

East Meets West in the Laboratory

Henry Ehrlich
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Thank you, Susan.

Just so you know, Susan's wonderful husband referred to me at her birthday party as their "Rabbi." I have a title for her, too. For fans of the Godfather, I call her my "consigliere." I can't tell you how important her friendship and wisdom have been to me.

(Look around)

Gosh, I haven't been in front of an audience like this since I quit my job at Chippendales.

I have enjoyed productive conversations with many of you. People like Jenny Dare Mitchell Sprague, our fairy godmother. How she put this together I'll never know. She's so busy she needs two middle names. She only made one mistake—she originally had me down for 90 minutes. I guess she mistook me for Fidel Castro. Otherwise, she has been perfect. Let's give it up for Jenny.

I'd also like to mention Anne Russell whom I met in person for the first time this weekend. Anne has not only been a stellar contributor to our website, but she also helped shape the way it looks and our overall standards. I think Anne is one of the visionary thinkers about the actual practice of allergy medicine. And one of the people whose opinion about my new book I really value. Thank you, Anne for everything.

Speechwriting books will tell you that at this point, you're supposed to give a content-related joke, anecdote, or quotation that will neatly set up the subject at hand. I know this because I wrote such a book. (Hold up *Writing Effective Speeches*)

But I have to say something about my cousin Paul whom many of you met and who is now headed back to New York because he has to see patients tomorrow. Just like him. Loves his patients, and it's that attitude that has shaped all our activity at Asthma Allergies Children world headquarters. I gather that's not the case with every allergist.

Thank you, Paul.

The history of science is replete with dramatic moments, some real and some apocryphal, that inspired important discoveries. For example, Galileo's experiments dropping balls from the Leaning Tower of Pisa. The apple falling on Isaac Newton's head. Benjamin Franklin flying his kite in a thunderstorm. Madame Curie learning about radioactivity from staring at radium in the dark. Einstein's perception of relativity while riding a Zurich street car. Dr. Emmett Brown falling off his toilet and conceiving the flux capacitor, which made time travel possible.

Wait a minute—that was in the movie *Back to the Future*.

But I want to tell you about a real such moment, one that I hope will profoundly affect the people in this room for the better.

Let's go back to the early 1990s to one of New York's most romantic restaurants, the River Café, built on a barge on the Brooklyn side of New York Harbor. The engineering masterpiece, the Brooklyn Bridge, looms to the right. The lights of Manhattan flicker on the water in the foreground and boats are going by. If you look high enough at the skyline over Wall Street, you can see the tops of the Twin Towers, now, tragically no longer there.

The restaurant is closed tonight to the public for a special event. Among those present is a thirty-something Chinese-born MD, who has come to the event with her colleagues to do something that comes naturally to every girl raised in a Communist country. Put on her best outfit and raise money for a good cause.

Dr. Xiu-Min Li, who has arrived in New York via Baltimore and Palo Alto, spent five days a week doing research on food allergies at Mount Sinai with Dr. Hugh Sampson, and Saturdays treating eczema so bad that other doctors couldn't help, at a private clinic, using traditional Chinese medicine--TCM.

At the time, their research focused on peanut vaccine using mice. They were studying whether a plasmid DNA encoding Ara h2 gene therapy could prevent peanut anaphylaxis. The idea was that if mouse host cells could express Ara h2 genes and make Ara h2 proteins, the immune cells might be fooled into believing that Aha h2 is their own protein so they wouldn't react.

They tried 10 different approaches even more esoteric that didn't work or made matters worse. Dr. Li said, "None of our tested immunotherapy was satisfactory in mouse models, which didn't hold out much promise for eventual human treatment."

But now we come to our Galileo, Newton, Einstein moment. Our young doctor was sitting at a table with a group of women very much like all of you. Loving mothers who wanted the best for their children, only to find that nature had played a dirty trick. Life-**changing** –and life-**threatening**--food allergies.

Dr. Li described the excellent results she was getting with the herbal treatments for

eczema. One of the mothers said she hoped Dr. Li could some day do the same with children like hers. She described her daughter's life in poignant detail. One by one, the mothers took turns talking about their own children.

As Dr. Li told me not long ago, "***From that moment, I felt that as a physician scientist I had an obligation to find a cure for these families.***"

Xiu-Min began studying the symptoms these mothers described, and something sounded familiar. She says, "I had memorized hundreds of formulas that used 500 different herbs. The connection with food allergies was blurry at first, but the symptoms began to sound like parasites."

She presented her ideas to Hugh Sampson who told me, "At that point, I was interested in anything that might be used to treat food allergies." Unfamiliar with the Chinese tradition, he was skeptical, but nevertheless gave the go-ahead with the condition that he would be active in the research at every stage.

Thus began an effort that is now 20 years old. It has been my distinct privilege to get to know Dr. Li in the last three years, and to work for the past year on my forthcoming book—***Food Allergies: Traditional Chinese Medicine, Western Science, and the Search for a Cure***. In the 18th century, Dr. Samuel Johnson had James Boswell. In the 21st century, Dr. Li has me, and for the time being that will have to do.

As a speaker, I have a wonderful advantage. I have spent a long time immersed in a subject, and I could easily spend the remainder of my time recapitulating what I have learned.

But I'm also at a disadvantage for the same reason—in a couple of months, all that I have learned will be on the market. So if I tell you too much maybe you will feel you don't need to bother buying it. In which case I will have done myself, and my beautiful 22-month old granddaughter, to whom this book is most lovingly dedicated, a disservice.

So being as circumspect as I can, I will tell you what the book does, and why it is important, without ruining the story. With luck, you will be so captivated, you will do me a favor and whet the appetites of your readers and inundate Amazon, Barnes and Noble, Kindle, and others with orders at the first possible moment.

Now, as I like to tell people, I am not a doctor, but I play one on the Internet.

Neither am I a scientist, but I have written a book that is about science, often in great detail. Dr. Arnold Levinson Emeritus Professor at the University of Pennsylvania and the Director of the Penn Center for Clinical Immunology (and incidentally a colleague of Paul's four decades ago at Walter Reed Army Medical Center) paid me the highest compliment after he read my manuscript.

He said, “You have done a masterful job of distilling a lot of complex material into verbiage that can be understood by the non-scientist, albeit a sharp non-scientist. And you have accomplished this in an entertaining style. Hopefully, your readers will not drown in the alphabet soup of cytokines and other immunologic reactants.”

The book is what I like to call a love letter to science.

Xiu-Min started with a pharmacopeia that had a proven record of efficacy going back in some cases THOUSANDS of years. The problem for her and her team was to show how and why it works, and that these ancient remedies could be used to treat modern maladies. What I like to call an **epidemic of progress**.

The results could be described in some ways as miraculous, if you happen to believe in miracles. Which I don't. Instead the results are a testament to the power of nature to combine certain properties in botanical form on the one hand

(raise left hand),

and the infinite patience of Chinese doctors to test that power in centuries of trial and error on the other

(raise right hand).

As Dr. Scott Sicherer, puts it, “In China, what we call Traditional Chinese Medicine is just medicine.” Still, it doesn't come easily to someone raised on Benadryl and aspirin to take seriously something called “Cool the Bones Powder” which “clears heat from deficiency and alleviates steaming bone disorder” or “Sweet Wormwood and Soft-Shell Turtle Shell Decoction Version 1” which is used for the same thing. I wonder what the people who named Avastin and Celebrex would do with that.

When I was growing up, the only people I knew who were interested in Chinese medicine were more interested in smoking herbs than taking them for illness.

On the THIRD hand, (raise closest hand of person nearby) --may I borrow this?

On the third hand there is the power of modern science to unlock these secrets. Don't forget—Chinese doctors had been using these preparations to treat disease for centuries when European alchemists were still trying to turn lead into gold.

There are no Chinese molecules and western molecules. Says Dr. Sicherer, “The good news for science is that this is being done by pharmaceutical protocols. Just because something is natural and it works doesn't mean it can be safely used. Dr. Li's work starts with safety before effectiveness, even though she has this body of medicine from China to draw on, and studies animals before humans. She meets all regulatory and ethical requirements.”

This lucky combination of these three elements—the herbs, the R&D done by centuries of Chinese healers, and our modern science—is what makes this story very special, for in some ways it represents a turning point in medical exploration. Dr. Sicherer also pointed out to me, “Western medicine looks at individual molecules to treat specific conditions, but it may be that many molecules or ingredients can do better, and can affect the larger immune system. By looking at them one at a time, we may be missing out.” He says, even if a specific therapy doesn’t work we have already learned things about the immune system we didn’t know before.

I feel the same way. To me, Dr. Li sits between the traditions like a Rosetta Stone, providing the key to translating the ancient into the modern. Dr. Li’s herbal formula is now the most advanced investigational drug in the history of the National Center for Complementary and Alternative Medicine, a branch of the NIH.

The crux of the book is a detailed look at how science works. Most of this is a step-by-step look at a series of experiments, but *science* is not just *science*. It isn’t just about test tubes and assays and mice. It also encompasses the red tape and customs of proof. I believe this is also a big part of the story, for it involves both the things we hate about the NIH and the FDA, and the things we should be grateful for.

I would guess that there isn’t one person in this audience who is satisfied with the pace of research. Anyone who is satisfied raise your hand—**(raise hand and look around expectantly, eyebrows up)**.

Just as I thought.

Some of you I met in Facebook discussions of oral immunotherapy. The day we posted Dr. Hugh Sampson’s article entitled “Not Ready for Prime Time” was the biggest day our site has ever had. It crashed us, and made my life very tense for about 48 hours. Any of you ever tried to contact a web developer in Sri Lanka on short notice?

I’m not going to talk about OIT at any length. I happen to believe that it, like TCM, will occupy a place in a repertoire of treatments for food allergy for a certain portion of the food allergy population *when we know who they are*. But why take my word for it? This is what Hugh Sampson and Anna Nowak-Wegrzyn in a 2011 review article in JACI about a series of studies.

Overall, approximately 50% to 75% achieve and tolerate the maintenance dose. The majority of children tolerate more than 5 grams of the allergenic food during therapy, but it remains to be determined whether partially desensitized subjects might become tolerant with a longer duration of OIT. It is also unclear whether failure of desensitization is associated with the most severe and likely permanent food allergy phenotype, as opposed to the successful desensitization and tolerance induction that might be associated

with a transient clinical phenotype and higher chances of spontaneous resolution of food allergy.

Everything clear?

At this point, I want to clarify the distinctions between OIT and what Dr. Li does. The OIT case has been discussed more publicly without always being fully understood, and I want to make sure that perception of the TCM approach isn't filtered through the OIT lens.

Without promising anything, the differences coalesce around two words. The first, for OIT, is "desensitization." The second, for TCM, is "cure."

As Dr. Li puts it, "OIT doesn't fundamentally alter the immune system. The Th2 cells that regulate production of IgE antibodies may be stimulated to produce it until they are worn out, but new ones are created all the time. Without new allergen exposure to exhaust their IgE output in early stages, they may regain their strength." Allergy shots produce long-term protection. Insect venom needs regular boosting. We don't really know where OIT will fall on that scale.

The idea of a cure is based on modulating the immune system. Inducing the helper cells to do the things they are supposed to do, but at the right time and in the right proportion. IgE is the least abundant immunoglobulin, but in very allergic people it is 10 to 100 times normal because of prolific Th2 cells. As Dr. Li puts it, "We want to turn bad boys into good boys." While, I must add, at the same time not turning good girls into bad ones, which would be the case if Th1 were ramped up.

And how do we do that? Or rather how do *they* that do that—the marvelous team of MDs and post-doctoral fellows?

This is where the story becomes magical. It becomes magical by taking the magic out of it. Lots of laboratory science, so-called bench work, is not for everyone. But some people love it.

The quality of the science is critical. So it was imperative that the story not rely on the anecdotal successes—and there were many—that emerged from Dr. Li's clinic. Instead the overwhelming power of this story was the fact that modern science allows its practitioners to show what makes these compounds work.

It has to be explainable in defined increments, which have to be negotiated with the NIH. Xiu-Min says, "Regulators don't like novelty."

Neither do peer reviewers. That's why all those articles in medical journals are written in such numbing detail. That's why each article begins with a litany of citations describing the extent and nature of the problem and all the previous experiments.

It reminds me of my favorite TV programs (sonorous) “*Previously on The Wire.*” All those one-sentence summaries with all those little footnotes—it’s like singing the 12 Days of Christmas. And instead of 8 maids a milking, you get 8 mice with edema, seven of whom also have pruritus, six of whom have their body temperature falling by two degrees Celsius, and also turn blue because the blue dye you injected is leaking from their capillaries into their little paws as their blood pressure plummets.

You always order the same strain of mice from the same laboratory. You always induce peanut allergy in the same way, by tube feeding peanut extract and cholera toxin. You segregate some animals for treatment, others for sham treatment, and you leave some of them naïve. You carefully plan all challenges, treatment schedules, as well as schedules for “sacrificing” some of them, drawing blood from others. You take their temperatures rectally with the same three-quarter of an inch probe attached to a five-foot cable attached to a computer. And so on.

Each experiment must be replicable. Anyone should be able to follow the breadcrumbs to the same result, if they have the tens of thousands of dollars worth of equipment and the same expertise.

In some cases it means weighing classical formulas against modern FDA concerns.

You replace *Zhi Fu Zi* (Radix Lateralis Aconiti Carmichaeli Praeparata) and *Xi Xin* (Herba Asari). Both contain alkaloids, which have safety problems.

This isn’t like, say, modifying the Ten Commandments to read, “Thou shalt not steal but instead add fees and hidden costs”, or “Thou shalt not bear false witness against your neighbor but instead post something anonymously on the Internet.” That’s one thing about stone tablets: it’s hard to carve fine print.

(Oh, wait a minute. Wrong Mount Sinai.)

There are other herbs that can be substituted. Ginger root—aka *Gan Jiang*—for stomach pain. *Ling Zhi*—the magic mushroom—for combatting the symptoms of anaphylaxis and save lives, as it did thousands of years ago in one of China’s most beloved folktales.

This process means “fingerprinting” the active ingredients, studying their pharmacokinetics, (defined as what the body does to the drug, as opposed to what the drug does to the body, which is called pharmacodynamics). It means monitoring absorption, first in cell lines, then mice, and then human subjects. So that eventually they may be able to assemble in the laboratory those unique combinations given to us by nature, should economic development or climate change ever threaten the habitats where these things grow. It also means that you can show that the combination of the ingredients is more effective than any lesser combination.

The more I think about what these scientists are able to accomplish in the laboratory, the more awesome it becomes, and when I use that word, I feel my father hovering over my shoulder. He compiled the first edition of the Oxford American Dictionary, in which he defined awe as “respect combined with fear or wonder.”

In a book called *The Genius Within: Discovering the Intelligence of Every Living Thing*, author Frank T. Vertosick, Jr. wrote “The immune system must learn and recall billions, perhaps trillions, of different molecular patterns. Our lives depend on its ability to make instant discriminations between friend and foe, not an easy task.”

Dr. Jerome Groopman describes “the elegant choreography of [the T cells]...coordinating scores of enzymes and releasing a repertoire of proteins that, in the body, amounts to a solid wall of immune defense.”

These are the things you can see under the microscope. Things you can assay in a flask. Things that are skewed in allergic people. And things that can be nudged in the right direction by the judicious application of these botanical compounds.

I’ve been talking for a long time now. So I’m going to start winding up. We are all eagerly awaiting the results of the latest phase of the human trials. I certainly don’t know what they are. All the researchers are in a state of—wonderful word—EQUIPOISE—which means that they don’t know the answers yet either and are waiting for the numbers to be crunched. If the results I do report in my book for mice hold up for people, we have a lot to look forward to.

This is the point I get weak in the knees and simultaneously awestruck and pretentious. Because the science begins to feel like those German physicists must have felt when they built the first electron microscope in the 1930s and got the first glimpse of the building blocks of matter.

Consider the other research Xiu-Min has enabled. If it only works for food allergies, asthma, and environmental allergies, it would be enough. But this has implications well beyond food allergies.

At a farewell luncheon for one of her fellows a couple of years ago, I met Dr. Jessica Reid-Adams. She was about to go on leave to have her third child, but what she told me about her ambitions etched itself into my brain. She is a pediatric nephrologist, which means her typical patient is a 2-year-old in late stage kidney failure, whose choices—or whose parents’ choices were dialysis, transplantation or—well you know....

Transplantation typically involves a full-sized adult kidney, and as with all transplants, it is subject to rejection. Think of what happens to your child when he or she encounters a taste of peanut or hazelnut or shrimp or egg. Micrograms of

alien protein. And think about what will happen to a 30-pound child carrying five ounces of donated kidney. Surgeons dreamed of transplantation for centuries, but it only became tenable with the development of powerful immunosuppressants, which, as any of you dealing with chronic asthma know, have problems of their own. Yet, they must be used day in, day out. And to make matters worse, the typical transplanted kidney lasts around five years. Finally, just to place a current events context on this problem, let me remind you that when the Affordable Care Act was being written, stories emerged in the press about organ transplants. To wit, insurance would pay for an operation, but there would be a cap on how much cyclosporin or sirolimus/rapamycin they would pay for. The organ might last five years, or, in the case of singer David Crosby's liver, 18 years, or for only one, like Lou Reed's liver. But your insurance company might pay for only two years of drugs.

So it became Dr. Reid-Adams' ambition to find a way to mitigate the toxic effects of those drugs and possibly extend the life of the organs. She went to see Dr. Li, who turned her loose on her herb database to study the ones that affected kidney function. She screened extracts from 53 herbs for their ability to suppress human alloreactive T cells—T cells mobilized by the presence of transplanted tissue. They reasoned that herbs would ideally inhibit production of the proinflammatory cytokine interferon-gamma (IFN γ) and simultaneously augment production of the immunoregulatory cytokine IL-10. Says Reid-Adam, "An increase in IFN γ is good for allergies, but bad for organ rejection. However, IL-10, which sometimes indicates greater Th2 activity but not really Th1, can be a beneficial indicator for allergies and also good for transplantation."

(Say that five times fast!)

Employing an in-vitro version of transplantation—culturing cells from one individual and then exposing them to cells from another--they analyzed the cytokines in the presence of each herb and identified *Qu Mai*, a member of the carnation family, as a candidate. Dr. Reid-Adam says, "There isn't much written about it in Western literature, but TCM practitioners use it to treat blood in urine and urinary infection, indicating a connection to the kidney, and for skin inflammation. It achieves the decrease in an important proinflammatory cytokine without killing immune cells."

Clearly, this is not hippie medicine!

Dr. Reid-Adams' research has now been published ENTHUSIASTICALLY in the world's foremost transplantation journal. This gives me chills. You've heard the expression, to see the universe in a grain of sand? How about human life in a flower?

Is this THE answer? Well, who knows? My great friend Dr. Mark Cullen of Stanford takes great delight in cautioning me against my amateur enthusiasm. Thank you, Mark. I stand warned.

But I'll tell you, it's hard not to look at this work and the vast database Xiu-Min has amassed and the experience and wisdom she has acquired and not be impressed. It's hard to look at the complex, co-morbid allergic conditions being treated in her private clinic—eczema, food allergies, EoE—and not be excited. It's impossible to look at the early stages of research into what I call “corrective epigenetics” and not feel for the first time a measure of hope that the intergenerational tendencies of allergic disease might some day meet their match.

(Pause)

As I indicated earlier, I used to be a speechwriter. I worked in the 1980s to help deregulate the financial industry. During the financial collapse of 2008 and 2009, people who knew me back when would come up to me on the street and shake their fists at me and say, “It's your fault.”

I still like writing speeches. I particularly like the money. I don't do much of it anymore. But there's one more speech I'd like to write one day if I still have all my marbles. And I won't even charge for it.

That's the speech that that Dr. Xiu-Min Li gives some day when she goes to Stockholm to accept her Nobel Prize.

Thank you.

Henry Ehrlich is editor of www.Asthmaallergieschildren.com, co-author of *Asthma Allergies Children: a parent's guide* and the new book *Food Allergies: Traditional Chinese Medicine, Western Science, and the Search for a Cure*. Both allergy books are published by Third Avenue Books. Speechwriters of a certain age will remember his book *Writing Effective Speeches*.