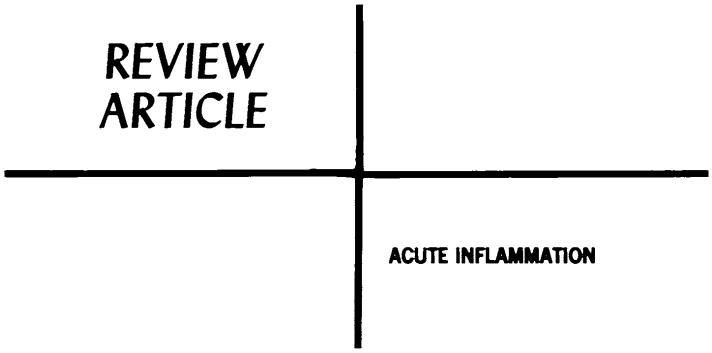

ACUTE INFLAMMATION

Acute Inflammation

A Review

Graeme B. Ryan, MB, BS, PhD, and Guido Majno, MD

INFLAMMATION has been a favored topic for research in recent years. It has graduated to a three-volume treatise, duly bound in red;[1] symposia and monographs are plentiful;[2-9] there is an Inflammation Club, an Inflammation Bulletin;[10] and a new (red) Inflammation journal has just appeared.[11] There is even a book on the future trends in inflammation.[12]

To those who are not specialized, this avalanche of literature has become difficult to analyze; the present review was therefore conceived as a short and critical guide to that part of the field generally known as *acute inflammation*.

History—The Saga of the Fifth Sign

A history of inflammation starting from the earliest times can be found in a recent book, where it is interwoven with the history of the wound.[13] In summary, we can say that the idea of comparing a red, hot, swollen skin lesion to something ablaze may be as old as medicine. In the cuneiform writings of Mesopotamia, several medical terms can be translated as *inflamed* or *inflammation; ummu*, for instance, means "the hot thing" and is used in a context that suggests either local or general heat (inflammation or fever). Another word meaning inflamed was derived from the verb *napāhu*, "to blow": thus an inflamed finger would have been called a "blown finger." This peculiar expression becomes logical if one stops to consider that fire, in those days, was lit by twirling a fire-stick: a procedure which involved a lot of blowing to kindle the first sparks into a flame (the same notion of "inflating" is implied in the old term *spina ventosa* for long bones of the hand or foot slowly expanded by a mass of tuberculous tissue). In ancient Egypt, again, we find several words that can be translated as inflammation (e.g., *seref, shememet*). When these words are written in the original hieroglyphs, their meaning becomes obvious (or at least believable) even to the non-Egyptologist, because both words are followed by a special hieroglyph called a *determinative*. This sign was not pronounced, and served to convey the general idea of

From the Department of Pathology, Harvard Medical School, Boston, Massachusetts, and the Department of Pathology, University of Massachusetts Medical School, Worcester, Massachusetts.

Supported in part by Grant HL-16952 from the National Institutes of Health.

Address reprint requests to Dr. Graeme B. Ryan, Department of Pathology, University of Melbourne, Parkville, Victoria 3052, Australia.

the preceding word. For *seref* and *shememet* it is a flaming brazier, symbolizing the notion "hot thing."

The Greek term for inflammation was *phlegmoné*, "the fiery thing" (phlox = flame). Ancient medical students must have wondered how this fiery condition could arise from *phlegm*, the cold and moist humor (whence we have the term *phlegmatic*). The contradiction was unexplained even in ancient times.

We will not bore the reader by repeating the Four Cardinal Signs of Celsus, but we do want to rectify the pedigree of the Fifth Sign, which was not added by Galen as the tradition holds. (Celsus, by the way, lived around the year 30 AD, and Galen between 130 and 200 AD: the dates are reversed in several textbooks [14]). It was L. Rather who first pointed out that Galen never added a Fifth Sign;[14] indeed, it would have been against his grain to do so, because he was so Greek at heart that he had little use for a Roman author, let alone for one who wrote in the language of the vulgar (Latin!) like Celsus. Throughout his monumental writings, he never even quotes Celsus. But who, then, originated the Fifth Sign?

It was, believe it or not, Virchow himself, in his *Cellular Pathology* (1858).[13,15] The episode is a magnificent example of the subtle, yet overwhelming influence that Virchow exerted over the world of pathology and over the thought processes of his peers. Virchow's statements had a way of becoming accepted as pure knowledge, as all-time truths. So, he dropped—just once—the remark that it was high time to add a fifth cardinal sign, the *functio laesa*, at least "according to the modern schools" (he does not explain which were these modern schools, but we suspect that "we, Virchow" was referring to his own "schools"). It took only a few years for the fifth sign to become a standard notion in Pathology texts; another few years later it metamorphosed, unaccountably, into an ancestral truth—promulgated by Galen.[13,14] This story is also an excellent example to show how medical legends arise and how textbooks carry them through, from generation to generation, unchecked.

Some Thoughts on Inflammation

The concept of inflammation and some of its satellite terms (such as acute and chronic) have come down to us from such remote antiquity that they carry with them, inevitably, a fair amount of vagueness; this tends to foster imprecise usage. We will, therefore, begin by defining some of the pertinent terms.

Most pathologists would probably agree that inflammation represents a response of living tissue to local injury; that it leads to the local accumulation of blood cells and fluid; and that the overall process, seen against the

broad perspective of evolution, is a useful one, its primary significance being (in all likelihood) that of a defense against microscopic invaders. Good discussions on this overall issue can be found in the major textbooks of general pathology: those by Payling-Wright,[16] Pérez Tamayo,[17] and Florey.[18]

Inflammation and *injury* are often confused. By injury we will mean here the *passive* changes induced by a noxious agent. These changes may affect the cells, the extracellular materials, or both; from the injured area arise signals—chemical and perhaps also physical—which call forth the inflammatory reaction.

The twin terms *acute* and *chronic*, as applied to disease in general and to inflammation in particular, have now survived well into their third millennium; they are obviously practical and we can assume that they are here to stay. It is easy to use them in a loose fashion, especially in a clinical context, but more difficult to define their significance in terms of modern biologic science. In this regard, there are today two schools of thought. Some pathologists (probably most) firmly believed that acute and chronic inflammation represent two distinct aspects of the inflammatory reaction; others preach inflammation as a single entity, which cannot be split on the basis of its course in time. Our own view is that the ancient dual terminology is rooted in definite biologic (and histologic) events, and therefore should be retained; its use, however, is subject to a number of qualifications, as we will discuss below.

It is obvious that local injuries of all sorts induce an *immediate, acute* response which is basically the same whatever the agent; this immediate response is triggered by a variety of chemical "mediators" which can appear within the tissues in a matter of seconds and act primarily on the microcirculation, with two main effects: a) exudation of fluid, and b) exudation of white blood cells, primarily polymorphonuclear leukocytes (PMNs). This is, in essence, a *stereotyped, nonspecific response*. It is a beautifully planned mechanism of defense, with multiple pathways leading to similar useful effects, no matter what the cause.

If we go on to examine a typical focus of chronic inflammation, as caused by, for example, tuberculosis, we notice in the first place that it is teeming with mononuclear cells. Now we have learned that the somewhat dull histologic aspect of such infiltrates is quite misleading: few cells are as specifically informed, or programmed, as the lymphocytes and plasma cells (macrophages alone tend to retain, by and large, a nonspecialized function). We are therefore dealing with a highly specific response. (Only a few years ago, an infiltrate of mononuclear cells would have been called nonspecific: those were the days when little was known about lym-

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.