Medical sleuthing without an MRI

As a medical student in the early 1960s, trained at Bart's Hospital (founded in 1123), I was extremely frustrated by some aspects of the teaching of clinical medicine. What I wanted to learn was exciting facts about the causes of illness, modern biochemistry, and the latest treatments. A number of years later when I worked as an intern for the late Dr Alan Spence, I felt confident enough to express my concerns. He replied that "50% of what I would have taught you would be wrong by the time you are middle aged, and biochemical tests change every 10 years." His job, he thought, was to teach me to use clinical judgment and to keep asking why does this happen, why are we doing this? I asked myself what motivated physicians in the past to carry out procedures, such as total dental extraction for colitis and rheumatoid arthritis!

Perhaps the most important person to ask "why" was William Harvey, the first physician appointed in Bart's. For the first 500 years of Bart's existence, they thought they could make do without physicians, running the hospital with nurses and administrators. At that time, Galenic philosophy was deeply carved in stone and taught as the basis of human physiology. Harvey, with only minimal support and apparatus, provided about 90% of the proof that blood circulates. It is difficult to understand that the idea of a heart acting as a pump was totally foreign at the time.

Analogously, I am certain there are many things that are wrong in modern medicine, even though great breakthroughs have been made in genetics, transplants, electrophysiology, and so on. In particular, I have a gut feeling that we have shied away from truly confronting the origins of a great puzzle—the so-called autoimmune diseases.

For the last 100 years, little progress has been made in understanding the true etiology and specific treatment of autoimmune diseases, such as rheumatoid arthritis, ulcerative colitis, Crohn disease, and disseminated lupus. These illnesses are thrown into a rat bag labeled "autoimmune." While admittedly there are design flaws in the human body, it does seem unusual that evolution has allowed the continuation of a mechanism whereby the body attacks itself. (In passing, some thought should be given to the concept that most organisms have a purpose. Bacteria and viruses, although they might kill the host, do carry out the basic tenet of nature: they reproduce and spread, thus fulfilling their goal. Such a goal is missing in all forms of cancer, which kill the host, and in the self-destructive autoimmune diseases.)

Over the last 80 years or more, great attention has been focused on the inflammatory cascade mechanisms of autoimmune disorders. We have nonsteroidal anti-inflammatory drugs, which suppress some of the pathology, disease-modifying agents that inhibit inflammation, and now the new anti–tumour necrosis factor agents. These all focus on the inflammation underlying autoimmune disorders, but none of them really address the underlying cause, the specific triggers that set the self-destructive autoimmune process in motion. The common factor in autoimmune diseases is that their true etiology remains unknown—we might be on the wrong track and persist in going down the wrong road.

A typical example of this frustrating situation is rheumatoid arthritis. Why is it symmetrical in distribution? It's not likely that the joints classically affected differ in cartilage structure from those that aren't. Moreover, why does a stroke prevent the development of the disease in the paralyzed limb? In animal studies, either surgically or chemically destroying the afferent nerves to joints prevents the appearance of arthritis in those joints.[1] As Harvey might have noted, the same blood circulates around these joints—so why the sparing? I was surprised to observe that a great many papers in the peer-reviewed medical literature refer to a phenomenon that is virtually ignored in clinical medicine—the neurogenic origins of arthritis.[2]

The final stimulus that motivated me to write this letter was encountering reports from the early part of the 20th century that sectioning the sympathetic nervous system often provided amazing relief in arthritis. Not double-blind studies, but great work by great medical scientists.

There is considerable evidence that substance P (SP) is a key trigger for arthritic inflammation.[3,4] Substance P is found in the terminals of afferent nerves densely innervating the joints affected by rheumatoid arthritis. The puzzle that no one can solve is why small afferent nerves carry 2-way traffic—sending sensory impulses centrally while at the same time releasing vesicles of SP antidromically. (The author will donate a case of

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wine for the first correct answer!) In rodents, neonatal depletion of SP from afferent joint nerve endings markedly reduces the induction of arthritis with Freund adjuvant—the classic experimental model of autoimmune arthritis.[2,5,6]

The neurogenic theory of arthropathy might explain why anticonvulsants often appear to exert a positive effect on so-called autoimmune diseases. Patients with epilepsy taking phenytoin seem to be at lower risk for autoimmune disorders.[7] Scleroderma, very difficult to treat, was reported to respond to anticonvulsant drugs in studies conducted in the 1970s.[8,9] Moreover, scleroderma might not afflict paralyzed limbs; a similar observation has been made with psoriasis.[10]

Our treatment of the so-called inflammatory cascade is passable: it provides pain relief and some disease modification—but it does not deal with the underlying cause of the cascade. Animal experimentation points clearly to the direct effect of a neurogenic influence, which I would humbly suggest is the initial stimulus. All of our attention in the past has been focused on the inflammatory cascade—its effect on blood chemistry and its response to therapeutic agents, such as steroids or nonsteroidal anti-inflammatory drugs—but we continue to ignore the cause.

Perhaps the greatest defect in modern medicine is that once we have gone down the wrong path, it is difficult to change direction or admit failure. Better sooner than later! Most have forgotten that for centuries we got the circulation of the blood wrong. A modern example is the hilarity and disdain that greeted the scientists who dared to propose that infection with *Helicobacter pylori* was the fundamental cause of ulcers. To quote a popular song—When will we ever learn?

The critical test is to electrically stimulate the afferent nerves innervating joints in animals to see if this can trigger inflammatory arthropathy—a very fast, very cheap experiment. Would anticonvulsant drugs provide protection also?

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Competing interests?

The article by Flook et al[1] on management of undiagnosed chest pain suggests a therapeutic trial of a proton pump inhibitor. While this approach sounds wholly reasonable, this particular article raises a serious issue of credibility. The authors state, under competing interests, "None declared." At the same time, Dr Karlson (one of the contributing authors) discloses that he works for AstraZeneca, who manufacture one of the proton pumps recommended. I do not doubt that the good doctor *declared* that he had no competing interests, but I would suggest that, absent some good evidence to the contrary, it would certainly appear otherwise.

In recent years, increasing attention has been paid by journal editors to ensuring the scientific accuracy and validity of articles published under their banner. I fully appreciate that it is simply impossible for

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