CHAPTER 22

Nutraceuticals: Reflections

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Although the three following categories of discussion are different in subject matter, they are intertwined. The intent is to demonstrate the rationale and critical need for a substantial increase in funding for both basic and clinical nutraceutical research and development (R & D), which will markedly accelerate medical-health discovery. Research on nutraceuticals, and in combination with other therapies, is urgently needed.

The “nutraceutical revolution” has stalled. This is bad news for the nutraceutical research and development communities. Conversely, the good news is that there is something that can be quickly done to establish a vigorous, well-funded research sector, and that something is the Nutraceutical Research and Education Act (NREA).

My involvement in the nutraceutical revolution began in 1965 after I conducted the first U.S. clinical study on carnitine as a “drug” or “pharmaceutical” in patients with hyperthyroidism. Carnitine is a natural substance found in practically all human cells, whose primary action is to transport fatty acids across mitochondria membranes to produce energy or ATP. It also has a number of other functions. While pursuing the thyroid lead in a clinical study, I stumbled on a serendipitous moment that focused my carnitine basic and clinical research efforts on its medical promise in cardiovascular disease.

With the enthusiasm of youth, I began my long journey with this natural substance, which continues to this day. The results of the cardiovascular studies were both broad based and extremely positive, ranging from the reversal of myocardial ischemia to toxic shock caused by Russell’s viper venom.
When I tried to find pharmaceutical companies to sponsor additional clinical studies necessary to obtain an FDA-approved NDA, I ran into a stone wall. This was my first lesson in medical economics and politics. Because carnitine is a natural substance, it is extremely difficult to obtain a sufficiently strong patent to justify the enormous cost that a pharmaceutical company must expend to obtain an NDA. Lacking a strong patent, generic competitors would enter the market. Put another way, the company spends hundreds of millions of dollars on research and development, whereas the generic company spends none and charges a lower price. This is no way to run a business!

Then I encountered another huge, unexpected obstacle. Carnitine suddenly appeared on the shelves of the health food stores freely available to consumers at a low cost. Its presence virtually put the nail in the coffin of any company willing to sponsor a carnitine NDA.

The nutraceutical revolution followed shortly after. It began with a big bang after a consensus group of medical experts, under the auspices of the National Institutes of Health (NIH), recommended, primarily based on clinical data, calcium supplementation for the prevention of postmenopausal osteoporosis. This gave an image of legitimacy, heretofore virtually absent to dietary supplements in the medical community. Physicians and their patients began to discuss nutrition, which was a revolutionary event. There then followed studies on omega fatty acids for lipid reduction, *Ginkgo biloba* for memory loss, beta-carotene for the prevention of lung cancer, St. John’s Wort for depression, vitamin E for heart disease, *Echinacea* for the common cold, and Ocean Spray Cranberry Juice for urinary tract infection, among others. The national impact of these benefits was rapid and enormous. The largest companies in the United States, regardless of the amounts of marketing dollars spent, could not achieve such product recognition.

The three basic components of this nutraceutical phenomenon were clinical data, beginning physicians’ acceptance of nutraceuticals based on such data, and extensive mass media coverage. Physicians became the cornerstone of nutraceutical legitimacy, and it will remain so. It is important to note that the source of the clinical data had the largest physician impact. In the case of calcium, it was the NIH consensus group, and with vitamin E, a survey study published in the prestigious *New England Journal of Medicine* that brought them aboard.

However, there was another highly desirable impact that has gone unnoticed; the “ping-pong effect” blossomed. Significant numbers of basic and clinical studies ensued to further delineate the clinical claims. In addition, companies rushed to create new formulations to deliver the nutraceuticals to the consumer.

(Taking a step backward in time, in 1976, I established the nonprofit organization Foundation for Innovation in Medicine [FIM]. FIM is an educational foundation whose charge is to inform the key players in the health sector in ways to accelerate medical discovery or innovation. FIM has a particular interest in natural substances. The first conference was held at Columbia University entitled “The Promise and Problems of Natural Substances in Medicine”)

Getting back to nutraceuticals, because I am a physician trained in the methodology of pharmaceutical-controlled clinical trials and realizing that most of the
nutraceutical clinical studies lacked statistical proofs or algorithms, I was impressed by the consistency of the findings. It seemed improbable to me that so many positive clinical findings just happened by chance.

During the late 1980s and 1990s, FIM held a series of nutraceutical conferences in Manhattan and Washington, D.C., in an attempt to create an R & D-intensive nutraceutical health sector. Although I am a firm believer in the potential medical and health benefits of nutraceuticals, I warned that, because of their wide consumption, controlled clinical trials would soon follow, which would either confirm or negate the findings of the previous ones. My enthusiasm was high, yet my pharmaceutical instincts told me to cool the optimism until more controlled studies were conducted.

I remember that, at one of the conferences, a presentation was made summarizing approximately a dozen clinical studies on the positive effect of beta-carotene in preventing pulmonary cancer. Frankly speaking, after a brief review of the data, I was surprised by the degree of consistency of the findings. One of the panel members was my physician colleague and friend who was a professor of nutrition at Harvard University. I asked him whether, based on the clinical studies, he would recommend beta-carotene as a pulmonary nutritional supplement. He would not. When I asked him why he would not, he replied that, in addition to serious flaws in the design of other studies, a lack of any response in the control group of the best study made him a doubter.

Then, as I predicted, controlled clinical trials were done on many nutraceuticals, including beta-carotene, which did not support positive findings of previous studies.

I must confess that the biggest surprise of all happened with vitamin E. Scientific and clinical studies very persuasively supported this vitamin’s cardio-protective effect. Plus, there was a solid scientific rationale behind it. There was little doubt in my mind that it was an effective supplement. Then, as with beta-carotene, the controlled clinical trials that followed did not support vitamin E’s clinical efficacy.

These, and other negative clinical findings, truly dampened the promise of nutraceuticals and R & D support, which continues today, but I emphatically do not believe that the results of the studies reflect the real world. The designs of these controlled clinical trials were based on a pharmaceutical philosophy of evaluating a single “magic bullet,” such as insulin, a statin, and Viagra. Nutraceuticals, although they can act as single magic bullets, more often than not work in teams or combinations.

For instance, a meal, the most efficacious and king of all nutraceuticals, is a combination of nutritional ingredients that work together to sustain life by maintaining health. No matter where you are in the world, from Madagascar to Brooklyn, the nutraceutical meal, no matter what the ingredients, keeps you alive! The clinical studies with vitamin E should have included other active cardiovascular nutraceuticals, such as carnitine, magnesium, folic acid, and other ingredients, which work together to achieve a common goal. The combination approach represents the real world, in which consumers usually take multiple dietary supplements daily. This could explain why a number of survey types of studies on the cardiovascular benefits of vitamin E were positive.

What was truly disappointing was a lack of response from all segments of the nutrition community to criticize both the design and the results of negative magic
bullet nutraceutical clinical studies, calling for more logically designed combination ones. Despite my efforts, I could not find a single leader or group to lead the charge.

Getting back to the pharmaceutical and nutraceutical carnitine, let’s begin with the former. During the early 1980s, sparked by the television series *The Odd Couple*, the main theme being the unavailability of drugs for patients with rare diseases, Congress enacted the Orphan Drug Act, which significantly reduced the amount of preclinical and clinical data and, therefore, the cost, to obtain an NDA. More importantly, however, it granted the sponsor of the NDA the exclusive right to make a medical claim for a seven-year period, which, in effect, is similar to a methods patent. Although not the strongest type, it is oftentimes good enough. The combination of these two provisions led to an enormous success. There were very few approved orphan drugs before the act. Today, there are hundreds, either approved or in the process of development. (Note that the FDA has defined an orphan population as 200,000 patients or less).

Because of the Orphan Drug Act, I managed to convince a friend and philanthropist, Dr. Claudio Cavazza, the proprietor of the pharmaceutical company Sigma Tau S.p.A. (Rome, Italy), to sponsor the NDA effort to develop carnitine for the treatment of primary carnitine deficiency, a rare and often fatal disease in children. A subsequent carnitine orphan drug NDA was approved for renal dialysis patients.

The carnitine NDA clinical studies and numerous additional ones sparked an enormous number of basic research studies, which then sparked additional clinical research studies. I called this the ping-pong effect. Basic research begets clinical research, and clinical research begets basic research. There are now literally thousands of both basic and clinical papers published on carnitine, and the number continues to rapidly grow.

Now let’s turn to the nutraceutical carnitine. It was in Greenwich Village that I first saw the dietary supplement carnitine on the shelves of a large health food store. I was very much surprised by the vast array of products displayed and began to wonder what this world was all about. I stayed for about an hour and eavesdropped on the conversations of a number of customers and employees who exchanged information on the medical-health benefits of various products ranging from fatigue relief to cancer prevention. I then began to review the dietary supplement literature primarily to determine whether there was sufficient clinical evidence of certain dietary supplements, which supported the claims. I was also surprised and disappointed by the paucity of even reasonably conducted clinical trials. In addition, most of the publications reported highly favorable response rates. After speaking to friends, colleagues, and others who were loyal dietary supplement takers, I don’t recall anyone responding in a negative way. I was struck by our overwhelming blind acceptance of and faith in dietary supplements, with meager evidence regarding their actual clinical benefits. Contrast this to our national suspicion, sometimes bordering on hostility, of pharmaceuticals, which undergo multiple controlled clinical studies evaluating both effectiveness and safety before FDA approval.
After wondering about it all, I drew several conclusions. Many of the products sold are placebos, which, in my opinion, are oftentimes a good thing. These substances deliver a national placebo response that immensely benefits the people. This leads to a significant reduction in physician and hospital visits and substantially lowers healthcare costs. Also, these substances are relatively safe. Think of this: if we were to remove all the dietary supplements from the shelves of health food stores and replace them with FDA-approved pharmaceuticals where customers could purchase them without a physician’s prescription, half of America would be either dead or on its way within six months.

I decided to try to conceive a new nutraceutical regulatory system that would lead to a quantum leap in both basic and clinical research to bring about the ping-pong effect.

First, I decided that an act of Congress was necessary, and second, it was essential to specifically define this entity necessary for congressional consideration.

In 1989, while in Rome, after a very good meal, good wine, and an excellent grappa, I decided to take a stroll in the Piazza Navona to try to come up with both the magic name and its definition. The uplifting vibrations of late night Roman life were everywhere. Maestro Stefano—owner of a restaurant by the same name, whom I knew for many years—saw me, called me over, and invited me in for another grappa. This was beyond my limit, but I thought “Why not?” in one of those tough-to-come-by beautiful moments in life. While discussing his favorite subject, the meaning of life, the term “nutraceutical” jumped to mind, but I couldn’t come up with the definition.

After I returned to the United States, I finally came up with a definition. “A nutraceutical is a food or part of a food that has a medical or health benefit, including the prevention and treatment of disease.” If you think about it, this includes almost everything one consumes. It includes foods, functional foods, pharmafoods, and herbal remedies, among others. The term hit the media and became widely used. It is even now in the Oxford English Dictionary, which also credits me for coining the term. What was disturbing was that others then created their own nutraceutical definitions primarily for marketing purposes, which has had a negative impact on my efforts. Now armed with a new term and a specific definition, I needed to propose a specific law for Congress to enact. It occurred to me, no grappa this time, that the Orphan Drug Act sparked the boon in the R & D of the pharmaceutical carnitine and other drugs. I decided that the same principles and ground rules should be involved in what I termed the NREA, which can be found on my website, http://www.findefelice.org. Also, there is an additional critical provision of the act: the right for a company to make a disease claim based on the results of clinical studies.

Current regulations severely limit “disease” or medical claims of nutraceuticals, particularly with dietary supplements. “Health” claims, however, can be made. Thus, if carnitine is shown to prevent myocardial ischemia in patients with coronary artery disease—and it has!—the company cannot make the claim. It may, instead, be permitted to claim that carnitine maintains a healthy heart. In other words, the regulations force companies not to tell the truth. Speaking about our health care system! Also, these regulations profoundly discourage clinical research and rob us
of new medical remedies. Why should a company fund both basic and then clinical research on a nutraceutical if it cannot make the claim?

The NREA has a provision that permits a company to make the claim, be it health, disease, medical, or whatever, based on the results of the clinical studies. In addition, it, as with an orphan drug, grants a seven-year exclusivity period to the company to make the claim.

During one of my FIM nutraceutical conferences, which were, as usual, heavily attended by influential people, I pushed hard for the need of the NREA. Congressman Frank Pallone (D-NJ), a major player in the health sector, who was in the audience, came to the podium and announced that he would introduce the NREA in the Congress which extends the claim-exclusivity period to 10 years. And so he did, in 1999 (http://www.fimdefelice.org). Despite my full-throated efforts to gather support for the legislation from influential elements of the nutritional community, which Mr. Pallone critically needed to convince his colleagues to join him in passing the act, not one person, company, or other organization, including nutritional scientists, came forward to support the act. Unlike the pharmaceutical industry, the food and dietary supplement industries are market driven, not R&D driven. Thus, unnoticed, it faded away, and, although it is still buried, it is not yet dead. My old stethoscope still detects a faint heartbeat, which tells me that it is, Lazarus-like, capable of resuscitation by an effective advocacy group.

Because there is currently no advocacy group, the next logical step is to create one. This presents a rare opportunity for nutraceutical researchers of all types. This group should be very familiar with the corridors of Congress as well as media contacts. The good news is that there are currently powerful Congressional members who would be favorably disposed to the NREA concept.

In addition, strong consumer support exists, as evidenced by the following: FIM conducted a consumer survey to determine whether there are concerns regarding the safety and effectiveness of the foods and dietary supplements that they take. Also, the importance of clinical studies to assess these concerns was outlined. More than 90% of the responders were very much concerned and strongly supported increased clinical research and the creation of the NREA.

In conclusion, the two major nutraceutical players already exist. What is needed is an effective advocacy group, perhaps supported by only a single major corporation, to coordinate the effort. The ping-pong effect would follow quickly.

THE BIOLOGICAL-MEDICAL LESSONS OF MY CARNITINE EXPERIENCE

The carnitine experience continues to open new ideas and avenues, for both basic and clinical research. My primary concern is attacking disease, and I view both types of research with that goal in mind. I, however, fully appreciate pure scientific research because it often leads to ideas regarding goal-oriented medical research. The following are examples of fundamental lessons learned:
1. The nutraceutical rejection need-acceptance concept: Carnitine performs few biological functions when given to both healthy animals and humans. For example, only by the administration of enormous intravenous doses in animals can a cardiac inotropic effect be elicited. This early observation, about 30 years ago, got me thinking about this biologic principle.

Applying this concept, I am currently planning a clinical study to attempt to partially reverse both the mental and physical deterioration of aging. Although the cause of aging is not known, there is little doubt that the loss of energy (or ATP production) is the clinical hallmark of this inexorable process. Young folks run faster than old ones and take to the computer much more easily. Tens of millions of U.S. consumers take dietary supplements daily that are, either directly or indirectly, involved in ATP production. Still, the aging process continues unabated. I have concluded that, for reasons not yet known, aging cells do not perceive a “need” for them and, therefore, “reject” their use, whereas, in scorbatic patients, the cells perceive a need for vitamin C and do not reject, but instead “accept” and use it.

Perhaps the aging cell can be stimulated to create acceptance and use of the ATP-producing supplements. For example, testosterone and growth hormone stimulate muscle cells to grow and enlarge in humans, increasing energy requirements. If the proper ATP-producing supplements are also given, these cells might recognize a need and use them, further increasing ATP production.

This condition most likely holds true with dietary supplements in many diverse conditions.

2. Acute part of organ deficiency: Sufficient cardiac cell levels of carnitine are critical to maintain normal cardiac function. In acute myocardial ischemia, the ischemic portion of the myocardium only loses carnitine. Although the blood levels are normal, a sufficient amount does not exist to replenish the ischemic cells. After ischemia occurs, cardiac arrhythmias appear, followed by cardiac arrest and death. In both animal and clinical studies, carnitine administration restores carnitine levels in the ischemic cells and dramatically prevents or reverses the ischemic changes. (Too often, dietary supplements are considered in terms of prevention, whereas—hold your breath—I believe their use as treatment has greater promise).

3. Whole organ carnitine deficiency: In chronic cardiomyopathy and congestive heart failure, the entire myocardium is carnitine deficient. In animal studies, carnitine increases cardiac output. The clinical studies to date have reported mixed results.

4. Subacute carnitine deficiency: In burn patients, for example, large amounts of carnitine are lost. The reported clinical benefits of carnitine administration are mixed, most likely attributable to inadequate dosing.

5. Chronic carnitine deficiency: In primary carnitine deficiency, a rare and oftentimes fatal disease in children, carnitine blood and tissue levels are very low. Patients respond dramatically to carnitine administration (an FDA-approved indication).

6. Pharmacologically-induced carnitine deficiency: The chemotherapeutic agent doxorubicin is cardiotoxic. It causes both an absolute and relative carnitine deficiency. In numerous preclinical studies, the administration of carnitine, both as prevention and treatment, dramatically eliminates these toxic effects. Although my former colleague, James Vick, and I made the initial observation using isolated Langendorf heart models during the late 1960s, since that time, for reasons that are inexplicable, no definitive clinical trial has been done. I learned a sad lesson from this and similar experiences. Physicians are not aware of nutraceutical studies because, unlike the pharmaceutical industry, which makes available educational material, the nutritional industry does not.

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If carnitine were a strongly patented pharmaceutical, every cardiologist and oncologist would have known about it soon after the initial laboratory studies and perhaps saved or prolonged cancer patients’ lives.

7. Pharmaceutical-nutraceutical additive or synergistic effects: In human ovarian cancer cell cultures, carnitine itself destroyed more than 50% of the cells. Doxorubicin, itself, did the same. When given together, the cell kill capacity of the combination was greater than either alone. I was very fortunate to find an oncologist who was willing to conduct an early Phase II clinical trial in late-stage ovarian cancer. The study will begin shortly. Cross your fingers!

8. Medical device-induced carnitine deficiency: The renal dialysis procedure removes carnitine from the body. Dialysis patients have many problems, ranging from severe fatigue to cardiac failure. Carnitine administration ameliorates some of these manifestations (an FDA-approved indication).

9. Herbal remedies: Although included in the nutraceutical definition, herbal remedies are sufficiently distinct to warrant special consideration. Unlike carnitine and other nutraceuticals, the cell need condition does not necessarily hold. These natural remedies are active under most conditions. What is an herbal remedy? Are St. John’s Wort, broccoli rabe, and the cocoa plant herbal remedies all? An epistemologist is urgently needed to delineate the category. Basic science research clearly tells us that these substances are active pumping up, for example, neurotransmitters and the immune system and doing other things. But not so in man. To date, the clinical data are woefully disappointing. I am as puzzled as anyone regarding the reasons. It could be a simple matter of dosing and kinetics. There are other concerns regarding negative clinical effects. St. John’s Wort increases hepatic systems, which are used to detoxify drugs, one result being lowered blood levels of certain drugs, including those given to AIDS patients. Not too long ago, approximately 20% of FDA-approved drugs were of plant origin. These substances work as pharmaceuticals but, to date, not as nutraceuticals. Go figure it!

MY PERSONAL EXPERIENCE TO FORM THE FIRST NUTRACEUTICAL COMPANY

The carnitine experience convinced me that, in many conditions, nutraceutical blood levels do not reflect intracellular ones and also that normal blood levels are insufficient to replenish them. Diabetics frequently have normal magnesium blood levels but low cell levels. The same pattern holds true with potassium in patients on certain diuretics. Supplementation is needed in such cases.

In the past, I was highly connected in both the food and pharmaceutical industries, and I tried to convince companies, particularly as joint ventures, to enter this health sector. There was little interest. Then, I decided to form my own company, Intracellular Health (ICH), and find private investors whom I thought would be more bullish. Not so. Interestingly enough, their major concern was FDA’s regulatory position on prohibiting disease claims. The FDA allows claims to be made about how certain supplements affect the body, but it prohibits disease-related claims. Money was not the problem. If the NREA were in place, it would have been an easy sell.
I was about to throw in the towel, when I received a call from a high-level executive of one of the world’s largest and most innovative companies in the chemical, agricultural, and raw material supplies business. The level of interest in this company was high enough that the board of directors requested that I present a rationale and an outline of a plan to enter the nutraceutical health sector.

The board was quite receptive to innovative ideas and asked the right questions, which I thought I answered satisfactorily enough.

I proposed that the company sign an agreement with one of the world’s most prestigious hospitals to measure the nutraceutical intracellular levels, including biopsies, of patients with specific high-prevalence diseases. Those with specific deficiencies would then receive tailored design nutraceutical supplements to correct such deficiencies. Clinical outcomes would then be evaluated in studies. I pointed out that unique formulation technology would be one key to success, ranging from once-a-day dosing to taste masking. Because, in many cases, large doses of nutraceuticals would often be required, food and not pill formulations would be critical for patient compliance. Also, because of daily dosing limitations in some cases, even with food technology, it would not be necessary to administer the same high daily dose but a varied one, taking advantage of the kinetics and distribution of fat- and water-soluble nutraceuticals. With the proper know-how, it would be possible to obtain formulation patents that offer lead time in the marketplace.

The give-and-take exchange lasted for precisely 3 h. I detected a tone of high-level curiosity during the last hour. I thought that I had finally accomplished my goal of establishing the first bona fide nutraceutical company and departed a happy trooper. I was wrong. There were just too many unknowns and risks for a public company to take. Once more, as with ICH, if the NREA existed, it would have been a different story. The ping-pong effect would have been in full swing, and patients—we are all patients in one form or another—would have benefited enormously.