In an earlier issue of this newsletter, I briefly chronicled the uphill battle waged through the 20th century to convince the medical profession that a high blood cholesterol level was a major cause of heart attacks. Many in the field were convinced of this as early as the 1960s but only in 1984 did the National Institutes of Health finally make it an official public health goal to lower cholesterol levels to prevent heart disease. My book in preparation, The Cholesterol Wars, explores the several reasons for the initial reluctance of the medical profession to accept the causal relationship despite a considerable body of evidence. One important reason was the unavailability of safe, potent drugs for lowering cholesterol levels. If you can’t do anything about it anyway, why bother your head? So the discovery of the statin drugs, drugs that lower cholesterol levels dramatically and safely (by inhibiting the body’s own synthesis of cholesterol), played a major role in ending “The Great Cholesterol Controversy.”

First, it was necessary to overcome concerns about the feasibility and safety of inhibiting the natural synthesis of cholesterol. The human body can make all the cholesterol it needs by breaking down other foodstuffs (fats and carbohydrates) and converting the fragments into cholesterol. In fact, most people make as much cholesterol every day as they consume in their diet. Because of this ability to manufacture cholesterol, the body does not rely on cholesterol in the diet; cholesterol is not an essential foodstuff.

However, while cholesterol in the diet is not essential, the presence of cholesterol in all the cells of the body is. What if you had a low dietary cholesterol intake and in addition took a drug that prevented the cells from making their own cholesterol? That might cause trouble. Indeed, when inhibition of cholesterol synthesis was first proposed as a way of treating high blood cholesterol, the notion was met with great skepticism. What the skeptics failed to consider is that no one was proposing to block cholesterol synthesis completely; that very well might be bad. But if you could titrate the dose of the inhibitor so as to achieve a lowering of blood cholesterol without reducing the amount of intracellular cholesterol needed for optimal health, you might have a novel way to correct hypercholesterolemia.

That was the gist of the proposal put forward in the early 1950s by Jean Cottet and his collaborators in France and by Steinberg and Fredrickson here. However, neither group came up with a clinically effective compound. It turned out that the drug introduced by Cottet and coworkers (alpha-phenylbutyric acid) was inhibiting the incorporation of a radioactively labeled precursor into cholesterol but not actually blocking net production of cholesterol molecules. Steinberg and Fredrickson, following up on observations made by Tomkins, Sheppard and Chaikoff at Berkeley, confirmed that a close chemical relative of cholesterol (delta-4-cholestenone) could inhibit cholesterol synthesis and went on to show that it reduced blood cholesterol levels. However, the toxic side-effects of the compound precluded
At this point. They went on to try compactin in dogs and there the results were quite different. In dogs they saw a very significant and consistent lowering of blood cholesterol levels. They also showed that it worked in rabbits, hens, and monkeys. Finally, in 1980 Endo and colleagues reported that compactin given by mouth at a dose of 50 mg per day decreased cholesterol levels in patients with hypercholesterolemia by an average of 27%. In some, the drop was as much as 30 to 35%. A second clinical study in seven patients with familial hypercholesterolemia, which is much harder to treat, was published in the prestigious New England Journal of Medicine. It showed a highly significant drop in total cholesterol levels from 390 down to 303. There was no doubt now that, barring the possibility of some unsuspected toxicity showing up in larger and longer clinical trials, this drug and others like it were going to be wonder drugs.

Endo's dramatic clinical findings with compactin caught the eye of the pharmaceutical industry. Merck, Sharp and Dohme was first out of the gate. Shortly after Endo's paper appeared, Merck signed a confidentiality agreement with Sankyo and obtained samples of compactin with which they conducted their own screening program, under P. Roy Vagelos, Director of the Research Laboratories, and Alfred W. Alberts, a long-time collaborator who had moved with Vagelos from Washington University. In October 1978 and were lucky enough to hit pay dirt with sample No. 18, just two weeks into their program. Quite a contrast to Endo's experience of screening about 6,000 broths before hitting something promising!

These drugs are so remarkably safe that some, half in jest, have proposed putting it in "the drinking water" or at least selling it over-the-counter. We may not be quite ready to go that far but it is noteworthy that such proposals are no longer "unthinkable."

Andy Wright (witty and acerbic as ever), Bob Eliot, Sig Burkhardt, and the inimitable and unflappable Roy Harvey Pearce. And now we could get on with it.

David Mahlon Bonner was born in 1916 and died in 1964, only four years after his arrival at La Jolla. In 1952 he was diagnosed with Hodgkin's disease, which is terminal, and died in 1964, only four years after his diagnosis. His friends and family gathered to celebrate his life and his legacy. He was a wonderful companion.

As a result of the statin studies, the "ideal" LDL cholesterol level has dropped to somewhere around 70 mg/dl. These drugs are so remarkably safe that some, half in jest, have proposed putting it in "the drinking water" or at least selling it over-the-counter. We may not be quite ready to go that far but it is noteworthy that such proposals are no longer "unthinkable."

[The author is indebted to Drs. Akira Endo and P. Ray Vegelos for in depth interviews.]
Richard Atkinson Still A Good Choice As the Namesake of UCSD’s Sixth College

—by Sandy Lakoff

When the announcement that Sixth College would be named for UC President Emeritus Richard Atkinson caused controversy, he asked that his name be withdrawn from consideration because he felt that UCSD students had not been sufficiently involved in the decision. This was a statesman-like move on his part, but it should not be the final word.

It took quite a while before Third College was finally named for Thurgood Marshall rather than for the ideological hothouses’ choice, Lumumba-Zapata-Allende. The job of finding a name for Sixth College needn’t have been prolonged, but it should now be reopened, with adequate consultation of students, faculty, administrators, alumni, and friends of the university. If the cause for honoring Atkinson is properly presented, it should be enthusiastically received, even though there is something to be said for taking ethnic and gender diversity into account, as was done when the roster of UCSD colleges was adorned with the illustrious names of Marshall and Eleanor Roosevelt.

In other instances, chancellors have been honored by having buildings designated for them. But Atkinson was the longest-serving of our chancellors, having held the of ce from 1980 to 1995, during a period of major growth. When he left to become UC President—the first UCSD chancellor to be so elevated—this campus was well established as one of the great success stories of modern higher education. As president of the UC system for eight years, he also served with distinction. This is an extraordinary record of service, which deserves extraordinary recognition. It bears comparison with the contributions of Roger Revelle, for whom our first college was named.

And that’s not all that should be said in Atkinson’s behalf. He has done major academic work in psychology. (Some of this work has been done with his wife Rita, so maybe it would be a good idea, for the sake of diversity, to recognize their partnership by naming the college for both of them, after the precedent of the Jacobs School of Engineering, which has been named for Joan and Irwin.) Before becoming chancellor, he was director of the National Science Foundation, one of the government’s major agencies for supporting basic research.

As UC president, he forced a re-vamping of the SAT when an inquiry he ordered found that it was not as good a predictor of academic success as claimed. And student radicals might note that he resisted efforts by the Regents to end affirmative action (or preferential treatment) in admissions based on race, ethnicity, and gender, and when that failed, reoriented outreach programs to focus on low-performing high schools; shifted emphasis from aptitude tests to achievement tests in admissions; expanded transfer programs from community colleges; instituted “comprehensive review” of applicants; and created a new path to admissions called “Eligibility in Local Context,” making the top-performing four percent of each high school eligible for admission to UC campuses—all in order to boost minority enrollment.

As an administrator, Atkinson was devoted to incremental improvement rather than any grand pedagogical passion. When he was up for reappointment as chancellor, the then UC president, David P. Gardner, came to the campus to interview people about his performance. I was among the faculty members he talked to. I gave Atkinson very high marks on most scores, but then Gardner threw me a curve.

“Does the faculty agree with his philosophy of education?” he asked.

For a moment I was stumped, but then I thought the right answer. “If he had one,” I said, “I think we’d Lynch him.”

Gardner had a good laugh at this answer, perhaps because he too did not have a pronounced philosophy of education. Like Atkinson, he was one of the few chancellors to come up through the ranks of the university’s teaching faculty, and he did not have the potential to become a billion-dollar-a-year product. The day’s discussions went well and spirits were high.

Then, toward the end of the day, right in the middle of a wrap-up session, Vagelos was called out to take an urgent phone call from the head of Merck’s Japanese division, H. Boyd Woodruff. Sankyo had just suddenly terminated all its clinical studies with compactin. They had given no reasons for this startling move and were unwilling to answer questions. Woodruff said that rumors were circulating to the effect that the company had discovered intestinal lymphomas, a form of cancer, in dogs treated with large doses. Woodruff had tried to verify the rumors but the company would not comment. No one seemed to know what was going on. But one thing seemed almost certain: Sankyo would never have aborted a potentially multi-million dollar program unless they had encountered something really ominous.

So, what had been a warm and fuzzy, even self-congratulatory, company-get-together became something of a wake. Lovastatin only differed in structure from compactin by one carbon atom. They both worked on cholesterol synthesis in the same way. So if compactin was carcinogenic it was very likely that lovastatin would be too. On the other hand, the carcinogenicity that had allegedly been encountered might be related not to the cholesterol-lowering effect of the drug per se but to some unrelated effect of the compactin molecule. Conceivably, the one extra carbon on lovastatin might abolish any carcinogenic potential. However, that was a long shot. Merck was already carrying out studies on the effects of lovastatin in men, so they had not encountered any intestinal cancers but their studies were so far of fairly short duration. Longer exposures might confirm the Japanese findings with compactin. Merck had already invested millions of dollars on this project. What to do?

Vagelos did the right thing. He immediately called a halt to all clinical studies and notified the FDA. He also began an all-out effort to get to the bottom of the rumors. At Absecon, N.J., the mood was somber. Vagelos tried every way he could to get more information about the findings that had prompted Sankyo to drop its clinical trials, including letters and phone calls to the company’s executives. Sankyo was unwilling to comment. So Vagelos and Barry Cohen, who was in charge of Merck’s international businesses, went to Japan themselves. Vagelos offered a business deal: “If you help us solve this problem, we’ll share Mevacor with you.” Sankyo responded that they would like to cooperate but that there were “others” who objected. Vagelos returned empty handed, puzzled.... and angry.

Merck continued long-term trials of lovastatin in dogs and never encountered any lymphomas or any other cancers. In retrospect we can say with confidence that neither lovastatin nor any other of the statins is carcinogenic. Dr. Endo believes the pathologists at Sankyo had misinterpreted the cellular changes in the lymphomas (a small possibility), for which thousands of subjects have received either a placebo or a statin have shown no change at all in cancer incidence. In the early 1980s, however, the level of anxiety both at Sankyo and at Merck was high.... and we came close to losing these wonder drugs.

It is difficult to overstate the impact the statins have had on the management of atherosclerosis, particularly coronary heart disease. Second, the statin studies laid to rest the concerns that lowering cholesterol levels might be intrinsically dangerous. In the Scandinavian 4S study with simvastatin there was actually a highly significant decrease in total mortality as well as in coronary heart disease.

Lovastatin, the compound discovered by Alberts, had a structure only very slightly different from that of compactin and it had very similar biological properties. Preliminary clinical trials were begun in 1980 and the early results looked promising indeed. But in 1980 the whole Merck program was suddenly shut down. The story behind that is an intriguing one.

In the fall of 1980 Merck held its usual annual four-day research “retreat.” That year it was held at the Seaview Resort at Absecon, New Jersey. P. Roy Vagelos, recently promoted to Vice-President for Research, had been driven down that morning for the meeting and he recalls very vividly the dramatic events of that afternoon. Merck was in excellent financial condition (net income about $400 million) but Vagelos knew that maintaining Merck’s leadership role required that there be a continuing input of new products into the “pipelines.” As Vagelos puts it, “That’s why we were all so in love with lovastatin.” It was so closely and that’s why we were all so upbeat about our research program. We thought [lovastatin] had the potential to become a billion-dollar-a-year product.” The day’s discussions went well and spirits were high.

Then, toward the end of the day, right in the middle of a wrap-up session, Vagelos was called out to take an urgent phone call from the head of Merck’s Japanese division, H. Boyd Woodruff. Sankyo had just suddenly terminated all its clinical studies with compactin. They had given no reasons for this startling move and were unwilling to answer questions. Woodruff said that rumors were circulating to the effect that the company had discovered intestinal lymphomas, a form of cancer, in dogs treated with large doses. Woodruff had tried to verify the rumors but the company would not comment. No one seemed to know what was going on. But one thing seemed almost certain: Sankyo would never have aborted a potentially multi-million dollar program unless they had encountered something really ominous.

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It is difficult to overstate the impact the statins have had on the management of atherosclerosis, particularly coronary heart disease.

First of all, because they lowered blood cholesterol so much more effectively than any diet or drug treatment that had gone before, it suddenly became much easier to demonstrate the decrease in coronary heart disease events in clinical trials and to do so in an unarguable way.

Second, the statin studies laid to rest the concerns that lowering blood cholesterol levels might be intrinsically dangerous. In the Scandinavian 4S study with simvastatin there was actually a highly significant decrease in total mortality as well as in coronary heart disease.
Remembering David Bonner

—by Stanley E. Mills
Professor Emeritus Professor of Biology

This is a brief appreciation of David Bonner and his participation in some of the early events in the history of UCSD. The narrative unfortunately issues from a failing memory, is based mainly on conversations with David, and is biased by personal affection and admiration. It also neglects, with regret, the contributions of other participants; I was simply unaware of their roles.

I met David at Yale when I was a graduate student in biology. He was the dominant spirit in the department. Breezy and engaging, he had a group of lively, energetic students all of whom went on to rewarding careers. Since I was a group of one I naturally gravitated to them and their activities, later working for David briefly before leaving for a post-doctoral position. David’s status at Yale was a mystery to us. He had the biggest lab in the department, the prerogatives of a full professor, but was never admitted to the tenured faculty. Why? As students we could only speculate. He was at YALE, but he dressed in khakis, mingled with us on a first-name basis, spoke his own version of English, laced with some earthy Anglo-Saxonisms, and appeared careless about academic formalism.

Certainly, whatever kept him from an appointment could not have been his achievements. Having studied with some of the great pioneers of genetics at Stanford, he had established his own formidable reputation in microbial genetics, a discipline to which he remained deeply devoted during his lifetime. Still, it was evident that with no future at Yale, he had to get a job. While on a seminar/job tour he got a call from Bill Bels, a recent graduate of our department, then at SIO. Bels suggested that it might be a good idea, to drop down and meet Roger Revelle who was putting together a campus at La Jolla. It was a good idea. When Bonner and Revelle met, each discovered that his life was now complete; Revelle with his towering reputation, and David with his zest and industry.

Before assessing his role in the ensuing few years, one must allude to the faculty already here, and gathering. They were in the main scientists and an extraordinary group. To name just a few: in addition to Revelle, there were the Nobel Laureates Harold Urey and Maria Mayer, and their exemplary colleagues, Joe Mayer, James Arnold, Bruno Zimm, and Keith Bruckner. It couldn’t get any better. Individually and collectively they approved of the new guy. They liked his style, his willingness to take a chance, and crucially, they gave him leeway on many matters. And he used their support unhesitatingly.

To set the stage, UCSD evolved “top-down,” with a graduate school established first. In biology we arrived in late 1960. Graduate classes began in 1961. The undergraduate division was scheduled, and did start in 1964. This meant, of course, that the faculty in place, mainly scientists, had to recruit faculty for the remaining departments. With no one here to misguide them, here are some of the things that occurred.

1. Languages and Linguistics. The traditional teaching of foreign languages via reading and grammar is an exercise somewhat akin to mathematics. It was the dominant method in higher education. There was however, an alternative. The armed forces, the diplomatic corps, and surely others, used “total immersion” as a foreign language teaching tool. On the assumption that the life of a language is verbal communication, with precedence over its derivatives, and with no proprietary interests here to protest, the campus chose to abandon tradition and go after a speaking program, now in place. Further, the job of implementing this approach was given to a new department, linguistics, not literature (which did not yet exist), and had the good fortune to Leonard Newmark to make it a solid functioning enterprise. I can attest David’s fine hand as a major determinant in this event.

2. The Medical School. When we arrived in late 1960, UC medicine had at best a modest reputation, somewhere between O.K. and not so O.K. The time was then ripe to add a medical school in San Diego since the area was growing in population and perforce in political importance. Accordingly, the great men from the San Francisco Medical School, wearing ties and statements, came down to teach the facts of medical school life to the local undergraduates.

The sentiment here was that a critical reason for UC medicine’s avoidance of distinction was the use of part-time faculty (the major schools were full-time). Part-time faculty are just that; their salaries are earned in part by faculty time, the rest from private practice. When the notorious bank robber, Willie Sutton, was asked why he robbed banks, he said that’s where the money was. In medicine, the money is, or was then, in private practice. Money often equals commitment.

Bonner’s version of me to the ensuing negotiations can be summarized. They told us how, when, and where they would build the school. We were polite. You are the experts; build it where and as you like. But part-time people will never be admitted to membership in the UCSD academic senate. The temperature did rise a bit. But each and every Bonner, as the faculty point guard, was challenged, he pointed to his faculty support.

To these events I can contribute a minor anecdote, which I recall with absolute clarity. In those halcyon days UC held a yearly all-campus conference about this and at the Davis campus (uh the wines, the winies). As a mere assistant professor I was volunteered as our representative.

While sitting in the rotunda of the Davis meeting hall, a slight, balding, immaculately dressed gentleman came up to me. It was Clark Kerr, though I didn’t know him then. The dialogue went like this:

“You’re Mills, aren’t you?” (Good staff work, I thought.)

“Yes, sir.”

“You tell Dave Bonner he can’t get away with it!”

“Of course, but which of what he is doing can’t he get away with?”

“The Medical School.”

And off he went. It is difficult to convey the somewhat charged exchanges and atmosphere that occurred 40 years ago. But the upshot? Today we have a full-time faculty medical faculty as have all the UC medical schools and UC medicine is highly regarded.

I would be remiss not to note that David’s support included not only our faculty but also that of Sherman Mellinkoff, the new dean of UCLA Medicine, a good friend of UCSD; and, in particular, Robert Hamburger. Robert came with us from Yale as a fellow in immunology and genetics.

He was David’s indispensable guide, counselor, and tutor in the complexities of medical culture. Some day I trust he will write an authentic account of the events that occurred. And finally, a nod to Jon Singer who kept the department together while David cruised off on his adventures.

3. The Arts. Those were heady times back in the early sixties. A university was to be put together, undergraduates were coming in 1964, and missing were the arts, social sciences, literature. How was the ingathering to occur? The faculty in place had to rely on their own experience, and I can recount the way it went in just one more case, the recruitment of the arts faculty.

The argument of David and his colleagues went something like the following. From the local vantage point it appeared that university music and art departments were largely staffed by historians, philosophers, and critics with the occasional composer or artist in display roles, altogether at variance with science, medicine, and engineering. So if scientists do sciences, physicians do medicine, and engineers do engineering at universities, why can’t musicians do music and artists do art? Well, they can and they do. The creative outpouring of the artists and musicians at UCSD issuing from departments that are second to none amply justifies the vision of David and his colleagues to bring in working creative artists and musicians.

And as a coda to this short memoir, toward the time the undergraduates were supposed to appear, we were a little frantic about the absence of literature. David had tried, in the spirit suggested in the above paragraphs, to recruit his friend Wallace Stegner, the California novelist and environmentalist, to come here and take over. Stegner was running a writing workshop, part-time, at UCLA but David couldn’t convince him and his wife (“David,” she asked, “do they have plumbing in San Diego?”) to abandon San Francisco. But the gods were kind. A fracas at Ohio State made available the grand Ohio State Quartet.