

The Germination of Alexander Keynan (1921-2012)

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The subject, one might say also the object, of Alex Keynan's life was germination. Alex worked a great deal on the *Bacillus subtilis*, the hay or grass bacillus. *Bacillus subtilis* has the ability to form a tough, protective endospore, allowing the organism to tolerate extreme environmental conditions, including cooking. Such spores may remain dormant for years, indeed for centuries.

Unlike several well-known closely related species, *Bacillus subtilis* causes disease only in severely immune-compromised patients, and conversely serves as a probiotic in healthy individuals. Soldiers used it during World War II to counteract dysentery, as Bedouins had done since ever. It is a characteristically Levantine organism.

Bacillus subtilis was Alex' favorite model organism. Probiotics have become a popular notion, but Alex had chosen this as his favorite long before health food companies began to pepper us with adds for the multitude of friendly microorganisms that bring us benefits.

The titles of some of Alex' most influential papers included "Activation of bacterial endospores," "Spore structure and its relation to resistance, dormancy, and germination," and "Transformation of a dormant spore into a vegetative cell." These papers were co-authored with his many life-long friends, including Cyrus Levinthal, Harlyn Halvorson, Woody Hastings, and Hans Kornberg.

Alex was fascinated and tempted by dormancy, apparent metabolic inactivity. In Alex' view dormancy had two distinct meanings. Dormancy usually described the apparent metabolic inactivity of the spore stage as compared with the vegetative cell. But it could also describe a spore suspension that responds poorly or not at all to germination agents under conditions that permit rapid germination of aged or heat-activated spores. This latter sense of unexploited potential, only needing an extra stimulus, especially fascinated Alex.

It is noteworthy in the papers that Alex would induce germination through both warmth and acid. He preferred warmth, which Alex and his extraordinary wife Malka generated so naturally, but when a bit of acid was required he would apply it.

To summarize his work as a microbiologist, Alex analyzed inhibitors of synthesis.

I was introduced to Alex in 1989 by Joshua Lederberg, with whom he had been friends since about 1950, from meetings at the Cold Spring Harbor Laboratory. I was directing a study funded by another close friend of Alex, David Hamburg, then President of the Carnegie Corporation of New York, on the use of technical expertise by the US government, a vast desert of dormant spores. We wanted some views of US behavior from outside the US. Alex had long experience in cooperation with the US, bilaterally with Israel, trilaterally with the Israel and Egypt, and multilaterally through the World Health Organization.

During a sabbatical at The Rockefeller University in 1990 in New York City, Alex wrote an insightful and diplomatic essay, almost 100 pages, titled :“The United States as a partner in scientific and technological cooperation : some perspectives from across the Atlantic.” Published in 1991, the essay documented many spores that the US had neglected to germinate.

Alex had co-chaired the Committee for Scientific Cooperation between Israel and Egypt from 1979 to 1984, so he understood about political spores and dormancy. In fact, the subject of the history of studies of scientists' roles in international conflict resolution became a great subject of the rest of Alex' life, neatly parallel to cryptobiosis.

After the bombs of World War II, scientists became increasingly aware of their social responsibilities. Some scientists used their communication networks not only for cooperation in science, but also to reach across international lines of conflict, in attempts to mitigate such conflicts. Some of these activities are well known and documented -- for instance, the activities of the international Pugwash movement, with which Alex had been involved for many years. Many other activities of similar nature but smaller in scope, or limited to regional conflict, were little known and less documented. Scholars had not examined these activities and their influence on international relations. Alex was aware of their increasing scope and concluded that they merited serious study. Their recognition spring some out of a vegetative state.

In 1995, Alex launched studies on "Scientific Cooperation and Conflict Resolution" cultivated especially during summers at his beloved Marine Biological Laboratory in Woods Hole, Massachusetts, where he had first worked on cryptogenesis about 1960. In 1996 Carnegie Corporation supported a 3-year project conducted under the auspices of the New York Academy of Sciences. The project began with case studies on particular conflicts (such as Israel-Egypt and US-USSR), institutions (such as Pugwash), and natural science disciplines (such as seismology). Most of the studies were conducted by scientists who themselves participated in attempts to use scientific cooperation for international conflict mitigation and drew on many interviews with other scientists involved in these activities.

An international conference in 1998 at the New York Academy of Sciences on Scientific Cooperation, *State Conflict: the Role of Scientists in Mitigating International Discord* discussed the case studies as well as a synthesis of the literature that Alex prepared. The New York Academy of Sciences (NYAS) published selected papers from the conference in 1998, edited by Alex. The volume contains 10 examinations of scientists' efforts to mitigate international conflicts as well as Alex' introductory essay summarizing the literature, case studies, and discussions at the meeting. At publication this volume was the most complete (and probably the only) study on this subject based on much empirical data.

Alex' own essays for volume included not only the over view on *The Political Impact of Scientific Cooperation on Nations in Conflict*, but also "Scientific cooperation in agriculture and medical research as a means for normalizing relations between Egypt and Israel" with Dany Shoham.

Although the NYAS project included a case study of the Argentina-Brazil conflict, it emphasized U.S. experience during the Cold War and the Middle Eastern conflict. Attendees at the New York conference pointed to the wealth of experience of cooperation among European scientists after World War II within Europe. Moreover, the NYAS project did not include studies of cooperation in the social sciences nor make much use of the analytic frameworks of the social sciences for examining the experiences in question.

Mindful of these omissions, the French historian of science Jean-Jacques Salomon, another activated friend of Alex, offered to convene a conference based on European experience, broadening the scope of scholarly networks considered to include such disciplines as economics, and deepening the perspectives offered by political economy and other fields. The meeting, titled "The Impact of Scientific Cooperation between Nations: Preventing and Solving Conflicts," was held in Paris. Sponsors of the meeting included NATO's Scientific Division and the *Ministere francais des affaires etrangeres*. The organizing committee included Andre Lebeau, founder of the European Space Agency, and Hugues de Jouvenel, son of Bertrand de Jouvenel, author of the classic "On power: The Natural History of Its Growth," written during World War II in occupied France. De Jouvenel wrote that politics is the last repository of hope, but perhaps science is truly the last repository of hope. The result of the Paris project was a volume, *Scientists, War, and Diplomacy: European Perspectives*, *Technology in Society* 23(3), 2001, rich in history and nuance and re-examining forgotten spores (table of content attached).

Meanwhile, Alex continued his long interest in luminous bacteria. Luminescence had led him to the now burgeoning topic of quorum sensing. Quorum sensing is a system of stimulus and response correlated to the density of a population of bacteria and perhaps larger organisms too. Many kinds of bacteria use quorum sensing to coordinate gene expression

depending on the density of their local population. Some social insects use quorum sensing to determine where to nest.

Bacteria that use quorum sensing secrete signaling molecules, often pheromones. The bacteria also have a receptor that can detect the signaling molecule. When the inducer binds the receptor, it activates transcription of certain genes, including those for inducer synthesis. One bacterium is unlikely to encounter or detect its own secreted inducer. Thus, for gene transcription to be activated, the cell will likely have encountered signaling molecules secreted by other cells in its environment. If few bacteria of the same kind are present, diffusion reduces the concentration of the inducer in the surrounding medium to near zero, so the bacteria in turn produce little inducer. As population rises, the concentration of the inducer passes a threshold and causes more inducer to be synthesized. The positive feedback loop can fully activate the receptor.

Coordinated behavior of bacterial cells can, for instance, cause bioluminescence. The bright Luciferase produced by *Vibrio fischeri* would not be visible if it were produced by only a single cell.

Quorum sensing implies cooperative behavior. Cooperative concepts tend to be challenged for their evolutionary implication, which favors the selfish. Alex had no problem seeing evolution as a balance of cooperative and selfish processes. The final technical paper he co-authored was titled "Quorum Sensing Influences *Vibrio harveyi* Growth Rates in a Manner Not Fully Accounted For by the Marker Effect of Bioluminescence" in 2008 in PLoS One with Zeena Nackerdien, Bonnie Bassler, Joshua Lederberg, and David Thaler. The paper has been viewed more than 7,000 times, healthy for a scientist who published his first scientific paper almost 60 years earlier.

The theme of Alex' long career was remarkably consistent, from microbiology to macro politics. He was concerned with inhibitors of germination. As we have heard these past two days, he was remarkably effective at overcoming these inhibitions, in the laboratory, in the careers of his colleagues, in universities and other research institutions, in science as a whole, in Israel, between nations in conflict. The consequence was the many careers, institutions, and programs he caused to germinate and the remarkable network of "The Friends of Alex." Many are here today, and I bring greetings from another dozen in the USA, including in alphabetical order Gary Borisy, David Hamburg, Woody Hastings, Howard Hiatt, David Kirsch, Hans Kornberg, Marguerite Lederberg, Paul Marks, Rodney Nichols, and David Thaler as well as Doris Manville and Iddo Wernick from my own group. I am sure the Revson and Rudin foundations would also want to be mentioned. And if they were still with us Josh Lederberg, Norton Zinder, and Harlyn Halvorson.

At one time or another Alex found all of us in an ametabolic state and with lots of warmth and occasionally just a little acid brought us to life. May we carry on his work of germination and the cooperative behavior he found so deeply rooted in biology. Thank you very much.

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