What is “inflammation”? Are we ready to move beyond Celsius?

A Scott, K M Khan, J L Cook, V Duronio

Different definitions of inflammation are a cause for concern

Inflammation, a term coined by the ancients, is widely used in sports medicine. But what is meant when a clinician tells a patient that symptoms are probably due to inflammation? The question of whether inflammation is helpful or harmful to healing can only be answered after inflammation is defined. This brief analysis of inflammation reveals that the term’s definition has changed dramatically since it was first used by Celsus nearly 2000 years ago. The definition also depends on the type of lens the viewer is using—whether it be clinical, cellular, or molecular.

INFLAMMATION—WIDELY USED (AND ABUSED)

On the one hand, the label inflammation is ascribed to a wide range of potential presentations in musculoskeletal medicine, but on the other, few clinicians would be able to define this complex biological cascade any better than Cornelius Celsus did in the 1st century AD. Nevertheless, this limited understanding of pathobiology does not limit therapeutic enthusiasm; American physicians prescribe drugs to block inflammation at a rate that costs patients over a billion US dollars annually. There has been an explosion of knowledge about inflammation over the second half of the 20th century, yet our clinical concepts about inflammation have remained relatively resistant to change. This leader highlights the evolution of the term inflammation as a prelude to a detailed update of modern concepts relevant to sports induced inflammation.

A HISTORICAL PERSPECTIVE

The word inflammation comes from the Latin inflammare (to set on fire). The Roman Celsus is credited as first documenting (1st century AD) the four cardinal signs of inflammation: rubor tumor calore et dolore (redness and swelling with heat and pain). This definition of inflammation recognises what we would today know as a “classical” acute inflammatory response—for example, following a traumatic event such as a macroscopic tear of ligament or muscle. Thus, in its genesis, inflammation was defined by a combination of clinical signs and symptoms not by specific pathophysiology (table 1).

Defining inflammation according to clinical signs and symptoms has major limitations, as in most cases the cellular processes and signals that underlie the cardinal signs occur at a subclinical level and do not give rise to any heat, redness, swelling, or pain. For example, the inflammation of delayed onset muscular soreness may cause tenderness on palpation or mild discomfort, but no redness or swelling. Broadening the definition of inflammation to include one or a subset of the cardinal signs is not a solution, as areas of swelling, pain, and tenderness may have a wide variety of non-inflammatory causes. For example, regions of muscle spasm (sometimes called “myositis”) and many cases of tendinosis (often called “tendinitis”) are often confused with inflammation, because of the local pain and swollen nature of the tissue.

Two centuries after Celsus, Galen was influential in promoting the humoral view of inflammation. In his model, inflammation (and pus specifically) was part of the beneficial response to injury, rather than a superimposed pathology. This humoral view of inflammation persisted into the 19th century when the fifth cardinal sign—function laesa, loss of function—was added in 1871 by Virchow (table 1). In contrast with Galen, however, Virchow viewed inflammation as inherently pathological.

Advances in microscopy and cell biology in the 19th century gave rise to cell based definitions of inflammation (table 2). This represented a completely novel way of understanding and defining inflammation. By the end of the 19th century it was acknowledged that changing cell populations arising from both the blood and local proliferation were a key feature of many models of inflammation. With the advent of the microscope, such a complexity of events underlying inflammatory reactions was revealed that researchers began to question whether inflammation was indeed a single process. A prominent German biologist, Neumann, defined inflammation more loosely as a “series of local phenomena developing as the result of primary lesions to the tissues and that tend to restore their health”.2

In one sense, the most cited sports medicine model could be seen as an elaboration of this 19th century vessel-cell hierarchy. In the classic monograph Sports-induced inflammation, Leadbetter describes a stereotyped cellular response that follows trauma to vessels. These phases progress from activation of platelets and endothelium, through recruitment and activation of leucocytes, to proliferation and repair by endothelium and fibroblasts. In this view, inflammation is defined as a necessary phase in the repair response after an injury in which the vessels are disrupted.

INFLAMMATION TODAY: A COMPLEX CASCADE

Modern molecular biology superimposes additional layers of complexity on this commonly accepted model. Firstly, a tissue may be influenced by proinflammatory signalling molecules, even in the absence of inflammatory cell invasion. For example, chondrocytes respond to a proinflammatory cytokine, interleukin 1, which is released by synoviocytes, to catabolise the surrounding cartilage matrix by upregulating their expression of matrix metalloproteases. This cartilage degeneration occurs in the absence of inflammatory cells. Secondly, aspects of both inflammation and repair can be

Table 1 Cardinal signs of inflammation

<table>
<thead>
<tr>
<th>English</th>
<th>Latin</th>
<th>Cause</th>
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</thead>
<tbody>
<tr>
<td>Heat</td>
<td>Calor</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Redness</td>
<td>Rubor</td>
<td>Vasodilation</td>
</tr>
<tr>
<td>Swelling</td>
<td>Tumor</td>
<td>Increased vascular permeability</td>
</tr>
<tr>
<td>Pain</td>
<td>Dolor</td>
<td>Increased granulation tissue</td>
</tr>
<tr>
<td>Loss of function</td>
<td>Functio laesa</td>
<td>Physical and chemical stimulation of nociceptors</td>
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</tbody>
</table>

Table 2  Key advances in developing a definition of inflammation between 1st and 20th centuries AD

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Quotation</th>
<th>Historical interpretation</th>
<th>Modern significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Celsus, 1st century AD</td>
<td>“rubor et tumor cum dolore”</td>
<td>First documentation of cardinal signs of inflammation</td>
<td>Emphasised the importance of clinical observations rather than philosophy based medicine</td>
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<td>Galen, 3rd century AD</td>
<td>“Laudable pus”</td>
<td>Infection and inflammation are beneficial to repair of wounds</td>
<td>Inflammation was seen as an expression of humoral theory well into the 19th century</td>
</tr>
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<td>Virchow, 1871</td>
<td>“The inflammatory reaction is a consequence of an excessive intake by interstitial cells of food... filtering through the vessel wall”</td>
<td>Inflammation as a pathological proliferation of cells due to leakage of nutrients from vessels</td>
<td>Recognised cellular nature of inflammatory response</td>
</tr>
<tr>
<td>Cohnheim, 1873</td>
<td>“Finally... there lies outside the vessel... a colourless blood corpuscle.”</td>
<td>Blood corpuscles were seen as pathological mechanisms by which infections spread, secondary to vascular injury</td>
<td>First description of diapedesis</td>
</tr>
<tr>
<td>Metchnikoff, 1908</td>
<td>“the primum movens of the inflammatory reaction is a digestive action... toward the noxious agent”</td>
<td>Inflammation as a defensive cellular response to pathogens, guided by the vessels rather than an aspect of the pathology itself</td>
<td>First to express the view that phagocytes were protective, not pathological</td>
</tr>
<tr>
<td>Lewis, 1927</td>
<td>Inflammation as the “triple response” to injury</td>
<td>Inflammation is characterized by vascular events mediated both by local chemicals and by axons</td>
<td>First recognition of neurogenic inflammation; first physiological characterisation of vascular events</td>
</tr>
<tr>
<td>Rocha e Silva, 1974</td>
<td>Inflammation as a “multi-mediated phenomenon, of a pattern type in which all mediators would come and go at the appropriate moment... increasing vascular permeability, attracting leucocytes, producing pain, local edema and necrosis”</td>
<td>Biochemical definition of inflammation</td>
<td></td>
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CLINICAL IMPLICATION

The clinical implication is that the term inflammation embraces a great variety of biological processes. Whether inflammation is involved in a patient’s symptoms is not a straightforward question. Knowing whether an anti-inflammatory drug is likely to benefit or harm a patient’s healing response is complex despite the knee jerk reaction for many patients to self-administer these compounds. In summary, this leader shows that (a) inflammation is not a single process and (b) it is not simply binary in nature (“on” or “off”), but it can be modulated by many factors in the cell’s environment. There remains a great deal of scope for understanding how mechanical loading (exercise as either sport or rehabilitation) influences the many faces of the complex cascade that is inflammation.


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REFERENCES
