Chronicles

Newsletter of the UCSD Emeriti Association

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Arthritis: Not a Disease, but a Symptom

—by Dr. Nathan Zvaifler

This issue of **Chronicles** *has three articles by Emeriti that pertain to health issues. For the first of these, we should all thank Dr.* ***Helen Ranney*** *for getting* ***Nate Zvaifler*** *to write such a valuable article for his fellow Emeriti. Helen wrote the following to identify and introduce Nate to those who don't know him. —Ed.*

"Dr. ***Nathan Zvaifler*** *who was head of the Division of Rheumatology in the Department of Medicine at UCSD from 1970 to 1990 is internationally recognized as a master clinician and skilled researcher. Already known in 1970 for his research on central nervous system involvement in an autoimmune disease (lupus erythematosis), Dr. Zvaifler built an outstanding clinical and research program in the Division that has grown from the original two to its present complement of 20 members with ample research funding. From 1972 to 1974, a crucial two years in the development of the new School of Medicine at UCSD, Dr. Zvaifler was Acting Chairman of the Department of Medicine.*

Dr. Zvaifler has published more than 100 research papers in addition to 100+ invited articles. He has received honors from many institutions in different countries, among them the Heberden Society in England, where he was the Heberden Orator in 1990; named lectureships in Holland, Germany, Greece, Japan, and the University of Pennsylvania; and Visiting Professorships at Harvard, the Hospital for Special Surgery (New York City), Rockefeller University, and Hammersmith Hospital (London). Having retired in 2000, Dr. Zvaifler continues many academic activities in the Division of Rheumatology as Professor of Medicine Emeritus. We are grateful to him for sharing his wisdom about arthritis with us."

Arthritis (arthros=joint + itis=inflammation) is not a disease, it's a symptom. The American College of Rheumatology recognizes more than 100 conditions associated with joint complaints. Many are uncommon or inconsequential, but two, osteoarthritis and rheumatoid arthritis, account for almost 20% of all office visits to primary care physicians. Osteoarthritis is a metabolic or degenerative process (so the "itis" is a misnomer), while rheumatoid arthritis is an inflammatory, destructive process mediated by the immune system. The origins of both are still obscure. A number of misconceptions about joint diseases persist: "It's only arthritis, nothing can be done about it"; "Why see a doctor, they'll only tell you to take aspirin." These erroneous beliefs overlook the considerable progress, both past and present, that has occurred in this field. For instance, two previously common, severe diseases associated with joint symptoms, namely rheumatic fever and gouty arthritis, are things of the past. The former, caused by a streptococcal infection, succumbed to improved hygiene and penicillin; while the latter, once the underlying metabolic processes were delineated, is now easily managed with drugs.

Rheumatoid arthritis is illustrative of this progress. How an obscure disease whose treatment was based on ignorance, superstition, and serendipity became amenable to treatment is a triumph of modern molecular medicine. Unlike gout, a disease of antiquity, descriptions of rheumatoid arthritis are lacking in skeletons, paintings, and classical writings prior to the 18th century. This is surprising given that the characteristic finger deformities are so easily recognized. Reports of a disease resembling rheumatoid arthritis appeared in the medical literature in the 1700's, but the first convincing

description that allowed rheumatoid arthritis to be separated from other joint diseases was published in 1800. The relative newness of the disease was consistent with the appearance of a novel infection and conformed to the "germ theory of disease" that was prevalent in the late 19th and early 20th centuries. As a consequence, normal teeth, tonsils, appendixes, and uteruses were removed from rheumatoid patients in a misguided attempt to eradicate a presumed "focus of infection." Prior to modern antibiotics, chronic infections like syphilis and tuberculosis were treated with heavy metals, such as arsenic, mercury, and gold. The latter improved some rheumatoid patients, and while there is no credible evidence of an infectious agent causing rheumatoid arthritis, gold remained a mainstay of treatment for the next 50 years.

In 1942, a Swedish investigator described a novel protein (the rheumatoid factor) in the blood of some patients with rheumatoid arthritis. Because of World War II, this important observation was overlooked until the following decade, at a time when the discipline of immunology was just being applied to clinical medicine. The rheumatoid factor proved to be an antibody made against a normal protein in the patient's own blood, thus an "autoantibody," and rheumatoid arthritis joined the expanding number of "autoimmune diseases." Research in this area has advanced along two fronts. First, were attempts to define the substances or molecules (called antigens) that provoke the aberrant immune response. Normally, although the immune system responds vigorously to foreign material, it recognizes and tolerates its own tissues; thus, autoimmunity seems an oxymoron. An autoimmune response is thought to develop when normal tissues are modified by injury or inflammation (altered self) or when a foreign agent or material is so similar to a normal body constituent (mimicry) as to fool the immune system. For example, the cell wall of the streptococcus bacterium contains molecules that are almost identical to molecules in heart muscle. As a consequence, some people who get a streptococcal sore throat also develop a severe immune-mediated disease of the heart muscle and valves (rheumatic fever). If the inciting antigen(s) is/are identified, treatment becomes possible. For example, penicillin eliminates the streptococcal organism and rheumatic fever is no longer a problem. To date, however, no specific rheumatoid arthritis antigen has been found.

Another approach is to control the harmful immune response, either by eliminating the participating cells or neutralizing their deleterious products. A number of anticancer drugs known to kill immune cells were given to rheumatoid arthritis patients. Most proved too toxic; but one, methotrexate, was very successful and has replaced many older treatments. Of interest, the benefits of methotrexate are probably due to anti-inflammatory rather than cytotoxic effects. Another example of the right result for the wrong reason. Compounds produced by molecular biologic technology are the latest approach to the treatment of rheumatoid patients. Early findings with antibodies that target and eliminate specific immune cells are encouraging, but the most spectacular results have been seen with antibodies that trap tumor necrosis factor (TNF), one of the most inflammatory and bio-toxic products of immune reactions. More than half of the rheumatoid arthritis patients treated with anti-TNF get significant improvement of symptoms, some have a complete remission, and joint destruction and deformity is halted in all. Important limitations include the expense ($10,000-$15,000 a year), a predisposition to develop certain infections, and the return of disease activity shortly after the treatment is discontinued. Thus, the arthritis is suppressed, but not cured. Nevertheless, most patients with rheumatoid arthritis now have a manageable disease. Laboratory studies at UCSD in the early 1990's predicted this remarkable outcome.

Degenerative diseases are becoming increasingly important as the population ages. Paramount among them is degenerative (osteo)arthritis, a complex disorder of mechanical, biochemical, metabolic, and genetic factors. Joint cartilage, the smooth, white, elastic substance that covers the end of bones, is the target of the disease. Degenerating cartilage can't withstand compressive forces and becomes friable and irregular, compromising joint motion, causing pain and leading to compensatory new bone formation ("bone spurs"). These produce typical deformities, especially in the finger joints and the spine. The source of the problem is unknown and probably differs depending on the joints involved. Most researchers have sought defects in the cells (chondrocytes) that produce the mucinous material that provides resistance to compression or to the collagen that gives cartilage its tensile strength. Others have focused on inflammatory substances (cytokines) that can compromise chondrocyte metabolism. At UCSD an alternative approach is under investigation; namely, that the problem does not begin in cartilage, but in the quality of the underlying bone. If the bone is stiffer, it will place increased stress on the cartilage and hasten its disintegration. Genes responsible for bone growth and remodeling are known from studies in developmental biology; some of them operate in adulthood. Evidence for alterations in their expression or function are currently under investigation in populations with specific forms of osteoarthritis.

The treatment of osteoarthritis remains symptomatic. Some medications are used for pain relief (e.g., Tylenol) and some to reduce inflammation (e.g. Motrin, Vio, Celebrex); but, to date, nothing has altered the course of the disease. Artificial (prosthetic) joints can successfully replace worn-out hips or knees, but attempts to resurrect damaged cartilage are still unsuccessful. In the future the degenerative process may be reversed by inserting normal chondrocytes or specific genes into diseased cartilage. Currently there is enthusiasm for glucosamine and chondroitin sulfate, constituents of normal cartilage that decline as cartilage ages or

degenerates. Symptoms of osteoarthritis improve in some patients who take these supplements, but so far there is no evidence that either or both of these molecules are incorporated into cartilage or slow the degenerative process.

Editor's Lament

Given the special importance of **Clark Kerr** to this campus and thus to San Diego as a whole, I found the perfunctory *San Diego Union*'s obituary marking his recent death to be ignorant and insulting to those of us who recognized his importance in supporting our unique way of starting a great university at its most critical early stages of development. I note that the *New York Times* was far more cognizant of Kerr's importance as a national leader in education than our local journalists were of his importance to UCSD and San Diego. To be sure, some of my colleagues thought that Kerr opposed what we wanted to create during those early years, pointing to his recalcitrance in getting our medical school and our library the extraorinarily rich funding we all thought they deserved because they were needed for the extraordinary campus we thought we were building.

In reading Kerr's account of those years and talking with him up close and personal at a time when he had nothing to gain by self-serving, I became convinced that he was telling the truth when he said that he (and the Regents) shunted funds our way that other of the new and some of the old campuses were clamoring for, and permitted us special exemptions from restrictions that applied on other campuses, because he thought that UCSD, of all the campuses, offered the most promising chance for future greatness. This, despite his personal affection for his friend Dean **McHenry**'s utopian Santa Cruz campus — tragically dashed during the wild antiwar days of 1969 when graduating students at the first Santa Cruz commencement ceremony inflicted derisive personal attacks on him and on McHenry.

Kerr particularly regretted that he was unable to get **Roger Revelle** approved as our first chancellor over the objections of the two most powerful Regents of that era. As for his failure to get us the special funding we needed for our ambitious medical school and library — both of which he actually liked for their ambitiousness — he argued that it was the insistence of Chancellor **Galbraith** for the library and Dean **Stokes** for the medical school on <u>immediate</u> funding, rather than any reluctance on his part to try to get them the money, that led to their frustration, the cause of which was really the legislature's pressure on the university to tighten its budgetary belt. He felt terribly unappreciated by some campus colleagues for what he did for us; they seemed to remember only what he was not able to do.

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Mark Your Calendar!

UCSD Emeriti Association Meetings

Wednesday, January 21
3:30-5:00 PM
Price Center Davis/Riverside Room

Nicholas Spitzer

"Building the Brain: Nature and Nurture"

Professor Nicholas Spitzer is one of the world's leading investigators in the study of brain development. In recognition of his scientific contributions, he was elected last year to the prestigious American Association of Arts and Sciences. Nick has been an academic leader on our campus both within the Division of Biological Sciences and on the campus as a whole since joining UCSD in 1972. He has played a major role in positioning this campus as first among the basic neuroscience programs in our country. He is presently a councilor for the Society for Neurosciences. Nick received his Ph.D. from Harvard and carried out his postdoctoral work at that institution prior to joining UCSD. In addition to hearing a gifted speaker, this is an opportunity for Emeriti to learn of some of the latest scientific developments in one of the forefront research areas of the biological sciences.

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Wednesday, February 18
3:30-5:00 PM
Price Center Davis/Riverside Room

Jonathan Saville

"Character"

Back at the December 1999 meeting of our Association, we heard an intriguing talk on "The Universal Principles of Plot Development" by Professor Emeritus Jonathan Saville. I suspect that his companion talk on "Character" at our February meeting this year will be no less intriguing, since Jonathan prefers not to expand that title in order to enhance the mystery of his subject.

Professor Saville began his distinguished career at UCSD over 30 years ago, first in the Department of Literature and then in the Department of Theatre. Writing often for the *San Diego Reader* since 1972, his perceptive articles on theatre, music, and the visual arts have won him a loyal following and great acclaim. Since retirement, he has continued his productive activities without letup.