Much contemporary nephrological literature deals with inflammation. Articles in many issues of renal journals address the subject. Some of them describe human observations, some animal models, and some in vitro experimentation. Some explore histological manifestations, some cellular and humoral aspects, and some the inter-relations between molecular items. Some consider causal mechanisms, some pathogenetic mechanisms, and some manifestations. They virtually all address aspects of a process that they label as inflammation without explaining what they mean by the comprehensive subject whose subsidiary aspects they address.

They perhaps imply that the meaning of the word inflammation is so obvious that further definition is unnecessary. This, however, is clearly not so since – although a superficial examination of the word suggests that it relates to heat – much current literature applies the term to phenomena not obviously related to heat. So does the word now describe a process quite unrelated to its etymological origin, or is heat now a non-obligatory feature, or has the word become so fashionable that contemporary investigators apply it loosely to things unrelated to true inflammation, or is there some other explanation? These questions obviously require answers if we are to think clearly about the subject, yet the literature dealing with it is quite scanty (1).
Languages have similarly derived words so an etymological analysis of it is unlikely to assist in understanding inflammation. A satisfactory explanation of inflammation, nevertheless, will have to account for its relationship to fever.

**ANCIENT INFLAMMATION: RED, HOT, SWOLLEN, AND TENDER**

Linguistics, therefore, offer little help in understanding the evolution of ideas about inflammation. Perhaps, however, an historical analysis may provide more insight. Medical sources from ancient Mesopotamia and Egypt contain references to fevers and perhaps to inflammation (3). Ideas associated with these words certainly had currency in Classical Greece in about 400 BC as Hippocrates referred repeatedly to topics that modern translators have invariably described as fevers and as inflammation. Much of Hippocrates’ *Book of Prognostics*, as well as others of his works, deal with what one must interpret as infective diseases and their consequences (4), such as his reference in *On Airs, Waters, and Places* to symptoms suggestive of urinary tract infection and inflammation associated with urinary calculi that he perceived as a localized process caused by stones.

Celsius, the Roman encyclopaedist who wrote in about AD 30, was also interested in inflammation. Commentators have credited him with being the first to associate it with the localized signs of heat, redness, swelling, and pain (5). Galen, writing in Rome some two centuries later, emphasized the association of inflammation with the development of pus in wounds that developed as a consequence of injuries, but also portrayed this as a localized – and indeed desirable – phenomenon (6). Avicenna summarized much of the previously available information that had accumulated before the year 1000. He linked pus with fever and inflammation, the latter manifested by localized pain, induration and redness (7). It was not until about 1275 that William of Saliceto (who worked in Bologna) challenged Galen’s contention that the formation of pus was a desirable aspect of the development of inflammation in wounds (8), but this did not alter the interpretation of inflammation as being a localized event. People also recognized that inflammation could affect solid organs, such as the kidney, with the first recorded use of the word *nephritis* appearing in the English language in 1580, when the author of a veterinary treatise made the statement: “The inflammation of the kidneys, which is called of them Nephritis” (9).

Bartholomew Castello, in the 1651 edition of his medical dictionary, indicated that the idea of inflammatory processes being solely of a local nature persisted well beyond the Renaissance, since his concepts differed little from those of Celsius (10). Assumption of a localized nature for the process indeed still continued in 1726 when John Quincy offered the following definition:

*Inflammation* is when the Blood Is obstructed so as to crowd in a greater Quantity into any particular Part, and give it a greater Colour and Heat than usual. See *Phlegmon*.

*Phlegmon* [derived from the Greek word, ‘to burn’], in the Acceptation of *Hippocrates*, and our practical Surgeons, signifies a Tumour with Inflammation and Heat.

Quincy also recognized that inflammation could occur in internal organs, citing nephritis as one example of this and arthritis as another. He, like his predecessors, attributed nephritis solely to the presence of calculi:

*Nephritis, or Nephriticus Dolor ...* is the Distemper call’d the *Stone* because that Part is reckon’d to be principally the Seat, or in Fault.

The implication here was that any disease that affected a particular part of the body (and stones, in the case of the kidneys, were the principally recognized culprits) might produce inflammation manifested by heat and pain. The heat was in fact presumably due to the secondary infection that could complicate a stone in the urinary tract, but the interpretation was that a stone (rather than the then unrecognized infection) was the culprit. Quincy’s mention of obstruction to blood flow in his definition alluded to iatrophysical theory, the assumptions of which then carried over into his idea of fever which he identified as ‘an augmented Velocity of Blood’ for which there was an almost infinite variety of causes, appearances and cures (11).

People throughout this era recognized that inflammation in wounds was often associated with fever, but that this was not an invariable association. They also recognized that many fevers had no apparent association with localized inflammation. The resulting enigma challenged the ingenuity of contemporary physicians who sought to devise explanations that simultaneously conformed to their empirical observations and to the theoretical constructs that dominated their thinking. Resolution of their confusion could not occur until improved technology enabled examination of previously obscure aspects. Access to microscopy was crucial to understanding what was happening in the local lesions, whilst a method to measure temperature was crucial to understand fever.
18TH CENTURY INFLAMMATION: PHYSICS TRIUMPHANT

Physics dominated science in the 17th and 18th centuries – an era of mechanical theory and technological development. Anatomists like Marcello Malpighi (1628-1694) first used lenses to discover such items as the renal glomeruli when, in 1666, he created a simple microscope that magnified up to 30 times to display multicellular structural outlines, but that failed to show the cellular detail of inflamed tissues. The latter required further technological improvements.

A similar situation existed with regard to thermometry. Daniel Gabriel Fahrenheit (1686-1736), who was born in Danzig (now Gdańsk), developed the first reliable method for measuring temperature in about 1720 (12). He had been apprenticed to a merchant in Amsterdam where he lived for much of his adult life; and, whilst travelling in Denmark, was intrigued by some primitive thermometers that the astronomer Rømer had made. He thereupon decided to try to create reliable thermometers and barometers that would provide reproducible and standardized readings. Scholars such as Herman Boerhaave (1668-1738) and members of The Royal Society of London (who elected him as a Fellow in 1724) respected him, despite other academics criticizing his lack of formal university training.

Fahrenheit managed to surmount several difficulties that had previously bedevilled the construction of thermometers. He substituted mercury for alcohol as the thermometric liquid. He then identified varieties of glass whose coefficients of expansion best suited mercury and established a temperature scale that relied upon the physical properties of water rather than having ‘healthy’ body temperature as its upper marker. He improved methods of glass-blowing to manufacture and fill the thermometers, and developed ways to produce multiple instruments that all gave similar readings in similar physical circumstances. He thus made temperature a reliably measurable parameter and gave physicists appropriate instruments with which to measure it. Clinicians eventually followed suit, although it took another century and a half for them to do so systematically.

The association of inflammation with heat, and the iatrophysical assumption that localized heat in part of the body must indicate increased blood flow to it, suggested a close linkage between inflammation and the circulation. The term inflammation thus came by the late 18th century to indicate any ‘irritation’ that produced increased local circulation (13). The irritation could be external or internal, local or universal. Alleged causes included wounds, bruises, sudden and excessive cold, dislocations, and fractures. Theoreticians made several suggestions to explain the pathogenetic mechanisms involved: for Boerhaave obstructive stasis occurred in the small vessels (14); for John Hunter a process occurred in small vessels that restored or damaged tissues, and often resulted from fever (15); whilst for Gaubius irritability prevailed (16). Most observers nevertheless believed that irritated nerves led to increased blood flow through local vessels, producing heat and redness. Distended vessels purportedly caused pain (sometimes preceded by itch). Increased heat acted on the tissues to cause swelling, and irritation of the local capillaries could cause them to spasm and produce dry skin. The heart would beat rapidly as it tried, in the words of one commentator, ‘to free its subservient vessels from any injury they sustain from accidental, or preternatural, irritation’. Various clinicians created such subdivisions as erythematous inflammations (that affected the skin), secretory inflammations (that affected mucous membranes), and phlegmatous inflammations (that caused swelling of internal organs without pus formation). Nephritis was an example of the phlegmatous group. Overarching all of this, the diagnosis of inflammation depended upon identifying the classical manifestations that included heat, pain, swelling, redness, and a rapid pulse.

Physicians thus increasingly developed the idea that other forms of inflammation existed apart from that which affected open wounds. They identified localized inflammation that occurred in various parts of the body such as the bladder, bones, breasts, eyes, heart, intestines, joints, kidneys, mediastinum, peritoneum, spleen, stomach, uterus, and vagina. They added new terminology (such as carditis, gastritis, and enteritis) to the words that they were already using such as nephritis. Cullen introduced the word cystitis into the English language in 1776; and Motherby described this as a pressing and burning pain in the region of the bladder and perineum with fever, sometimes accompanied by retention of urine, ‘a constant stimulus in its evacuation’, dribbling, a rapid pulse, cold extremities, anxiety, restlessness, vomiting, and delirium. He commented that ‘This disorder usually terminates soon, either in a recovery or death; frequently the latter.’

Motherby described nephritis as a word that indicated ‘any distemper of the kidneys’. He considered that it was uncommon. Wounds, contusions, running, violent riding, excessive heat, poisons, abscesses, and tumors could, on his analysis, produce ‘a long continued spasmodic contraction of these vessels…forcibly convey[ing] the thicker parts of the blood into the urinary ducts’. He considered that spasm of the renal vessels could produce oliguria or anuria, haematuria, lo-
calized pain sometimes radiating to the testicle, nausea, vomiting, diarrhoea, fainting, and convulsions. He noted that, although early recovery could occur, abscesses would sometimes form and discharge, and that persistence of symptoms for longer than two weeks often presaged a fatal outcome.

The term inflammation thus seemed, by the late 18th century, to imply the presence of disease of any type in a local area of the body that was associated either with pain and heat and redness, or with a febrile illness. Observers usually attributed local inflammation (often tenuously) to an external insult, and assumed that its pathogenetic mechanisms involved the local blood vessels. Speculative issues relating to its pathogenesis and causation were now playing an important role in the concept.

19TH CENTURY INFLAMMATION: FEVERS AND CELLS

Early attempts at developing microscopes and thermometers produced instruments that were too inefficient for routine clinical use, with the result that investigators had to wait until the mid-19th century before the technology in these fields improved sufficiently to advance the understanding of inflammation and fever. The single lens of a simple microscope provided inadequate magnification to reveal the cellular detail involved in inflammation. The obvious solution to its lack of power was to use a second lens to expand the image produced by the first lens; but blurring and discolouration of the resultant images due to a phenomenon known as chromatic aberration foiled this exercise. It was not until an English lens maker, John Lister (1786-1869), discovered that making the two lenses out of different types of glass would mutually counteract their individual distorting refractive properties that convenient compound microscopes capable of magnifying up to 300 times became possible (17).

The measurement of temperature similarly required improvement before clinicians could elucidate fever. The Swedish astronomer, Anders Celsius (1701-1744) extended Fahrenheit’s ideas in 1742 by calibrating thermometers in a centigrade scale of 100 units, with 100 degrees set at the freezing point of water and 0 degrees at its boiling point. His approach gained widespread acceptance on the Continent after the temperature scale was inverted, although the English-speaking world preferred the Fahrenheit scale. Occasional clinicians measured the temperature of patients suffering from different stages of various diseases during the next century, but their cumbersome instruments and a lack of conventions by which to interpret their observations stymied their efforts. Interest in the subject however increased in several countries after 1851 when Carl Wunderlich (1815-1877), the Professor of Medicine in Leipzig, started recording the temperatures of all his patients in a systematic way and accumulated ‘some millions’ of readings on nearly 25,000 patients (18, 19). His thermometers were, however, awkward, measuring up to 30 cm long, with bulbs up to 0.75 cm in diameter, and having to sit in the axilla for almost 30 minutes. Clifford (later Sir Clifford) Allbutt of Leeds in England eventually popularized thermometry when he commissioned some inexpensive instruments in 1867 that were 7cm long, and that recorded the axillary temperature in 5 minutes (20). They gained widespread support as soon as a Fahrenheit version became available, rather than the original centigrade version!

The late 18th and early 19th centuries were marked by the development of a series of classifications of diseases, almost all of which had groupings of fevers and inflammations (21, 22). Some groups included distinctive types of febrile illnesses, especially exanthemata such as scarlet fever. Others focussed upon localized inflammation, to which they applied either that word or synonyms. Their efforts at nosology, however, demonstrated little advance in the understanding of the diseases that they classified, such that the general understanding of inflammation in the early part of the 19th century differed little from that of 50 to 100 years before. Samuel Cooper gave as a typical definition of that era (23):

By the term, inflammation, is generally understood, the state of a part, in which it is painful, hotter, redder, and somewhat more turgid, than it naturally is; which topical symptoms, when present in any considerable degree, or when they affect very sensible parts, are attended with fever, or a general diseased action of the system.

It was only after about 1860 that definitions started to reflect the advances in understanding that resulted from improved methods of microscopy and thermometry (24).

The earliest recognition of cellular involvement in the process of inflammation resulted from the identification in 1840 by William Addison (1802-1881), of Malvern in England, of leukocytes in the blood, and his further observation two years later that these migrated through vessel walls in locally inflamed areas (25, 26). Struggles by various people to understand the role of cells in inflammation during the next few years culminated in the views expressed by Rudolf Virchow (1821-1902) of Berlin in his epic publication, Die Cellularpathologie, that appeared in 1858. He thought that the focus of understanding about inflam-
nflammation had moved historically from heat to redness, then from redness to swelling, and finally from swelling to irritation. External irritants, he suggested, could cause changes within the structure of cells that impaired their function to produce exudation if they lay on the surface of the body (secretory inflammation) or swelling if they occurred internally (parenchymatous inflammation) (27). This classification thereby imposed a cellular perspective upon the established 18th century ideas.

Another development that the availability of improved microscopy facilitated during the 1860s was research into experimental pathology. Workers such as Julius Cohnheim (1839-1884) in Berlin and Simon Samuel (1833-1899) in Königsberg worked on inflammation, examining respectively the changes that occurred in the microvasculature of frogs’ corneas (Cohnheim) and rabbits’ ears (Samuel) subjected to artificial irritation. This field thereafter attracted many other investigators, but Elie Metchnikoff’s (1845-1916) observation in 1884 of phagocytosis by polymorphonuclear leukocytes (‘microphages’) in the blood and mononuclear macrophages in the tissues was the one that generated greatest interest and led to a new definition of inflammation.

Metchnikoff, a Russian, was a zoologist who had a particular interest in marine biology. He had held an academic position at the University of Odessa, but resigned and moved to Messina in Sicily where he performed experiments that demonstrated macrophages phagocytosing splinters of wood that he had poked into transparent starfish larvae. This stimulated him to propose that inflammation is an essentially protective phenomenon that occurs as a result of phagocytes eating foreign material to protect their hosts, rather than merely eating to ensure their own survival. He considered this to be a fundamental characteristic of living organisms, to the extent that inflammation became central to ideas that he developed about animal life. He then proposed a new definition (28):

Inflammation generally must be regarded as a phagocytic reaction on the part of the organism against irritants. This reaction is carried out by the mobile phagocytes sometimes alone, sometimes with the aid of the vascular phagocytes or of the nervous system.

This marked a categorical change in ideas. Here, for the first time, was an attempt to describe inflammation in terms that did not derive from its manifestations. Metchnikoff’s view was, rather, a mechanistic one that arose primarily from teleological considerations: inflammation exists, he said, and it does so for the purpose of defending an organism against external attack. Heat received no mention in his proposal; pain received no mention; swelling received no mention; redness received no mention; and he totally disregarded interference with function. Metchnikoff became, thereby, the first person truly to extinguish the fire of inflammation.

Fevers, nevertheless, persisted and a revolution in the understanding of them was occurring simultaneously. One of the greatest scientific achievements of the late 19th century was the discovery of bacteria, made possible by the improvements that had occurred in microscopy. Identification of the microbiological basis of so many diseases immediately impacted upon ideas about causes of inflammation. Whereas observers had previously successfully identified only occasional external sources of irritation that led to inflammation, they could now confidently identify micro-organisms in a causal role for many diseases. Much that had formerly seemed totally obscure became clear. Whether one adopted the classical approach of regarding inflammation in terms of its manifestations, or instead focussed upon its pathogenetic mechanisms, the discovery of invading organisms in so many diseases provided incontrovertible evidence of a third and ineluctable component of the process – an external causal factor. These organisms furthermore provided the explanation for the linkage between inflammation and fever. The Swiss surgeon, Emil Kocher (1841-1917), expressed this in the simplest of terms when he wrote that (29):

There is only a difference of degree, a quantitative difference between a simple localized acute inflammation and cases of the most acute pyemia.

The identification in 1880 of staphylococci and streptococci by the Scot, Alexander Ogston (1844-1929), and his demonstration that injection of organisms derived from abscesses into animals could cause responses identical to those of septicemia, clarified yet other previously obscure aspects. The relevance of the discovery of bacteria extended to the urinary tract as several investigators cultured organisms from the urine between 1885 and 1890, culminating in the realization by Ali Krogius (1864-1939) in 1892 that the most important of these was identical to Bacterium coli commune (later renamed as Escherichia coli) that Theodore Escherich (1857-1911) of Vienna had identified in 1885 as the predominant organism inhabiting the bowels of normal humans. Speculation nevertheless continued about the pathogenetic mechanisms of inflammation – with the result that the cellular theory, despite its attraction, failed to
gain universal support. Ideas of chemical mechanisms of disease, derived ultimately from the Galenic theory of the four humors, had influential supporters, especially among German pathologists such as Baumgarten of Berlin. Their opposition to Metchnikoff’s vigorous advocacy from his influential new position at the Pasteur Institute in Paris even developed nationalistic overtones (30). Their case nevertheless received its first objective support from the identification in 1888 by George Nuttall (1862-1937) of bactericidal properties in the cell-free serum of animals (31). The prompt extension of this observation to normal humans and to humans immunized against various infectious diseases, and the discovery of complement during the next year by Hans Buchner (originally named alexin) as the chemical responsible for this, created further difficulties (32). Emil von Behring (1854-1917) and Shibasaburo Kitasato (1852-1931) exacerbated these when they discovered antibodies to diphtheria and tetanus and so opened the way for the development over the next decade of a general theory of antigen-antibody reactions as the mechanism of humoral immunity (33).

These developments had a profound effect not only on ideas about immunity, but also on the concept of inflammation. Compare the definition of inflammation provided by a widely used medical dictionary in 1875 (34):

A state of disease characterized by redness, pain, heat, and swelling; attended or not with fever.

with the definition provided by a comparable dictionary in 1886 (35):

Inflammation is a series of changes in a part identical with those that are produced in the same part by injury; and, for the sake of precision, injury by a chemical or physical irritant.

The final quarter of the 19th century was therefore the time when the heat went out of inflammation and its emphasis irrevocably moved from manifestations to mechanisms and to causes.

Ideas about diseases of particular organs evolved concurrently with the evolution of general ideas about inflammation. The situation with regard to urinary tract diseases amply demonstrates this point. The great challenge during the 19th century was for people to reach some understanding of what they described as Bright’s disease, although there was also some reference to pyelitis, pyelonephritis, and related conditions. Many authors also wrote about nephritis, although they included a wide variety of conditions under this heading that few 20th century commentators would regard as inflammatory.

Richard Bright (1789-1858) was the person responsible for stimulating much of the discussion about diffuse renal diseases. He referred occasionally to the condition that came to be called after him in terms such as ‘a decidedly inflammatory state of the kidney itself’ (36), but one suspects that he was cautious about using this term as it appears only very rarely in his writings. He, like virtually all his successors, associated the development of many (but not all) cases of nephritis with a preceding attack of scarlet fever and had a notion that some poison resulting from that condition had damaged the kidneys. He was, however, primarily an observer who focussed upon recording his observations with accuracy, rather than upon speculating philosophically about their implications. He certainly avoided indicating an opinion about the relationship of fevers to inflammation or what he understood by the term inflammation.

Pierre Rayer (1793-1867), on the other hand, regarded nephritis (under which term he included Bright’s disease) as an inflammatory condition, or group of conditions, and also wrote of pyelitis and pyelonephritis as forms of inflammation (37). He contrasted starkly with Robert Christison (1797-1882) who mirrored Bright in the caution that he displayed in addressing the theoretical aspects of the topic. Christison gave his 1839 book on the subject the title of On Granular Degeneration of the Kidneys, and its Connection with Dropsy, Inflammations, and other Diseases, so he obviously had no great reticence in referring to inflammation, but an examination of this work demonstrates that, whereas he perceived some of the secondary manifestations of uremia that appeared in distant organs such as the pericardium and pleura as being inflammatory (presumably on the basis that they generated exudates), he hesitated to apply that term to the primary disease in the kidneys themselves. He indeed commented of Bright’s disease that ‘Its inflammatory character in many instances may be doubted’ (38). George Johnson (1818-1896), writing in 1852, adopted a similar position to Christison in that he made one reference to ‘acute inflammation of the kidney’ in relation to post-scarlatinal nephritis and similar diseases, but appeared reluctant to use the term in this context, in contrast to his frequent reference to ‘suppurative inflammation’ when describing conditions associated with the presence of pus in the urine (39).

William Basham (1804-1877) was a slightly later author who wrote repeatedly about diffuse diseases of the kidneys. A comparison of his ideas expressed in 1862 with those of 1870 shows how use of the term inflammation was evolving at the time. Basham commented in 1862 that ‘the inflammatory origin of the
disease is the most apparent and most readily demonstrated’ in post-scarlatinal nephritis, but this did not provide him with his principal method of sub-classifying diffuse diseases of the kidneys (40). By 1870, however, he had moved to make his major subdivision of renal diseases depend upon whether they were inflammatory or not, with acute kidney diseases typifying to him the former and chronic diseases the latter. He recognised, nevertheless, that his distinction was imprecise since he commented at the very beginning of his 1870 book that ‘For clinical purposes, under the term Nephritis several disordered or disturbed states of the kidneys are included which are not in a strictly pathological sense inflammatory’ (41). Jean Charcot (1825-1893), writing in 1877, made it clear in contrast that he favored the non-speculative position of the earlier British authors. He thus carefully avoided using the term inflammation when describing the various types of kidney disease, but – like Christison – labeled several of the complications of uremia that affected serous membranes as being of an inflammatory nature (42). British viewpoints were, however, changing and William Dickinson (1832-1913), wrote in 1881 of diseases of the kidneys in which there was a ‘morbidly increased cell growth’ as exhibiting inflammation (43).

This all suggests that concepts that related inflammation to urinary tract diseases changed only slowly during the 19th century. Such conditions as pyelitis and pyelonephritis – that displayed the classical manifestations of heat and pain, sometimes with redness and swelling – were clearly inflammatory. Bright’s disease and nephritis, however, posed such difficulties, to the extent that most authors expressed a vague belief about their inflammatory nature, but few did so comfortably until late in the century.

20TH CENTURY INFLAMMATION: THE EVIL HUMORS
TRIUMPH

Several landmark observations occurred just before World War I that resulted from experimental investigations in animals. The most prominent of these were of anaphylaxis, serum sickness, and the Arthus reaction – for which subsequent workers have elucidated the underlying mechanisms that have shed much light on the relationship between immune processes and inflammation.

Anaphylaxis, first described by Paul Portier (1866-1962) and Charles Richet (1850-1935) in 1902, is a generalized condition. It develops within minutes when a second injection of a foreign protein is given at least ten days after a previous injection of the same protein. The first injection induces the formation of antibodies that fix to mast cells; antigen from the second injection reacts with those antibodies; and the damaged cells release vasoactive histamine that causes systemic manifestations (44).

Serum sickness that Clemens von Pirquet (1874-1929) and Bela Schick (1877-1967) described in 1905 is also a generalized condition. It develops eight or more days after an intravenous injection of a foreign protein. The injection induces the formation of complement fixing antigen-antibody complexes that deposit in the microvasculature of various organs (skin, lymph nodes, spleen, joints, and kidneys) and cause localized inflammation, generalized fever, and malaise (45).

The reaction that Maurice Arthus (1862-1945) described in 1903 is a localized condition. It develops over several hours when a subcutaneous injection of a foreign protein is given at least ten days after a previous injection of the same protein. The first injection induces the formation of antibodies that circulate; antigen from the second injection reacts at the injection site with those antibodies and with complement, producing a cellular inflammatory response (46).

Henry (later Sir Henry) Dale (1875-1968) and Patrick (later Sir Patrick) Laidlaw (1881-1940) identified the physiological action of histamine in 1911 and associated it with anaphylaxis (47), but it was not until 1927 that Sir Thomas Lewis (1881-1945) proposed that this and similar vasoactive chemicals mediate many clinical manifestations of inflammation (48). Valy Menkin (1901-1960) took up the challenge in 1929 of understanding the basis of inflammation and later of trying to identify additional chemical mediators (49). He eventually isolated a substance that he called leukotaxine that increased capillary permeability (50), but also later found evidence to support the existence of several other factors including pyrexin (that he believed caused fever) (51), necrosin, and growth-promoting factor.

Major advances in developing a theoretical understanding of immunology occurred between 1930 and 1960, with a focus on circulating and tissue-fixed humoral factors all of which played roles in inflammation. Ideas about endogenous pyrogen emerged in 1953, and interferon in 1957, the latter due to the work of Alick Isaacs (1921-1967) and Jean Lindenmann (born 1924) (52). The development of tissue culture techniques facilitated the investigation of the products of pure strains of cells, with the result that several new substances had entered the discussion by the early 1970s. Research thereafter focussed upon identifying ever more examples of these and the roles of various cells in producing them. They included...
leukocyte mitogenic or blastogenic factors (LMF/BF), macrophage migration inhibitory factors (MIFs), macrophage activating factor (MAF), vasopermeability factor (VPF), vascular endothelial growth factor (VEGF), slow-reacting substance of anaphylaxis (SRS), endothelial derived relaxation factor (EDRF), and tumor necrosis factor (TNF). The term interleukins appeared in the late 1970s to describe factors released by macrophages (interleukin-1) and lymphocytes (interleukin-2) that promoted T-cell proliferation. The proliferation of identified substances that moved between cells led to the proposal in 1974 of the term cytokines to describe them (53). Their numbers also grew rapidly (more than a hundred have now been identified), as did an awareness of their integral role in mediating inflammation. The result is that cytokines are now depicted as ‘soluble extracellular proteins that regulate non-specific as well as immunologically dependent inflammatory reactions, cell growth, differentiation, and development and repair processes culminating in the restoration of homeostasis’ (54, 55).

Further evolution of the idea of inflammation resulted from all this laboratory activity. An increasing awareness during the 20th century of the complex roles played by the various cellular and humoral factors in the pathogenesis of tissue damage left observers struggling for a comprehensive descriptive term. Inflammation became the one that most adopted — and this caused its definition to change. Hence, by the 1930s, some medical dictionaries were stating that (56):

**Inflammation** (inflammation, I set on fire) may be defined as the reaction of the tissues to any injury, short of one sufficiently severe to cause their immediate death. The term is limited sometimes to the changes which take place when bacteria enter the body, but the changes in the latter case, though specially severe, are essentially the same as those produced by any other source of irritation.

They thus reflected the views of Valy Menkin, the most prolific writer on the subject in the middle years of the century, who stated that (57):

The term inflammation refers to the aggregation of several interdependent reactions incited by the presence in normal vertebrate tissue of a foreign body or so-called irritant. The injurious agent may be living or non-living; it may be of exogenous or even of endogenous origin. Inflammation as such, is a basic phenomenon in infectious processes ...Inflammation is essentially one, among others, of the various manifestations of cellular injury. It represents the complex response on the part of normal tissue to relatively severe damage.

Although some writers still continued to predicate inflammation upon the traditional findings of heat, redness, pain and swelling (58), most definitions had long left that notion behind as several examples demonstrate:

The non-specific immune response that occurs in response to any type of bodily injury (59).

A fundamental pathologic process consisting of a dynamic complex of cytopathic and chemical reactions that occur in the affected blood vessels and adjacent tissues in response to an injury or abnormal stimulation caused by a physical, chemical, or biological agent, including: 1) the local reactions and resulting morphologic changes, 2) the destruction or removal of the injurious material, 3) the responses that lead to repair and healing (60). The reactive state of hyperemia and exudation from its blood vessels, with consequent redness, heat, swelling, and pain, which a tissue enters in response to physical or chemical injury or bacterial invasion (61).

[Collection of the vascular, tissue and humoral changes produced in multicellular beings by any attack on the integrity of their tissues] (62).

The question then arises of the clinical impact that these various definitions exert. How, for example, did they improve understanding of kidney disease? Friedrich von Mueller (1858-1941) of Marburg supported a major role for inflammation when he drew a clear distinction in 1905 between inflammatory types of renal parenchymal disease (nephritis, in his terminology) and degenerative types (nephrosis) (63). Franz Volhard (1872-1950) and Theodor Fahr (1877-1945) in Mannheim continued this terminology in their various writings. The presence of cellular proliferation within the glomeruli was, to them, the feature that distinguished a particular lesion as inflammatory. This convention persisted in the writing of most commentators over the following half-century (64-67).

Awareness of the possible involvement of humoral factors grew only slowly despite occasional case reports having appeared from early in the 20th century that associated hypocomplementemia with inflammatory types of glomerulonephritis. The association with previous streptococcal infection and the latent period of some 10 to 20 days after the time of infection with these inflammatory lesions was also highly suggestive. It was not, however, until the development of kidney biopsy techniques with fluorescent antibody staining to identify the deposition of immunoglobulins and complement factors, that the potential role of circulating factors developed a credible place in the understanding of glomerular inflammation (68). This then
led to an avalanche of research as each new interferon, interleukin, and cytokine was examined for roles and interactions with other circulating and tissue-fixed factors in each natural and experimental variety of glomerulonephritis, each systemic immunological disease, and each disease with a vascular component that affected the kidneys. Few of the latter showed any evidence of the classical manifestations of inflammation (of redness, swelling, heat or pain) although for an increasing number of them evidence emerged of some external factor (usually infectious or chemical) that played a causal role. And the frenzy of this type of work continues to the present.

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