

A Medical Application of Matzinger's Danger Model: Coley's Cancer Vaccine

Gar Hildenbrand
Lecture and PowerPoint presentation
to the American Academy of Anti-Aging Medicine Fellowship
in Integrative Cancer Therapy: Module II;
August 14, 2010;
Boca Raton, Florida
Fellowship Dir: Mark Rosenberg, M.D.



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Abstract

For many years, cancer was believed to be invisible to the immune system; therefore, serious attempts to develop immunotherapeutic agents were dismissed, and funding was nearly nonexistent. Now, from the laboratory of Matzinger comes an explication of the tissue-controlled immune system, in which danger signals replace “self/not-self recognition”. In the Danger Model, merely wounding a tumor can cause it to release danger signals that awaken dendritic cells, which in turn activate an effector class of lymphocytes that can clear tumors. Coley's Toxins, first introduced in the late 1890s, can be considered the prime example of a medical application of the Danger Model.

Introduction

Let me just say, while the device is booting here, that on our way here we stopped at the laboratory for T-cell Tolerance and Memory at NIH and visited professor Matzinger there, Dr. Polly Matzinger, and I have some interesting news to tell you about that — stay tuned. That's a teaser, right? They do it on radio all the time — you won't believe what we found; stay tuned for the third hour!

The other scientist we visited was Dr. Stephen Groft, who is the director of the Office of Rare Diseases Research, and was a prior executive director of the White House Commission on Complementary and Alternative Medicine Policy. And where I'm going with this is that we are trying to do something about getting this mixed microbial vaccine created by Coley studied, in-house at NIH, with taxpayer funding without the involvement of unnecessary leaches from big Pharma. And it looks pretty good.

So (*looking at computer screen*) I'm watching a little pinwheel that says we have slides. Are we up? Oh, that's wonderful — an abstract which is not in your course book. It was funny. I got one of the course books this morning, took it back to the room and looked at it, and it had been bound on the wrong side so I was looking at everybody's lectures backwards, and I thought maybe I should trade this in. The rest are good I think.

There is no abstract in the slides that you have in your manual there, so let me just read this out loud as is my wont — I adhere to the Pauling principal, and I'm not doing it this time; I can apologize for that; I've got something up there and I'm saying something else. Linus Pauling hated that so much that he made a point of putting up a slide at the beginning of his talks, and then asking that it be taken down, and he lectured without notes, even at age 93. His one gripe, well two gripes, were when you put something up and then say something other than what's on the screen, and that you print with white letters on a black background. He couldn't stand it. I'm with him on both counts; I'm using a white background with black letters.

A Medical Application of the Matzinger Danger Model. How many of you are familiar already with Matzinger's danger model? How many know Charlie Janeway's self-not-self model of immunity? No self-not-self models? Surveillance army of immune cells floating through the bloodstream; they know self; they're going to attack anything that is not self? This is what you were raised with actually; this is what you were taught, is self-not-self. The danger model is, in the nature of Kuhnian scientific revolutions, the new paradigm that has emerged that is larger than the older paradigms and fits them nicely into context, explains their deficiencies, ties them together. The danger model, you are going to love this, it was first published in 1994. It is all over the literature. All you have to know is too look for the words "danger signal" and you will see that it is absolutely permeating research.

For many years — I am going to read this now — cancer was believed to be invisible to the immune system; therefore, serious attempts to develop immunotherapeutic agents were dismissed, and funding was nearly nonexistent. Now, from the laboratory of Matzinger comes an explication of the tissue-controlled immune system — let that sink in, the tissue-controlled immune system — in which danger signals replace "self/not-self recognition." In the Danger Model, merely wounding a tumor can cause it to release danger signals — this would be like intracellular ATP or mitochondria coming outside the cellular membranes, hyppos, other molecules that belong behind the cloak of cellular membranes; if these are outside, these are danger signals — that awaken dendritic cells, which in turn activate an effector class of lymphocytes that can clear tumors — and I would hastily add, in our observations of Coley's toxins, yes, the lymphocytes lead the show. As Robert Good pointed out, these are T-cell mediated immunities. The T-cells kind of lead the show. But I would add that, as the good doctor was discussing, the neutrophils play an enormous role in an anti-cancer surge by first the innate and then the adaptive immune system; and I don't think you can separate the two. Coley's Toxins, first introduced in the late 1890s, can be considered the prime example of a medical application of the Danger Model.

We'll start with a walk down memory lane for Coley's Toxins; this is a historical review. I'd like to give the nod to Lloyd Old, who pointed out that Coley is the father of tumor immunotherapy, *per se*. William Bradford Coley lived a full life. It was over by 1936. He had been injecting his vaccine for four decades at the time that he died, and publishing in every good journal.

To turn to a quote by Charlie Starnes — some of you may know Charlie Starnes as the director of Oncology Research at Amgen. Charlie, in this article in *Nature* — this was an answer to a letter writer. A letter writer had gotten very excited. Charlie had written an article about Coley's Toxins. The letter writer had gotten very excited about cytokines, and had written back enthusing about, you know, where we're going to go with tumor necrosis factor and interleukin 2, and Charlie wrote him back and said: *I specifically stated that "...serious consideration should be given to a return to an aggressive use of the vaccine..."; not TNF-related or toxin-related therapy, but specifically the Coley vaccine itself. This is a point made in deference to the fact that the clinical accomplishments of Coley and his contemporaries were much beyond what we would be able to offer these same patients today. If we are going to make changes or improvisations in treatment, this should not be*

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Slide 1

Coley's toxins

A historical review of the first anticancer vaccine and a discussion of its potential role in the contemporary context

Slide 2

Starnes, Charlie O.,* *Nature* Vol 360, 5 Nov, 1992

I specifically stated that "...serious consideration should be given to a return to an aggressive use of the vaccine..."; not TNF-related or toxin-related therapy, but specifically the Coley vaccine itself. This is a point made in deference to the fact that the clinical accomplishments of Coley and his contemporaries were much beyond what we would be able to offer these same patients today. If we are going to make changes or improvisations in treatment, this should not be done until after we have at least managed to reproduce the original, basic observations.

*Director Oncology Research, Amgen

Slide 3

done until after we have at least managed to reproduce the original, basic observations. Truer words were ne'er spake.

And Charlie goes on to say, in a way that only he can, Coley today is revered as the 'father of present day immunotherapy' and awards are periodically presented in his name, most of the time for accomplishments, which while very important in and of their own right, yet at best, share only a peripheral association with Coley's work as a clinician...

As Sylvia Formenti, who is the Radiation Oncology Chief at NYU, is wont to say regarding the lack of interest in clinical approaches, as opposed to new drugs and devices, "I want to scream!" That's what she says, and she says it in front of people, "I want to scream!"

At the same time, in our current clinical efforts with recombinant cytokines, we find decisions being made empirically, by trial and error, that could have well been made in advance, had we expressed a true appreciation of Coley's work by simply reading his papers. Had we chosen to do so, we would have also learned that there is much more to be expected out of this arena than that which we have managed to accomplish thus far.

I've got to tell you, Christeene started some course work, some degree work, and she started a pull on Coley's literature and I got involved, I got engaged. We were working out of San Diego, so we used UCSD's Biomedical Library, interlibrary loans, and then we got a research dispensation at National Library of Medicine and we went to the History Division there with unlimited pull capabilities, and we yanked and jerked and cranked and copied this stuff, and we took it home, and we read it. You know, what happened to Charlie Starnes and Bernadette Wiemann is they had a religious experience; they read it and it was epiphany time. It was also "Oh, my God, what happened to this?" time. Where did this go? What are we doing with the current approaches? Why are we not still hooked in here with the Coley Vaccine? To cite Lloyd Old — you know who Lloyd Old is? He's current head of Ludwig Cancer Center in New York and permanent board member of Memorial —

Clinical support for the idea that the immune system might restrain the development of cancer emerged in the 1800s, when physicians noticed that tumors sometimes regressed in cancer patients who contracted bacterial infections. William B. Coley, a surgeon at Memorial Hospital in New York City from 1892 to 1936, dedicated his life to creating therapies based on this observation.

Now, the observation is not a pretty one. I'm going to throw you back into medical-school nightmare city by citing from Stanley Robbins. You are all, undoubtedly, familiar with Stanley Robbins. But this is germane to the Coley.

Wiemann B, Starnes, C. Coley's toxins, tumor necrosis factor and cancer research: A Historical Perspective. *Pharmac Ther.* 1994;64:529-564.

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Weimann & Starnes, cont.

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Old, L.J. Immunotherapy for cancer. *Sci Am*; Sept. 1996:136-43.

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*Humans owe to inflammation and repair their ability to contain injuries and heal defects. This is the chapter we skipped, right? This is the chapter called *Inflammation and repair*. It's the longest chapter in Robbins' Pathology, just for what its worth; the longest chapter: *Inflammation and repair. Without inflammation, infections would go unchecked, wounds would never heal, and injured organs might remain permanent festering sores.**

The inflammatory response is closely intertwined with the process of repair — Two sides of the same coin — Inflammation serves to destroy, dilute, or wall off the injurious agent, but in turn sets into motion a complex series of events that, as far as possible, heal and reconstitute the damaged tissue.

Anyone who has suffered a severe sore throat or a respiratory infection has experienced the systemic manifestations of acute inflammation. Fever is one of the most prominent systemic manifestations, especially when the inflammation is associated with bacteremia. Bacteremia usually induces fever with dramatic swings in temperature — Is this coming back? Right? — producing so-called spikes on the temperature chart. Violent shaking chills are known to all those who have had the flu.

These days fever is typically regarded as an unpleasant, unnecessary, weakening state, which should, by default be prevented. Its 'guilt by association' remains firmly entrenched in most areas of current medicine. This opposition to fever was not always the case... Parmenides (about 540-480 BC) said: "Give me the power to induce fever, and I cure all diseases."

Now, this is from Professor Uwe Hobohm, who has been firing off articles in an attempt to bring back to focus an original, cardinal observation that tumors sometimes cleared as collateral damage when the body has a robust inflammatory response to another challenge.

*In the issue of 13 March 1868, of the *Berliner Klinische Wochenschrift*, Prof. Busch reported — this is Wilhelm Busch — perhaps for the first time, an experiment with a human patient in which an attempt was made to treat cancer by fever induction. Busch had previously observed a resorption of tumor mass in some patients with sarcoma of the face or neck after they got an erysipela: a severe skin infection caused by *Streptococcus pyogenes*, which is accompanied by a heavy and acute inflammatory reaction.*

Hobohm, U. Fever and cancer in perspective.
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Stanley Robbins, Ramzi Cotran, Vinay Kumar.
Inflammation and repair. In: Pathologic Basis of Disease.
3rd Ed., Philadelphia; WB Saunders Co.; 1984:40.

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Slide 7

Robbins S. 1984 (cont)

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Slide 8

Robbins S. 1984 (cont)

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Hobohm U. 2001 (cont)

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Actually, the back story is more interesting than Dr. Hobohm is letting on here. Busch was operating a patient who had seven sarcomata on her face and neck. He cleaved one of them off and apparently was already working in a hospital with a “dangerous” ward and dangerous beds. Now in the old days you couldn’t disinfect the hospital if Streptococcus or gangrene got into the facility; you had to burn it down and build a new one. The dangerous-bed concept was coming to be at this time, and Prof. Busch profited from this.

His first patient, operated more cosmetically than functionally for these sarcomas, contracted erysipelas and experienced weeks of racking fevers, and completely absorbed the remaining tumors. Busch published this in 1866, and then again it happened to him the next year with another patient — in the same facility. And at that point, in addition to publishing, he made plans to wound a patient’s tumor and place that patient in a dangerous bed. And that worked. And he published that case. Now this last case wasn’t such a happy outcome. There was a lot of tumor; there was spinal tumor. The masses shrank very, very rapidly, and by the historical record, it looks very much like tumor-lysis syndrome occurred, and the patient was lost due to toxic overload and multiorgan failure.

The historical context for *Streptococcus pyogenes* is nothing less than fascinating. This is a microbe that has to be studied, because the microbe appears to elicit from the human immune system a response of a very singular nature, or maybe I should say a very complex nature. Other infections are really not very utilitarian. But it was established, already in the 1820s, that skin diseases that were chronic and/or acute and morbid would be caused to go into remission if an erysipelas infection intervened; and the Faculty of (Medicine in) Paris made a point of encouraging research into contamination or cross-inoculation of *S. pyogenes* — unknown then — it was erysipelas. It was not until Fehleisen in the 1880s that we named it, right? Because Koch’s postulate hadn’t come out yet. But at the Faculty of (Medicine in) Paris it was well known that you could trade advanced syphilis for a short-term *Streptococcus* infection. Who wouldn’t? Who wouldn’t? And then, of course, Busch with his *Über den Einfluß, welchen heftige Erysipiele zuweilen auf organisirte Neubildungen ausüben* (Regarding the occasional influence of severe erysipelas on unresolved neoplasms). Amazing stuff.

Fehleisen, in 1882, identified *Streptococcus erysipelatos* (now called *Streptococcus pyogenes*) as the pathogen leading to erysipelas, and he achieved three remissions by injecting cultured living bacteria into seven cancer patients. Parenthetically, I would add that he killed several whose time had not come because, seriously, *Streptococcus pyogenes* then was a hellacious bug. It had a 10% mortality rate, even in the doctors and nurses who contracted it. Today, it’s nothing. Penicillin wipes it out easily and reliably. But then, it was a bad deal.

So, Prof. Hobohm continues, *Thus, William Coley (1862-1936) was not the inventor of the treatment of cancer using bacterial infections. However, he was the first to do it systematically on a large number of patients.* And, I would add, you have no idea how large a number. It is a *tour de force* in the literature and it’s much to the great shame of our predecessors in the medical, pharmaceutical, and research development complex that they did not enshrine and bring forward Coley’s work. It’s just not nice; it just wasn’t right.

Historical context: diseases improved by erysipelas (*Streptococcus pyogenes*)

- Chronic or acute morbid processes of the skin. *Med Chir Trans.* 1828;14(Pt 1):1-80.
- Syphilis. Sabatier JC. *Recherches Historiques sur la Faculté de Médecine de Paris, Depuis son Origine jusqu’ à nos Jours.* Paris, Baillière, 1837.
- Cancer. Busch W. Über den Einfluß, welchen heftige Erysipiele zuweilen auf organisirte Neubildungen ausüben. *Berliner klin Wochenschr.* 1866;13:245-6.

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Slide 13

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Hobohm continued, *In 1950, Shear reported that brief remissions in children with untreated leukemia were observed in about 10% of the patients. Three quarters of those remissions were preceded by an episode of acute infection. In a remarkably lucid statement, he wrote: 'Are pathogenic and non-pathogenic microorganisms one of Nature's controls of microscopic foci of malignant tissue, and, in making progress in the control of infectious diseases, are we not removing one of Nature's controls of cancer? Think of your immune system as a couch potato; it's a move-it-or-lose-it kind of system.*

And now I am going to turn to my colleague who was here yesterday, Prof. Stephen Hoption-Cann from UBC, because I love quoting from his brilliant paper, *Spontaneous regression: a hidden treasure buried in time* which was published in the now-defunct *Medical Hypotheses*. Some of you know about what happened to *Medical Hypotheses*; a big battle ensued because they were acquired in a merger-mania and suddenly this journal was no longer to be umpired; it was to be peer-reviewed. And if there is anything that staunches the free-flow of new ideas into the literature, it's democratically selecting reviewers of average intelligence from the pool, because they tend only to approve of ideas with which they are already familiar, and they tend to be allergic, they have a high antibody titer to anything they haven't seen before.

So, as Stephen wrote, *By the 1890's, William Coley refined this approach with a bacterial vaccine which, when administered properly, could induce complete regression of extensive metastatic disease. Unfortunately, after Coley's death, his vaccine and technique fell into obscurity.*

A key aspect that Coley found to be necessary for tumor regression was the induction of a mild to moderate fever. Stephen lectured about fever yesterday and it is a fascinating — I love that lecture, actually, I think it's fantastic. (Coley) would thus gauge dosage levels according to individual patient responses and increase the dose as necessary to avoid vaccine tolerance. Can you imagine what a freaking nightmare that is for people who want to do an RCT, and they want to define the dose? To simulate the effects of a chronic infection in his patients, he would inject the tumor vicinity daily or every other day for the first month or two.

Hobohm, U. 2001 (cont)

In 1950, Shear reported that brief remissions in children with untreated leukemia were observed in about 10% of the patients. Three quarters of those remissions were preceded by an episode of acute infection. In a remarkably lucid statement, he wrote: 'Are pathogenic and non-pathogenic microorganisms one of Nature's controls of microscopic foci of malignant tissue, and, in making progress in the control of infectious diseases, are we not removing one of Nature's controls of cancer?

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Spontaneous regression: a hidden treasure buried in time.

S.A. Hoption Cann,^{1,2,3} J.P. van Netten,^{1,2} C. van Netten,³ D.W. Glover¹

¹Special Development Laboratory, Royal Jubilee Hospital, Victoria, British Columbia, Canada;

²Department of Biology, University of Victoria, Victoria, British Columbia, Canada; ³Department of Health Care and Epidemiology, University of British Columbia, Vancouver, British Columbia, Canada.

Medical Hypothesis (2002) 58(2); 115-119.

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Hoption-Cann S. 2002 (cont)

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Hoption-Cann S. 2002 (cont)

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Despite the 'crude' approach taken by Coley, his vaccine stimulated a complex immune response that could induce the complete regression of both extensive primary and metastatic lesions. Furthermore, his vaccine was universally effective against many types of malignancies.

When you parse this literature, you find this to be true, and its not just Coley, of course; there are colleagues; there are publications: *New England Journal of Medicine* is a journal which was Coley's venue; *The Proceedings of the Royal Academy of Sciences*, you know, all the good journals of the time; case after case, series after series of patients.

Tumors that were observed to partially or completely regress following treatment with Coley's vaccine included: lymphomas, melanomas, myelomas, sarcomas and a wide spectrum of carcinomas.

Modern investigations have shown how difficult it is to reproduce this complex immune response, and correspondingly tumor regression, when more precise — I don't know if that is the right word — tumor-specific antigens and cytokines are used. In contrast to such immunotherapies, Coley's vaccine could be produced at a nominal cost, be used for a wide spectrum of cancers, and still provide a significant benefit to patients at all stages of disease.

Other interesting observations by Coley were that the toxins led to a marked relief of pain — We just found an article that was published by Dr. Kline in which he was treating arthritis patients and he was getting this wonderful shrinkage of these inflamed and distorted joints with sequential injections of Coley's vaccine at a level a little bit below fever, in fact — so that patients could often discontinue using narcotics; and, as these injections often followed surgery or were injected into ulcerated tumors, there was an extraordinary enhancement of wound healing and even bone regeneration. Similar observations on infectious amelioration of cancer pain and enhancement of wound healing have been reported by others.

Decline in the use of Coley's toxins came about after Coley's death in 1936. by the 1950s, antibiotics came into general use for surgery, greatly reducing the chance of infection following tumor excision. Furthermore, radiation and chemotherapy became mainstays of treatment as they required less individualization

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Decline in the use of Coley's toxins came about after Coley's death in 1936. By the 1950s, antibiotics came into general use for surgery, greatly reducing the chance of infection following tumor excision. Furthermore, radiation and chemotherapy became mainstays of treatment as they required less individualization and the immediate results were more predictable, although it soon became apparent that such treatments often led to cures of a short duration...

Slide 23

tion and the immediate results were more predictable, although it soon became apparent that such treatments often led to cures of a short duration — more of a parlor trick —

Chemotherapy, and to varying degrees radiation, is highly immunosuppressive, and therefore infections in the cancer patient cause little immunostimulation, and in any case, are rapidly treated with antibiotics. Thus, it is not surprising that reports of spontaneous regression have become rare. Still, an association with acute infections prevails in the few recent reports of this phenomenon.

Professor Bauer, one of the founders of the German Cancer Research Institute (DKFZ) in Heidelberg, in his founding talk for the DKFZ in 1965, claimed that, 'the human body has no cancer fighting capabilities.' This is Dr. Hobohm talking. This highly ignorant view was not substantiated even at that time, when hundreds of case studies of spontaneous remissions had been published.

Even worse, we have to admit that this dogma was preserved in clinical standard therapy until the late 1980's, and we still find a majority of clinical oncologists who do not consider immunological measures. Everybody in here is hopped up on vitamin D. Why? Because you care about the host. Not so in the cancer wards. The persisting ignorance of clinical oncology towards the impact of a well-functioning immune system and the potential power of a stimulated immune response is one of the saddest examples of the occasional immobility of modern medical practice.

The effects of the Busch-Coley treatment and the frequent concurrence of spontaneous remissions with fever might both be explained by the following hypothetical cascade of events: — Home in on this because Hobohm is basically right — fever generates inflammatory factors with co-stimulatory activity, which activate resting dendritic cells (DC), leading to the activation of anergic T-cells, maybe accompanied by a second process, where a possible physical damage of cancer cells leads to a sudden supply of cancer antigens to DC.

It's close. As we get into the theoretical basics of Matzinger, we'll see that there were a few holes in Prof. Hobohm's explanation, which is largely derived from the concept of pathogen-associated molecular patterns, which is still about the self-not-self model, mostly.

Hobohm, concluding — Today we can induce and control fever much better than 100

Hopton-Cann S. 2002 (cont)

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Slide 27

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Hobohm U. 2001 (cont)

Today we can induce and control fever much better than 100 years ago, we have a much better understanding at the molecular level, and we have a plethora of additional immune-stimulators available, which might be combined into a synergistic therapy regimen. It is time to scrutinize fever therapy again.

Slide 28

years ago, we have a much better understanding at the molecular level, and we have a plethora of additional immune-stimulators available, which might be combined into a synergistic therapy regimen. It is time to scrutinize fever therapy again.

To look at an analysis that Helen Nauts did of a few of the pathologies — now I've included a big breakdown of cancers in the slides there that you can barely read because it's so tiny; you could use a magnifying glass (see Slide 114, pg. 36). But, let's look at a couple of these rates that were broken out. Now I want to point out that this was a review of 896 cases that were validated out of more than a thousand. Dr. Lloyd Old is the man who actually requested the histological specimens and pathologically validated them himself. So this is not just Helen Nauts, the daughter of William Coley, but Lloyd Old and the people that he brings with him, his entourage, looking at this and asking how well did Coley do?

As you see, Non-Hodgkins Lymphoma with a sample of 86 patients, there was a 5-year survival of 49%. These were all so-called inoperable cases; in other words, they have an extent of disease that maps them up at least stage III, and more often than not, stage IV.

Hodgkin's disease: with an n of 15, ten of these patients out at five years. This is no mean accomplishment, there was no chemotherapy then, there were no immunosuppressive steroids at the time. If you think about that, that's quite remarkable. And do remember that Coley is working in a vacuum; they didn't even have insulin until 1926. There's no propranolol, there's no beta blockers, there's no nothin'. You get pre-septic symptoms, you just watch that blood pressure plummet and stick with the patient. You could give them oxygen; we had that then. And Coley, I've got to tell you, Coley didn't alter life-style; he took them as they came. If they were drinking Seagram's for breakfast and having bacon three times a day, he treated them as they came.

Ovarian: ten of fifteen patients out five years. Think about that. One of my wife's favorite examples of immunogenic cancers, cancers that are immunoresponsive, is ovarian, because we worked for a couple years — we went around the world for former Congressman Berkley Bedell's National Foundation for Alternative Medicine doing nothing but best case series, and there were always one, or two, or three ovarian cases where women had often-times been operated but refused chemotherapy for the mop up. If you know FIGO Stage IIIC cancers and above, the studding of the retroperitoneum is left alone, nothing smaller than 1 cm is going to be removed by the surgeon, because there is too much of it; you wait for the chemo to mop it up. These are people who did their mop ups with immunotherapy, whether the physician was Thomas Rau's Dr. Braun; or Wöppel over at Hufeland Klinik; the Gerson group in Mexico; everyone had ovarian cancer patients.

Now, breast. Non-surgical cases of breast cancer: 65% five years — 65% of these patients; and often times with complete remissions, because you could get at the tumor. We'll explain with Dr. Matzinger's model why that would happen. Melanoma — of a sample of seventeen, you got 60% five-year survival. Melanoma — that's a fast cancer. If you're thinking, well breast, it's variable, you know, we've seen breast cancer patients do better, think about melanoma patients who have done better as a group. You can't. — Giant cell sarcoma — sample size of 19; you've got 79% five-year survivorship.

Historical 5-yr survival rates
Nauts HC. *Cancer Res Inst Monograph* #18, 1984

Non Hodgkins Lymphoma $n = 86$
5-yr survival = 42 (49%)

Hodgkins disease $n = 15$
5-yr survival = 10 (67%)

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Historical 5-yr survival rates
Nauts HC. *Cancer Res Inst Monograph* #18, 1984

Ovarian (nonsurgical) $n = 15$
5-yr survival = 10 (67%)

Breast (nonsurgical) $n = 20$
5-yr survival = 13 (65%)

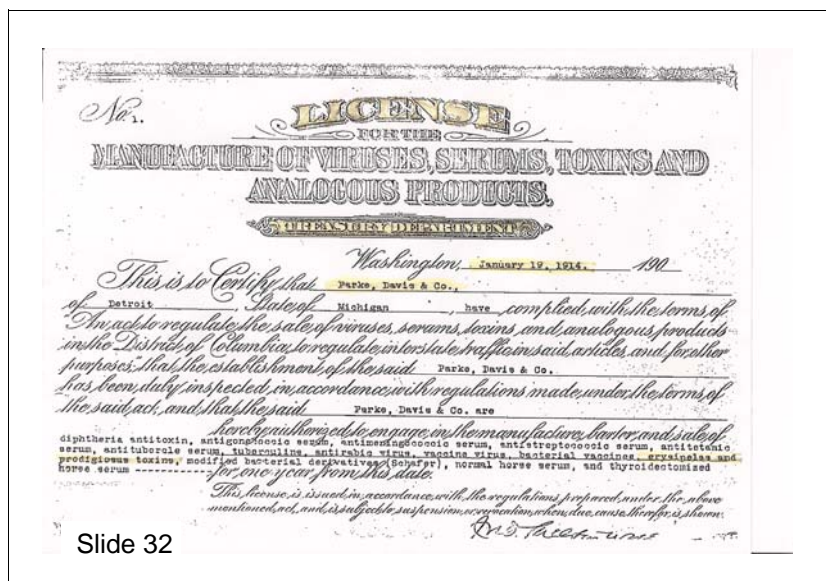
Slide 30

Historical 5-yr survival rates
Nauts HC. *Cancer Res Inst Monograph* #18, 1984

Melanoma (nonsurgical) $n = 17$
5-yr survival = 10 (60%)

Giant cell sarcoma (nonsurgical) $n = 19$
5-yr survival = 15 (79%)

Slide 31



Slide 32



Slide 33

This is what the license looked like (above). This is the license for Parke Davis, this is in 1914, the one that we found in the National Archives, to manufacture Coley Fluid. Parke Davis made this stuff for more than a half a century; more than half a century.

This is Parke Davis (above right). .

A little bit about the legislative opportunities; and the opportunities for reparations and remedy before we break for lunch.

The sole U.S. commercial license to manufacture Coley Fluid was held by Parke, Davis & Co. for more than 50 years, from 1899 until an indeterminate point in the early 1950s. The license, issued by the U.S. Treasury, was regulated by the Hygienic Laboratory of the Public Health & Marine Hospital Service. In 1934, the Hygienic Lab was renamed the National Institutes of Health. It is probable that Parke, Davis & Co. had to request revocation, and its reasons for doing this are, as yet, unknown.

We started an FOIA request in September of 2007; got nothing until two weeks after Obama was inaugurated, and then we got a reply. Before that, I would call and be told, "Oh there's a long queue and you'll have to wait; we have no idea when anything will be forthcoming." And two weeks after Obama takes office, we have got the most helpful people; we've got the contents of a three-ring binder that was a working document from within the office of the Commissioner of the FDA, having to do with streptococcus pyogenes.

(Academy member: Just a quick question; Parke Davis had the manufacturing license from 1899 to the 1950s; is that the product that William Coley was using? I don't think so.)

can answer that briefly. There's a lot of scuttlebutt about what Parke Davis made. It is true that in the beginning they made a pretty weak vaccine, and if there were any stores of that vaccine sitting around, they were pretty puny. But Parke Davis did — and we found the record in the Archives — did respond to Martha Tracy's advancements by nitrogen fixation of the replicability of the batches of the vaccine, and so we're relatively confident that Parke Davis was manufacturing a competent vaccine toward the end of its duration. Martha Tracey was in Buxton's laboratory at Columbia, and she is credited with having developed the two most potent batches of Coley.

(Academy member: I'm not sure if it's really answering what I'm asking. Is that the product that William Coley used?)

Commercial licensure

The sole U.S. commercial license to manufacture Coley Fluid was held by Parke, Davis & Co. for more than 50 years, from 1899 until an indeterminate point in the early 1950s. The license, issued by the U.S. Treasury, was regulated by the Hygienic Laboratory of the Public Health & Marine Hospital Service. In 1934, the Hygienic Lab was renamed the National Institutes of Health. It is probable that Parke, Davis & Co. had to request revocation, and its reasons for doing this are, as yet, unknown.

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Yes, Coley was involved with Parke Davis, intimately. There's correspondence back and forth. He was always over there — they worked for him and with him. Coley was remarkably well-respected and connected. We found an entire box of correspondence between Coley and the Director of National Institutes of Health asking Coley for help evaluating a new vaccine. Coley was very much "in;" you couldn't get any more "in." Thank you for asking the question, because there are — there's a kind of a lingering effect of the disinformation campaigns against Coley that occurred — and these were *ad hominem* attacks after the guy had been dead for several decades — and you hear it all; you hear that Parke Davis was crappy and that's why it needed to be done another way. I'm not so sure that is true. The historical record is pretty clear that William Coley and Martha Tracey were deeply involved; Parke Davis was responsive; and what happened with the revocation of the licensure remains a mystery. I don't know that we're ever going to find out, but we're trying.

Sustained efforts were made by the Cancer Research Institute, under the leadership of Helen Coley Nauts — you know, the Cancer Research Institute still raises millions for Sloan-Kettering every year — to attract a corporate developer to bring the vaccine back. So these are just the cites: Barbara Johnston did two trials, and then JJ Chandler led trials, these were in the sixties; however, in the sixties, especially 1965, a well-known fund-raising outfit by the name of the American Cancer Society bell-weathered an industry-wide propaganda campaign. And this is what it looked like.

This was published in *Cancer — A Cancer Journal for Clinicians* — a so-called journal. Grabstaldt — I have no idea who Grabstaldt is, or where Grabstaldt's expertise came from. But this is the nature of the propaganda:

After careful study of the literature — meaning he didn't read it — and other information available to it, and in view of the length of time which these toxins have been under investigation without any scientifically acceptable favorable reports, the American Cancer Society has found no evidence that treatment with Coley's mixed toxins results in any objective benefit in the treatment of cancer in human beings.

Those people, the Lasker Foundation, those were the enemies of the truth. They were the friends of a couple of fat cats in the good ol' boys network of industry. The problem persists today, as you well know.

So despite the atmosphere investigators kept publishing. 1969 saw Chandler looking at the treatment of breast cancer with chemotherapy and Coley's combined.

Sustained efforts were made by the Cancer Research Institute, under the leadership of Helen Coley Nauts, to attract a corporate developer to bring the vaccine back

- Johnston BJ. Clinical effect of Coley's toxin. I. A controlled study. *Cancer Chem Reports*. **1962**;21:43-68.
- Johnston BJ, Novales ET. Clinical effects of Coley's toxins. II. A seven-year study. *Cancer Chem Reports*. **1962**;21:43-68.
- Chandler JJ, Stark DB, Allen CV, Fletcher WS. Observations on the treatment of cancer by bacterial toxins. *Amer Surg*. **1965**;31:443-449.

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The environment for development was hostile. The American Cancer Society bellweathered an industry-wide propaganda campaign.



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Grabstaldt H. Unproven Methods of Cancer Treatment: Coley's Mixed Toxins. *Cancer: A Cancer Journal for Clinicians*. * 1965;15:139-140.

After careful study of the literature and other information available to it, and in view of the length of time which these toxins have been under investigation without any scientifically acceptable favorable reports, the American Cancer Society has found no evidence that treatment with Coley's mixed toxins results in any objective benefit in the treatment of cancer in human beings.

* An American Cancer Society "Journal"

Slide 37

Despite the atmosphere, investigators kept publishing

- Chandler JJ, Crisera RV, Fletcher WS. Coley's toxins and chemotherapy in treatment of breast carcinosarcoma: case report. *Amer Surg*. **1969**;35:377-383.

Slide 38

William Donald Regelson, who was a charming scholarly oncologist and professor from the Commonwealth University of Virginia, wrote an article called, *The 'Grand Conspiracy' Against the Cancer Cure* for the *JAMA* in 1980, and he cited three examples of errors made by the cancer establishment. He didn't think there was a conspiracy — there was, but he didn't think there was — and I'll cut him some slack. I was involved in a government process at the time that the Getzendanner decision of Wilk vs the AMA uncovered and explicated the conspiracy against cancer managements that were outside the industry picks. So, what did Bill have to say?

There is no question that inappropriate judgments have resulted in injury to good observations: if we look at Coley's toxin, a turn-of-the-century pyrogenic bacterial endotoxin anti-cancer treatment, we see a valid approach to nonspecific host resistance set back by being falsely labeled a 'quack remedy' by the American Cancer Society. The other two were Charles Lincoln and his bacteriophage, Staphage Lysate it was also called; and Max Gerson's dietary treatment for cancer. These were Dr. Regelson's observed victims of the American Cancer Society's industry-wide campaign against 'quackery.'

Oh, yes, and then there were more trials.

Axelrod in 1988, Kolmel in 1991... Tang and Zhao in 1991 — and Havas in 1993. And for none of this work was an appropriate response seen from a pharmaceutical giant. You know, that's the model since 1902, with the passage of the Pure Food and Drug Act; only giant corporations were allowed to be the developers of biologicals and vaccines. There was always one big winner; always one.

Regelson W. The 'Grand Conspiracy' Against the Cancer Cure. *JAMA* 1980;243(4):337-339.

There is no question that inappropriate judgments have resulted in injury to good observations: if we look at Coley's toxin, a turn-of-the-century pyrogenic bacterial endotoxin anti-cancer treatment, we see a valid approach to nonspecific host resistance set back by being falsely labeled a 'quack remedy' by the American Cancer Society.

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More trials were conducted

- Axelrod RS, Havas HF, Murasko DM, Bushness B, Guan CF. Effect of the mixed bacterial vaccine on the immune response of patients with non-small cell lung cancer and refractory malignancies. *Cancer*. 1988;61:2219-30.
- Kolmel KF, Vehmeyer K, et al. Treatment of Advanced Malignant Melanoma by a Pyrogenic Bacterial Lysate. A pilot study. *Onkologie* 1991;14:411-417.

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And more

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- Tang ZY, Zhao HY, Zhao G, et al. Preliminary result of mixed bacterial vaccine as adjuvant treatment of hepatocellular carcinoma. *Med Oncol Tumor Pharmacother*. 1991;8:23-28.
- Zhao You Tang, et al. Preliminary Result of Mixed Bacterial Vaccine as Adjuvant Treatment of Hepatocellular Carcinoma. *Med Oncol & Tumor Pharmacother* 1991;8(1):23-28.

etc.

- Havas HF, Axelrod RS, Burns MM, Murasko D, Goonewardene M. Clinical results and immunologic effects of a mixed bacterial vaccine in cancer patients. *Med Oncol Tumor Pharmacother*. 1993;10(4):145-58.

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Now, I took this from Bradley Coley Jr., Jr's. — I think the grandson's — website.

Following the tragedy of thalidomide in Europe in 1963, the Kefauver bill was passed enabling the Food and Drug Administration (FDA) to establish very stringent regulations regarding clinical trials of new drugs. Though the Coley toxins were 70 years old, the FDA ruled it was a new drug requiring special permits and endless red tape to use it clinically, hence all those who were using it stopped.

He was wrong. He was just flat out wrong, and I'll tell you why — and I'll tell you why I know it first. Christeene figured out how to follow FDA docket numbers in the Federal Register — they change, so it is a mind-bending exercise, to follow these dockets, but she followed them — and what she found was that, in the first place, historically, it was completely impossible for the FDA to have control over the vaccine in 1963, because all biologicals were controlled by NIH until 1972, when a payola scandal having to do with the awarding of one of them big vaccine contracts to somebody's buddy, resulted in Congress, in a fit of ire, pulling regulation of biologicals from NIH and plopping it right down into FDA — 1972, not 1963. And it's true that the Kefauver did have an effect on things being studied; it's true that there was controversy; but there was no clear evidence that this perspective is correct.

So here we have our little slide: *The real reason no corporate partner stepped up — according to results of a Sept. 2007 (ongoing) Freedom of Information Act inquiry into FDA by the Gerson Research Organization — that's my little "epi" group — All biologicals were overseen by NIH (chartered by Congress in 1934) until a conflict-of-interest scandal led Congress to transfer them en bloc to FDA in 1972. Beginning in 1972, FDA put existing biologicals on hold for 7 years; then, in 1979, it banned all Strep A products from interstate commerce, stating concerns about putative delayed toxic effects. — This could be caused by injecting it more than once. — The ban was not lifted until June of 2006. Because of this, progress ossified for more than 3 decades, right up to the present time.*

The ban occurred at a time when Eli Lilly and Co had developed a Strep-A intravenous vaccine for rheumatoid arthritis, an intractable condition that causes much suffering. And the early clinical outcomes were stellar, so much so, that when Commissioner Kennedy announced the ban, doctors and patients and family members swarmed FDA and begged for a hearing to keep the Lilly vaccine accessible, to which Commissioner Donald Kennedy replied, persons, such as yourselves have no standing to request a hearing, only an FDA-licensed corporation can request a hearing. How many libertarians in the bunch here? I thought so. I'm progressive myself, so I'm sympathetic.

This is like Citizens (United) in medicine. It's like, what do you mean people can't request a hearing from the FDA? But it was a fact. When the ban was lifted, the commentators from the modern FDA said, essentially, we don't know why they banned it, but we can say that now the technology exists to fully characterize the microbe and all its components and so there is no need for the ban to be continued. So, as of that time, it had been okay to attract a corporate sponsor, but the prime movers and shakers who had committed decades to trying to get this exhumed and revived, pretty much said screw it, I'm going home; I can't handle it anymore; I'm beating my head against the wall. So now it comes to yet another generation. Lloyd is twenty-five years my senior, he gave up. Helen died five years ago. So now it's our turn. I'm happy to say, it looks like the time might be right to actually get this stuff studied at intramurals in NIH with appropriate basic, translational, and clinical investigations running simultaneously. We'll see, we'll see. Don't hold me to it; but it is a possibility, and it hadn't been before.

COLEY TOXINS



<http://www.coleytoxins.com/1893.htm#top>

- Following the tragedy of thalidomide in Europe in 1963, the Kefauver bill was passed enabling the Food and Drug Administration (FDA) to establish very stringent regulations regarding clinical trials of new drugs. Though the Coley toxins were 70 years old, the FDA ruled it was a new drug requiring special permits and endless red tape to use it clinically, hence all those who were using it stopped.

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The real reason no corporate partner stepped up — according to results of a Sept. 2007 (ongoing) Freedom of Information Act inquiry into FDA by the Gerson Research Organization

- All biologicals were overseen by NIH (chartered by Congress in 1934) until a conflict-of-interest scandal led Congress to transfer them *en bloc* to FDA in 1972.
- Beginning in 1972, FDA put existing biologicals on hold for 7 years; then, in 1979, it banned all Strep A products from interstate commerce, stating concerns about putative delayed toxic effects.
- The ban was not lifted until June, 2006. Because of this, progress ossified for more than 3 decades, right up to the present time.

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So, to conclude this segment and take a lunch break — As Prof. Hoption-Cann concluded his article:

Modern approaches to treatment have reduced the occurrence of spontaneous regressions. Aseptic techniques and antibiotics significantly reduce postoperative infections, while chemotherapy and radiation impair immune activation even when an infection does occur.

We are about to embark on a period of time during which we may see the liberation or the un-jailing of the immune system from the biomedicine research paradigm and returned to its rightful place at the center ring. Enjoy your lunch. See you in about an hour.

Hoption-Cann. *Medical Hypothesis* (2002) 58(2):115-119.

Modern approaches to treatment have reduced the occurrence of spontaneous regressions. Aseptic techniques and antibiotics significantly reduce postoperative infections, while chemotherapy and radiation impair immune activation even when an infection does occur.

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PART II

All right, I think we're ready to go here. This next module — I think I'm supposed to go for an hour this time, right, and then we're going to take a stretch break, and then another couple? This module is a little walk through the past in between Coley and now. I am a Gerson scholar, and because of that, I'm a scholar of the golden age of German medicine. And most of us now don't read medical German, but if you're eighty years old and a researcher, you still know medical German, because you had to back then, because what was happening in Germany, their medical education system, was so much superior to what was happening in the United States, that you had to go to Germany to perfect your training; you had to do it.

So, we're going to look briefly at Gerson: *A brief historical review of (Gerson's dietotherapy's) acceptance and a set of general measures useful in the treatment of tuberculosis and its cross-over application to the management of malignant disease.* And to start off with, I'd like to point out that Gerson was thoroughly vetted by the same people that vetted Coley, and the propaganda machine was in high dudgeon against him.

Council on Pharmacy and Chemistry of the American Medical Association reported in 1955, *The Council ended its statement on the Gerson treatment by saying, "There is no scientific evidence whatsoever to indicate that modifications in the dietary intake of food or other nutritional essentials are of any specific value in the control of cancer."*

(Academy members: Wow. Wow. Wow.)

I know.

(Academy members: (General laughter).)

It seems ludicrous to us now, it seems positively ridiculous, but these people were in control. They were the learned sages; they were the authorities. They had the pulpit and they could do quite a bit to change the mindset of the population. By the nineties, that had changed, and you see, for example, RK Chandra writing in *The American Journal of Clinical Nutrition* that *Nutrition is a critical determinant of immune responses and malnutrition the most common cause of immunodeficiency worldwide.*

Gerson's dietotherapy

A brief historical review of its acceptance as a set of general measures useful in the treatment of tuberculosis, and its crossover application to the management of malignant disease

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Council on Pharmacy and Chemistry of the American Medical Association In: Gagan V. The Gerson Cancer Treatment. Cancer Reports Section, National Cancer Institute, March 8, 1955.

The Council ended its statement on the Gerson treatment by saying, *"There is no scientific evidence whatsoever to indicate that modifications in the dietary intake of food or other nutritional essentials are of any specific value in the control of cancer."*

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— and of course, Robert Good was a pioneer in showing the world that nutritional repletion could have enormous effects on immunity, and that restriction of certain components, certain macronutrients, i.e., calories and protein, could be enormously beneficial to the functions of the immune system — *Protein-energy malnutrition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentrations, and cytokine production... Deficiency of single nutrients also results in altered immune responses: this is observed even when the deficiency state is relatively mild. Of the micro-nutrients, zinc; selenium; iron; copper; vitamins A, C, E, and B-6; and folic acid have important influences on immune responses. Overnutrition and obesity also reduce immunity.* Well, you all know this.

I am fond of reminiscing that when Dr. Good — you know, one of your colleagues here was involved with Dr. Good in Alexandria in his feeding experiments, when he was called to Egypt to consult. The first thing he wanted was he wanted immune profiles of the kids who were, you know, impoverished kids. They were energy and protein deficient; they were deprived. And there wasn't one single thing about their immune profiles that was correct, so it was impossible to vaccinate them, because they wouldn't make antibodies. So you had to set up a feeding program — that's what you were involved in, right? Setting up that feeding program and getting these kids on some well balanced nutrition.

And just remember, since the time of the Golden Age of German Medicine, we have had four positive food groups. We want people to eat whole vegetables, whole fruits, whole grains, and dairy, cultured dairy, you know; usually, of course now it has to be organic because otherwise it's a bacterial swill, but you know — you can just kill the bacteria by ultra pasteurization, you can kill the bacteria, but you don't get rid of it — so its sort of like an oral vaccine.

At any rate, the German's knew a lot about nutrition. A couple of months ago, I did a module on Gerson that began with a discussion of the 1926 unveiling of Sigwald Bommer's results in the treatment of lupus vulgaris which is cutaneous tuberculosis, in which it was clearly demonstrated that controlling the nutrition, feeding a lot of plants — a lot of plants — and restricting greasy, salty meat-based foods would result in the healing of previously refractory cases of cutaneous tuberculosis in even severely advanced cases. Seventy-five cases were demonstrated in 1926 at that particular symposium. So, there was a demonstration that was paid for by the Austrian and German federal governments and received a lot of attention. Gerson was a household name then in Germany and all of Europe and, in fact, in the United States. In fact, I grew up forty miles from Lincoln General Hospital in Nebraska, where Clarence Emerson wrote in the Nebraska State Medical Journal in an article called, *"Treatment of tuberculosis by altering metabolism through dietary management (Gerson-Sauerbruch-Herrmannsdorfer method),"*

That *It may be further stated that the "Munich diet" has become in the Lincoln General hospital almost the routine medical management of tuberculosis by members of the staff. Dr JM Mayhew, chief of staff and head of the Department of Internal Medicine, and others in that department report very favorably on it.*

Chandra RK. Nutrition and the immune system: an introduction. *Am J Clin Nutr.*1997;66:460S-463S

Nutrition is a critical determinant of immune responses and malnutrition the most common cause of immunodeficiency worldwide. Protein-energy malnutrition is associated with a significant impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobulin A antibody concentrations, and cytokine production.

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Chandra RK. 1997 (cont)

Deficiency of single nutrients also results in altered immune responses: this is observed even when the deficiency state is relatively mild. Of the micro-nutrients, zinc; selenium; iron; copper; vitamins A, C, E, and B-6; and folic acid have important influences on immune responses. Overnutrition and obesity also reduce immunity.

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Emerson C. "Treatment of tuberculosis by altering metabolism through dietary management (Gerson-Sauerbruch-Herrmannsdorfer method)." *Nebraska State Medical Journal.* 1929;14:10-107.

It may be further stated that the "Munich diet" has become in the Lincoln General hospital almost the routine medical management of tuberculosis by members of the staff. Dr JM Mayhew, chief of staff and head of the Department of Internal Medicine, and others in that department report very favorably on it.

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I would note that, you know, we like to think of tuberculosis as manageable, if you've got antibiotics and you've the public health people to follow and birdog the patients to make sure they are compliant with the antibiotics over a period of time; but if we fed them right — if we fed 'em right — it would take a lot less drugs — a lot less drugs. I'm not saying that antibiotics have no place; I'm just saying, boy, you know, trying to get there using only one of the tools in your tool box is sort of a silly exercise.

Edgar Mayer and IN Kugelmass — Edgar Mayer was sort of the *sine qua non* in tuberculosis in the United States — writing in *“Basic ‘vitamin’ feeding in tuberculosis” in the JAMA in 1929: My own experiences very largely agree with the evaluation of it made by the Hamburg Medical Congress that the diet is a distinct therapeutic advance as an aid generally effective in the treatment of lupus vulgaris and occasionally in bone and joint tuberculosis, and that its value in other forms, more particularly pulmonary tuberculosis, is yet to be determined. The leading authorities report favorable effects from this diet in the treatment of lupus vulgaris.*

Edgar Mayer was the founding director and chairman of the medical and scientific advisory board of the Will Rogers Hospital, and Isaac Newton Kugelmass, IN Kugelmass, was a professor of chemistry at Howard College.

AL Banyai was at the Lake Saranac Sanitorium in Wisconsin, and wrote in the *American Review of Tuberculosis: Favorable results were seen in 36% of our pulmonary cases. Gain in weight, decrease in cough, expectoration, temperature and pulse rate, improved appetite, and complete or partial abatement of subjective and objective symptoms were recorded. Considering the fact that 82% of our pulmonary cases had far advanced tuberculosis, with serious complications in many instances, we feel that the beneficial results found justify the further application of the Sauerbruch, Hermannsdorfer, Gerson diet in the treatment of tuberculosis.*

Sauerbruch, you may remember, Ferdinand Sauerbruch was the most famous and the richest surgeon in the world. He developed open-thoracic surgery, the surgery to let a lung rest from tuberculosis, in other words, pneumothorax, and he developed Sauerbruch's cabinet which was an antiseptic cabinet where the surgeon stood to perform open thoracic surgery. So, he's quite a guy, and he literally pulled Gerson out of obscurity. Gerson was practicing in Bielefeld which is one of those little country hamlets that you miss if you sneeze, you know, so it was very fortunate for Gerson that Sauerbruch brought him to Berlin, first to the Charité Hospital, then secured him an appointment as an adjunct professor at the University of Munich in the Department of Tuberculosis, where he was a trialist, an interventional trialist.

Erich Urbach was the grand dean of American dermatology, and he wrote a number of monographs. This first one in 1932, *“Skin Diseases and Nutrition: including the dermatoses of children”* — *Since both dietaries (Gerson, and Sauerbruch and Hermannsdorfer)* — I want to point out, Gerson was more strict, Sauerbruch and Hermannsdorfer said, “oh the poor patients should have a little animal protein,” right? So there was a divide, and the divide was along scientific investigatory

Mayer E, Kugelmass IN. “Basic ‘vitamin’ feeding in tuberculosis.” *JAMA*. 1929;93(24):1856-1862.

My own experiences very largely agree with the evaluation of it made by the Hamburg Medical Congress that the diet is a distinct therapeutic advance as an aid generally effective in the treatment of lupus vulgaris and occasionally in bone and joint tuberculosis, and that its value in other forms, more particularly pulmonary tuberculosis, is yet to be determined. The leading authorities report favorable effects from this diet in the treatment of lupus vulgaris.

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Banyai AL. “The dietary treatment of tuberculosis.” *Am Rev Tuberc*. 1931;23:546-575.

Favorable results were seen in 36% of our pulmonary cases. Gain in weight, decrease in cough, expectoration, temperature and pulse rate, improved appetite, and complete or partial abatement of subjective and objective symptoms were recorded. Considering the fact that 82% of our pulmonary cases had far advanced tuberculosis, with serious complications in many instances, we feel that the beneficial results found justify the further application of the Sauerbruch, Hermannsdorfer, Gerson diet in the treatment of tuberculosis.

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Urbach, E., *Skin Diseases and Nutrition: including the dermatoses of children*. Vienna; Wilhelm Maudrich; 1932: 186.

Since both dietaries (Gerson, and Sauerbruch and Hermannsdorfer) have successfully stood trial in the largest Austrian and German hospitals and institutions over a period of 6 years, it is safe to say that dietotherapy constitutes one of our best weapons in fighting cutaneous tuberculosis.

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rationales. We talk about the Gerson diet and the Sauerbruch-Herrmannsdorfer Diet — *have successfully stood trial in the largest Austrian and German hospitals* — and remember Austria and Germany are the Valhalla in investigative science at the time; the U.S. was not a player; Great Britain was in the shadow of Germany. In fact, ninety percent of all research initiatives came from Otto Warburg's laboratory at the Planck Institute — ninety percent of all biomedical research initiatives were coming from Warburg — *so the largest Austrian and German hospitals and institutions over a period of 6 years, it is safe to say that dietotherapy constitutes one of our best weapons in fighting cutaneous tuberculosis.*

And then we've got Goeckerman, William Henry Goeckerman, writing on the *Effect of a diet low in salt in cases of tuberculosis of the skin*. He's writing in the *Proceedings of the Staff Meetings of the Mayo Clinic* in 1932. You all know Mayo up in Rochester. *Although the last word on the (Gerson) diet as such, or on the mechanism by which it acts, probably has not been said, it must be conceded that good clinical results have been obtained.* Now, during his years at Mayo, William Henry Goeckerman innovated the treatment of psoriasis that this day bears his name. It is a coal tar and ultraviolet-B light treatment for psoriasis, and he became a clinical professor in dermatology at the University of Southern California. And I think his expertise was such that he was certainly qualified to comment on whether or not this was working.

Goeckerman WH. "Effect of a diet low in salt in cases of tuberculosis of the skin. *Proceedings of the Staff Meetings of the Mayo Clinic*. 1932;7(6):73-78.

Although the last word on the (Gerson) diet as such, or on the mechanism by which it acts, probably has not been said, it must be conceded that good clinical results have been obtained.

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Urbach again, in 1932, and I happen to love this particular quote: *"The treatment of tuberculosis of the skin has been immeasurably enriched by the dietetic methods of Gerson as well as Sauerbruch and Herrmannsdorfer. It is true that Struwe as long as 100 years ago, prescribed a salt-poor diet for the treatment of cutaneous tuberculosis and that H. Straub emphasized long ago the importance of chloride-poor nutrition for various diseases, but it is to Gerson's everlasting credit that he profited by a fortuitous observation to inaugurate the dietotherapy of tuberculosis of the skin and carefully studied the influence of a salt-restricted and vitamin-rich dietary on the clinical course of this disease."*

And now in 1946, with a summary, which I'll read really fast, here is Urbach just trying to drive home the point that this is established:

"(Gerson's) dietary therapy for cutaneous tuberculosis has been extensively tested and approved by the majority of authors (Jesionek, Jesionek and Bernhardt, Bommer, Volk, Wichmann, Jadassohn, Stuempke and Mohrmann, Brunsgaard, Scolari, Dundas-Grant, Stokes, and others). Particularly noteworthy are the investigations which Jacobson and Brill and Gawalowski carried out over a number of years on extensive material — That's what we used to call patients, extensive material. — The Russian authors treated 124 patients who were under observation for five years, while the Czechoslovak investigator followed 127 cases. Both groups showed marked improvement. Interesting, too, is the report submitted by Simon and Kaplanskaja which shows the necessity of adhering to the salt-poor diet for an adequate period of time.

Urbach, E., *Skin Diseases and Nutrition: Including the Dermatoses of Children*. Vienna; Wilhelm Maudrich; 1932: 183.

"The treatment of tuberculosis of the skin has been immeasurably enriched by the dietetic methods of Gerson as well as Sauerbruch and Herrmannsdorfer. It is true that Struwe as long as 100 years ago, prescribed a salt-poor diet for the treatment of cutaneous tuberculosis and that H. Straub emphasized long ago the importance of chloride-poor nutrition for various diseases, but it is to Gerson's everlasting credit that he profited by a fortuitous observation to inaugurate the dietotherapy of tuberculosis of the skin and carefully studied the influence of a salt-restricted and vitamin-rich dietary on the clinical course of this disease."

Slide 55

Slide 56

Urbach, Erich and LeWinn, Edward. *Skin Diseases, Nutrition and Metabolism*. New York; Grune&Stratton; 1946:530-537.

(Gerson's) dietary therapy for cutaneous tuberculosis has been extensively tested and approved by the majority of authors (Jesionek, Jesionek and Bernhardt, Bommer, Volk, Wichmann, Jadassohn, Stuempke and Mohrmann, Brunsgaard, Scolari, Dundas-Grant, Stokes, and others). Particularly noteworthy are the investigations which Jacobson and Brill and Gawalowski carried out over a number of years on extensive material. The Russian authors treated 124 patients who were under observation for five years, while the Czechoslovak investigator followed 127 cases. Both groups showed marked improvement. Interesting, too, is the report submitted by Simon and Kaplanskaja which shows the necessity of adhering to the salt-poor diet for an adequate period of time.

So much for the history; now to visit a quote by Patricia Spain Ward, the late Patricia Spain Ward, who was campus historian for the University of Illinois at Chicago, the schools of Dentistry, Medicine and Nursing. She was contracted by the Office of Technology Assessment. It is a deceased, former watchdog agency that was killed by the Gingrich revolution. It was mothballed because, frankly, it was doing very, very good work, and it was responsible for a lot of pro-health regulatory actions taken by Congress. Dr. Ward read the record and this is the opening sentence of her contract report for the OTA on Gerson: *It is one of the least edifying facts of recent American medical history that the profession's leadership so long rejected as quackish the idea that nutrition affects health... A scholar's scholar and a superlative observer of clinical phenomena, Gerson was a product of the German medical education which Americans in the late 19th and early 20th centuries considered so superior to our own that all who could afford it went to Germany to perfect their training.*

You know, Gerson got into trouble because in 1945, he was asked by then-Senator Claude Pepper to give testimony on a bill that Senator Pepper's Subcommittee on Foreign Relations had aimed at providing \$100 million for an international clearinghouse of cancer research. So Gerson was definitely not an insider to that; he was part of the dog-and-pony show. But he was very obliging; he brought with him a number of patients and a number of abstracted cases, and the patients took the witness stand, one after another. One that was particularly impressive was a paraplegic — formerly paraplegic — girl by the name of Alice Hirsch, who had been operated for an intradural glioblastoma and who had gone into remission under Gerson's care, and who walked to the witness stand and carefully explained who she was and where she had been treated; and then Gerson explained the details of the case as it was treated at Beth Israel Hospital in Newark. Gerson made some mistakes, and within several months of his testimony at the hearings, angry editorials appeared in the pages of the *JAMA* in the absolutely unmistakable style of Morris Fishbein, the former long-time editor and bulldog for the AMA. Professor Eli Seifter got up in front the American Chemical Society in 1985, and spoke on Gerson's behalf and explained that what Gerson did wrong, what caused him to be ridiculed by the United States Public Health Service and the American Cancer Society, was that he thought that people could influence their health by changing their diets, and that he recommended more vegetables and more fruits, cut the salt, cut the fat, cut the meat, lower their alcohol consumption and stop smoking.

Dr. Ward explained to us that it was, in fact, the smoking critique that Gerson gave that resulted in the editorials in the *JAMA*. Because the *JAMA* — in 1926, Fishbein, when he was ascendant to his role as editor of the *JAMA* and voice of American medicine — Fishbein had gone to Phillip Morris, and had proposed that they change their rabbit dermatological testing with cigarette challenges, that they cure the tobaccos with ethylene glycol rather than glucose, because the smoke was certain to be less irritating to rabbit skin. And if they would do this, and publish the results, then the American Medical Association would publish full-page, four-color advertisements in the *JAMA* for cigarettes. You can still find them, just go to the old annex and look at the old journals, and they're there. And the AMA then would provide speaker's bureaus to go to the PTA, to go to the Chamber of Commerce, to whomever, to explain why cigarettes of this brand or that brand were good for you, and that was the time during which the war of the physicians pimping cigarettes occurred where, you know, you were told that if Pall Malls bother your throat, switch to Chesterfields, because your otolaryngologist tells you they're toasted and milder.

Dr. Patricia Spain Ward, "History of the Gerson therapy" contracted for "Unconventional Cancer Treatments." OTA-H-405, Sept. 1990.

It is one of the least edifying facts of recent American medical history that the profession's leadership so long rejected as quackish the idea that nutrition affects health.

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Ward PS. 1990 (cont)

A scholar's scholar and a superlative observer of clinical phenomena, Gerson was a product of the German medical education which Americans in the late 19th and early 20th centuries considered so superior to our own that all who could afford it went to Germany to perfect their training.

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(Christeene: You should show it.)

I should show it, do I have it here?

(Christeene: I think it's on your desk top.)

Let me see if I can improvise with this. I may be able to do that.

(Christeene: How many of you have seen this? How many of you haven't seen what I'm talking about?)

(Academy member: You mean the doctor relaxing at the end of the day one?)

(Christeene: Uh huh.)

No, its not in power point so I can't make it show.

(Christeene: Oh. Go on the Google on cigarettes — its on Youtube. It's worth such a good laugh.)

It's embarrassing, isn't it, that the people who had the professorships and who trained you did that kind of stuff? But they did. Here we go.

A colleague and friend, Pete Lechner — I copublished with him — had an extraordinary opportunity. He was sent over to study with the Mexican doctors at a time when the Gerson Research Organization was still part of the Gerson Institute, before we made it an epidemiology group, and when everyone was cohesive at one hospital. Lechner's CEO sent him over. The CEO's aunt had chided him about not taking Gerson's work seriously, and now there was an opportunity to look at, clinically, a little group in Mexico was doing it, and he should just send somebody to study it. So Pete got the charge. He came over and studied it, and he was so taken by the results he had seen, including rapid, complete clearing of opaque lungs on X-ray — it was a woman named Pansy Hannides — and Peter had driven her to the x-ray exam and driven her back to the facility himself. He took all this stuff back, and he pitched having an expanded laboratory, beds, an ambulance, and outpatient facility, and at the end of six years of adjuvant diet therapy in conjunction with surgical oncology, this is what he came to report.

These were his definitive findings: *Tumor cachexia was prevented or delayed. Fewer post-operative complications/infections occurred. Lessor side effects when radiation and chemotherapy were used. Significantly less analgesics/psychotropic drugs than controls. Good psychological state. Slower progression of existing liver metastases. Less marked occurrence of malignant effusions* — and as he said at that time and it still holds true: *"These results encourage us to continue and, within our possibilities, to intensify the use of dietary therapy measures, and we are seeking cooperation with all those who are experienced in this — at present still highly controversial — area of work."* He didn't get any nibbles, you know, because you can't blister pack a coffee enema; there's no way to mass produce this stuff.

Lechner P, Kronenberger I. "Experiences with the use of dietary therapy in surgical oncology."
Aktuelle Ernährungsmedizin. 1990;2(15).

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"After nearly six years of using adjuvant dietary therapy in conjunction with surgical oncology, we are able to report the following preliminary results:

- Tumor cachexia prevented or delayed.
- Fewer post-operative complications/infections.
- Lessor side effects of radiation and chemotherapy.
- Significantly less analgesics/psychotropic drugs than controls.
- Good psychological state.
- Slower progression of existing liver metastases.
- Less marked occurrence of malignant effusions.

These results encourage us to continue and, within our possibilities, to intensify the use of dietary therapy measures, and we are seeking cooperation with all those who are experienced in this — at present still highly controversial — area of work."

What we did — the findings that we published and that we presented at the POMES Conference at NIH, a methodology conference in which I was opposite Ernst Wynder, which was a great honor for me, since he had published his findings on cigarette smoke and cancer the year I was born; it was really quite something. — At any rate, we found that none of the Gerson patients died of stage I or II melanoma, and that in stage IIIA, where you have small early lymphatic metastases, there was an 82% five-year survivorship. In stage IIIA and B cumulative, there was a 70% five year survivorship, and even with the disease skipping from one quadrant to another in early IVA — Stage IVA we invented; all that we're saying is it's not visceral yet. IVA, we proposed, was a way of describing the disease jumping from one quadrant to another, but not leaving the skin and the lymphatics for internal structures. But even at that you had a 39% five year survivorship which is an extraordinary number; something that should have been noted.

And then we published in the *Journal of Naturopathic Medicine*, because we knew this would largely be an audience for Gerson's work, the role of surgery in diet therapy. And what we demonstrated was that, in patients who were willing to have their disease debulked surgically, that eleven out of twelve IIIA, and eight out of ten IIIB patients, and four out of seven IVA patients were alive and disease free at the five year window; meaning that it doesn't hurt if you can reduce the bulk of the disease — it certainly doesn't hurt to do that.

We also demonstrated that in Duke's C colorectal cancer that, if the patients were operated, you had a 64% five-year survivorship out of eleven patients. Admittedly, if we wanted to do statistical significance, we'd have to have forty-five patients in the series; but, you know, if you're not a stickler for statistical significance, you can see clinical significance when it happens; this is clinical significance.

I think the ovarian findings speak for themselves. There were twenty-one stage III patients in the diet therapy cohort, but thirteen of them had had chemotherapy following their surgeries, one of them dropped out — in other words, lost to follow up — and the other twelve are deceased. But of eight who refused chemotherapy following surgery and used diet therapy instead, although two are deceased and one is lost to follow up, five are alive and well, and we're looking at fifteen and a half to thirty-two and a half years at the time that I presented this, last November I think it was.

Hildenbrand *et al.* Five-year survival rates of melanoma patients treated by diet therapy after the manner of Gerson: a retrospective review. *Alt Ther Health Med.* 1995;1(4):29-37.

100% n = 14 Stage I and II patients (local disease)
Balch reported 82% in a meta-analysis *Semin Surg Oncol* 1992;8:400-414. Gerson sample too small for significance
82% n = 17 Stage IIIA patients (early lymph mets)
ACS reported 39% of 103 Cancer. 1993;71:1239-46.
Significant. Chi-square 9.48, 1df, p=.002, power=.887
70% n = 33 Stage IIIA/B (early to late lymph mets)
ACS (cited above) reported 41% of 134 alive at 5 years.
Significant. Chi-square 7.62, 1df, P<.006, power=.802
39% n=18 Stage IVA (distant skin + lymph mets)
ECOG reported 6% of 194 Cancer. 1993;71:2995-3005.
Significant. Chi-square 19.3, 1df, P<.0001, power=.997

Slide 60

Surgery & diet in prevention of recurrence

Hildenbrand *et al.* "The role of follow-up and retrospective data analysis in alternative cancer management: the Gerson experience. *J Naturopath Med.* 1996: In Press.

n = 49 combined Stage IIIA, IIIB + IVA melanoma
75% n = 32 operated patients alive at 5 years
35% n = 17 patients who avoided surgery
Significant. Fisher Exact Test, P = 0.013

11 of 12 (92%) operated IIIA alive at 5 yrs
8 of 10 (80%) operated IIIB alive at 5 yrs
4 of 7 (57%) operated IVA alive at 5 yrs

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PREVENTION OF RECURRENCE 5-year survival rates of Duke's C colorectal cancer

- Moertel *et al* [*Ann Intern Med* 1995;122(5):321-6] report 60% n = 304 operated-to-cure patients alive at 5 years with 5FU plus Levamisole (compared to 47% of 315 controls).
- Records of the Gerson facilities reveal 64% n = 11 operated-to-cure patients alive at 5 years with dietotherapy.

While the above rates are similar, the Gerson sample size would have to be at least 45 patients with the same percentage of survivors to achieve statistical significance. Only prospective data collection can establish the validity of this early trend in the data.

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Retrospective survival assessment of women with FIGO stage III ovarian cancer who used dietotherapy instead of chemotherapy following optimal surgical debulking

n = 21 stage III patients were in the dietotherapy cohort
5 (24%) of 21 have lived >5 years disease free
5-10% 5-year survival rates are the norm in standard oncology; *Practical Oncology*, 1994;Lange:352.
n=13 (62%) of the above 21 were treated postsurgically with chemotherapy.
– 12 (92%) are known deceased, 1 dropped out
n = 8 (38%) refused chemotherapy and instead began dietotherapy immediately after surgery. This is a distinct subpopulation, of which 2 are deceased, 1 is lost to follow-up and
5 (63%) of 8 are alive & well at 15½ to 32½ years

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And a quick look at the Hodgkin's cohort, or the non-Hodgkin's, I'm sorry, non-Hodgkin's lymphoma cohort, what we did was we threw these into the Working Group Formula, so we had low grade, intermediate grade, and high grade, and you can see there that these are assessable charts documenting only complete regressions with dietotherapy as sole influence, right? So, this is a pretty impressive little collection. What it suggests is that it can be replicated; and some of these patients had massive disease.

Now, to quote from my teacher, Freeman Widener Cope, who was known as the father of supramolecular biology, and the author and editor of the *Journal of Physiology Chemistry and Physics and Medical Magnetic Resonance Imaging*, writing an article in 1978 called *A medical application of the Ling Association-Induction Hypothesis: the high potassium, low sodium diet of the Gerson cancer therapy: From the nature of the measures that gave good results, and from the laboratory medical science available at that time, Gerson attempted to deduce the reasons why his therapy was effective in curing cancer. His deductions led to some unconventional ideas regarding the nature of human cancer and the mechanisms of therapy. Some of his hypotheses were vaguely stated and incompletely validated, but they are of great importance because they imply that those approaches to cancer therapy that will be effective are mostly different from those now used.* Freeman was a great man and a great teacher.

We have to visit — one more time — we have to visit William Donald Regelson with his comment in the *Journal of the American Medical Association* on Gerson, *We may shortly have to ask if Gerson's low-sodium diet, with its bizarre coffee enemas and thyroid supplementation, was an approach that altered the mitotic regulating effect of intracellular sodium for occasional clinical validity in those patients with the stamina to survive it. Was the Establishment correct in turning its back on these programs?* I would point out that he was referring to the work of Clarence and Virginia Cone in a series of experiments, elegant experiments, published in the *Annals of New York Academy of Sciences*, in which the Cones came to the conclusion that sodium is the malignant mitotic trigger — the malignant mitotic trigger — and they demonstrated meticulously that raising the potassium gradient in extracellular fluid would cause partial differentiation of malignant cells, and that raising the sodium in the extracellular fluid would cause sudden recovery of mitotic function and endless mitosis.

I would also comment on Regelson's comment on coffee enemas. When a scientist like Bill Regelson says that something is bizarre, that means he's very interested; and he confided in me that he thought that the coffee enema was probably the most intelligent thing that Gerson had contributed. And he explained in terms of veterinary pathology — I didn't know anything about it — he said, you know the name Visik — V-I-S-I-K — and I said, no. He said, "Well that's the school of ammonia-pathophysiology. It was Visik who proposed the antibiosing of feedlot animals to increase carcass weight gain during grain feeding in the stock yards." He said the problem with grain feeding, when you push the grains, is that you create gut dysbiosis, and when you do that you get an acid environment, such an acid environment, that you're breeding acid-fast E coli.

Non Hodgkin's Lymphoma

On a first pass through the diet-treated cohort, 13 of the assessable charts documented complete regressions of adult non-Hodgkins lymphoma with dietotherapy as sole therapeutic influence

2 low grade

1A- 17 years; 1C - 8 years

7 intermediate grade

3D - 8 years, 13 years, 45 years

2E - 7 years, 4 years

2F - 9 years, 5 years

2 high grade

2H - 10 years, 5 years

2 histology pending review

7 years, 17 years

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Cope FW. A medical application of the Ling Association-Induction Hypothesis: the high potassium, low sodium diet of the Gerson cancer therapy.

Physiol Chem Phys Med MRI. 1978;10(5):465-468.

From the nature of the measures that gave good results, and from the laboratory medical science available at that time, Gerson attempted to deduce the reasons why his therapy was effective in curing cancer. His deductions led to some unconventional ideas regarding the nature of human cancer and the mechanisms of therapy. Some of his hypotheses were vaguely stated and incompletely validated, but they are of great importance because they imply that those approaches to cancer therapy that will be effective are mostly different from those now used.

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Regelson WD, "The conspiracy against the cancer cure." *JAMA* 1980;234(4).

We may shortly have to ask if Gerson's low-sodium diet, with its bizarre coffee enemas and thyroid supplementation, was an approach that altered the mitotic regulating effect of intracellular sodium for occasional clinical validity in those patients with the stamina to survive it. Was the Establishment correct in turning its back on these programs?

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So, when you read about Burger King killing people, it's because of the antibiotics in the grain feeding and the breeding of acid-fast E coli that can survive the acid bath of the human stomach and go on down and set up housekeeping in the small gut and the colon. And, after explaining this to me, and making the logical connection between Gerson's really high-carb feeding, which was augmented, of course, with juices, which are sweet, and suggesting that, yes, you need to manage that in the human, and the coffee enema was a way to do that — the way that Gerson managed that in order to hyperalimint his patients with phytochemicals — he said, regarding the feedlot animals, that you could have gotten the same results, instead of using antibiotics, by using coffee enemas in the cattle, but you never would have gotten the stock yard managers to comply with that.

All right, we'll go through this next little section and then we'll take a leg stretch before we get into the meat of why we are here, which is the Danger model, which ties everything together; the tissue controlled immune system. That will be a little bit more — it's not going to be 101-level, it is going to be 8000 level — you'll like it.

Moving on, one of my favorite stories to recount is the story of Bill Allaben and Kevin Keenan working for the FDA to try to establish the nature of laboratory feeding. This is the story that came out in 1995 — we are fifteen years out on this.

San Jose — The nation's lab rats are eating themselves into oblivion. Locked into their cages with bottomless bowls of chow, the rodents have nothing to do but snack. In some cases, they become so fat and sickly that it's hard to interpret the results of studies that are designed to tell whether a chemical is deadly or safe, say researchers for the federal Food and Drug Administration (FDA). The situation is so grave that the FDA will soon suggest that scientists cut back on feeding the animals to keep them healthy. — Now I would note that this is happening at FDA — for the rats — but not for the general population of humans, all right, and I think that is just ironic.

Bill Allaben said, *"They're just blobs of fat with legs"* — of these rats. And you will note that Bill is a toxicologist with the National Center for Toxicological Research at Food and Drug.

And Kevin Keenan said, *"It was a joke in our laboratory — although not a very funny one — that the most toxic substance we've tested... over the past 20 years was the food"* — Kevin is at Merck.

Under normal circumstances, — most rats and mice live a little more than two years. But in some two-year studies, so few animals were left alive that Merck came close to having the results rejected by the FDA — jeopardizing years of work that cost \$2 million to \$3 million. Sometimes, the rats exposed to a dangerous chemical fared even better than their untreated cousins, Keenan said. Apparently the chemical ruined their appetites, which kept them slim and healthy

Fat Rats

— *San Diego Union-Tribune*, Nov. 8, 1995

San Jose — The nation's lab rats are eating themselves into oblivion. Locked into their cages with bottomless bowls of chow, the rodents have nothing to do but snack. In some cases, they become so fat and sickly that it's hard to interpret the results of studies that are designed to tell whether a chemical is deadly or safe, say researchers for the federal Food and Drug Administration (FDA). The situation is so grave that the FDA will soon suggest that scientists cut back on feeding the animals to keep them healthy.

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Fat Rats (cont)

"They're just blobs of fat with legs."

— **William Allaben**, toxicologist

National Center for Toxicological Research
US Food and Drug Administration

Slide 68

Fat Rats (cont)

"It was a joke in our laboratory — although not a very funny one — that the most toxic substance we've tested...over the past 20 years was the food."

— **Kevin Keenan**, veterinary pathologist
Merck Research Laboratories

Slide 69

Fat Rats (cont)

Under normal circumstances, most rats and mice live a little more than two years. But in some two-year studies, so few animals were left alive that Merck came close to having the results rejected by the FDA — jeopardizing years of work that cost \$2 million to \$3 million. Sometimes, the rats exposed to a dangerous chemical fared even better than their untreated cousins, Keenan said. Apparently the chemical ruined their appetites, which kept them slim and healthy enough to counter the ill effects of the chemical.

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enough to counter the ill effects of the chemical. You never have to make it up, right? There's no future in fiction.

Scientists who study aging and nutrition have known for years that animals live longer when their diets are cut back by a moderate amount. It works in rats, fruit flies and worms, and there are indications it may work in people, too.

Bill Allaben again, *A lab rat that's allowed to eat its fill tends to have rough hair, it's yellowish in color, it has horrible-looking teeth, it just looks horrible by the time it reaches middle age.* Think about your last high school reunion and what you saw. How many of you are over sixty? You know what happens after sixty in people that don't pay attention. *In contrast, a rat on a restricted diet looks young, healthy, slim, shiny, more active.*

And finally, Keenan again, *If you want to live a long time, you will do that by simply moderating your food intake.*

Now, to the very graphic examples of Dick Weindruch's rhesus monkeys; if you haven't seen them, welcome to the real world.

Canto is twenty-seven; Owen is twenty-nine. Canto is restricted, meaning Canto is fed what Canto's body can metabolize in the way of calories. Owen is ad libitum, meaning Owen eats more than he can burn. You'll note right away that Canto, Christeene said I should use one of these things (*holding laser pointer*) — look it's a little red dot, isn't that great? Canto is animated. He's up because the photographer is out there and he's looking; he's like, "What are you doing here?" But Owen is just like dazed and confused, I think you would call it.

Fat Rats (cont)

Scientists who study aging and nutrition have known for years that animals live longer when their diets are cut back by a moderate amount. It works in rats, fruit flies and worms, and there are indications it may work in people, too.

Slide 71

Fat Rats (cont)

"A lab rat that's allowed to eat its fill tends to have rough hair, it's yellowish in color, it has horrible-looking teeth, it just looks horrible by the time it reaches middle age. In contrast, a rat on a restricted diet looks young, healthy, slim, shiny, more active."

— William Allaben, toxicologist
National Center for Toxicological Research
US Food and Drug Administration

Slide 72

Fat Rats (cont)

"If you want to live a long time, you will do that by simply moderating your food intake."

— Kevin Keenan, veterinary pathologist
Merck Research Laboratories

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Dick Weindruch's rhesus monkeys

<http://www.news.wisc.edu/newsphotos/monkeyDiet09.html>

Canto, 27

May 28, 2009

Owen, 29



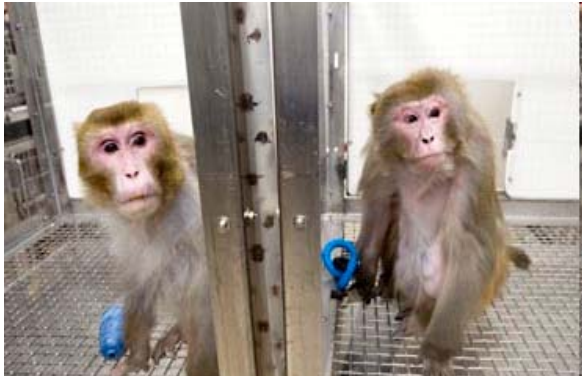
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Dick Weindruch's rhesus monkeys
<http://www.news.wisc.edu/newsphotos/monkeyDiet09.html>
Canto, 27 May 28, 2009 Owen, 29



Slide 75

Dick Weindruch's rhesus monkeys
<http://www.news.wisc.edu/newsphotos/monkeyDiet09.html>
Canto, 27 May 28, 2009 Owen, 29



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And you see it again. There's Canto; he can't sit still. Owen's got the camera in his eyes, but he just sort of doesn't care, but Canto is up — he's just there. He's so engaged and involved. They are almost exactly the same physiologic age, but as Indiana Jones once quipped, "It ain't the years, it's the mileage." And if you want to do mileage, overfeed yourself, right? As Denham Harman said, we don't so much age as rust — we oxidize.

And now for the gross truth, we're going to look at these slides. We're putting Canto's — I just took this from the source — Canto's brain is going to be on your right now, so we're going to look at the young monkey's brain, it's going to be over here. There it is. Look at the difference between the restricted monkey's grey matter and the fluid, and the poor *ad libitum* monkey's grey matter in atrophy — in wretched atrophy. This is what we don't want to have happen to us, because we use our brains to earn our paychecks, right? So this is what makes you want to learn that first, most vital form of exercise at the dinner table, the *push-off*, the *stop-eating-before-you're-satisfied*. And remember, that if you're metabolically of a thin body habitus, that is no guarantee against the ravages of this type of tissue depletion, because cellular senescence doesn't care whether your belly is big or small. If you are overfeeding, you will accelerate the destruction of your telomeres — you're going to fall apart at the level of the genome, and your cells are not going to stay alive, they're going to *not* replace. So, do yourselves a favor, practice what you preach, be Canto not Owen.

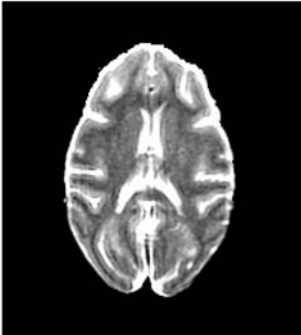
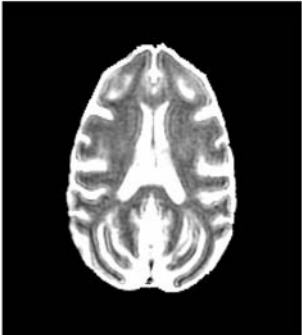
Dick Weindruch's rhesus monkeys
<http://www.news.wisc.edu/newsphotos/monkeyDiet09.html>
Canto, 27 May 28, 2009 Owen, 29



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Their brains

Owen, 29 May 28, 2009 Canto, 27
(ad libitum feeding) (calorie-restricted)



Brain scan of control animal on an unrestricted diet Brain scan of animal on a restricted calorie diet

Lost grey matter, increased fluid Maintenance of grey Slide 78

And now a little interlude, this is something that was shot on that little camera that Christeene is filming with right now, and edited in this (MacBook Pro), and it was a love letter to Tom Harkin — more about that after the break, when we come back here. We want these therapies to be put back where they belong, so we asked some patients to talk to the senator, who now has Ted Kennedy's chair in the Senate Health Committee, the most powerful man in Washington right now regarding health, and our friend, believe me. Senator Harkin is our friend. You're going to like this guy, if you get up close to him; it's hard to.

(FILM)

All right, let's take a stretch.

PART III

The Danger Model is, in the sense of Thomas Kuhn's (*Structure of Scientific Revolutions*), the new paradigm, and it really helps us in so many ways, as we confront the issue of malignant disease, to know how our immune systems work. So, let me again adhere to the Pauling principal and speak the words that are on the screen: *The picture of a tissue-controlled immune system is emerging, which subsumes and contextualizes both the old self-non-self model (SNF) and the more recent pattern-recognition-receptor model (PRR). The Danger model was created by Polly Matzinger, Chief, Senior Investigator, of the T-Cell Tolerance and Memory Section (also called The Ghost Lab), of the Laboratory of Cellular and Molecular Immunology of the National Institute of Allergy and Infectious Diseases.*

It's called the Ghost Lab because Polly, who is an iconic, eccentric, and brilliantly gifted scientist, was given the assignment as the senior investigator and chief of this laboratory, but she was interested in possible applications of string theory to human pathophysiology, and didn't show up at the lab for the first nine months; hence the name, Ghost Lab. We visited Polly, Monday, on the way here.

And that's what she looks like. That's what the most brilliant immunologist on the planet looks like; the guy next to her is her disciple. Isn't she? She's remarkable. When you talk with her its all sheep dogs and sheep — and I'm not kidding. She raises sheep. When I called her to get together with her, she said, "What time on Monday?" I said, "I don't know, eleven?" She said, "That's hard for me; I have to worm my sheep." One night, Polly was listening to the sounds of nighttime, and her sheep began to make sounds of distress. And then her sheep dog, Annie, began to bark anxiously, and she had an insight that would become the Danger model. The sheep were the tissue, and the tissue was calling for help. The sheep dog was a dendritic cell, an antigen-presenting cell. And I asked Polly, "Does that make you the lymphocyte?" And she thought about it, and she thought first maybe somebody with a gun, but then she said, "Well...but I don't have any guns and, I guess maybe I am the lymphocyte."

The Danger model

The picture of a tissue-controlled immune system is emerging, which subsumes and contextualizes both the old *self-non-self model* (SNF) and the more recent *pattern-recognition receptor model* (PRR).

The Danger model was created by **Polly Matzinger**, Chief, Senior Investigator, T-Cell Tolerance and Memory Section (The Ghost Lab), Laboratory of Cellular and Molecular Immunology, National Institute of Allergy and Infectious Diseases.

<http://www3.niaid.nih.gov/labs/aboutlabs/lcmi/tCellToleranceMemorySection/matzinger.htm>

Polly Matzinger (and disciple)



Dr. Palazon, writing in *Inmunologia* in 2008, wrote about Polly Matzinger's "danger model" — *[it] finds its predicted danger-denoting self moieties. The beauty of a theory is that it stands as an attempt to explain diverse experimental observations and makes some testable predictions. In the danger theory its simplicity deserves admiration. Still, it clashes with previous theories and psychological resistance to change. Most of us are very fond of what we learn in textbooks and therefore reluctant to abandon old paradigms. After all, we all were trained with the "mantras" of self/non-self discrimination.*

That and the fact that Charlie Janeway is so cool. That's the guy who invented the self-not-self paradigm of immunity. So it's hard to resist a guy like Charlie Janeway. I'm sorry the visual translation, here, isn't quite right — Charlie's hat is vivid red, and his shirt is patched with red as well; and you can't really see that with the way this slide is played out.

So, let's look at Polly Matzinger's central concept. *Friendly and dangerous signals: Is the tissue in control?* — This is from *Nature Immunology* in 2007: *In their own defense, tissues send a panoply of signals that initiate immunity and guide the choice of effector class. T_H1 - T_H2 and T_{reg} is far too simple a representation of the breathtaking variety of the resulting responses.* Each tissue can command its own form of immunity. As we were discussing this, Polly said she had a paper in for peer review at *Nature Reviews Immunology*, and that it's about the types of tissue, and the types of immunities they request. For example, the gut would never want a T-cell-mediated immune response in it. It would just be horrendous, and it could lead to bleeding, inflammatory — colitis types of diseases — inflammatory diseases. The brain could never tolerate a T-cell-mediated immune response. These tissues want immune globulins, and they ask for them, and they receive them. This is totally different from the self-not-self model, in which a circulating army of T lymphocytes and B lymphocytes and B- and T-memory cells look for things that are not self. That's the old model. The new model is, they are not circulating looking for anything, not really. The tissue is going to do the talking.

What causes an immune response? In the self-not-self model, a foreign threat is seen by the T cells and the B cells. In the pattern-recognition-receptor model, viral or bacterial pathogen-associated molecular patterns, PAMPs, are recognized, again by T and B cells. In the danger model, damage-associated molecular patterns, or DAMPs, are recognized first by antigen-presenting cells that have costimulatory capabilities to make lymphocytes into effector cells.

There are danger molecules or danger signals that are universal to life. *Hydrophobic portions (Hyppos) of molecules which hold membranes together, shape complex proteins, and originate from bacteria* — these are a key danger signal — *Possibly all molecules that bind*

Palazon A, et al. Polly Matzinger's "danger model" finds its predicted danger-denoting self moieties. *Inmunologia*. 2008;27(4):205-211

The beauty of a theory is that it stands as an attempt to explain diverse experimental observations and makes some testable predictions. In the danger theory its simplicity deserves admiration. Still, it clashes with previous theories and psychological resistance to change. Most of us are very fond of what we learn in textbooks and therefore reluctant to abandon old paradigms. After all, we all were trained with the "mantras" of self/non-self discrimination.

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Charlie Janeway



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Matzinger, P. Friendly and dangerous signals: is the tissue in control? *Nature Immunol.* Jan 2007;8(1):11-13.

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Matzinger P. 2007 (cont)

What causes an immune response?

SNS model = foreign threat seen by T & B cells

PRR model = viral or bacterial pathogen-associated molecular pattern (PAMP)

Danger model = damage-associated molecular pattern (DAMP)

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toll-like receptors (TLR) on — dendritic cells — antigen-presenting cells (APC) are Hyppos — and then we've got Nucleic acid (DNA and RNA) — (these) can activate (Antigen Presenting Cells). Now, it's important that we recognize that these things are normally behind a couple of two or three membranes. If they are suddenly exposed in the bloodstream, a dendritic cell will see this as a danger signal, because they're not where they belong. They indicate tissue damage. DNA from both bacteria and eukaryotic cells contains the APC stimulant, unmethylated CpG (groups). When cells are damaged, they spill CpG-rich DNA which, outside the cell, signals danger. I would note that Cooley's *Streptococcus pyogenes* is rich with CpG, unmethylated CpG.

Dr. Aymeric, writing in *Cancer Research* this year, in an article called *Tumor Cell Death and ATP Release Prime Dendritic Cells and Efficient Anticancer Immunity*, pointed out that although the dosages, timing and administration are universally wrong in standard oncology that the mechanism by which any tumor remission or shrinkage happens at all, is likely to turn out to be the immune system. *By destroying tumor cells, conventional anticancer therapies may stimulate the host immune system to eliminate residual disease. Anthracyclines, oxaliplatin, and ionizing irradiation activate a type of tumor cell death that elicits efficient anticancer immune responses depending on IFN γ and the IFN γ receptor. Thus, dying tumor cells emit danger signals that are perceived by DCs, which link innate and cognate immune responses. Our results identify tumor-derived ATP as a new DAMP, which is required for cancer cell death to be immunogenic.* I would just point out that, you know, back in the 40's, in the *Index Medicus*, there are all these articles about how terribly wrong efforts went to administer ATP to build cellular energy in people who were obviously wasting and needed mitochondrial function. You can't put ATP into the blood stream because you wake up all the antigen presenting cells — they freak out. And you get a huge — they used to call it toxicity; well it's not toxicity. You're causing an immune cascade. You might as well be using interleukin 2 as ATP.

Dr. Matzinger, again: *Each organ is a complex combination of tissues, delicately balanced to perform a particular function: a function that can easily be compromised by the powerful effector mechanisms wielded by the immune system. Thus, tissues use all sorts of mechanisms to keep the cells and molecules of the immune system out until they need them and to control them when they arrive* — a totally different way to look at it; one in which, immediately, pro-host therapies suddenly have context. If the tissue has got to function to ask for the kind of immunity it wants, you can't just dump cytokines into the patient. You have to make sure their tissue is functioning as well as it can function. There is no way to do that other than pro-host management. It is the only way.

If we accept that at least some immune responses can be initiated by tissue-derived signals that activate APCs, it is but a short step

Matzinger P. 2007 (cont)

Crosscutting DAMPs — universal aspects of life

- Hydrophobic portions (Hyppos) of molecules hold membranes together, shape complex proteins, and originate from bacteria. Possibly all molecules that bind toll-like receptors (TLR) on antigen-presenting cells (APC) are Hyppos.
- Nucleic acid (DNA and RNA) can activate APC. DNA from both bacteria and eukaryotic cells contains the APC stimulant, unmethylated CpG. When cells are damaged, they spill CpG-rich DNA which, outside the cell, signals danger

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Aymeric L, et al. Tumor Cell Death and ATP Release Prime Dendritic Cells and Efficient Anticancer Immunity. *Cancer Res.* 2010;70(3):856-858.

By destroying tumor cells, conventional anticancer therapies may stimulate the host immune system to eliminate residual disease. Anthracyclines, oxaliplatin, and ionizing irradiation activate a type of tumor cell death that elicits efficient anticancer immune responses depending on IFN γ and the IFN γ receptor. Thus, dying tumor cells emit danger signals that are perceived by DCs, which link innate and cognate immune responses.

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Matzinger P. 2007 (cont)

Each organ is a complex combination of tissues, delicately balanced to perform a particular function: a function that can easily be compromised by the powerful effector mechanisms wielded by the immune system. Thus, tissues use all sorts of mechanisms to keep the cells and molecules of the immune system out until they need them and to control them when they arrive.

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Matzinger P. 2007 (cont)

If we accept that at least some immune responses can be initiated by tissue-derived signals that activate APCs, it is but a short step to suggest that there are also tissue-derived signals that educate those APCs in order to control the effector class of an immune response.

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to suggest that there are also tissue-derived signals that educate those APCs in order to control the effector class of an immune response.

The danger model suggests that healthy fetuses should not be rejected because they do not send alarm signals. Transplants, however, cannot be performed without surgical and/or ischemic damage. Thus, to induce the acceptance of transplants without lifelong immunosuppression, we should mimic the body's own way of inducing tolerance, i.e., by blocking the endogenous alarm and/or costimulatory signals.

I had neglected to mention that Dr. Matzinger's work is of importance, huge importance, in transplantation science. It's rewriting transplant medicine.

To tumors; this is Polly's voice: *This is where I think the Danger model has the potential for the most immediate practical impact. It is also an area in which it becomes clear that the way we think influences the way we act. I firmly believe that we have the ability, today — her italics, not mine — to cure a substantial percentage of tumor patients through immunization but we do not do it because we are working within the wrong paradigm.*

*Tumors should not stimulate immunity, either because they are not associated with microbial stimulators, or because they are healthy growing cells that do not send alarm signals. Thus, to eradicate a tumor, we should **infect it**, or **cause it repeated damage** to alert the local APCs (as Bill Coley did in the late 1800s), or we should vaccinate repeatedly with a tumor vaccine that stimulates immunity.* I would note here that many people involved here in the immunology of cancer think of William Bradford Coley as Bill. We think of him as a friend, as somebody we know, or we ought to know, right? And Polly is no exception; she calls him Bill.

So, let's look at what happens with infection. Now there are a couple of models — I sent these articles to Polly and subject was "brain candy" — a couple of German animal models, looking at *Streptococcus pyogenes*, the central microbe of the Coley vaccine, and asking, "What if we just infect the animal with a live strep?" Right?

The researcher was Maletzki, the article, *Pancreatic cancer regression by intratumoural injection of live Streptococcus pyogenes in a syngeneic mouse model. In the present study, we sought to address the question of whether bacteriolytic therapy using S pyogenes is applicable for pancreatic carcinoma. To achieve this goal, we analysed the impact of a single intratumoral injection of S pyogenes on established murine pancreatic tumors in a syngeneic mouse model. This single application of S pyogenes resulted in complete tumour regression within 4 weeks.* This is Wilhelm Busch's observation. This is

Matzinger P. An innate sense of danger. *Ann NY Acad Sci.* 2002;961:341-342.

The danger model suggests that healthy fetuses should not be rejected because they do not send alarm signals. Transplants, however, cannot be performed without surgical and/or ischemic damage. Thus, to induce the acceptance of transplants without lifelong immunosuppression, we should mimic the body's own way of inducing tolerance, i.e., by blocking the endogenous alarm and/or costimulatory signals.

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Matzinger P. An innate sense of danger. *Sem Immunol.* 1998;10:399-415.

Tumors

This is where I think the Danger model has the potential for the most immediate practical impact. It is also an area in which it becomes clear that the way we think influences the way we act. I firmly believe that we have the ability, *today*, to cure a substantial percentage of tumor patients through immunization but we do not do it because we are working within the wrong paradigm.

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Maletzki C, et al. Pancreatic cancer regression by intratumoural injection of live *Streptococcus pyogenes* in a syngeneic mouse model. *Gut.* 2008;57:483-491.

In the present study, we sought to address the question of whether bacteriolytic therapy using *S pyogenes* is applicable for pancreatic carcinoma. To achieve this goal, we analysed the impact of a single intratumoral injection of *S pyogenes* on established murine pancreatic tumors in a syngeneic mouse model. This single application of *S pyogenes* resulted in complete tumour regression within 4 weeks.

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erysipelas, in a mouse, being administered to a target organ, the pancreas. And this is not a grafted tumor, this is a mouse tumor. We're not playing with a human tumor in a murine model, so there is no question about this being a difficult, difficult challenge for the mouse's immune system.

Let's continue: *A massive activation of immune response mechanisms secondary to infection accompanied the regression and contributed to eradication of the tumours. In summary, S pyogenes may be an excellent candidate for the evaluation of an active antitumour therapy. These findings may be of special clinical interest for additive treatment of patients with pancreatic tumours* — we always have to say “additive.” Of course we'd do the chemo first; I mean, we're good boy scouts and girl scouts. We're going to do it first, because the FDA says we have to do chemo first — horsefeathers. But I understand, he had to get published, so we call it additive therapy.

The intratumoural administration of S pyogenes did not — this is so fascinating, anybody that's going to be doing immunotherapy, some of these examples are just, they're what you need — *affect pancreatic carcinoma growth within the first 4 days*. The treatment's a failure, right? Four days; can you imagine in a clinic, with humans? Four days; no response? People don't wait well, right? Especially not the family members of the cancer patient; they do not wait well. *Palpable tumours continued to grow* — Oh, my God, it's a disaster, right? — *and reached an average size of 11.8 mm³ which was comparable with the tumour sizes of the vehicle-treated animals. Thereafter, about 6-8 days after infection, tumours in the infection group became noticeably and quantitatively smaller than those of the control groups (p<0.05)* — But you are a week into it, right? before that happens — *(they) were frequently ulcerous and apparently necrotised 10-14 days after infection. This finally resulted in nearly* — What an interesting spelling of “nearly,” neeeeearly — *complete regression within 4 weeks*. Four weeks, a month — a month you're having to do psychotherapy on the patient, right? And the family — more the family.

There was — and complications — *There was massive splenomegaly only in tumour-carrying mice that had undergone bacteriolytic therapy (an approximately seven- to eightfold increase in size at all time points). Interestingly, spleens of tumour-free mice infected with S pyogenes were macroscopically not enlarged*. What that says is that the tumor — and the tumor micro-environment, as many of you know, is at least 50% tumor-associated macrophages packed into the stroma — this has become enormously activated, the macrophages become confused about where their allegiances and loyalties lie; the spleen becomes terrifically hypermetabolic and involved. So immunotherapy is not without consequences, not without symptoms, it's not without the need to do supportive care, big time, supportive care.

Maletzki C. 2008 (cont)

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In summary, *S pyogenes* may be an excellent candidate for the evaluation of an active antitumour therapy. These findings may be of special clinical interest for additive treatment of patients with pancreatic tumours.

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Maletzki C. 2008 (cont)

The intratumoural administration of *S pyogenes* did not affect pancreatic carcinoma growth within the first 4 days. Palpable tumours continued to grow and reached an average size of 11.8 mm³ which was comparable with the tumour sizes of the vehicle-treated animals.

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Maletzki C. 2008 (cont)

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Maletzki C. 2008 (cont)

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In order to test to what extent the bacteriolytic therapy not only led to tumour regression but also induced protective immunological memory towards a re-exposure to Panc02 tumour cell — this is a mouse-line of tumor cells — a tumour rechallenge experiment was performed... Four weeks after tumour inoculation, the M49-C (control) mice displayed growing tumours... In the rechallenge group, tumour development was significantly restrained, with one animal remaining tumour-free until the end of the experiment. This is very instructive. You are taking a bolus of live malignant cells and injecting them into these animals — they are resisting re-infundment. They are resisting this tumor taking just on the strength of what they have already accomplished. And this is astounding that this could be done four weeks later, because, as we'll learn, as we study Dr. Matzinger, that the T-cell response really doesn't last that long. So there have to be other subtle aspects of immune memory that are alive and well there.

Now, looking a little further here, Linnebacher contributed to the Maletzki study by doing *lysates of S pyogenes Serotype M49 Induce Pancreatic Tumor Growth Delay by Specific and Unspecific Antitumor Immune Responses*. Lysates of *S pyogenes* were used. This is Coley's vaccine, the first formula before he added Serratia. Serratia, by the way, was only added to potentiate the *S pyogenes*. So, in this experiment, *After tumor establishment on day 9 (mean size: 60 mm³), animals were randomized. One group of animals received 2 intratumoral injections of the bacterial lysate (days 0 and 4, 50µL volume, dissolved in phosphate-buffered saline), and there were 28 mice in the study.*

Established Panc02 tumors rapidly stopped growing and started to macroscopically necrotize within 7 days. This is with the lysate, all right? Which is why Coley realized — when he used live injections and couldn't get the infection to take, because it's hard to get that to happen, too — the tumors were still shrinking, and that led Coley to understand that it was the body's response and not the agent that he was injecting that was leading to tumor shrinkage, which led him to the realization that he could safely sterilize the microbe, still get the tumor response, and not risk killing his patients. That was the trajectory of his thought. *At the end of the experiment (day 28), tumors of the lysate-treated animals were still quantitatively smaller with large necrotic lesions at the injection site. Moreover, complete regression of Panc02 tumors was found in 2 of 7 lysate-treated animals.* Now I would point out that Dr. Matzinger would just ask, "Why did they stop injecting? Why didn't they keep injecting?" Because you will learn that Dr. Matzinger loves the idea of reawakening the immune system again and again and again until the tumor is gone.

Therapeutic treatment with the lysate was well tolerated by all animals, resulting in a 100% survival rate with no signs of...

Maletzki C. 2008 (cont)

In order to test to what extent the bacteriolytic therapy not only led to tumour regression but also induced protective immunological memory towards a re-exposure to Panc02 tumour cell, a tumour rechallenge experiment was performed.

Four weeks after tumour inoculation, the M49-C (control) mice displayed growing tumours.

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Linnebacher M, et al. Lysates of *S. pyogenes* Serotype M49 Induce Pancreatic Tumor Growth Delay by Specific and Unspecific Antitumor Immune Responses. *J. Immunother.* 2008;31(8):704-713.

After tumor establishment on day 9 (mean size: 60 mm³), animals were randomized. One group of animals received 2 i.t. injections of the bacterial lysate (days 0 and 4, 50µL volume, dissolved in phosphate-buffered saline, n = 28).

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Linnebacher M, 2008 (cont).

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Linnebacher M, 2008 (cont).

Therapeutic treatment with the lysate was well tolerated by all animals, resulting in a 100% survival rate with no signs of tumor-associated clinical symptoms like anorexia or weight loss. Moreover, examination of the inner organs revealed no marginal changes except a slight splenomegaly in animals that had been treated with lysate.

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tumor-associated clinical symptoms like anorexia or weight loss. Moreover, examination of the inner organs revealed no marginal changes except a slight splenomegaly in animals that had been treated with lysate.

The most striking result of the current study was the tumor growth cessation subsequent to 2 consecutive i.t. administrations of bacterial lysate. This effect suggests participation of immune cells with cytotoxic potential. The strong infiltration of remaining tumor tissues with CD8⁺ T cells additionally supports this interpretation. Furthermore, we could show that Panc02 cells are specifically recognized by lymphocytes of treated animals in IFN- γ -ELISpot analysis. Right?

And just a little graph that shows that the animals that were treated by yet another bacteriolytic, and this was C novyi, could enjoy tumor regression: *Bacteriolytic therapy can generate a potent immune response against experimental tumors*. As Polly was saying, we should infect them, we should infect tumors, right?

This particular study has some fascinating findings in it: *When C novyi-NT spores were intravenously injected into mice with CT26 tumors, bacteria germinated exclusively within the tumors*. The reason they chose this is that this microbe homes in on anaerobic locations, so it is going to preferentially find those pockets of the tumor that are depleted of oxygen. *By 24 h after treatment, hemorrhagic necrosis could be observed at the centers of most of the tumors. Three to 4 weeks later, the tumors had regrown from the small nonnecrotic region at the periphery in 66% (31 of 47) of the animals. In the other 34% of the mice, the tumors had completely regressed, and the mice remained tumor free until the end of the experiment (>60 days).*

Now, we're looking at rabbits here and *Seven of 23 (30%) rabbits were cured*. I think you're going to find this segment fascinating if you're actually thinking about engaging in immunotherapy with any of your cancer patients. Just remember how important it is that people be kept in a state of confidence and belief, and most of your time is spent reassuring them. A rabbit you can't talk to, but this is what one rabbit that underwent PET in addition to CT scanning revealed. *There was a single liver tumor present on day 14, 1 day before treatment with C novyi-NT. Treatment with C novyi-NT destroyed this lesion as is evident by the lack of FDG uptake 1 week later (day 22). But by that time, a second tumor not visible on day 14 had become apparent as a result of local extension or metastasis. Oh, my God, a new tumor. We better throw out the immunotherapy and get onto chemotherapy like good boys and girls, right? Because that's, of course, what we have to do. We have to abandon it and return to radiation and chemo; that's always the argument. This second lesion presumably arose after the initial germination event and was not effectively colonized by the bacteria, as is evident by its robust PET signal (day 22).*

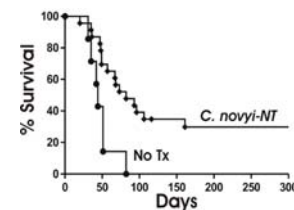
Linnebacher M, 2008 (cont).

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Bacteriolytic therapy can generate a potent immune response against experimental tumors.

Agrawal N, et al.
Proc Natl Acad Sci U S A. 2004 Oct 19;101(42):15172-7.



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Fig. 10. Kaplan-Meier survival curves. The median survival increased from 44 to 82 days in the treatment arm ($P < 0.01$). The cure rate was 30%. Seven rabbits were used in the control arm and 23 in the *C. novyi-NT* treatment arm.

Agrawal N. 2004 (cont).

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Agrawal N. 2004 (cont).

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Seven of 23 (30%) rabbits were cured.

One rabbit that underwent PET in addition to CT scanning was particularly informative. There was a single liver tumor present on day 14, 1 day before treatment with *C. novyi-NT* (figure 7, day 14). Treatment with *C. novyi-NT* destroyed this lesion as is evident by the lack of FDG uptake 1 week later (day 22). But by that time, a second tumor not visible on day 14 had become apparent as a result of local extension or metastasis. This second lesion presumably arose after the initial germination event and was not effectively colonized by the bacteria, as is evident by its robust PET signal (day 22).

A third lesion, an abdominal wall metastasis that also contained viable tumor cells evident on PET, was observed several weeks later (day 51). These are a little bit small, but you can see from the arrows — from the yellow and the blue and the red arrows — they're probably clearer in your book than they are on the screen. AV's got to fix the color.

(Academy member: They are unrecognizable in the book.)

They're not visible in the book? Okay, well, your citation is here. This line is, I think, in PubMed Central, free download on PDF. So you can get them that way. Essentially what you're seeing is the appearance of two tumors after the immunotherapy was begun — *Yet all lesions eventually disappeared in the absence of any further treatment... suggesting (but not proving) that they might have been eradicated by an immune response that occurred after the initial germination.* I don't know if you can see that — the yellow arrow is very clear, the other arrows are not so clear. There is the additional tumor down here. You've got your primary tumor, then you've got the second tumor, and then you've got your... you really can't see it. It's like I say, it's online and you can get it online — and the point is that they all went away.

So, Agrawal continues: *To obtain more direct evidence of the development of tumor immunity in these rabbits, we selected three that had been cured of their hepatic tumors by C novyi-NT and challenged them with an intramuscular (quadriceps) inoculation of 1×10^6 tumor cells. In 12 naïve animals, such inoculations always led to rapid tumor growth that destroyed the muscle and surrounding cutaneous tissues within a few weeks. However, no tumor growth occurred in C novyi-NT-cured rabbits after identical intramuscular injections, even though the injection sites were far from the site of the original hepatic tumors.*

So, again we are looking at an immune system waking up and remembering something for at least a period of time.

Back to Polly again: *This is not a new idea. It was first done at the turn of the century by Bill Coley, who injected tumors with a nasty mix of bacterial products dubbed 'Coley's toxin'. Though he cured about one-third of his patients, his method fell out of fashion, to be replaced by the combination of surgery, chemotherapy and radiation that have been used ever since.*

All right, a look at the microbes of Coley Fluid: Streptococcus pyogenes — you've all probably run into that in your practices. Serratia marcescens — until the 1950s, S marcescens was erroneously believed to be non-pathogenic, it was called a sacrophyte. Its reddish color was used in school experiments, infections were tracked with it. It has been used as a simulant in biological warfare testing by the United States military. On September twenty-sixth and twenty-seventh of 1950, the United States Navy conducted a secret experiment called

Agrawal N. 2004 (cont).

A third lesion, an abdominal wall metastasis that also contained viable tumor cells evident on PET, was observed several weeks later (day 51). Yet all lesions eventually disappeared in the absence of any further treatment with *C. novyi-NT* (day 455), suggesting (but not proving) that they might have been eradicated by an immune response that occurred after the initial germination.

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Agrawal N. 2004 (cont).

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The two microbes of Coley Fluid

- Streptococcus pyogenes
– Erysipelas
- Serratia marcescens
– Bacillus prodigiosus

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Operation Sea Spray in which *S. marcescens* was released by bursting balloons over urban areas of San Francisco Bay area in California. Although the Navy later claimed that the bacteria were totally harmless, serious urinary tract infections occurred and there were eleven patients at a local hospital with this very rare urinary tract infection; one of them died. His name was Edward Nebbin, for what it's worth. There were cases of pneumonia as well, they increased remarkably after *marcescens* was released — but it was regarded as non-pathogenic.

This is *Strep pyogenes* doing its usual thing in the pharynx and tonsils — uncomplicated bacterial pharyngitis and tonsillitis.

Some other examples: impetigo, scarlet fever, cellulitis. It's a nasty bug, right? But it does remarkable things to the immune system.

Coley, speaking out on the subject of *Serratia* in an article that he wrote in 1910 in the *Proceedings of the Royal Society of Medicine*, *The treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus)* — which is the old name for *Serratia marcescens* — *At this time, Roger's experiments with the prodigiosus cultures showed that if the Bacillus prodigiosus were grown together with the streptococcus of erysipelas the virulence of the latter was materially increased. Roger had never used the Bacillus prodigiosus alone or with the streptococcus of erysipelas on the human being, and had never, as far as I know, suggested it as a therapeutic agent.*

In order to intensify the virulence of the erysipelas, I decided to use the combined toxins of erysipelas and Bacillus prodigiosus, growing the two organisms together and sterilizing them with heat. The first preparation was made for me by Dr B H Buxton, then Fellow of Bacteriology of the Loomis Laboratory, and now for seven years Professor of Experimental Pathology of Cornell University.

And I did put this chart in there — I don't know if you can read it with a magnifying glass — in your manuals. (See next page). This is Lloyd Old's and Helen Coley Nauts' assessment of the impact of Coley's Toxin treatment in not only sarcomas, but take a good note, of carcinomas and dyscrasias. Think of the lymphosarcomas and the Hodgkin's disease as tumor-forming dyscrasias, but they really are serum cancers. And just to look at these numbers, the uterine sarcoma is quite tantalizing; a 73% five-year survival in inoperable cases. What is evident here is — this is from Coley's notebook; he kept one notebook, it had about a thousand plus cases in it. He noted the type of Coley formulation he used. He noted the demographics, he noted the disease, and he noted the follow up. The man followed up his patients. He published ongoing outcomes studies of his patients. And I think it's remarkable, again, this was occurring at a time before any of the normal bells and whistles of medicine were available. Before there

Strep Throat

- *S. pyogenes* is leading cause of uncomplicated bacterial pharyngitis and tonsillitis
- Common in winter and early spring in children over age 3
- Typical symptoms:
 - Pus in throat
 - Reddened and inflamed tonsils and uvula
 - Tiny, reddish-brown spots at back of throat
 - Swollen lymph nodes and tongue
- Treatment is best 48 hours after symptom onset



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Strep throat



Impetigo



Scarlet fever



Cellulitis



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Coley WB. The Treatment of Inoperable Sarcoma by Bacterial Toxins (the Mixed Toxins of the Streptococcus erysipelas and the Bacillus prodigiosus)
Proc R Soc Med. 1910; 3(Surg Sect): 1-48.

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Coley WB. 1910 (cont).

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-----5 year survival-----					
Type of tumor	No. of cases	No. INOPERABLE %		No. OPERABLE %	
Bone tumors					
Ewing's Sarcoma	114	11/52	21%	18/62	29%
Osteogenic Sarcoma	162	3/23	13%	43/139	31%
Retic Cell Sarcoma	72	9/49	18%	13/23	57%
Multiple Myeloma	12	4/8	50%	2/4	50%
Giant Cell Tumor	57	15/19	79%	33/38	87%
Soft Tissue Sarcomas					
Lymphosarcoma	86	42/86	49%	----	----
Hodgkin's Disease	15	10/15	67%	----	----
Other soft tissue sarcom	188	78/138	57%	36/50	73%
Gynecological Tumors					
Breast cancer	33	13/20	65%	13/13	100%
Ovarian Cancer	16	10/15	67%	1/1	(100%)
Cervical Cancer	3	2/3	67%	----	----
Uterine Sarcoma	11	8/11	73%	----	----
Other Tumors					
Testicular Cancer	64	14/43	34%	15/21	71%
Malignant melanoma	31	10/17	60%	10/14	71%
Colorectal Cancer	13	5/11	46%	2/2	(100%)
Renal Cancer (adult)	8	3/7	43%	1/1	(100%)
Wilms' Tumor	3	----	----	1/3	33%
Neuroblastoma	9	1/6	17%	2/3	67%
TOTAL	896	238/523	46	190/373	51

Table reprinted from *Breast Cancer: immunological factors affecting incidence, prognosis and survival* by Helen Coley Nauts, Cancer Research Institute Monograph #18, 1984.

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were internists, think about it, because there weren't drugs to speak of. There weren't all of the things that we're so accustomed to using. So...

The Danger model is a correct paradigm and, as such, it sees its roots in history. Prof. Alfred Pischinger (1899-1982) introduced the idea of a tissue, which he called the extracellular matrix, that originated immune responses. In the 1950s, Max Gerson relied on Pischinger's model to explain tumor responses to his own dietotherapy. Contemporary research focuses on signaling pathways initiated by extracellular matrix proteins, integrins and growth factor receptors that influence the biology of tumor cells and angiogenic endothelial cells — and as I note in the footnote here, PubMed responded to a July 17, 2010 search on "extracellular matrix" with more than 63-thousand references, none of them to Pischinger, of course, but it was his work, and it's always important to give a nod to the guy who saw it and articulated it.

Gerson, in his book, his monograph, from 1959, wrote: *Professor (Alfred) Pischinger places the activation of the mesenchyme more precisely into the foreground. This is remarkable; again, 1959: "The mesenchyme consists mostly of connective tissue cells which are distributed all over the body, especially between all organs and tissues. It contains several different types of cells. This tissue was long ignored until a few scientists discovered the importance of this so-called 'filling*

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Gerson M. A Cancer Therapy: Results of 50 cases, 1959, New York, NY, Dura Books.

Professor (Alfred) Pischinger places the activation of the mesenchyme more precisely into the foreground: "The mesenchyme consists mostly of connective tissue cells which are distributed all over the body, especially between all organs and tissues. It contains several different types of cells. This tissue was long ignored until a few scientists discovered the importance of this so-called 'filling tissue,' now characterized more precisely as the 'reticular system,' containing the mesenchymal defense and parenteral digestive apparatus."

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tissue,' now characterized more precisely as the 'reticular system,' containing the mesenchymal defense and parenteral digestive apparatus. We are talking about the innate immune system here, identified and characterized correctly more than half a century ago, but not popularized, not utilized to inform research or development.

"From the pathology we learn that almost every tumor is surrounded by such tissue, and the same tissue also embraces all new cancer establishments. This connective tissue is almost inactive and paralyzed in cancer, incapable of helping or protecting the body any longer in defense or healing." Now it is interesting that this observation is made by a man who managed to turn the peritumoral environment into a hyperactive, allergic-inflammatory, responsive tissue in enough cases that he attracted attention. It's a little bit at odds with Dr. Matzinger's Danger model, in that the Danger model would say, well, the tissue is not reacting to the tumor, because the tumor is not making danger signals. But the fact is that many tumors are sloppy enough that there is a small, constant supply of danger signals in the tumor, but the tissue around it is too narcotized and lethargic to do anything about it, if people are sticking with general nutrition, eating what comes in the car window half of the time, and receiving no soil microbes, no live plant materials in their nutrition. So, one can argue that, in part, this viewpoint is correct and that Dr. Matzinger has more to learn about what can help the body to recognize danger signals.

Gerson, again: *Let us cite Professor Sigmund (translated): "The theory of cancer is a question of the defense of the mesenchyme (connective tissue) especially a defense work of the whole organism against damages penetrated from outside or developed from inside. In the end, the therapy is a so-called parenteral digestion."* Now, parenteral digestion is neutrophils, macrophages, lymphocytes — all of our little white buddies who circulate around and clean up refuse.

Again with Gerson: *The body's capacity to produce an allergic inflammation (healing power) depends on a most complete detoxification and an equilibrium in the metabolism to near normal. The completely detoxified body is then able to produce an allergic inflammation if the healing apparatus (liver, visceral nervous system and reticulo-mesenchymal system) can be activated sufficiently.*

Everything that can help to bring about and strengthen the necessary allergic inflammation may be used for that purpose after the general detoxification has taken place — that only takes days — *Bacterial preparations (Coley and others) are effective as far as they can stimulate the visceral nervous system in connection with the liver and the mesenchymal defense and healing apparatus.* Now, because I am a Gerson scholar, I got into Coley the same way Sharon Brockman — the patient you saw in the film — did, through Gerson. Gerson was absolutely correct in calling for incorporation or integration of the Coley approach in his approach. All he was doing was making it more

Gerson M. 1959 (cont)

"From the pathology we learn that almost every tumor is surrounded by such tissue, and the same tissue also embraces all new cancer establishments. This connective tissue is almost inactive and paralyzed in cancer, incapable of helping or protecting the body any longer in defense or healing."

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Gerson M. "The Healing of Cancer" in *A Cancer Therapy: Results of Fifty Cases*. 1958, New York, Dura Books.

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Gerson MB. 1959 (cont)

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Gerson M. 1959 (cont)

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likely that the immune system was going to be active and responsive. The Coley was choosing the target and forcing Danger signals into the system. Let's go into how that works.

In the Danger model, everything starts in the tissue. The tissue controls both innate and adaptive immunity. Tissue responses to danger, death, destruction, and distress existed prior to the evolution of the thymus-mediated antigen-presentation system of innate and adaptive immunity. It is an evolutionarily conserved system. It's our ancient wisdom; it's how we got here. It's why we didn't die on the path. All right?

Tissue has three jobs. This is the gospel of Matzinger. Tissue does its main function: it makes insulin, for example, if it is a pancreas. It sends stress signals to activate antigen-presenting cells. And it presents its own antigens to unactivated lymphocytes to induce tolerance to itself. In short, tolerance and immunity both originate in the tissue itself. Just on point number three here, our lymphocytes do circulate; their primary job is to accept tissue-presented antigens that are lifted up on a major histocompatibility complex on the surface of the cell membrane for the lymphocyte to imbibe. If the lymphocyte receives that signal, that's signal one; without being costimulated, which would be called signal two, that lymphocyte will either rest down or delete, it will find its way floating back to the nearest lymph node, and the tissue represented by that antigen will be tolerized. That's why we don't attack our own tissue.

So, three rules govern T lymphocytes. These are Matzinger's rules of lymphototics, not lymphatics, but lymphototics. *T cells are deleted (die) if they bind an antigen (signal 1) but are not activated by APC (signal 2). Activation requires both signals 1 and 2. Only APC, and these are interdigitating dendritic cells and, perhaps, macrophages — under some circumstances. Only APC can activate (co-stimulate) both virgin and experienced T cells.* A virgin T cell has not taken up antigen; an experienced T cell has taken up antigen. *An experienced T cell can be reactivated by a B cell — this is a little corollary to rule two.* The third rule of lymphototics: *T cells only stay activated for a period of days, — about fourteen — after which they either die or return to a resting state, again requiring both signals 1 and 2 to be reactivated.*

There is a single exception to these rules. Are you ready? Do you want a little second? T cells are going to delete if they bind an antigen but don't get costimulated. Only DCs, and maybe macrophages, can costimulate. And T cells only stay active for awhile. These are the basics. These are the basics of transplant and tumor immunology.

The exception: *In the thymus gland, the evolutionary interface between tissue and lymphocytes, young T cells have not yet developed the pathways for antigen-presenting-cell co-stimulation (signal 2). Because of this, any young T cell that recognizes antigen presenting cell is deleted, inducing permanent systemic tolerance for antigen*

In the Danger model, everything starts in the tissue

- The tissue controls **both** innate and adaptive immunity
- Tissue responses to **danger, death, destruction**, and **distress** existed prior to the evolution of the thymus-mediated antigen-presentation system of innate and adaptive immunity.

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Tissue has 3 jobs

- It does its main function (e.g. makes insulin).
- It sends stress signals to activate antigen-presenting cells (APC).
- It presents its own antigens to unactivated lymphocytes to induce tolerance to itself.

In short, tolerance and immunity both originate in the tissue itself.

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3 rules govern T lymphocytes

- T cells are deleted (die) if they bind an antigen (**signal 1**) but are not activated by APC (**signal 2**). Activation requires *both* signals 1 and 2.
- Only APC (interdigitating dendritic cells and, perhaps, macrophages) can activate (co-stimulate) both virgin and experienced T cells. (An experienced T cell can be reactivated by a B cell).
- T cells only stay activated for a period of days, after which they either die or return to a resting state, again requiring both signals 1 and 2 to be reactivated.

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There is a single exception

*In the thymus gland, the evolutionary inter-face between tissue and lymphocytes, young T cells have not yet developed the pathways for APC co-stimulation (**signal 2**).*

Because of this, any young T cell that recognizes APC is deleted, inducing permanent systemic tolerance for APC.

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presenting cells. All right? In the thymus gland, T cells can't be co-stimulated, so if they eat a DC antigen, they delete and therefore tolerate the DCs to the system. That means we can't have immunity against our dendritic cells. So we're not going to be making mistakes, and that's a really helpful little rule, or exception.

New tissue is allowed to develop. This was a big fat hole in the self—not-self model that Charlie Janeway put out. *With the tissue in control, the body can change, e.g., women can go through puberty and their breast can begin to make (new) milk proteins without becoming autoimmune.* I read with some astonishment, and not a little bit of queasiness, an experimental vaccine being developed in mice — God willing that's where it stops — using beta lactalbumin. These are mice that always develop breast tumors, and the idea was to immunize them against milk protein. And it did work, I mean, because the mice didn't develop breasts when they were immunized with vaccine, and therefore no tumors are going to develop. But I just don't see it happening in the human. *Because no stress signals (signal 2) are sent by the changing tissue of the breast, T cells that bind the new antigens (signal 1) are deleted and the new tissue is tolerized.* This is why it is okay to get older and for your body to change its function and change what it manufactures, and why you are not going to suddenly become a massive autoimmune disease.

Tumors — unfortunately — are just new tissue to the immune system. Tumors express new antigens (signal 1) in the absence of stress signals (signal 2); if a tumor cell dies, it is by nontoxic apoptosis. There is no reason for the tissue (innate) immunities or the lymphocytic (adaptive) immunities to see developing tumors any more than any other rapidly dividing cells, e.g., gut cells, hematopoietic cells.

Spontaneous regression. Spontaneous regression of, for example, a melanoma might be induced by viral, bacterial or physical insult resulting in activation of local APC. This is a cannon of the gospel of Matzinger. *APC would capture tumor antigens and present them to passing T cells in — there's an extra "n" in the "in" — the draining lymph nodes. These and other tumor-specific experienced T cells that had not been deleted would be activated and attack the tumor, destroying it.*

Well, let's look at some extraordinary examples of the application of the Danger model. One of them is Dr. Silvia Formenti at New York University. She is Professor and Chair of the Department of Radiation Oncology — one of the good guys. Now, what Dr. Formenti did initially, to start her research ball rolling, was she applied Matzinger's Danger model to patients receiving chemo and radiation. The reason they were on chemo is that the institutional review board would not allow them to be treated without it. So, all of the patients had to be immune suppressed. In spite of this, Dr. Formenti designed a trial in

New tissue is allowed to develop

With the tissue in control, the body can change, e.g., women can go through puberty and their breast can begin to make (new) milk proteins without becoming autoimmune.

Because no stress signals (signal 2) are sent by the changing tissue of the breast, T cells that bind the new antigens (signal 1) are deleted and the new tissue is tolerized.

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Formenti SC *et al.* Ionizing radiation inhibition of distant untreated tumors (abscopal effect) is immune mediated. *Int J Radiat Oncol Biol Phys.* 2004 Mar 1;58(3):862-70..



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Sylvia Formenti, Prof. and Chair, Dept Rad Onc NYU

which the patients were given GM-CSF, and all of you probably know that granulocyte-macrophage-colony-stimulating-factor will lead to a greater activation, higher counts of white cells, and more dendritic cell activation *in vivo*.

The patients had to have three tumors, only one of which was targeted, because this was a demonstration of the abscopal effect — scopal = the target; ab = away from the target. The abscopal effect is a well-known phenomenon of radiation oncology in which tumors other than the one being irradiated shrinks. It was always brushed off the way that scientists have, in the past, brushed off things like the ability of the monarch butterfly to migrate from Canada to South America in four generations, the first one dying in the middle of the migration, the second generation born, continuing the migration and dying, the third one continuing the migration. When the fourth generation arrives, nobody asks, how do they do that? And I know you've heard the phrase, mere instinct; mere instinct, well, you know, its not very scientific not to be humbled and in awe of things we cannot understand. So, the apscopal effect really deserved to be studied, right? And Dr. Formenti ran a "proof-of principle" clinical trial. I apologize that this is a little fuzzy, but this is actually her presentation caught by camera.

To detect a response outside the radiation field after GM-CSF administration (as DC growth factor) in patients with metastatic tumors.

And, that's almost too small. What we're showing here is radiation and GM-CSF and what happens to the cells.

Enlarging it, you can see here that the main thrust of this is Polly Matzinger's; cancer cell death and antigen release — antigen release that causes a reaction by antigen-presenting cells.

Twenty-five patients were accrued to the trial. Twenty-three of twenty-five completed treatment, and twenty-two had PET/CT before and following therapy. One patient was evaluated only clinically, on skin metastasis outside the field. An abscopal response — and these are concomitantly-chemotherapy-treated patients, immune-suppressed patients — was detected — an abscopal response was detected in eleven of twenty-three — that's 47.8% -- defined as an objective response of at least one lesion outside the treatment field. Now, if you're getting ideas about GM-CSF, you know, there's a reason, and I would point out rapidly that Coley's vaccine induces endogenous GM-CSF production. And it is not uncommon to see somebody come in with a white blood count of six, and after the first Coley treatment or two, it's eleven. And when you do apheresis or mono-phoresis on them, you get a milky-white product out of that because you're enriching their white count. You've got leukocytosis.

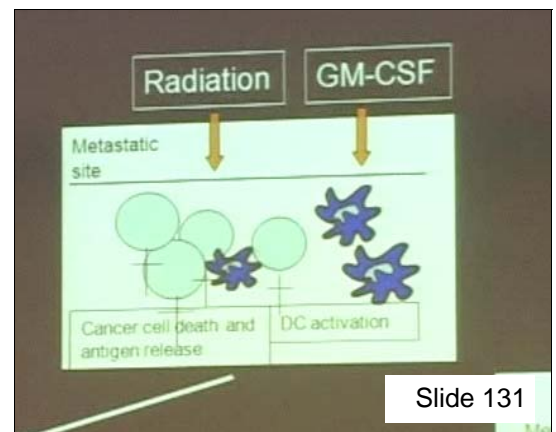
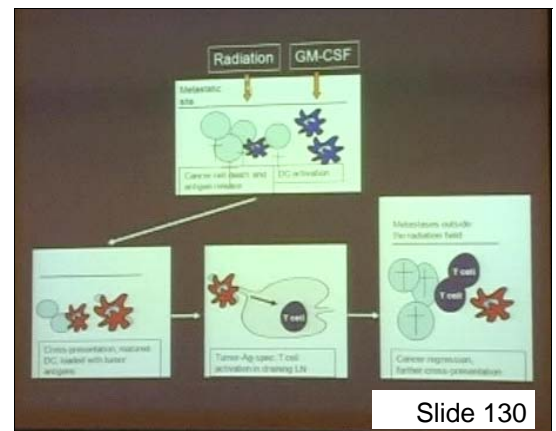
NYU 02-58

PILOT STUDY OF CHEMO-RADIATION INDUCED ABSCOPAL EFFECT IN METASTATIC SOLID TUMORS

A "proof-of principle" clinical trial

To detect a response outside the radiation field
after GM-CSF administration (as DC growth factor)
in patients with metastatic tumors

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RESULTS

25 patients accrued to the trial
23/25 completed treatment and 22 had PET/CT before and following therapy. One patient was evaluated only clinically, on skin metastasis outside the field

- An abscopal response was detected in 11/23 (47.8%) defined as an objective response of at least one lesion outside the treatment field

	CT+PET	CT only	PET only
# of patients	4	2	5*

* In 3/5 preceded by a flare

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This is a graphic showing that the treatment field was at the sternum, but that there's another problem down here in the lung; you see that? And the abscopal baseline was May 4th, and by July 12th, this is what's left. And by July 28th, the next year, it's gone, right? One year of follow up. That's the abscopal effect occurring in a GM-CSF-loaded patient, who received radiation to another tumor — another tumor. And it's always nice to see a PET/CT — if you're not using PET/CTs, you're missing out on seeing the metabolism of a tumor disappear.

And this is a three-month follow up on a patient whose abscopal effect tumor was disappearing — three months it took for that to disappear.

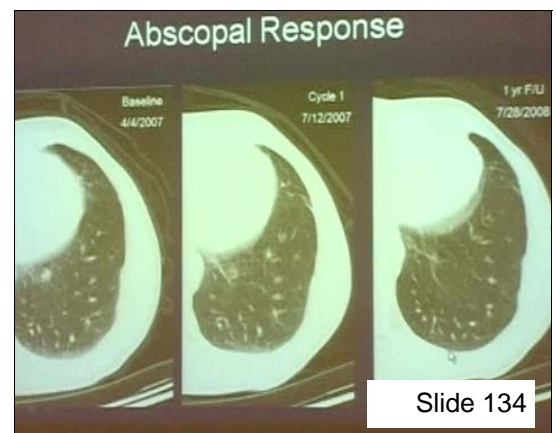
So the conclusion that Dr. Formenti derived from this trial was: *The addition of radiation therapy and GM-CSF resulted in a systemic effect outside the radiation field in eleven of twenty-three — almost half — of patients who either did not respond or progressed during the same chemotherapy.* These are all refractory — they did not respond or they progressed — they were all refractory. *This trial confirms feasibility and preliminary efficacy of harnessing local radiotherapy effects to synergize with immune therapy.* This is also the chair of radiation oncology at NYU seeing the light and turning the battleship. This is very, very good stuff, because we're finally going to be asking, not how often can we radiate, and how high can the dose be but, which one of these should we destroy with this material? If we can't reach it with a vaccine, if we can get it with radiation, which one should we use, and what should the immune profile look like before we do that? And what can we do to augment the antigen-presenting-cell population to the patient; These are all wonderful new considerations that are rapidly moving from bench and theoretical to the bedside and the clinic.

Only by studying the immune profile of patients who achieve an "abscopal response" we will be able to understand how to make progress.

2009 recipients of a grant from Manhasset Women's Coalition Against Breast Cancer. Support to conduct immune-monitoring in ten



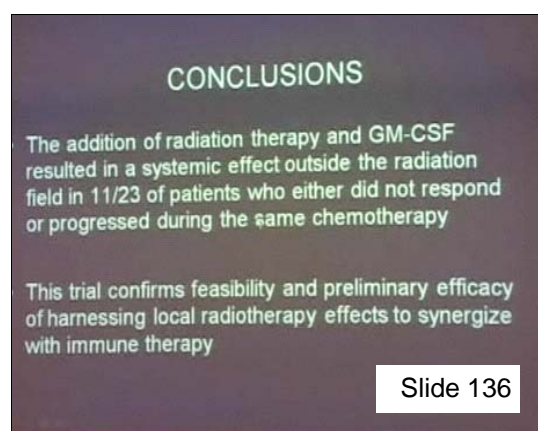
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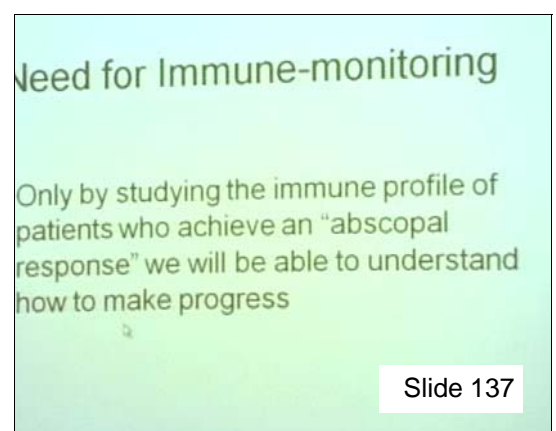
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patients — and she got Lloyd Old's people at Ludwig Institute to do the immune profiles; and I think it's a tremendous, tremendous advance.

Now, sequential immunizations — doing it more than once — why do we stop? Why do we stop immunizing when the tumor's shrinking? *Matzinger's Danger Model predicts that getting rid of tumors might be a simple matter of immunizing repeatedly with appropriate antigens. Repeated immunizations are necessary. A single immunization would initiate immunity, but the response would see [soon] die down for lack of repeated stimulus.* — It's not supposed to be "see"; it's supposed to be "soon" — *In the absence of repeated immunizations, the tumor would induce deletion of tumor-specific memory cells as they rested down, just like any other tissue expressing signal 1 without signal 2.*

So, what we may be calling failure — for example, Dr. Matzinger was speaking about Steven Rosenberg and his TIL experiment; he knows how to clone tumor infiltrating lymphocytes, Steve Rosenberg, at NCI. He's gotten beautiful responses, but he only treats them twice, with two injections of TILs. And Polly has been trying to get him to do more than that. She says, "Why don't you do more injections? Because what happens after two? The patients go into remission but they recur and they die. Why don't you do three; why don't you do four; why don't you do five?" And Dr. Rosenberg's response is, "Because I want them to not have to do more than two" — he's thinking about drug development — he's thinking about convenience — he's thinking about how to sell the material — but Dr. Matzinger is thinking about "how do you cure the patient"?

An innate sense of danger, from 1998, made the prediction: *We just have to let go of the old-fashioned idea that the immune system, once turned on, continues to fight until the antigen is gone. It won't. It will continue to fight until the Danger is gone, and it does not recognize most tumors as dangerous because the cells do not send alarm signals. In many cases a vaccine boost increases the number of animals that clear the tumor.* — This is Polly's voice -- *When I suggest another shot, the response has usually been "Why? We clearly induced immunity. In the animals that do not clear, the tumor must have escaped (or suppressed)." ... The important point is to keep boosting.*

Matzinger P. 1998 (cont)

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...The important point is to keep boosting.

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2009 recipients of a grant from
**Manhasset Women's Coalition
Against Breast Cancer**

- Support to conduct immune-monitoring in ten patients (in collaboration with the Ludwig Institute) enables us to derive the most important information from this trial
- Most importantly, it will translate into a substantial acceleration in the impact of this research on human lives

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Sequential immunizations

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- In the absence of repeated immunizations, the tumor would induce deletion of tumor-specific memory cells as they rested down, just like any other tissue expressing **signal 1** without **signal 2**.

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**Matzinger, P. "An innate sense of danger."
Sem Immunol. 1998;10:339-415.**

We just have to let go of the old-fashioned idea that the immune system, once turned on, continues to fight until the antigen is gone.

It won't.

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**Longo D. Idiotype Vaccination in Follicular Lymphoma: Knocking on the Doorway to Cure.
JNCI. 2006;98(18):1263-1265**

The Bendandi group* decided to assess the effect of idiotype vaccination by quantitating the duration of second remission in patients who had received an initial serious attempt at remission induction but who had relapsed.

*Bendandi M, et al. Clinical Benefit Associated With Idiotypic Vaccination in Patients With Follicular Lymphoma
JNCI. 2006;98(18):1263-1265

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Don Longo wrote an article about the Bendandi group's use of an idiotypic vaccination for follicular lymphoma, and his take on this was published in the *Journal of National Cancer Institute* four years ago. It was that this was a great example of an application of Matzinger's Danger model, an appropriate application, and it's another way to look at vaccination, per se. *The Bendandi group decided to assess the effect of idiotypic vaccination by quantitating the duration of second remission in patients who had received an initial serious attempt at remission induction but who had relapsed.* — This is a wonderful $n = 1$ study; each patient is his own control in repeated measures.

Patients on the study had relapsed from a combination chemotherapy-induced complete remission. They received a second course of combination chemotherapy and then were given Id-KLH vaccine. — That's idiotypic keyhole limpet hemocyanin vaccine. — The median duration of second remissions in response to nearly any conventional-dose treatment regimen, even to repeated courses of the therapy that induced the initial remission, is about 13 months.

Thus, the choice of the study design was the first innovation. Each patient would be his or her own control. Second remissions longer than first remissions would be an indication of therapeutic effect... The second innovation was the use of multiple repeat exposures to the idiotypic vaccine over a period of 2 years after completing chemotherapy. Patients received the vaccine monthly for 4 months, then received a boost 2 months later (at month 6), and then 5 additional boosts, one every 3 months.

Dr. Longo writes: *I am not aware of data suggesting that 10 vaccinations provide a wider spectrum of lymphocyte specificities than 3 or 4 vaccinations. I do not know why Bendandi used multiple vaccinations, but it worked. The results are remarkable. Of 25 patients who achieved a second chemotherapy-induced remission and were vaccinated with idiotypic, 20 made an immune response to the vaccine and 5 did not [respond] to the vaccine.*

Among the 20 immunologic responders, the median duration of the second complete response has not been reached after nearly 3 years of follow-up (durations range from 20+ to 51+ months), and in every case, the second remissions have been longer than the initial remissions. Only a single immunologic responder has relapsed, and that patient had an altered idiotypic at the time of relapse.

We talked — Polly and Chrissy and I talked — about why that patient relapsed, and Dr. Bendandi whose boss had brought Matzinger's concept to him; and that's why the multiple vaccinations. Dr. Bendandi said, "We ran out of idiotypic." To which Polly's response was, "For crying out loud, it's just a hybridoma; why didn't you make more? You know? — a little ethylene glycol to fuse the membranes? Why didn't you make more?" And that's a logical question for anybody dealing with vaccine therapy. If you're going to start, do you have enough?

Longo D. 2006 (cont).

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*Idiotypic keyhole limpet hemocyanin

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Longo D. 2006 (cont).

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Are you going to go forward with this long enough to induce a complete response? — Only a single responder relapsed.

Polly, again: *The Danger model has a very simple prescription for anyone using tumor vaccines. If you have a vaccine that makes a tumor get smaller..... Don't stop!..... Keep injecting until the last tumor cell is gone.*

And a final note here — *An organism in which the availability of 2nd signals (APC) governs immunity and tolerance needs no static definition of self. Its immune system is not a separate army protecting (and regulating) the rest of the organs of the body, but an extended, highly interactive network making its decisions on the basis of input from all bodily tissues. This is a flexible immune system that changes as the organism changes, that welcomes the presence of useful commensal organisms and allows the passage of harmless opportunistic ones. In short, this is an immune system that exists in harmony with both its internal and external environment.* — I know, I feel the same way; isn't that poetry? It's just marvelous. So, that's the end of my formal presentation. Any comments or questions?

(Academy member: I have to ask the question of the idiopathic (sic) keyhole limpet hemocyanin, when it was given, is it inducing fever, or this is not inducing like a Coley's fever reaction; otherwise there's an immune response, but its not at the level...)

No. This is a vaccine that is going to work more subtly.

(Academy member: Right.)

Remember that we are starting with minimal residual disease. We're starting with what should be a clean slate; we can't see any tumors anywhere. These are complete remissions from chemotherapy. So, in any patient, even in the Coley model, the burden of disease determines the severity and duration of the response. Breaking tolerance in a patient with a heavy tumor burden is onerous and full of all kinds of clinical side effects and urgent needs for supportive care. The patient who has minimum residual disease and begins a course of the Coley vaccine will have a very predictable, much less eventful, series of vaccinations. There will be forty-five minutes of wait time and, you know, prodromal feelings, and then you'll have rigors kick in. There will be chilling and shaking for maybe twenty or thirty minutes, after which that will calm down, and of course, the blood pressure will come back up, because its done a pre-septic drop, and then you'll begin the spike. The spike will be up and down within three or four hours in a patient with minimum residual disease. That's with the intravenous approach. Of course, as you know, if you go into subcutaneous tissue, these people could be walking around with bright red wheal, or even a whole upper arm that is bright red, and it can be a twenty-four-hour cytokine generator on their arm. Anyone else? You mean I'm done? It's Mark's turn? Okay, thank you.

(Applause.)

Matzinger P. 1998 (cont)

The Danger model has a very simple prescription for anyone using tumor vaccines. If you have a vaccine that makes a tumor get smaller..... *Don't stop!.....* Keep injecting until the last tumor cell is gone.

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Matzinger summarizes

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An organism in which the availability of 2nd signals (APC) governs immunity and tolerance needs no static definition of self. Its immune system is not a separate army protecting (and regulating) the rest of the organs of the body, but an extended, highly interactive network making its decisions on the basis of input from all bodily tissues. This is a flexible immune system that changes as the organism changes, that welcomes the presence of useful commensal organisms and allows the passage of harmless opportunistic ones. In short, this is an immune system that exists in harmony with both its internal and external environment.