Whither the Pauling Legacy? The Linus Pauling Institute and the Future of Medicine

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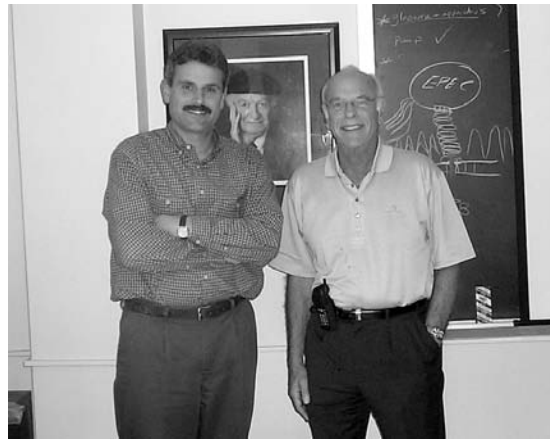
In these waning months of Linus Pauling's centennial year, it seems appropriate to ask what kind of permanent mark the great man has left on the world—although "marks" might be more appropriate for the activities of a man who changed his career focus every so often. Surely his contributions to chemistry will stand a hundred years from now, or a thousand, even if no one remembers his name: they are fundamental. His contributions to world peace may prove more evanescent. Smaller wars have persisted here and there because governments favor them, even though a *pax Americana* settled over the globe for a few years (effective, but probably not Pauling's ideal of peace), the horrors of September 11 proved how fragile that really was.



The author (right) with Balz Frei, Ph.D. director of LPI.

Will Pauling's final quest—to alleviate human suffering through orthomolecular medicine—attain the durability of his contributions to chemistry, and perhaps peace? That is the proper focus of a journal devoted to orthomolecular medicine, so I shall leave the bond angles, alpha helices, resonating electrons and pacifist initiatives to fend for themselves. Is "orthomolecular" a good idea? In the long run, will it matter to anybody?

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Pauling's Institute: The First Twenty Years

Pauling did not invent orthomolecular medicine; he simply identified the principle behind a type of therapy, and named it. So great was his stature in the scientific community that a number of forward-thinking physicians were drawn to his ideas and began to implement them. So defensive was the medical profession against interlopers that his theories generated disdain among even greater numbers of doctors. In 1973, Pauling, together with Arthur Robinson, established what later was named the Linus Pauling Institute for Science and Medicine (LPISM). Its mission was simple and relatively nonspecific: to alleviate human suffering by maintaining laboratories for biological research. Initial projects included application of the mass spectrometer toward diagnosing clinical illnesses. An early attempt was made, in conjunction with John Catchpool, M.D., to deliver orthomolecular services to patients.

Later the Institute moved to Palo Alto, where, under the leadership of Emile Zuckerkandl, its focus became research programs of fundamental biological relevance, with long-term prospects for human application. There was less that a medically-trained observer would identify as orthomolecular. The model for this phase of LPISM seemed to have been the

much larger, and highly endowed Salk Institute that pursued multiple independent projects in basic science. Small though it was, and lacking an endowment, LPISM did not lack influence: its "impact factor", calculated as the number of citations of its work divided by the number of papers cited, ranked it among the top 20 biomedical research institutes in the United States.

A summation, and in many ways a celebration, of the Institute's progress over 21 years took place in September, 1994, in the form of a conference on the therapeutic potential of antioxidants. Esteemed scientists from all over the world attended. Nobel laureate Henry Taube gave the keynote address. Unfortunately, Linus Pauling was not present for the occasion. After a long battle with prostatic cancer, he died only weeks before the meeting.

The financial history of LPISM through the years had been one of almost chronic instability. Although the financial situation stabilized before Pauling's death, that event precipitated uncertainties over LPISM's future ability to raise money from the public. Moreover, a change in property zoning threatened to raise the rent for LPISM's quarters more than tenfold. Lacking an endowment, the Institute felt the pressure to chart a new course before time and money ran out.

In 1996, under an agreement reached between the Linus Pauling Institute of Science and Medicine and Oregon State University (Pauling's old alma mater), the former's assets were used to establish the Linus Pauling Institute (LPI) at OSU. Included was $1.5 million from each of the two parties to establish the Director's chair. A new mission statement (which actually preceded the transfer to OSU) was drawn up by members of both institutions.

The new Institute's mission—more specific than that of its predecessor—was to investigate the function and role of micronutrients, phytochemicals and microconstituents of food in maintaining human health and preventing and treating disease, and to advance knowledge in areas that were of interest to Linus Pauling through research and education. The mission statement was later modified to include the role of oxidative stress and antioxidants in human health and disease.

Metamorphosis: New Focus, New Home

Five years have elapsed since the transfer. It is fair to ask: is the new LPI successful? Has progress in orthomolecular medicine occurred? Will Linus Pauling's crowning achievement be remembered as the orthomolecular foundation of medical practice? The answers are yes, definitely yes, and perhaps not.

The Linus Pauling Institute initiated a worldwide search for a Director, and found Balz Frei, who had published extensively on the role of vitamin C and other antioxidants in health and disease. Dr. Frei came from Boston University School of Medicine to join LPI a year after its founding. He initially insisted upon certain policies that have benefited LPI greatly, including tenure-track appointments for all faculty and the necessity of NIH grants; his policies have helped to recruit first-rate scientists and provide support for them. (LPI is in fact responsible for a disproportionately large share of NIH grants at OSU.)

The LPI presently employs about 40 scientists (of whom six are faculty) and staff, including 14 graduate students. Within LPI, different laboratories address antioxidants and vascular biology; vitamin E metabolism and biological activity; colon cancer and cancer chemoprevention by phyto-chemicals; the role of nitric oxide and oxidative stress in neurodegenerative diseases; and the role of oxidative stress and mitochondrial dysfunction in the aging process. LPI has already outgrown the space allotted to it on one floor of Weniger Hall.

Today's LPI is more tightly focussed than its predecessor, owing to its more

tightly drawn mission statement. The faculty are working toward common goals. Thus, the casual visitor is struck by the collegiality of the place, the easy manner in which one scientist might informally consult with his or her peers. The atmosphere is reminiscent of the California Institute of Technology; it fosters communication and creativity.

Critics of the new LPI have pointed to a certain conservatism, a lack of boldness and dash, but it is understandable. Making waves is not usually a ticket to popularity in academic circles, as Pauling himself well knew. Late in his career, Pauling was impervious to his colleagues' slings and arrows, and quite secure in his convictions. The younger generation at LPI does not yet own Pauling's armor.

One criticism of LPI might be its isolation from clinical medicine. Arguably, it belongs on the campus of a great medical school. To be sure, Oregon Health Sciences University is about an hour's drive north of OSU, and LPI is conducting some joint projects with OHSU, but some day-to-day contact with clinical medicine could be useful in maintaining the focus of an Institute whose mission statement includes maintaining health and treating disease.

Optimum Nutrition: State of the Art

Progress in orthomolecular medicine is occurring in laboratories throughout the world, although only the LPI, so far as we know, applies the sobriquet "orthomolecular" to the work. Some of the larger and more multi-faceted programs are located at Tufts and Harvard. The growing influence and relevance of orthomolecular research were fully evident at a conference on *Diet and Optimum Health* organized in Portland, Oregon by LPI in May 2001.

The roster of speakers at the *Diet and Optimum Health* conference reads like a Who's Who of scientific leaders. Their research interests range from cancer to cardiovascular disease to neuro-degeneration and aging, all in relation to nutrition and constituents of the diet. The fact of the speakers' diversity and high scientific credentials bodes well for the future of research in this field; their willingness to attend the conference (with one speaker going so far as to volunteer a paper and travel halfway around the world to give it) bespeaks the esteem in which the scientific community holds the LPI.

It is neither appropriate nor feasible to summarize the presentations of over 30 speakers in a short article such as this one. LPI has made the abstracts of the meeting accessible on the internet at http://osu.orst.edu/dept/lpi/conference/program2.html, and succinct summaries are scheduled for publication in LPI's fall/winter 2001 newsletter. The proceedings of the meeting were not recorded.

Although few physicians were in attendance, most of the presentations were highly relevant to the practice of orthomolecular medicine. In particular, this reviewer enjoyed Walter Willett's two lectures on trans and omega-3 fatty acids, and other dietary factors, in relation to cardiovascular disease risk. Dr. Willett is chairman of the department of nutrition at Harvard School of Public Health. I had hitherto been unaware of how undeniable the evidence against trans fatty acids has become. Not only do they have, on a gram-for-gram basis, twice the adverse effect on HDL/LDL ratio as saturated fats, they raise triglycerides and Lp(a) comparatively more, also. Thirty thousand or more premature deaths per year, attributable to coronary heart disease, could be prevented if trans fatty acids were not manufactured. Omega-3 fats protect against heart attacks, but perhaps not in the way we thought: amounts too small to affect platelet function nonetheless raise the threshold for ventricular fibrillation.

Dr. Willett also had negative words for high-glycemic-index foods (glycemic load being co-evil with trans fatty acids) and

obesity, as did some of the other speakers, notably Gerald Reaven of Stanford and David Ludwig of Boston Children's Hospital. The latter, who was among the speakers critical of the ubiquitous food pyramid, proposed a low-glycemic-index pyramid to help stem the nationwide epidemic of obesity.

Given the power and influence of the processed-foods industry, the scrapping of the existing food pyramid is unlikely. Indeed, the magnitude of that power and influence is implied in the remarkable absence of news media at this important meeting. The life-saving consensus of experts ought to have been emblazoned on every front page in the country.

If the words of such as Willett and Reaven should have been reported in the news, those of Kedar Prasad should have been printed in red ink and distributed to every practising oncologist. Dr. Prasad spoke on multiple antioxidants as an adjunct to standard cancer therapy. It has become sort of an urban legend among oncologists that antioxidants diminish radiation and chemotherapy. In fact, tumor response is demonstrably better, and host survival is enhanced, when antioxidants are used in combination with conventional therapy, under a variety of conditions. The NCI in conjunction with the NCCAM is planning to offer a workshop on combining antioxidants with radiation and chemotherapy.

The LPI's already strong position in aging research was recently bolstered by the appointment of Joseph Beckman to the Ava Helen Pauling Chair at LPI. At the meeting, Beckman chaired the section on cognition and neurodegenerative diseases. Earlier that day, the LPI's Tory Hagen had spoken on dietary amelioration of age-related mitochondrial dysfunction. This cutting-edge research opens the door to clinically restoring the function of age-damaged mitochondria (reversing their depolarized state) through judicious use of such substances as acetyl-L-carnitine and alpha-lipoic acid.

There was much more of interest at the conference, including exciting work from LPI and elsewhere on chemo-prevention of cancer by phytochemicals. Suffice it to say, in summary, that orthomolecular research has come of age (even if it didn't make the *New York Times*), and LPI is squarely in the mainstream of it.

Orthomolecular Matters: the Future

Even as managed-care medicine encourages quick diagnosis (instant categorization instead of analysis of processes) along with drug therapy (one or a few patented pharmaceuticals), medicine has begun to move away from that model. In part, the marketing of natural substances based upon recombinant DNA technology has begun to change the medical paradigm. To the extent that medical practice truly rests on science, we can expect the fledgling trend to gain momentum, for scientists like those at LPI and their colleagues will open doors and point the way for doctors. Already orthomolecular medicine is being reinvented, rediscovered, and yes, renamed. We have integrative, functional, complementary, and other names for our discipline; new ones are sure to arise.

What's in a name, anyhow? Maybe nothing, if one prefers the thing itself over the name we give it. Abram Hoffer once predicted that someday orthomolecular concepts would guide clinial medicine to such an extent that the modifier "orthomolecular" would become superfluous—the word "medicine" alone would suffice. Linus Pauling's part might well have been forgotten by the time that happens, but one doubts he would have minded much.

Acknowledgement

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