Reflux, revolution, and the role of forgotten research in medical paradigms

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Introduction

The conventional view of science as a plodding, methodical process free of entrenched interests and proceeding solely on the basis of observable facts permeates popular thinking. Scientists are often seen as seekers of truth, garbed all in white, using their sheer brainpower to piece together the innumerable parts of whatever grand puzzles capture their respective imaginations. In truth, though, science often progresses not only by evolution, but by revolution as well. In his seminal work of scientific sociology, "The Structure of Scientific Revolutions,"[1]Thomas Kuhn put forward the notion of the paradigm shift as the major mechanism for scientific change, and although the term has been popularized – almost to the point of losing its original meaning – it still retains immense relevance for the analysis of current events in the scientific and biomedical realms.

Kuhn posited that research into a particular scientific or medical problem takes place within the context of a research programme, an overarching framework that dictates the shape of the overall problem, as well as the nature of the specific results needed to solve it. It is perhaps best compared to a partially-solved jigsaw puzzle, in which the dimensions of the puzzle are clear, and the shapes of the missing pieces are discernible – one only has to find the missing pieces that fit into particular spots to complete the puzzle and construct a coherent image. However, sometimes one is left with puzzle pieces that don't seem to fit anywhere, and empty spots for which suitably-shaped pieces cannot be found. In this case, one is forced to question whether the attempt at the puzzle is, indeed, correct, or if perhaps the puzzle depicts something entirely different and needs to be rebuilt from scratch.

Such is the case with science as well: data that pose challenges to the dominant framework accumulate, and important research questions go unanswered by the research programme currently underway. A new theory is put forward that accounts not only for the previously established results, but also for the conflicting data that troubled the dominant paradigm, and while the new approach may not answer every remaining question, it does provide a direction for further research to follow. However, as will be demonstrated shortly, there is often considerable opposition to the introduction of a new paradigm. Careers and fortunes are often staked upon a widely-held paradigm, and even though researchers may have the best of intentions, the words of Max Planck too often hold true: "a new scientific truth does not triumph by convincing its opponents and making them see the light, but rather because its opponents eventually die, and a new generation grows up that is familiar with it."[1]

The case of peptic ulcers

The classic example of a paradigm shift in medical thinking relates to the etiology of peptic ulcers. Originally described by Marcello Donati in 1586,[2] gastric ulcers in particular came to be attributed to the acid milieu of the stomach, encapsulated in the famous proclamation of the Croatian surgeon Karl Schwatz: "No acid, no ulcer." Factors which increased the amount of acid, such as stress and spicy food, were naturally seen as contributing to the pathogenesis of the dread disease. However, blaming acid alone for the incidence of ulcers left several important facts unexplained. For one thing, until the advent of effective antacid medication, the prescribed treatment was often ineffective. More fundamentally, as early as 1875, it was proposed that bacteria had a role to play in the development of peptic ulcers, and in the late 1950s, it was recognized by some clinicians that ulcers could be successfully treated with antibiotics. The Greek physician John Lykoudis, for example, discovered that his chronic ulcer problem went into remission after he treated himself with antibiotics for a bout of gastroenteritis. He later took out a patent on his antibiotic ulcer preparation and attempted to publish an article in JAMA, only to be summarily rejected.[3] Lykoudis was eventually fined 4,000 drachmas (about $900, accounting for inflation) by the Greek medical disciplinary committee for his unorthodox treatment,[4] and the bacterial theory of peptic ulcers resumed its usual lowly place in the dominant paradigm until the work of Marshall and Warren in the 1980s finally set into motion the wheels of scientific revolution and established that gastric infection with *H. pylori* was a major cause of peptic ulcers.

What this paradigm shift serves to highlight is the role of forgotten research, the undercurrent of data supporting alternate etiological factors that were never incorporated into the dominant paradigm. That this research is generally ignored – or censured, as in the case of Lykoudis – is, in retrospect, difficult to justify scientifically, but ultimately understandable. Before the attribution of peptic ulcers to acid and acid alone, research in this area was in what Kuhn called the pre-paradigm phase, in which there is no consensus on a research programme, but the research being conducted is nonetheless valid and scientific. When the consensus of an acid etiology was reached, research began operating in the second phase of Kuhn's hierarchy: normal science, in which experiments and studies are conducted with the aim of filling in the missing pieces of a defined puzzle. Concurrent with the ascendancy of a particular paradigm is the frequent abandonment of earlier, pre-paradigm directions in research, not because of inherent invalidity, but because circumstances are such that further exploration is unfeasible: researchers may change to

a different field of study, there may not be sufficient supporting knowledge or technological gadgetry to investigate a theory, or sources of funding may shift to approaches that support the alternate, ascendant theory. When a dominant paradigm is established and other theoretical approaches are no longer *en vogue*, it is easy to all but forget the historical context that gave rise to the current situation, especially when the next generation of researchers comes through the ranks having not even been informed of any alternative theories to the dominant one.

Forgotten though they may be, alternate theories and dusty old data often survive in some form or another. In some cases, researchers outside the mainstream may continue to investigate older approaches, earning the scorn of their colleagues and collecting very little in the way of grant money and prestige. Alternatively, a researcher may, like John Lykoudis, discover quite accidentally through his or her own personal experience, that the current paradigm is lacking. Furthermore, an older theory may be resurrected when contemporary researchers independently turn up data that force them to dig through the literature for theories that might explain their findings. Thus, forgotten research has a vital role in maintaining one of the ultimate principles of scientific enquiry – that current knowledge is always subject to revision.

Forgotten research in neurology

Neurology is certainly a field that has its share of unsolved problems. The causative factors behind such diseases as epilepsy, ALS, and Parkinson's are still mostly unknown, even if we have made progress towards understanding their pathophysiology. Of all the theories currently circulating that attempt to explain some aspect of neurological disease, there is perhaps none as recently controversial and widely-publicized as the vascular theory of multiple sclerosis (MS), which contests the widely-held notion that MS is predominantly an auto-immune phenomenon. While this author is not in a position to comment on the ultimate validity of the theory, or the degree to which it explains the phenomena it claims to account for, an analysis of the issues surrounding the theory and the potential it has for sparking revolutionary science is worth contemplating.

As was the case for peptic ulcer disease, there have seemingly always been multiple theories accounting for the pathogenesis of MS. As early as 1839, just a year after the first recorded pathological description of multiple sclerotic lesions, it was noticed that MS lesions appeared to involve altered vasculature or hemodynamics, an observation that was later made by Charcot himself.[5] Intriguingly, an experimental study in dogs published in 1935 claimed that when the cerebral veins were artificially obstructed, lesions developed that were "so striking [in similarity to MS lesions] that the conclusion appears almost inevitable that venular obstruction is the essential immediate antecedent to the formation of typical sclerotic plaques."[6] The conclusion at the time was that such obstructions were likely a result of thrombosis, and as a result, treatment with anticoagulants was attempted, with mixed results.[7]

In the years following the second World War, there was increasing recognition that the inflammatory component of MS could be amenable to treatment. In 1969, researchers carried out a placebo-controlled study of adrenocorticotropic hormone (ACTH) in patients suffering from exacerbations of MS, and found that it was an effective symptomatic treatment.[8] This paved the way for decades of further research into pharmacotherapeutical initiatives aimed at curbing the inflammatory process. The vascular component was all but forgotten, and today, the majority of drugs used to treat MS target the immune system, and although they are often touted as breakthroughs, retrospective studies have shown that they have only modest effects on established disease and somewhat questionable efficacy in preventing disease progression.[9,10]

The modern attack on the dominant paradigm of MS began in late 2008, when Paolo Zamboni and colleagues showed that a particular set of extracranial venous anomalies were found in MS patients, but not in controls.[11] (It should be mentioned that Franz Schelling had attempted to resurrect the vascular theory of MS in 1986,[12] but his efforts to secure funding for experimentation were frustrated, and it was left to Zamboni to take the lead more than twenty years later.) News spread quickly, and just a few months later, patients were discussing the new findings and seeking treatment for their venous stenoses and malformations at centres all over the world. Internet forums were abuzz with talk of a real breakthrough, as well as the personal anecdotes of those who had undergone treatment and found that it had helped their symptoms improve. In late 2009, Zamboni published the results of an open-label pilot study, which showed that venous angioplasty reduced symptoms and disability measures in those MS patients who had demonstrated cerebrospinal venous insufficiency.[13] Notably, it should be pointed out that Zamboni does not argue that MS is *not* an auto-immune disease, but rather that the insult leading to inflammation and white matter lesions is often vascular in nature, and likely a congenital malformation.[14]

Comparing the timeline of research into peptic ulcers with that of MS, it appears that the two share a similar trajectory. Both have their origins in a stage of pre-paradigm science prior to the twentieth century, an ascendant paradigm and a consequent programme of normal science within the last hundred years, and a period of potentially revolutionary science within the last few decades. In both cases, researchers operating outside the mainstream demonstrated findings compatible with older theories that challenged the dominant paradigm, and in both cases, their findings were met with skepticism. Lest we forget, even Marshall's dramatic demonstration of the ulcerogenic properties of *H. pylori* (in 1984, he drank a culture of the bacterium and subsequently fell ill with an ulcer) was insufficient to convince the majority of clinicians; eight years later, an informal survey showed that two-thirds of gastroenterologists polled were still skeptical of the *H. pylori* claim.[15]

Conclusions

As the debate over MS paradigms rages on, it is instructive to analyze the situation at play and understand what it may mean for medicine in general. Looking back on a century or more of modern medicine, it is likely that at least some answers to the pressing medical questions of our time have already been found, but have been neglected amidst the inevitable turmoil of shifting paradigms, ever-accumulating data, and the cognitive dissonance stemming from overzealous adherence to a particular set of ideas. Luckily, advances in technology and increasing access to more and more sources of historical research data have provided us with a rich reservoir of science to review and learn from. Whatever the final outcome of the MS debate, it is a foregone conclusion that this will not be the last time forgotten research has its last laugh.

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Addendum

A precursor to this article was originally presented to the Harvey Club of London on April 20, 2010.

The author invites readers to submit further examples of forgotten research at a new website created explicitly for this purpose: www.forgottenresearch.com.