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Research in Jeopardy

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Since my talk is called Research in Jeopardy, I will introduce the subject with 5 questions in a *Jeopardy* game format, then take each one and use them to discuss the true objective of my talk, Research in Jeopardy.

1. Daniel Bovet won the 1957 Nobel Prize for Physiology or Medicine for his discovery of this substance that served as the basis for an effective therapy against allergic reactions and acid-related diseases. What is this substance?

The first answer is **Histamine**.

Let's start by looking at a typical parenteral nutrition (PN) bag. As most of you know the story of PN's development, I will tell a different story, one that relates to a single additive found in almost every bag of PN, ranitidine, a histamine-2 antagonist.

In fact, this story is really an investigation that moves from obscurity to discovery and then on to commercial success. The story began in 1910 with the discovery by Henry Dale of histamine on a group of unusual mold formations found on the grain rye. Dale worked for Wellcome Laboratories, a pharmaceutical company, and for this discovery he was subsequently knighted and awarded the Nobel Prize.[1] In this case, an initial investment in research by the pharmaceutical industry led to an entirely new venue of investigation. This was followed in 1937 by the discovery by a number of university investigators of the first antihistamine, one that would eventually become a common antihistamine that is, of course, now used by millions for cold and allergy symptoms.

In the 1950s, several investigators identified the unusual finding of histamine within the wall of the stomach, but its function and significance remained unknown. However, based on this scant preliminary evidence, the pharmaceutical industry again took up the investigation of antihistamines, this time under James Black and his research group. Their radical strategy was to block H2 action and control stomach acid secretion. Some 16 years later, they identified the first H2 antagonist, a compound that we now call Tagamet® or cimetidine, a drug that has a profound benefit in the treatment and prevention of peptic ulcers and is available at any pharmacy counter.

So 100 years later, one line of drugs, 62 years of investment and research, and the dedication and commitment of government funding, pharmaceutical support, and academic insight were able to achieve an incredible line of therapeutics. The total commercial sales for this class of drug totals roughly $58 billion from 1979 to today.[1]

2. What number do you get when you add 36 plus 36 and subtract 14?

The second *Jeopardy* answer is the **number 58**, or $58 billion, almost twice the 2014 National Institutes of Health (NIH) yearly budget.[2]

When you look at this incredible achievement, you observe that success was entirely due to a partnership between 3 critical entities: government funding, academic investigation, and the pharmaceutical industry. In synchrony with each other, this partnership has produced some incredible achievements, including novel drugs and important nutrient products, all of which have had an enormous impact on our patients' health (Figure 1).

However, when one of these elements fails, the gears falls out of synchrony. The results have far graver consequences than what may initially be perceived.

Where are we today? In fact, I am among the vast majority of researchers who are convinced that we have fallen out of this synchronized state.[2] Unfortunately, most pharmaceutical corporations and government funding agencies no longer demonstrate the dedication or commitment to support such long-term endeavors as the development of H2 antagonists. Many corporations are driven by yearly or even quarterly profit reports. A decline during any quarter may mean moving away from critical areas

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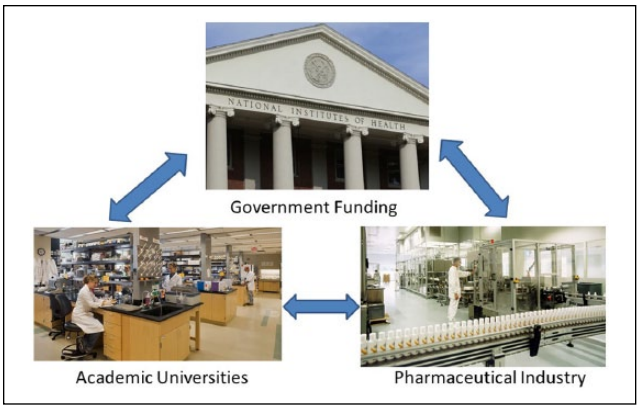

Figure 1. Partnerships to achieve research advancements.

of novel investigation, some of which might mean the next great nutrition advancement. A 62-year commitment just does not fly in our current world. Furthermore, most NIH study sections rarely support projects that last beyond 1–2 funding cycles.

3. What year did the song, "We Built This City," by Jefferson Starship reach number 1 as a billboard chart single?

Our next Jeopardy answer is **1985**.

While there had been tremendous increases in NIH funding in the early 1980s, then another jump in funding around the year 2000, when corrected for inflation, funding for U.S. research has not increased since 1985.[3]

In fact, funding has actually declined over the past decade. NIH funding, the key driver of innovative research and knowledge in U.S. academic institutions, has not changed in over 15 years and has declined by 20% since 2004.

So how does this match up with the general economic realities in the United States? During virtually this same period of time, despite low inflation rates, prices have not remained frozen. Looking at the economy 30 years ago in 1984 dollars, median salaries, the cost of a new home, and the price of a car have gone up dramatically.

4. Which animated Disney movie has main characters named Anna and Elsa?

The next Jeopardy answer is ***Frozen***.

I submit that research scientists have entered into a true ice age. In fact, the term *Frozen* very accurately describes our current state of research in the United States.

Classic funding via an NIH R01 grant, the main mechanism for most academic researchers, has remained fixed at $250,000 for the past 25 years. This leaves researchers in the terrible predicament of paying 2014 wages and 2014 laboratory supply costs with funding levels from almost 3 decades ago. Investigators are forced to go to extreme measures with a resulting decline in research productivity, fewer successfully funded laboratories, and far fewer young investigators who want to take up this challenge.

What are the implications of this decline? In a country with an economy that is otherwise growing, fixed levels of funding mean that far fewer scientists will receive NIH funding. The chances of a researcher receiving funding on a grant proposal after the first submission is only 8.5%, and even after resubmission, this rises only to 17%. One would do better with gambling at a blackjack table than submitting an NIH grant. And for those who do not make the narrow funding cut, the outcome is becoming quite dismal.

In fact, in 2014, more than 3500 established NIH investigators shut down their laboratories permanently, and 47% of scientists abandoned an area of potentially fruitful investigation. Think about that ergot mold growing on rye that generated $58 billion—would that ever have a chance of getting funded in this environment?

The loss of each laboratory leads to the loss of knowledge, experience, and a line of work that may never be replaced. The closure of a laboratory also represents the loss of future ideas and innovations. As each laboratory closes, one also closes an opportunity for our young scientists. Young and bright scientists begin in research as postdoctoral fellows, yet many move from research into other careers, such as consultancy, industry sales, clinical work, or teaching. While the reasons are varied, each clearly sees that the prospects of an academic research career are not what they once were. Less than 16% of PhDs will ever get a faculty position, and fewer than 10% of PhDs ever become a principal investigator.

5. Which Greek mythology character ignored his father's warnings and flew too close to the Sun, melting the wings that his father had made for them both to escape the island on which they were imprisoned by King Minos of Crete?

So now for our "final" *Jeopardy* question—the tough one: **Icarus**.

In an outstanding recent book by Seth Godin, *The Icarus Deception*, the author relates the ancient mythological story of Daedalus and his son Icarus, who are prisoners on the island of Crete. They cleverly escaped from their captor, King Minos, by building wings of wax and feathers. Now, many of us will remember the part about the father warning Icarus about flying too high and letting his wings melt. In fact, Daedalus warns Icarus of an even greater danger: flying too low, getting his wings wet on the seawater, and losing his lift.

To quote Godin: "It's far more dangerous to fly too low than too high, because it feels *safe* to fly low. We settle for low expectations and small dreams and guarantee ourselves less than we are capable of."[4]

I chose this example, as I know our research efforts in the United States are flying dangerously too low. We are setting

our expectations far too low. And, just as Daedalus warned his son, we are of course setting ourselves up for a potentially terrible demise.

So, what options do we as medical professionals have?

We are at a cusp, for without significant and doubling of NIH funding over the next decade, we will see that empty research laboratories and online advertisements selling off laboratory equipment will be our only legacy.

However, we can take a different direction, and I firmly believe we can move ahead. The past 20 years have resulted in the most dramatic advancements in all of medical history: the cloning of the human genome, stem cell technology, antiviral therapies, advanced imaging, and technological marvels such as robotic surgery.

Yet this is really just the beginning. We are at the verge of some incredible achievements in human health, all of which directly affect how we as medical professionals will nutritionally care for our patients.

Many of us may have heard President Obama talk about personalized medicine being the next forefront. In many ways, nutrition is a prime example of how we can tailor the nutrition needs of our patients in a highly individualized fashion that addresses their unique genetic and metabolic processes. Furthermore, advanced bioinformatics will allow us to align not just the human genome but also proteomics, metabolomics, and metagenomics. Tissue engineering and nanotechnology innovations hold tremendous promise for treating diseased organs and cancers in ways we have never before conceived. We should not let these incredibly valuable opportunities pass us by!

But what can we do?

First, I would like to call your attention to what the American Society for Parenteral and Enteral Nutrition (ASPEN) is doing to support research. Over the past 3 years, ASPEN, through the great work of Peggi Guenter and our Research Committee, has developed a detailed research agenda.[5] This agenda serves to help guide current and future researchers and investigators to the most critical areas where new research in nutrition support is needed. This was published 1 year ago in the *Journal of Parenteral and Enteral Nutrition*, and I ask that you take a look at this outstanding work.

Second, I want to emphasize the incredible work that the ASPEN Rhoads Research Foundation is doing. The 2015 Rhoads grant awardees are a spectacular group of individuals. Each year as I look at the quality of research in these proposals, I am completely blown away by how far our nutrition research efforts have advanced. Since 1994, more than $1.3 million has been awarded to over 65 individuals. Many of these awards have been to men and women in the audience today who represent our current and future nutrition leaders. I ask that each of you strongly consider making a contribution to this foundation and help to secure our future legacy in nutrition research.

Third, as Congress decides the next budget priorities this winter, it is very important that your senators and congressional representatives hear from you. While the Congress is set to keep research funding at *Frozen* levels, the Federation of American Societies for Experimental Biology and several other scientific groups have advocated for significant increases this year. I want to emphasize that this is not a question of Republicans vs Democrats. We need to speak as a common group for what is needed for our patients. With the U.S. economy stronger than it has been in the past decade, we should not let this opportunity pass us by.

Fourth, I encourage the leaders of our nutrition and pharmaceutical corporations to invest in research and development efforts to improve the nutrition care of our patients. They play a critical role in our success.

Each attendee to Clinical Nutrition Week and member of ASPEN will receive a brief message from me today. The message will guide you to contribute to our Rhoads research foundation. It will also provide you with a link to communicate to your congressional representatives and let them know that you want to see research funding advance in our country. I ask each of you to make a contribution and act as an advocate for research. If each of you in this audience could contribute $5, we could eventually help to fund 2 more small research grants. Please do not let this message slip by. If we do not act now, the future we are creating for our next generation of researchers will not be a pretty one!

To close, I hope that your time at Clinical Nutrition Week is enlightening, educational, and most of all enjoyable. I look forward to interacting with many of you over the next few days.

Acknowledgments

I want to thank Gordon Sacks for that great introduction. It was really appreciated. I want to thank several ASPEN leaders who I have been fortunate to have worked with and train under. My first exposure to nutrition was unfortunately not in medical school, a major issue our organization is trying to work on, but rather during my surgery residency.

Jeff Fabri, Jay Mirtallo, Ken Kudsk, and Phil Schneider were all at Ohio State at the time I was starting my general surgery residency. You can only imagine the incredible exposure and nutrition training I would get on a daily basis on my morning rounds with this incredible group of individuals, all of whom became future ASPEN presidents.

When I moved into the specialty of pediatric surgery, my next 2 mentors were Denis King at Columbus Children's Hospital and then John Wesley who had just left the University of Michigan by the time I had arrived there. Both of them left an indelible impact on my career. Both of these physicians impressed upon me an incredible knowledge and appreciation for the unique nutrition needs of infants and children. What I learned from all of these wonderful individuals I still use today, and each has helped me develop my academic career in this field.

And then came the incredible PEN (parenteral and enteral nutrition) team at Michigan for which I had the honor to work with so many wonderful professionals: David August, Nabil Khalidi,

Imad Btaiche, Carol Braunschweig, Deb Kovacevich, Theresa Han Markey, Bonnie Peterson, Annie Perrez, and Luisa Partipilo. In more recent years, our PEN team has evolved, and I have had the opportunity to work with many additional colleagues, including, Mike Kraft, Jenn Wooley, Jill Cherry, Petrea Cober, and Allison Blackmer. Now there is my current Intestinal Rehabilitation team—or ChIRP. Their work and dedication have been a real dream to see come to fruition and have been an incredible benefit to hundreds of children with this unfortunate disorder. Thank you for your lessons, mentorship, and support. Now I thought a lot about how to convey a message to our audience today that truly is dear to my heart.

I also want to thank several people for making this day possible. First, I want to give my thanks to an amazing board of directors. I encourage you to seek them out this week and get to know them these next 3 days. Second, I want to thank Debra BenAvram and her amazing staff of professionals at ASPEN. While they are almost always working behind the scenes, they are the true engine that makes ASPEN the success it is. And they certainly keep me from getting tangled up.

Finally, I want to thank my 3 children: Hannah (who was fortunately able to be here today), Abigail, and Rachel. Certainly I thank most my wife Mindy for being understanding and patient when I was gone these past few years at Clinical Nutrition Week, our monthly board meetings, and of course our memorable weekly Monday evening conference calls.

Note

Charlene Compher, PhD, RD, edited Dr. Teitelbaum's draft remarks slightly to prepare them for publication.

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