



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 erythematosus), 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 extraordinarily 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 immediate 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.

Leonard Newmark, ldnewmark@ucsd.edu

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.

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.



Wednesday, February 18

3:30-5:00 PM

Price Center Davis/Riverside Room

Jonathan Saville

“Character”

Reminiscences: Early UCSD History

Editor's Note

The following article is a first-person account of engineering at UCSD that fits very well with our *Chronicles* series aiming to provide a history of UCSD through the eyes of its early builders. Incidentally, the group of early engineering faculty alluded to in the article are **Paul Libby** himself, of course, as well as **Hugh Bradner**, **Shao-chi Lin**, **John W. Miles**, **Daniel B. Olfe**, **Stanford S. Penner**, **Sinai Rand**, and **Forman Williams**.

Changes in Engineering at UCSD: A Personal View

—by Paul A. Libby

The Irwin and Joan Jacobs School of Engineering (SOE) is presently housed in an impressive and growing set of buildings on the Warren Campus. Three no-name buildings, EBU-I and -II and EBU-III A (Bioengineering) are fully occupied, while EBU-III B (Computer Engineering) is presently coming out of the ground and the Cal-(IT)² building along the north edge of the old soccer field is becoming more massive each day. In addition, plans for a Structural Engineering building to be located south of Voigt Drive are underway. At the present time roughly 25% of UCSD undergraduates are engineering majors, and the engineering faculty number approximately 150.

All the activity implied by these buildings and these numbers evolved over forty years and was initiated by a small group of faculty recruited by Professor **S. S. Penner** in 1963-64. I was one of that group. The group constituted the Department of Aerospace and Mechanical Engineering Sciences (AMES). They were the first engineering faculty on campus and were housed in Revelle College. In 1966 a second engineering department, the Department of Applied Electrophysics (AEP), was established with Professor **Henry Booker** as Chair and was housed in Muir College. Several years later with the rapid growth of computing, the mission and name of this second department were changed to Applied Physics and Information Sciences

(APIS). What follows is a personal but incomplete and biased history of the changes in engineering at UCSD from this nucleus of faculty to the present. I shall focus primarily on AMES since I am most familiar with its history but shall note some of the developments in APIS.



Initially both of the engineering departments had a strong applied science in contrast with a technological emphasis. This was a consequence of the interests of the early faculty and consistent with the general academic tone of the campus at that time. This feature had a highly important consequence for the development of engineering at UCSD. In the late 60's there was concern statewide that an excess capacity for engineering education in the UC-system was developing. Accordingly, Dean **Fred Terman**, a distinguished former dean of engineering at Stanford, was asked to survey engineering on the various campuses of the university and to determine if indeed there was such excess. Dean Terman

concluded that there was no need for the emerging engineering programs at Santa Cruz and Riverside and that they should therefore be terminated. However, he recommended that the program at San Diego with its strong applied science emphasis should proceed. Engineering at Santa Cruz and Riverside was put on hold for twenty or so years, while we were allowed to proceed. Clearly my story would be significantly changed if a different recommendation for UCSD had been forthcoming.

The applied science emphasis of the department was reflected in the renaming of the department in the early 70's. The acronym was retained but we became the Department of Applied Mechanics and Engineering Sciences. That name prevailed until 2000 when the more conventional label, Department of Mechanical and Aerospace Engineering (MAE), was adopted. I discuss the reasons for this latter change and its implications later.

And so in the late 60's and early 70's, the two engineering departments grew in numbers, both faculty and students, both undergraduates and graduates, with the undergraduates receiving Bachelor of Arts degrees. In the early 70's I became Chair of AMES. It appeared to me to be appropriate to consider a second option for our undergraduates, one leading to B.S. degrees in engineering. I had in mind a program modeled after one that existed at UCLA at that time, the Boelter-

Tribus program. Involved was a largely uniform curriculum for all students for the first three years with specialization limited to the senior year. It seemed to me that such a general curriculum could be compatible with the requirements of the various colleges at UCSD and could retain the applied-science emphasis of the two departments. My proposal to offer such an option to the chair of APIS at the time was well received, but only in the sense of establishing a new engineering curriculum, one far more conventional than I had in mind. Moreover, the idea of minimizing specialization in the new program was immediately rejected by the faculty of both departments.

Over the years the curricula in the two departments have evolved so that more required engineering courses appeared, first in the sophomore year and more recently in the freshman year. These developments have had the consequence that our early applied-science emphasis and compatibility with the requirements of the various colleges at UCSD have been lost. Since UCSD engineering students must meet college as well as SOE requirements, many of them are enrolled in the college with the least stringent requirements. These developments were perhaps inevitable if a program accredited by the operative national organization and if an engineering school with national visibility and national stature are deemed desirable. Such goals were not considered in the early days when many less Olympian matters required attention. It should also be noted that many of the engineering faculty added over the years have been recruited from, and educated at conventional engineering schools, and as a consequence see little value in the college system.

In the early 80's **Richard Atkinson** became Chancellor at UCSD. His previous academic position had been at Stanford, which has a full-fledged School of Engineering. Since early in his tenure here, engineering undergraduates constituted roughly twenty percent of the student

body, Chancellor Atkinson asked that a committee be appointed to examine whether a School of Engineering should be established at UCSD. **David Miller** was appointed as Chair of such a committee and I was a member. Hearings and discussions were held, with the consequence that in 1982 the committee recommended the establishment of a Division of Engineering. A "division" required a Dean and in due course **M. Lea Rudee**, who had been Provost of Warren College and a faculty member in APIS, was appointed the first Dean of Engineering. I believe Dean Rudee was the first academic dean on the general campus. In 1994 the Division was renamed the School of Engineering, and so the efforts of Chancellor Atkinson were brought to fruition.

In recent years the original two departments have divided so that at present they number five. The first activity to secede was bioengineering, which must be considered the great, perhaps the only, real success of the **Bonner Plan**. The original idea of the Bonner Plan was that the appropriate departments on the general campus would handle the early basic training of the students of the School of Medicine (SOM). Early on, for example, faculty positions were deployed to Biology, Chemistry, and Mathematics. In addition, a bioengineering activity was started in AMES under the leadership of Professors **Y. C. Fung**, **Ben Zweifach**, and **Marcos Integlietta**, all of whom were recruited by Professor Penner. Although over the years many of the deployed FTE's were called back to meet immediate needs of the SOM, the bioengineering activity has prospered and led to active collaboration in teaching and research with faculty of the SOM, much as envisaged in the Bonner Plan. In the early 90's, bioengineering was set up as a separate department and now occupies a handsome building in the engineering complex. It is highly ranked nationally and has contributed significantly to San Diego becoming a center of the biotechnology industry.

Two other separations have occurred. The structural engineering component in AMES has become the Department of Structural Engineering with an important research facility for structural testing, the Powell Laboratory. Its faculty have played a significant role in retrofitting many California bridges to make them more resistant to earthquakes. Moreover APIS has divided into the Department of Electrical and Computer Engineering and the Department of Computer Science and Engineering. The latter will soon be housed in the building presently under construction.

In the last seven or eight years, a full-fledged School of Engineering at UCSD has been developed. Dean **Robert Conn** succeeded Dean Rudee and exerted strong leadership to this end. In particular, he solicited significant contributions from local high technology companies. Especially important were contributions from **Irwin Jacobs**, who had been an early faculty member in APIS and who subsequently founded Linkabit and Qualcomm, two successful San Diego companies. In 1999 he made an important financial contribution to UCSD, with the consequence that the SOE was named after him and his wife. As an additional step toward conventionality, Dean Conn encouraged the name change from AMES to the standard Department of Mechanical and Aerospace Engineering, i.e., to MAE. Dean Conn oversaw significant growth in students, research activity, and faculty and in the construction of new facilities. At present the national ranking of the SOE is now quite respectable for such a newcomer to the national scene, and all of our undergraduate programs are fully accredited. **Frieder Seible** became the third Dean of the SOE in 2002.

Our story has sketched the changes in engineering at UCSD over the past forty years. Many of the early faculty are no longer with us, but some of the original group are still active and taking note of further developments evolving from their early effort.

In the second of the articles in this issue that pertain to health matters, Gerhard Schrauzer provides information that will especially appeal to our common interest in health as old people. Professor Schrauzer submitted a longer version of this article in response to my request for articles about changes in his field during his academic life.—Ed.

What We Knew and What We Know: The Anticarcinogenic Action of Selenium

—by Gerhard Norbert Schrauzer

Introduction

Selenium was shown to be nutritionally essential in 1957, but was still registered as a carcinogen as late as in the early 1970's and subject to the now infamous Delaney Clause. Selenium accordingly could not be legally added to animal feed, making it impossible to prevent selenium deficiency diseases in livestock that continued to cause huge annual losses in many parts of the USA. At the same time, the degree to which selenium increases human cancer risk, if at all, was essentially unknown. When, finally in 1969, cancer mortalities in the United States were compared in relation to regional selenium occurrence, a surprising result was obtained: instead of being higher, the mortalities were actually lower than expected in the high-selenium regions! This study not only showed that selenium as naturally present in forage crops did not increase cancer risk, but even suggested that selenium could have cancer-protecting properties.

Important discoveries are often made simultaneously by more than one group. In my laboratory at UCSD, I was at that time not concerned with animal nutrition. I was interested in cancer, viewing it, in part, as a "disturbance of cellular respiration." Within this context, we investigated electron transfer reactions in simple systems, typically using thiols as the electron donors and reducible dyes as the acceptors. Such reactions are normally slow, but we found them to be greatly

accelerated by traces of certain metals, including selenium. This led us to re-investigate a previously utilized diagnostic "cancer test," which, though poorly understood, was widely used in the 1940's to 1950's at Massachusetts General Hospital and New York Medical College. The test consisted in the measurement of the methylene blue reduction time of human plasma and was originally believed to measure the amounts of protein sulfhydryl groups present. Our work established that the test actually responded to the amount of plasma selenium present. We thus were able to conclude that cancer patients tended to have low plasma selenium levels. Since the test was positive even in newly diagnosed patients having only very small tumors, this suggested that selenium acted as a cancer-protecting agent.

Preventing Mammary Tumors in Mice

In order to test this hypothesis, I wanted to study the effect of selenium in a suitable animal model. I was very fortunate to meet Dr. **Leonell Strong**, the discoverer of the famous C3H strain of mice whose females develop spontaneous tumors in the mammary gland, and to tell him about my plans. Using his mice, we were able to show that selenium at subtoxic levels significantly prevented the genesis of these tumors without causing any unwanted side-effects. The oncogenic agent in this animal tumor model system used to be called the Bittner Milk Factor, so

named because **Bittner** found it to be transmitted to the offspring through the milk of infected dams. The Bittner Milk Factor has since been identified as an RNA virus and is now referred to as the Murine Mammary Tumorvirus (MMTV). Its relevance to human breast cancer was originally doubted. However, recent studies demonstrated the presence of fragments of the same or very similar virus in a significant percentage of human breast cancer tissues. Since our studies indicated that the genesis of mammary tumors can be prevented with selenium, we concluded that this could also apply to humans.

Ecological Studies

Since breast cancer mortalities in different countries vary considerably, it seemed logical to assume that this was caused by differences in the dietary selenium intakes. Subsequent studies revealed that this is indeed the case. We also compared the selenium concentrations of blood samples collected from healthy donors in different countries and found them to be inversely correlated not only with the breast cancer mortalities, but also with the mortalities from cancer of the ovary, prostate, colon, rectum, lung, pancreas, and others. Based on these findings, I proposed in 1976 that "cancer mortalities in the U.S. and other Western industrialized nations would decline significantly if the dietary selenium intakes were increased to approximately twice the current average amount by the U.S. diet." In

other words, this meant that cancer could be prevented simply by taking a pill containing 200 micrograms of selenium. Understandably, granting agencies, colleagues, and even some of my best friends initially thought that this was a harebrained idea. However, the selenium-anticancer hypothesis received further support in the 1980's through case-control studies.

Case Control Studies

In a study published in 1983, **Walter Willett** and coworkers at Harvard showed that low serum Se is a prediagnostic indicator of higher cancer. They compared the Se levels of serum samples collected from American subjects 1-5 years prior to diagnosis of cancer and compared them to the levels of selenium in serum samples of subjects that had remained cancer-free during the same period. The association between low serum Se and cancer was the strongest for gastrointestinal and prostate cancer; low serum levels of vitamin A and E compounded the apparent cancer-protective effect of Se. Similar results were subsequently obtained in studies conducted in Finland and in Japan. In other nested case-control studies, low levels of Se in serum or plasma were found to be associated with increased risk of thyroid cancer, premalignant or malignant oral cavity lesions, and colorectal adenomas. Serum Se and vitamin E was also found to be lower in Japanese lung cancer patients and their family members. In three studies, low toenail Se values were associated with higher risks of developing cancers of lung, stomach, and invasive prostate cancer. In four studies, significantly lower Se levels in plasma or serum were also observed in breast cancer cases than in controls. What was now obviously needed was to test the selenium-anticancer hypothesis directly in humans.

Intervention Trials

In 1980 a young scientist, **Larry C. Clark**, then a graduate student working at the Institute for Environmental Studies at the University of North Carolina at Chapel Hill, became seriously

interested in conducting a human cancer-prevention study with selenium. While still at Chapel Hill, he wrote a dissertation entitled "A case control study of skin neoplasms and the anticarcinogenic effects of selenium." After obtaining his doctorate in epidemiology in 1982 he accepted a position as Assistant Professor of Epidemiology at Cornell University and was able to convince the National Cancer Institute to fund a large scale, placebo-controlled cancer-prevention trial with selenium. While supplemental Se had no effect on skin cancer recurrence, incidence and mortality from cancers in other organs were significantly reduced: in the placebo group, 117 non-epithelial cancers occurred, but in the Se group only 70, and overall cancer mortality was reduced by 56%. The incidence of prostate cancer was reduced by 63%, colorectal and lung cancer by 58% and 46%, respectively.

On the basis of all the available evidence the National Cancer Institute believes that only one additional intervention trial needs to be conducted before selenium supplementation can be officially recommended for cancer prevention. This study was started in the year 2001. Named SELECT, it will enroll 32,000 subjects in 400 centers in the USA and Canada and is scheduled to end in 2012.

Mechanisms of Anticarcinogenic action

The anticarcinogenic actions of Se occur at the systemic, cellular, and nuclear level, may involve the immune system, and thus cannot be interpreted by a single mechanism. The anticarcinogenic action of Se also depends on its chemical form, dosage, and the nature of the carcinogenic agent. At optimal levels for the prevention of carcinogenesis, Se is effective only prior to or in the early phases of malignant transformation. Cells

adequately supplied with Se are less susceptible to the damaging effects of endogenously or exogenously generated oxygen radicals that may attack cellular DNA, cause mutations and the oxidative activation of chemical carcinogens.



Concluding remarks

Whereas biological research during the past three decades has vastly deepened our understanding of the mechanisms of conversion of normal cells into cancer cells, the introduction of selenium into the field has added new dimensions of complexity. Obviously, much more research is still required for the full understanding of its multiple modes of action. However, the mechanistic complexity should not detract from what seems to be already well established at the practical level, that a daily extradietary supplement of 200 micrograms Se reduces cancer risk. In Se-adequate regions, the desired Se intakes of 200 to 300 micrograms Se/day may be attained through prudent diet choices alone, i.e., by maintaining a high consumption of Se-containing cereals and seafoods. However, for maximal protection, attention to Se alone is insufficient; all other established means of cancer prevention, such as the adherence to healthy life-style, the avoidance of exposures to known carcinogenic risk factors, the practice of regular self-examination and periodic medical checkups for early detection must remain in effect.

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happy
new year
2004

RETURN SERVICE REQUESTED

*Following up his report on the UC health insurance options in **Chronicles**, Volume III, No. 1, our Association's current president offers the following account of his discovery of an anomaly that may affect our Emeriti. — ed.*

The Kaiser Plan Anomaly and its Implications

—by Murray Rosenblatt

In the recent listing of medical plan options for University of California employees in the open enrollment for 2004, Kaiser plan fees for people with Medicare were greater than for those without Medicare. As far as I know, this was the first time this has occurred. Typically the fees for those with Medicare are somewhat less than the fees for those without Medicare; the lower cost of most medical plans with Medicare comes from the contribution that Medicare fees make to those plans. A natural question is: what accounts for the Kaiser anomaly? One of the great virtues of Medicare for consumers is that it tries to keep down costs by setting limits on charges for medical procedures and types of medical consultation. Reasons for the anomalous Kaiser charges, as transmitted to me by **Stan Kowalski** of the UC office of the President follow: "Medicare reimbursement by Centers for Medicare and Medicaid Services is capped at approximately

2% annually, which is not keeping pace with rising costs." In addition, "Kaiser is maintaining Medicare + Choice, while other providers are leaving the program entirely or are reducing the plan area for Medicare services."

These comments illustrate the great difficulties the Medicare program is likely to face in the future. The current national administration and Congress are also pushing private medical programs, sometimes with a claim that "competition" and "deregulation" make the medical system "more efficient." However, in the realm of medical services (as well as that of electricity regulation) past experiences have caused many people to have doubts. In any case it is clear that the future of Medicare is worrisome.

Joyce Rapaport, Sept. 12, 1921-Dec. 15, 2003
