The Living and Dead Chemical Called a Virus

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At a recent seminar at the University of California Irvine, Dr. Eckhard Wimmer of Stony Brook University presented a talk entitled "Studies on the life cycle of a chemical called poliovirus". During that seminar the question was posed: is a virus a chemical or is it alive? His answer to this question was **yes**. I agree completely with this seemingly vague answer that might appear to be nonsense to some. Yes is an appropriate answer because viruses are both chemicals and at times alive. In a recent article I published in Scientific American, I also presented the arguments for thinking of viruses as both chemicals and alive and argued for the need to include them in the tree of life. For Dr. Wimmer, with his early background in chemistry, thinking of viruses as chemicals is most appropriate. After all, it was Dr. Wimmer's group that first produced infectious poliovirus in a test tube (using in vitro translation systems). Dr. Wimmer often likes to start his seminars with the chemical formula of poliovirus ($C_{332,652}$ $H_{492,388}$ $N_{98,245}$ $O_{131,196}$ $P_{7,501}$ $S_{2,340}$). The crowning achievement along these lines was the chemical synthesis of poliovirus genome from scratch followed by the production of infectious virus in a test tube. Thus not only did Dr. Wimmer and colleagues make the chemical of poliovirus, they also reproduced its life cycle in a test tube.

Chemicals, even as complex as virus can be synthesized. However, Dr. Wimmer did not anticipate the irrational political firestorm that would result from his chemical synthesis as many came to believe that he had let the genie out of the bottle and would allow bioterrorist to custom order any virus via the internet. Irrational reactions to viruses and vaccines, even by virologists, however, have a long and proud tradition in all human cultures. After all, Jenner's smallpox vaccine was initially banned in Boston much as poliovirus vaccination was recently banned in Nigeria. The biological reality, however, is much more mundane. One need not bother with such molecular biological gymnastics to make a virus from scratch. Anyone wanting an authentic human-adapted viral pathogen would be much better off simply hanging out (in Africa for example) waiting for the next outbreak of take your pick; Ebola, Marburg, Monkeypox or poliovirus to occur. They would not have to wait too long as this year's outbreaks have shown. (Smallpox being an eradicated virus is another story but remains beyond the technical capacities of individuals). But wait one minute! Do chemicals cause epidemics?

It is, however, equally justified to think of viruses as alive, at least at times. Viruses can clearly be killed. They are subjected to the same evolutionary laws and principles of fitness as are any living organism. They have sex (via recombination) and produce many progeny. Although they may lack all the essential machinery for their own reproduction, as Dr. Wimmer showed, this can be provided in a test tube whose constituents are completely known, avoiding the need for invoking any vitalistic concept. Viruses have major consequence to the biosphere. During the living portion of their life cycle, they become one with their cellular host and replicate. They are able to invent genes in large numbers and can determine who will survive and who will parish. They (and their

defective derivatives) are found to reside in the genomes of all living things. Our very own DNA has much more endogenous retroviral elements then it has genes, for example. Thus viruses are embedded into the very fabric of all life. They must be alive.

This issue of whether viruses are dead chemicals or living agents is not just a theoretical musing of a bored virologist. The life and death of a virus matters very much to our own health. Consider, for example, the current global effort to eradicate poliovirus. Nigeria's irrational reaction to poliovirus vaccines threatens the entire world, as the recent outbreak in Indonesia has shown. The live poliovirus vaccine as originally developed by Sabin has been highly effective and economical in controlling poliovirus epidemics. However, a 'live' vaccine can create a life of its own by evolving beyond the intentions of its human developers. Living viruses, like these vaccines, generate genetic variation that drives adaptation and evolution. Selecting for increased replication can increase fitness, resulting in a fully infectious poliovirus able to cause outbreaks of paralytic disease. Thus use of these live vaccines is now often the evolutionary source of new poliovirus outbreaks. Pay attention anti-evolutionists: this is the applied science of evolution in its purest and simplest form and the survival of a person infected with HIV, hepatitis C virus or poliovirus will depend very much on the evolutionary trajectory taken by that virus. Not believing in evolution won't offer much protection. Although live poliovirus vaccines are cheaper to make and easy to administer in third world settings, live poliovirus vaccines must now be abandoned for dead vaccines (such as the Salk vaccine). Interestingly, the distinction between a live and dead version of poliovirus is not always clear-cut. It is possible to make an incapacitated version of poliovirus that is 'quasi-live', or mostly dead, depending on one's perspective. This concept is reminiscent of a scene from the movie "Princess Bride" in which the Miracle Max character played by Billy Crystal notes that the tortured prostate hero (the ever reborn Dread Pirate Roberts) is only 'mostly dead' and can still be revived. A 'quasi-live' virus is one whose genome is severely incapacitated, but can still replicate sufficiently in order to allow variants with a corrected template to be made resulting in the selection and growth of these more fit variants, but not growth of the original 'quasi-live' template. These viruses cross the very threshold of the living and chemical world. After all, a dead virus can simply be a chemical variant of a live one, a single well placed chemical bond can do the trick, separating live from dead. What is one chemical bond? An electron shared by two atomic nuclei that can separate the living from the dead. Can this be described by a wave equation? Well, yes. What would Erwin Schrodinger, author of *What is Life?* have said to that?

Such observations tend to confuse us and to question our very definitions. But perhaps our confusion is simply the result of our limited state of mind in which we strive to categorize things too neatly. In ending his seminar, Dr. Wimmer reminded us of a similar state of confusion that once existed in the physics community. Physicists once struggled to define an electron: is it a wave or a particle? The answer is yes. It is both, depending on how we measure it. Although we now accept the particle/wave duality concept of an electron, this concept can still boggle the mind if we contemplate it too much. Similarly, viruses are both living and dead chemicals. We need to expand our concept of what constitutes the threshold of these worlds and should thank Dr. Wimmer for this clarification of such a basic issue, not chastise him as an enabler of bioterrorism.