Introduction to the “Paradigm Shifts in Perspective” Series

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Published online: 12 June 2013
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The history of human knowledge has so uninterruptedly shown that to collateral, or incidental, or accidental events we are indebted for the most numerous and most valuable discoveries, that it has at length become necessary, in any prospective view of improvement, to make not only large, but the largest allowances for inventions that shall arise by chance, and quite out of the range of ordinary expectation.

—Edgar Allan Poe, *The Mystery of Marie Rogêt*, 1842

These words, voiced by Auguste Dupin, a fictional amateur sleuth, contain an inalienable truth regarding the nature of discovery. In science, the truly major advances, which substantially change the way we think, termed “paradigm shifts” [1], often arise from the most unexpected quarters by individuals not considered to be in the mainstream of investigators associated with a disease or observation. With this issue, *Digestive Diseases and Sciences* introduces a new series of articles entitled “Paradigm Shifts in Perspective” which is aimed at highlighting scientific findings that have had a major impact on the field of gastroenterology. One of the motivations for creating this series is to increase the appreciation for “small” science, driven mostly by intellectual curiosity informed by a desire to understand disease pathogenesis, the principal well-spring for these advances. We plan to highlight advances that were initially under-appreciated, scorned, or even forgotten, only to resurface or gain acceptance as the “game changers” of gastroenterology. Since it can take

decades for the full import of a discovery to manifest, most of the articles highlighted will be from the 1980s at the latest.

The first of these articles is by Daniel Hollander, who writes of his remarkable 1986 discovery in which he reports increased intestinal permeability in unaffected relatives of Crohn’s patients [2]. Although the familial nature of inflammatory bowel disease had been documented for decades previous, few disease biomarkers that would provide clues regarding its etiopathogenesis existed. Furthermore, at that time the concept of intestinal permeability as a static, intrinsic property of epithelia was widely held. Lastly, the concept that increased intestinal permeability could predispose to disease was virtually unknown.

The publication of Dr. Hollander’s paper in 1986 marked an important year for the understanding of the nature of intercellular junctions, with the publication of the cloning of one of the first junctional proteins, zonula occludens [ZO]-1. This finding, along with Dr. Hollander’s, marked the start of the current understanding of intercellular junctions as complex, dynamically regulated multiprotein structures, which have strong implications for disease pathogenesis. Although interventions have not yet targeted permeability, the observation that increased permeability could be a cause and not the effect of mucosal inflammation and injury changed the way we thought about IBD specifically and about mucosal injury in general. That junctional permeability could be under genetic control, as Dr. Hollander first reported, was a revolutionary finding, which helped ignite the current wide interest in the structure and function of intercellular junctions. Indeed, 20 years after its publication, several groups reported that increased intestinal permeability was present in relatives of patients with familial Crohn’s disease who bore specific mutations in the nucleotide-binding oligomerization domain-containing protein [NOD]2/caspase recruitment

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domain-containing protein [CARD]15 gene at a higher frequency than did control subjects [3, 4].

I hope that our readership will benefit from reading about the genesis of these important advances by having an increased appreciation for fundamental discovery in gastroenterology.

References

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