Interview Questions for Dr. Thomas A. Waldmann

Interest in Science, the NIH, and Mentorship

1. **How did you get interested in medicine after majoring in Philosophy?**

Essentially everyone at the University of Chicago in the [Robert Hutchins era] was a philosophy major. All of us had to take, or pass in advance, 16 courses. Then, so many of these, in essence, were of great philosophers. It was really, if anything, the most exciting and innovative time of my life. We asked critical questions. If someone said good morning, we replied, “What do you mean by good?”

But then, of course, the doctor’s draft and regular draft were on. It was between the Korean and Vietnam wars.

So, I had always been interested in biology. I was the nature and woodsmanship counselor from my camp. The other half of 3 years in college were the premedical aspects. Where did I get interested in science? [Sherm] Weissman at HMS [Harvard Medical School] and I received a $50 grant to study what we now know as erythropoietin. It was just discovered by Alan [Erslev]. We, in middle of the night - midnight to 6 am- would sneak out to the Harvard Dental School to study erythropoietin in rabbits.

Now, at this time we are having what some view as a tough time now. It was a tough time in the 1950s as well. Senator [Joseph] McCarthy and his committee came to HMS to search for communists in academia. In rebellion of this, someone painted all the toilet seats in Vanderbilt Hall of Medical Students red. I woke in the night to go to the bathroom and ticked my shoe against the red paint. The next thing I knew, I was in the Dean’s office. They were saying, “Tom Waldmann, we hold you morally and financially responsible.” But I was such a grinding person that no one believed that I would do this. Nevertheless, Sherm Weisman put a red jelly bean in my mailbox during that period.

Another event occurred that sort of interested me in immunology and the immune system. I went to Mass General Hospital (MGH) for an Internal Medicine Residency in 1955. That was with the last polio epidemic of our country, and I was rotating through a lesser service than medicine. Frank Autin and I were placed into the iron lung part of MGH. For the rest of the summer, MGH had 500 patients with polio. At that time next year, there was the discovery of the polio vaccine that was widely distributed in 1956. So, I was truly impressed with how effective a vaccine could be for preventing a very serious acute infectious disease. If you have an acute, self-limited infection, vaccines are outstanding.

At that time, the doctor’s draft was on. In lieu of 2 years of army time, I decided to apply to NIH. I was accepted. Maybe it was my $50 grant or whatever. I was rotating through services without going through [read on] and was assigned to the metabolism branch of Nathaniel Berlin. I was also there with Jesse Steinfeld, who became Surgeon General. He was tired of research at that moment, and I de facto became a tenured senior investigator with total research experience of my $50 grant. I came with Jesse, who was

interested in the metabolism of serum proteins and their loss into the intestinal tract. We knew about proteinuria but were interested in the massive loss of Igs [immunoglobulins] and lymphocytes into the bowel. We developed new techniques to study protein metabolism and loss into the GI [gastrointestinal] tract. We discovered disorders of lymphatic channels, intestinal lymphangiectasia or Waldmann's disease. The gene causing it was CD55. It was discovered by Mike [Ionardo], who began to study at NIH during this era.

For my career at NIH, I intended to be here for 2 years. That was 62 years ago. Despite what someone said to my wife, "Sooner or later, he'll get a real job," I delighted in staying at the NIH. My education has been in the corridors of the NIH. My education has been because of the proximity of the Clinical Center to research labs and the ability to have patient-oriented clinical research. A patient's disease teaches you, and postdocs and technicians teach you.

2. Can you describe your studies of the immune system?

Throughout this first era of my career, 1956-1980/1981, we were trying to understand the immune system. I cannot tell you how primitive the understanding of the immune system was. In 1956, a classical text said we don't know what lymphocyte is not involved in carrying lipids from the intestine to the liver. There was no understanding of it at present. There was no knowledge of B and T cells, retroviruses were not defined, receptors were unknown, etc. Nothing approaching our understanding of HIV or retroviruses. I studied HTLV-1 [Human T-cell leukemia virus type 1].

What we studied then were 3 sorts of approaches. We studied the genetic primary immunodeficiency diseases. At the time, we didn't have approaches to use knockout or transgenic animals. We used immunodeficiency diseases of genetic nature as experiments of nature. We studied patients to understand the error and from that we could understand the normal immune system. The second approach was to study leukemias of lymphocytes, especially T cells. There is a bewildering array of subsets and functions. It's a tower of Babel of different suppressor, cytotoxic, and helper cells all mixed together. But with leukemias, any one would have single function. We studied what is now [cezarae] or T cell malignancy leukemia of helper T cells, and we studied the leukemia now called adult T cell leukemia caused by HTLV-1 (which is a leukemia of suppressor cells now termed Tregs). We used leukemias with Sam Broder to understand different, unique functions of T cells. The 3rd approach was using radiolabeled Igs to study survival and synthesis of these proteins, which was defined in the late 50s. The survival of each of the 4 subclasses of IgG IgA IgM, IgD, IgE and subsets of IgG1-4 defined their survival characteristics. Now this is used for the rationale development and use of monoclonal Abs. Fragments of Ig survival are used for rational Ig use. Also, at this time we were able to show that very low levels of Igs in circulation was not only due to the failure to make them (a failure of synthesis) but also due to short survival in other patients. We showed IgG short survival in myotonic dystrophy. All Igs and albumin had short survival in familial hyperbolic anemia. Ig short survival when lost in intestinal tract defined new diseases and new disorders.

In 1981- serendipity - a chance for a prepared mind altered my career to one that has focused on the cytokines. These molecules are what the immune system uses to talk to one another. Hormones had long been used to know how tissues talk to one another. Here we were studying cytokines, specifically the gamma cytokines. They use the common gamma chain receptor and include IL-2/4/7/9/15/and 21. Our work focused on IL-2 and IL-15. The NIH has always been a great area of cooperation, but that has not always been true throughout the whole community. We wished to have Abs [antibodies] to what is now CD4, but they were not made available to us. [Toksah] and I wished to make Abs to CD4, so we used a leukemia that we knew expressed such an antigen. But, by chance, the Ab turned out to be IL-2Rα or CD25. So, our work focused on IL-2. Bill [Paul's] focused on IL-4, so we shared both a community of interest and interacted at the National Academy of Sciences often in a cooperative way. When we made Abs to IL-2Rα, we soon realized it couldn't be the only receptor. We further studied and defined IL-2Rβ.

I noted throughout the remainder of my career, a pattern: we would make a discovery, see a disorder in human disease, make a new agent (like a monoclonal Ab for IL-2Rα/ IL-2Rβ or new cytokine like IL-15), test that in mouse models and then in nonhuman primates, and finally test it in patients with leukemia, immunodeficiency diseases, or autoimmunity.

The FDA approved our agents for study. The first Ab was to what we now know is IL-2Rα/CD25. We showed that normal cells except these Tregs do not express this receptor in a resting state. It's expressed in situations where we wish to eliminate the cells. It's expressed in leukemia (HTLV-1 adult T cell leukemia). It's expressed in T cells involved in rejecting organ allografts and autoimmune diseases (MS and a blindness condition). We first used pure mouse Abs, but then we used the humanized form of the Ab and applied it first to leukemia (caused by a retrovirus) and then to other diseases. Steve Jacobsen studies [uveitis] and Bob then studied organ transplants. As we used this in 1997, after many clinical studies approved by FDA for its use in the prevention of allograft (foreign) graft rejection, it was further studied by Bibiana Bielekova, especially with her work in MS. A couple of years ago, it was approved for use in MS. The arc of a study from discovery to definition of disease association to production of an agent to evaluation in mouse and primates to people as a new therapy for conditions takes 15-20 years.

Second serendipity - studying this IL-2 and IL-2 receptor Abs in leukemia, we came upon a circumstance. A cell was making something like IL-2, but it didn't get neutralized by the Ab to IL-2. It was a new cytokine. Kenneth H. Grabstein discovered IL-15. We were able to show that IL-15 played an enormous role in the maintenance and development of NK cells and memory CD8 cells. IL-15 shared 2 receptors, the common gamma chain and beta chain, with IL-2. It, like IL-2, also has its own private receptor – IL-15Rα. As we studied these 2 pathways, at least with IL-15, first we showed it had an enormous role in NK cells and memory CD8 cells. We used it in the treatment of patients with cancer as a bolus infusion that is injected in 30 min by subcutaneous infusion and continuous I.V. infusion. Continuous I.V. infusion here showed a 30-fold increase in the number of NK

cells and over a 350-fold increase in an NK cell subset. The body has checkpoints to prevent autoimmunity, which is true of NK cells as well. We reasoned that we could use IL-15 to generate NK cells in combination therapay with monoclonal Abs directed against cancer. They need NK cells interacting with macrophages to become binders of monoclonal Abs and killers of tumors. In mouse model systems, the combination of IL-15 and anti-cancer monoclonal Abs shows great efficacy. In anti-cancer therapy initiated clinical trials to test it there have been encouraging results. Others studied it with CD8 cells and used combination therapy with anti-CD40 to take advantage of CD8 cells to treat patients with cancer. One use of IL-15 is the study of cancer therapy or vaccine design. The other arena is knowledge that there are disorders of IL-15 (like diseases of refractory celiac disease, type I diabetes, IL-15 cutaneous T cell lymphoma, alopecia, autoimmunity, and T cell malignancies). Many approaches use an Ab to the shared beta chain of the IL-2/IL-15 receptor. We made a separate Ab from 1 described earlier. This other approach reflects a recognition that in T cell malignancies, a subset of each form has normality of the gamma receptor. We dig into the pathway (JAK1/3 and STAT5). We are approaching these leukemias with JAK inhibitors. We are using IL-15 in combination therapy with monoclonal Abs and anti-CD40 to treat malignancy disorders of IL-15 and JAK/STAT signaling. We are treating T cell malignancy with Abs to the receptor and JAK/STAT pathway inhibitors.

Our studies parallel those of Bill Paul. Part of the reason choosing me for that talk was our close association over 4-5 decades. Both of us came to NIH as part of our army time and stayed to become branch chiefs in our own institutes. Our careers involved recognition and control of immune responses and disorders of control, immunodeficiency, autoimmunity, and leukemias. We translated insights to new approaches to therapy of diseases of focus within our institutes.

3. Can you describe the doctor's draft, your decision to work at NIH, and your initial experiences in the NCI Metabolism Service?

We now have a fully volunteer army. But in that period of the Korean and Vietnam wars (and through much of time), there was a generalized draft for men under 26 years of age. In addition to that draft, there was a draft for physicians. One needed physicians to take care of the injured in wars. Thus, there was a draft for doctors. I was at MGH and under 26 as an intern. Walter Bower looked at 4 of us under 26 and said, "You are doubly at risk for the general and doctor's draft. We can't afford to have all of our interns conscripted."

The demographics were different in 1956. The one woman on the house staff was Kathy Sprang from Case Western Reserve and Oberlin. Now, she is Kathy Waldmann. She was my boss when I was an intern, since she was an assistant resident.

The 4 of us (interns) who ultimately became branch chiefs (at NIH) and professors at Harvard were eligible for the doctor's draft. We were going to have to leave MGH and go to some place. I gave considerable thought to research and wanted to come to the newly formed NIH Clinical Center, which opened in 1953 with Harry Truman. I came here in

1956. Then, it was a great wonder how one could use thousands of square feet of space, but now we fight over it. Each of us came to NIH. Sherm and I came, as I said, to the Metabolism Branch. We were assigned to the branch. It was through the back door of immunology that I came here. Dr. Berlin had been with the Navy Research Institute and was recruited by Gordon Zubrod to chair the branch. Throughout this era, there were 22 members of the American Society for Clinical Investigation, 20 associate physicians, and members of the National Academy of Sciences.

In many cases, one had not planned to be a scientist. NIH was bewildering successful in capturing the interest of people and getting what we used to sardonically call “yellow berets.” They came here to get out of the army, and they came here, in the end, to learn science. For many cases, it was translational science. The remainder of the country is rich in basic sciences. NIH has had a very special contribution to translational research due to the proximity of the clinic and laboratories. We could recruit patients with rare diseases of great teaching value. At the hospital we have here, we could study a rare disease like HTLV-1 adult T cell leukemia, which is prevalent in Japan and the Caribbean but rare in the US. But, it’s of great heuristic and teaching value. Through this disease, we discovered co-receptors of the immune system. Through NIH, we discovered leukemias with retained function. This characteristic of understanding the basic science, the nature of diseases, is important.

Outside, research is often dominated by what industry wants you to study. At the NIH, you can study what you want as long as you have good site visits and get an outstanding rating. You’re allowed to continuously study what you will until you’re 87 years old and can still persist in bearing the fruits. Often these odysseys last 25-35 years, as with the IL-2 receptor and IL-15. It literally takes that long to take the basic discovery to FDA approval. It’s like planting an orange tree. The reason you stay is that you’re always waiting for oranges to mature and to get to the point where you can salvage the tree.

In the earliest eras, the branch was diverse. Metabolism was studied. Metabolic effects of cancer on the host has evolved. In the 1980s, it became an immunology branch. In the 2000s, it was one of molecular oncology under Lou Stout and it’s a continuation of immunology in our own era. Individuals in these eras have gone onto populate universities throughout the country and enrich the field (such as the Howard Hughes scientist Stan [Cormeyer]). They also went on to be branch chiefs throughout NIH (like Tom Fleischer who just retired). Scientists throughout the institutes have had training in our branch and some of them worked with me. One has delight in one’s scientific children and grandchildren, and the gestation is not 20 years between those generations. Many people who I continue to collaborate with worked in my lab during the early 1980s. They were especially involved in the cytokine field.

I think one of the government’s most fantastically valuable investments has been in the NIH. So, the Vanderberg committee that started the NIH, started under Harry Truman [this is incorrect: the Hygienic Laboratory began in 1887 and became the NIH (singular) in 1930, and the NIH (plural) in 1948]. The ability to have a central area meant that we moved from an era before WWII with science carried out, in part by the wealthy. HMS

researchers were often those who could afford to be a scientist rather than practice medicine. It was a single, individual endocrinologist, a single person in hematology oncology, etc. to an enormous expansion of science. Science merited financially the ability to do research, not favored by a professor but by way to compete for grants. One of the great aspects of the intramural program was the great training of physicians. It was also an area where one could study rare orphan diseases that were of value, not only for that particular disease but diseases in general. It's one area, if you think of huge of areas of great growth and great opportunity. There was the Greek era of 5 centuries B.C., 1500s and Italy, machine revolution of the 1800s, currently the West coast and chip technology, and the NIH and biotechnology are some of the great eras of advance. Those were some of the eras of enormous advance and we are in one of them now. Some of it is now in the south of San Francisco and some is around here. These are areas of enormous achievement of the country and I feel one of the great investments has been in the NIH (both extramurally and intramurally). The post-WWII period started and was enriched by the doctor's draft, which meant that people who might not have come chose it. [Michael] Brown, [Joseph] Goldstein, Bob Leftkowitz, etc. It was part of their development and, clearly in part, because of the doctor's draft.

4. Can you describe how your mentees have helped you during your career?

Reflecting backwards, Carolyn Goldman and Gene Becker may have been called technicians, but each one was with me for 37 years. I may be responsible for the big direction and global idea of where the lab should go. I joke that I make slides and give talks. But how to get things to work and how to have the patience to get the experiment to work was in a major way from Carolyn Goldman and from an administrative way, Gene Decker. A person who has been with me until this week for 19 years was Mellie Zhang. How to make a mouse experiment to work? You need someone who is no longer a renaissance person. One needs people at all skill levels. So, there were Halcyon periods crammed within 4 modules. These were Stan Korsmeyer, Warner Green, and Takosha Myomi/Yuchioma [name unclear].

Stan Korsmeyer, if he had not died of lung cancer, would've won the Nobel Prize for his studies of the death pathways of cells. He came to me with maybe 2-3 weeks of summer experience in a lab. He came at wonderful time when Phil Leder was defining the Ig gene rearrangements along with Tsunoma and Lee Hood. He said, "You, Waldmann, are studying genetic immunodeficiency diseases. Wouldn't it be interesting to study this in Ig gene rearrangement? You're studying leukemias too. Wouldn't that be critical to study as well?" Stan went to Phil Leder to learn Ig and TCR rearrangement. He was able to use these insights.

The most important question, perhaps ever, in immunology was "how can the immune system identify millions of foreign antigens by B cells and T cells with a limited amount of genetic material?" It's the same way, in part, that alphabet can generate Shakespeare's plays through the rearrangement of letters. Units of the immune system rearranged in different patterns for different combinatorial events. Other events are hypermutations and so forth. This was amplified by Phil Leder and Lee Hood. Stan Korsmeyer played a dominant role and defined that we could use Ig and TCR rearrangement to define the

clonality of leukemias (or state of maturation at different stages of development). By studying these rearrangements, we could follow the efficacy of therapy of B or T cell malignancies.

As I said, Yuchioma came when we wanted to make a monoclonal Ab to CD4, but by accident made an Ab only reactive to cells that were activated (and not resting). It couldn't be CD4. Warner Leonard and Warner Green, with me, showed they were defining IL-2Rα only present on activated cells. We also used those Abs to clone the gene for IL-2Rα. One, with the trio's effort, entered the field of Ig gene rearrangement and Il-2. It's their ability to see what could not be explained by a prevailing paradigm. One has to think in new ways. Each of these opened up a whole new field that has stayed open for many decades. That was an era of great value. We are now in the era of IL-15. Again, we have the basic science of IL-15 with Millie Zheng doing animal studies and Miloslavich and Kevin Conlan doing clinical trials of combination therapy. The pathway of seeing and testing things remains: first using *ex vivo* cells from a patient, then cell lines, mouse models; then, developing new agents with the biopharma program at NCI for patients and collaborating with others; next, FDA approval.

Many times, getting it to work had been at the level of the technician. Getting it to interpret new insights though these people, who were in many cases coming to NIH due to the draft, the attractiveness of possibilities of cytokines and their Abs in the treatment of autoimmune diseases and leukemia, etc. One cannot emphasize too strongly how important the people in the lab are. It's not by chance that we are meeting in an office. This is where I live, whereas I depend on their actions. We interact, we talk, and we have meetings. It is through their hands that it gets done.

Cancer Immunology Research

5. What excites you about your research studying the IL-2/IL-15 receptor pathways in lymphocytes and their role in diseases?

Number 2 – developing new approaches to treatments of T cell leukemias, lymphomas and orphan diseases. There's often no standard for therapy.

Number 1 is combination therpay with IL-15. We have recognized the enormity of the impact of IL-15 on not only mouse and rhesus monkeys, but the human immune system. To become effective and make great advances in the immunotherapy of cancer, it needs to be used in combination therapy. You and I both know immunotherapy has become a hugely important aspect. It's important in removing checkpoints - removing the brake. Just like a car has a brake to stop, the immune system has PD1 and CTLA-4. We can block these with antibodies. I view IL-15 in combination therapy as a gas pedal of the immune system by increasing action. I also realize that because the immune system has so many brakes that would prevent IL-15 from acting on its own, it would need to be used in combination therapy. One is in the clinic being evaluated for action in 4-5 new clinical trials. They are just going through the review process. Each of which involve IL-15 to increase NK cell and macrophage activation. Used with a monoclonal Ab with (adcc/anti-CD40), IL-15 increases CD8 ccytotoxic lymphocytes. A 3rd study is underway

using IL-15 with checkpoint inhibitors (anti-CTLA-4/PD-1) to simultaneously have checkpoint release (get rid of hand and foot brake) and IL-15 as an accelerator. IL-15 in cancer immunotherapy could potentially be part of a multi-drug approach for therapy. I wish to continue until I know the outcome of the story in these areas.

Personal

6. What led to your interest in photography? Can you talk about this hobby?

When I was very young, for a short period of time, we (my family) had a car. For the most part, we lived during the Depression and WWII and did not have a car. When we had a car and went to the apple blossom festival in VA, my father bought me a $15 camera. I took pictures of the festival and the local camera dealer was so impressed that he gave me a $1.15 in exchange for a picture a $1.15 camera. My father was interested in photography and he had a roloflex that he took pictures with. Then, as I came to NIH I joined their photography group. Now, Sherm Weissman (who I should've mentioned, since we really went to the University of Chicago, HMS, and the NCI metabolism Branch together, as well as were Best Men at each other's weddings) in this context, was a demanding task master. One night a month, I went to the NIH camera club. In that era, I took color slide pictures in 2 large veins. One was nature photography - echoing my interest in nature and large-scale closeups. The other was in experimental photography to make (codol) and posterization for competitions at the NIH camera club. For 19/20 competitions, I was color slide photographer of the year. I still do it now, but it's focused on close portraits of my grandchildren. In part, this reflected the fact that it became so close to what you do in lab. But, now, with a modern camera, one could do what we couldn't do with a film camera. To do experimental photography to make a poster took a weekend - codeless to color and combinations of superimposed images. Experimental artist photography we can now do with a digital camera in a half hour to half a minute. It lost the competitive advantage. As science becomes more complex, more demanding, more in large measure, with the exception of pictures of family, I've stopped doing it. If I ever retire, it would be to go back to photography. The walls still have pictures of large prints in color of my wife's 60th anniversary and 90th birthday, a large volume of 8x10 pictures of family, all of them with portraits.

The same thing has the impact of scientific slides - simplicity and lighting. In other words, I often use the image "Where's Waldo?" Show people you know your slides are like "Where's Waldo?" If cut out and put on a background alone, you see him immediately. Keep simplicity and think about backlighting.

Being interested in nature meant I could have a lunomoth or monarch butterfly placed in position with a black background or icicle from the roof with the sun shining behind it. One was able to do things that were fun. And so, I do think that the same things can be held true to object and images projected on slides and as images in a printed research article. It's hard if you have it very complicated. I never use a pointer. I don't say, "I'm going to have to take you through this complicated slide." I will use multiple slides rather than a complicated image. It's an aspect of trying to keep a story. How do you start your story? I argue with people in my group. They have a certain way of doing a phase 1 trial.

What is the story? What is new? What is the impact? That's what I want the title to be and in the abstract. I want the story to develop in a rationale way and end with a discussion about the future, why it's exciting, and why they should be interested in what we told you because of what it implies. IL-15, even though it hasn't cured cancer, it has this opportunity to do so. I learned from photography for science. If you listened, I had no training in research at all.

The project we have going on, we can't afford to abandon. We want to see the orange out of the orange tree. Others left NIH to learn molecular biology or whatever else. I stayed, in part, because there was never an opportune moment to leave. It was always fun to stay.

7. **What about you would surprise most people?**

That I have become a cook. Until a few months ago, I had not cooked. Being lactose intolerant (not able to take cream, milk, or cheese) restricts where I can eat at outside restaurants. If I'm to eat a fancy mushroom soup, I have to make it myself or it will contain cream. No one would know me as a cook. Even my kids wouldn't know me as a cook. They certainly wouldn't know the red toilet seat story.

Final Question

8. **Anything else? Is there something we haven't talked about that you'd like to talk about?**

I think the polio story is one of the enormity of advances, both in medicine and immunology, that have occurred through the work of so many people. At a so-called 100 anniversary of NIH, Paul Berg and others gave a lecture and likened science to a river. That is, there may be a few eddies and backflows, but there are constantly additions and tributaries adding to it so the flow is always advancing. One may never do better than Beethoven in art, but science builds on what goes on in the past. All of us are enormously helped by science of past and by the huge number of people that contribute to the field. Certainly, the field of immunology has changed from looking through a glass darkly during a tough time (as the stepchild of biochemistry) and so forth. It was really very valuable and hypothetically moved from a phenomenal effort to unbelievably rigorous science. After years, it has taken full place with the therapy of patients. Jenner is a critical element. It is not chance that every institute of NIH has an immunological component. It is the openness and cooperativeness of the immunological community of NIH that I have learned so much. That aspect of NIH exceeds for certain my alma mater of Harvard, where it's very competitive. Here, I feel the cooperativeness. Five decades ago, a meeting started with 5 people interested in the theory of the immune system and how it could make Abs. That has blossomed to full meetings at Lipsett [Auditorium] and cooperative groups that meet in Masur auditorium.

It's intriguing that something that occurred 50 years ago in 1959 - almost 60 years ago - could have a hyperbolic gene discovered. We had a brother and sister who had low albumin and gammaglobulin, as well as were hypercatabolic. Their proteins were rapidly destroyed and had short survival and did not know why. Decades later, someone from

Cincinnati called us and asked, “Can you send us tissue from those patients?” From the serum, they were able to define the gene that was wrong. It was beta 2 microglobulin, which is involved in the protection system of albumin. We often learn by research and going back to problems. We go a certain distance forward with research techniques at the moment. Go back 3- 5 decades later, and you get new insights into molecular errors and rationale therapies to diseases that were enigmatic. The theme of returning to issues of past where we define new diseases, new molecular errors, and new therapies.

The greatest strength is making connections and combinations of associations. If we are having a lecture, it is of value to me if I can associate it with my own work or some other thought.