes-pathways that are operative, but understand the same pathways can be impacted by separate influences.

2. Unlike in acute diseases where the usual aim is to cure, in chronic disease, “the task of the physician is to manage the course of disease over time.” In this scheme “…it is the patient who sets the goals and is an essential contributor to achieving and monitoring progress.”

3. Our healthcare system is mainly based on acute care and needs to be adopted more to the many needs of chronic care.

Hoping, thus far, I have not done any injustice to what Holman said, I propose here several additional thought barriers: 1. an irresistible urge to “lump” diseases; 2. an incomprehensible resistance to include diseased control groups in genetic association studies; and 3. the misuse of the controlled clinical trial.

Lumping Diseases

A certain amount of soul searching may be in order prior to further discussion of “lumping diseases.” My docent’s thesis 33 years ago was about disproving that Behçet’s syndrome was among the great rheumatologic “lump” of seronegative spondarthritides, as was then claimed. Later, I also disagreed that it was a bona fide autoimmune disease in the line of rheumatoid arthritis or systemic lupus erythematosus (SLE). Currently, I disagree with those who call Behçet’s syndrome an autoimmune disease, and I have some difficulty in classifying it with the primary vasculitides. The fact of the matter is that there are elements of Behçet’s that go along with seronegative spondarthritides. There surely are immunological aberrations in Behçet’s; the unique pathergy phenomenon of Behçet’s represents a bona fide increased inflammatory propensity, and there can be vasculitis in this curious condition from the minute venule all the way to the left ventricle. On the other hand, no single nosological “lump” explains the majority of what is going on in Behçet’s. Not only does it not explain, it has the potential of delaying our understanding of what is going on.

Among many others, one main objection some of us had against the inclusion of Behçet’s within the seronegative spondarthritides was our inability to show increased sacroiliitis in controlled studies. However, we have now realized 1. acne lesions of Behçet’s syndrome and arthritis often go together; 2. the pustular lesions are not sterile; and 3. there is increased enthesopathy among the acne-arthritis cluster of patients. On the other hand, there is no increased frequency of HLA B27 or sacroiliitis in these patients, and we have recent evidence that this cluster might be more present in familial Behçet patients. After all these years, I now reason that had we considered that there might have been some elements that could have been common to the other diseases in the seronegative spondarthritides “lump,” our debate would have taken a more fruitful course.

Similarly, the separation of ankylosing spondylitis (AS) from rheumatoid arthritis (RA) in the early 1960s was surely an intellectual and clinical accomplishment. The separated AS population made-up the back bone of the seronegative spondarthritides “lump” a decade later, especially with the addition of the HLA B27 association. However, the separation of AS from RA has perhaps been too complete. Including one publication from our unit, there have been reports that HLA B27 is also associated with RA to some degree and more importantly, there is the important observation that AS is more commonly seen in the families of RA patients. It was an “eye opener” for me to learn recently that among the first-degree relatives of a patient with RA, the odds ratio of having AS is definitely higher than having systemic lupus erythematosus (SLE) or Hashimoto’s thyroiditis, conditions which we always take as more closely related than AS is, with RA. In this line, I found it interesting that no reference, either backing or refuting, was made to the RA/AS/HLA B27 association I have been discussing, in a very recent and comprehensive publication on a “systemic comparison” of RA and AS. Forty years after its discovery, we still do not know what the HLA B27 means in AS. Would it be “heresy” to suggest that perhaps what we call RA and AS also have some common, granted considerably more separate, biological pathways which also have something to do with carrying the HLA B27 molecule?

The Genetic Association Studies and the Lack of Diseased Controls

The importance of diseased controls for the specificity of our observations is obvious. This being so, it is to me truly amazing why (as a rule!) genetic association studies in general, for example, 90% in our best journals, lack such controls. I was privileged to be in the meeting when the FMF (familial Mediterranean fever)–MEFV (pyrin) association was first presented (1st International Conference on FMF, Jerusalem, 2007). I vividly remember the industry booths in
the coffee break area already promising the genetic diagnosis probes. However, as said, the seeding work of two consortia from the United States and Europe did not include diseased controls, and it shortly became apparent that MEFV mutations were not specific for FMF. We now know that MEFV mutations, although very important in our understanding of inflammation in general, are not specific, or for that matter are even only about 70% sensitive for what we call FMF. However, almost 80% of the articles I read or review on FMF still open with a sentence to the effect that FMF is caused by MEFV mutations. Recently, as we were pointing out that “had the initial FMF-pyrin work included diseased controls, for example patients with other auto- or otherwise inflammatory conditions, the students of FMF would have been ‘where they are now’ quite a number of years ago.” One reviewer objected saying, “…had the two FMF consortia used a Behçet or Crohn’s disease control group, they might still be searching for the gene now…” I guess our reviewer had some more genes up his-her sleeve yet to disclose to our benefit.

This singular and curious resistance of the students of genetics to diseased controls is perhaps best reflected in the multi-investigator 2009 STREGA (Strengthening the Reporting of the Genetic Association) study guidelines simultaneously published in our highest impact basic and clinical science journals. This excellent position paper indeed, does provide a very useful list of guideline points in designing more meaningful association studies. The inclusion of diseased controls, however, is, as expected, not among the list.

Misuse of the Controlled Clinical Trial
I was given the opportunity to discuss this last “thought barrier” at some length in a previous issue. In brief, I closed my discussion by pointing out that the prevailing “inductive reasoning” of our times was perhaps the culprit of the abuse of this very important research tool. This last point takes me directly to my conclusion.

Conclusion
While I hope the “sweet music of cozy lumping” is not also misleading me into a dangerous generalization, I propose that our contemporary inductive and seductive reasoning is mainly responsible for our disease “lumping” and for our omission of diseased controls in the genetic association studies, a major area of our work. We are so “happy and keen” to prove rather than to falsify ourselves. The “truths,” lumps if you will, of our discussion are there to be reproved or complied with, and we take anything that lessens the strength of our argument or hinders our way to these truths as unfriendly and to be avoided.

It would be an injustice not to bring up here that, in his article, Professor Holman gives the Kuhn approach to scientific discoveries as the main frame of thought when he teases out the thought barriers he discusses. It is the revolutionary paradigm shift and not the gradual and peaceful accumulation of observations that is at the core of scientific progress. On the other hand, I strongly suspect, as others did, that the essence of this shift perhaps has always largely been the healthy Popperian falsification.

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References
8. Hatemi G, Fresko I, Tascilar K, Yazici H. Increased enthesopathy among Behçet’s syndrome patients with acne and

Table 1 Important Clinical Attributes in Understanding Diseases

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<td>• Same diagnosis, different target organ involvement between patients and within the same patient at different times.</td>
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<td>• Same diagnosis, different disease severity between patients and within the same patient at different times.</td>
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<td>• Discordance between the clinic and the laboratory. How often does a laboratory represent the response to rather than the cause of the disease?</td>
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<td>• What determines the age of onset of a genetic defect?</td>
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<td>• There is varying response to therapy among patients with same severity of disease.</td>
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