

Science and Judaism: Chemist's Perspective

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Shabbat Shalom.

It is a pleasure and honor to open up a season of discussions that will explore the intersection of science and Judaism. It is rich and open territory, and I only wish today to start the conversation which is an extension of the program Rim started last year around cosmology and Judaism. Science and religion are generally thought of as being at odds, especially since one is based on theory, testing, and observation to explain reality whereas the other is based on the interpretation of ancient scrolls often describing occurrences beyond our experience and imagination. It is not my goal to reconcile this or to describe how passages of the Torah allegorically interpreted are not inconsistent with scientific knowledge. My practice of Judaism however has come naturally from my scientific experience as Judaism invites QUESTIONING, REASONING and DEBATE. The Bible is not meant to be taken literally and there is no authoritative or definitive interpretation. In the biochemistry I practice, I obsess with understanding our natural world and how to use that knowledge to improve the state of man and his environment. In Judaism, I obsess with understanding our human place in our natural world, and how I can make the world a better place. Tikkun Olam is at the heart of my practice of both science and Judaism.

Religious practice and science both invite us to ponder “why and how are we here.” In a few days, we celebrate the birthday of the world, which is according to the Torah is 5779 years old, whereas science informs us that it is indeed billions of years older. As a chemist, I am more fascinated by the question of the mechanics and mechanism of how the building blocks of life were selected and how they agglomerated into the entities we know as cells, how replication came about to perpetuate life, and how the high level of organization of even single cells, never mind whole organisms could become energetically stabilized against the tendency of systems to devolve towards chaotic states. In my early career, I studied methanogenic bacteria, the oldest organisms on earth, originating perhaps 3.5 billion years ago, just 1 billion years after the earth was formed. The formation of life on earth seems quick and inevitable--given that it has been around for most of the time the earth has existed. But life as we know it is vastly improbable as well and the subject of limitless speculation and inquiry as to its origin. Methanogens live at extreme temperatures in deep sea vents and thrive in the absence of oxygen—sounds like the best place for life on earth to have originated but extreme conditions may have enhanced chemical reactivity needed to create life's molecules. A famous biochemical experiment involved electrolysis of a noxious soup of ammonia, methane, carbon monoxide and sulfur dioxide, essentially mimicking the extreme conditions of a primordial earth. This reaction yielded nucleic acids and amino acids, the building blocks of DNA and proteins. Was it as simple as this??? A flash of lightning started life on earth? That explanation of life's origins is but a fragment of knowledge needed to account for the improbability of life as

we know it. How did these building blocks condense into polymers and organize into molecular machinery? Just think—the possible proteins of 100 amino acids in length constitute more combinations than there are atoms in the universe, and yet, and yet life has selected the 10,000 or so that work. A single protein unwound can assume more shapes or conformations than there are stars, yet it folds into a discrete form that conducts a specific chemical or physical task. How could these functions have been selected for when the combinations are seemingly endless and infinite? A recent theory posits that life actually originated from RNA, the oft ignored step child of DNA, as it can hold genetic information but also is chemically reactive in a way that DNA is not. More pieces, but still, there are many missing links from building blocks to replicating cells. When we utter the words *B'reishit*, in the beginning, we are lost in the complexity and the infinite possibilities. Scientific theories, however close to the truth they may be are still filled with improbabilities and wonder, and so this is certainly one area where science and the divine meet—in the unknown of how we are here and why where we are here. We can attempt to drill down to answer questions, but we are limited by the resolving power of our lens, not by our imagination. To me, both the scientific and the religious explanations are ultimately wanting on a literal level.

The difficulty of answering a “simple” question such as the origin of life is part of my daily scientific experience. Scientific answers and solutions are frustratingly hard to get to, definitive experiments are difficult to design, and new layers of information are always waiting to be discovered. It is an ongoing collaborative process requiring years of learning, and generations of supporting knowledge, not unlike Torah interpretations. So, personally, I have started to consider where my scientific life and my Jewish life intersect. It is not honest to say that that my Jewish identity informs my scientific approach, and I came to science long before I came to Judaism. Rather, my understanding, practice, love and frustration with science has found resonance in my practice and celebration of Judaism and in the teachings of Torah.

The story of Abram as told in Lech Lecha is an epic story of the founding of the Jewish lineage, the creation of a covenant with God, it is the story of self discovery and the destiny of a people. It is quite out of proportion with the perils and challenges of scientific discovery, but still illustrative in an allegorical sense. I have started on many a scientific journey with some idea of the destination and an ultimate goal, but nevertheless filled with trepidation, little assurance of where I will end up, even less assurance of when and if I will ever get there. Frequently, one ends up in a scientific Egypt—a safe haven, but temporary and certainly off course from the true direction. Motivated by a higher sense of purpose, (for me patients in need), and a faith in achieving success one is able to recognize that further journeying and resilience is required to persevere through these challenges. And adaptability and an open mind is needed as well. Sara's insistence that Abram conceive a child through the nursemaid Hagar was not his preferred path to assuring the multiplicity of his descendants, but it was the option that he chose when presented with a more promising opportunity.

I work in the pharmaceutical industry. The success rate in pharmaceutical development is about 5%--incredibly low. 95% of drug development programs fail somewhere in between initial discovery and the ultimate proving ground of Phase 3 trials. With that kind of batting average, you wouldn't make it very far with Red Sox, and it would probably lead to a depressing obsession with futility. In my first job, I was assigned the task of discovering and designing an imaging agent to visualize blood clots on an MRI. Over 100,000 people annually get potentially life threatening clots, including myself, that are difficult to diagnose via conventional methods. I needed to find a compound that would home in on clots specifically, wherever they may be (lung, heart, legs) and meanwhile ignore tissues in the body, and especially, the constituents of blood. This posed an initial problem as blood clots are essentially made up of blood. But in understanding the molecular differences between unclotted and clotted blood, I could develop a strategy for screening compounds to bind to the clots and not get washed away in the blood components. I screened through over 10 billion different peptides to find two or three unique compounds with the right specificity and binding properties. And this was only the beginning of an eight-year process. Stability of the compound in the body needed to be increased. The peptide needed to be modified to increase its binding affinity to clots, and it needed to be chemically modified so as to light up in an MRI scan. At each step of refinement and up to the point that the compound went into patients, it was unclear as to whether it would work—would it last long enough in circulation to home in on the clot? Would it buildup to a high enough level to make the clot detectable? Would there be undesirable side effects? Yes, it did work and indeed this agent revealed images in an eighty year old woman with clots detected not only where they were suspected but elsewhere where they were not. So incredibly gratifying that this long process of inquiry and engineering could lead to something beneficial and even life saving for people. But... it is still unrealized, the compound sitting on a shelf. As quoted from Pirkei Avot, one hour of pleasure in the world to come is better than all the time in this world.

In a second journey, for the last 12 years, I am trying to find new drugs to treat cystic fibrosis, a debilitating and lethal disease. 20 years ago, the life expectancy was about 18 years old. Today, through medical and scientific expanses, life expectancy has advanced beyond 40 years, a truly remarkable achievement, but finding a cure remains a critical unmet need. If not now, when?

We have screened through over 1 million compounds to find just a handful that have the potential to ameliorate this condition. Among these several have already failed upon further examination. For other remaining leads, further optimization and then clinical testing is required. Despite all this, still being so far from the goal even after plugging away at it for so long, the potential impact to tens of thousands of patients and their families and communities is immeasurable. So another reminder from Pirkei Avot, the compendium of rabbinical wisdom, rings true--it is not incumbent on you to complete the work but neither are you to desist from it. And in this endeavor, we are at the very least creating hope. But the power of

hope, and here is another point of intersection with the divine, cannot be underestimated. The knowledge that we have identified compounds that could fully reverse the underlying dysfunctions in cystic fibrosis provide a motivation for patients to continue on their time consuming and life dominating therapeutic regimes with the expectation that improvements that will be further life extending will be soon available.

Creating new molecules is in a sense a continuation of the process of creation that I described earlier. Rather than considering a moment of creation, our creativity as scientists is a continuum from The Beginning--*B'reishit*. As chaotic chemical reactivity may have given rise to life, chemist use controlled methods, selecting the proper starting materials and reaction conditions so that new entities that did not previously exist may emerge with beneficial properties for our lives. Perhaps that can be regarded as Godlike or divine, and certainly the ability to attack disease using chemistry and rational thought is a divine gift. Or at least I think it is. And the reason that I come to Shir Tikvah is to get closer to recognizing, nurturing and being thankful for that gift despite the challenges and burdens it brings.