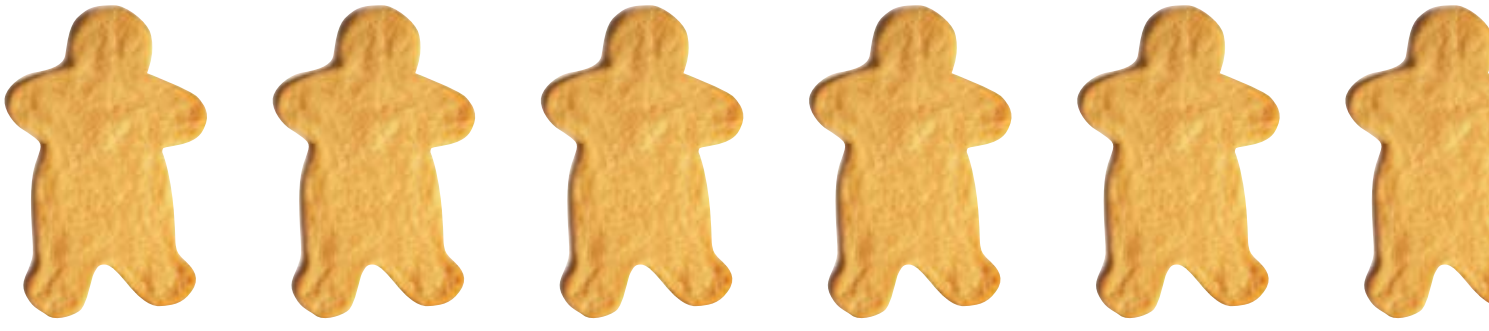
AVERAGE IS NOT GOOD ENOUGH: THE FUTURE OF Individualized Medicine

BY JANET STITES

The first thing to understand about Avidan Neumann is that he is not a medical doctor. However, his impact on the field makes this a benefit rather than a drawback. Armed with a Ph.D. in physics and mathematical biology from Bar-Ilan University in Israel and the École Normale Supérieure in Paris, Neumann has shown how mathematical modeling can help us understand disease. Now, he is doing the same for the individual patient.

Much of his work has been in the field of viral kinetics, in particular the study of Hepatitis C and B, HIV/AIDS, and the use of mathematical modeling of viral dynamics for drug development.

After completing a postdoctoral fellowship at the Weizmann Institute, Neumann worked as a postdoc for four years in the mid-1990s at the Santa Fe Institute and Los Alamos National Laboratory under the guidance of Los Alamos Senior Fellow and SFI External Professor Alan Perelson. Now he is an associate professor on the faculty of life sciences at Bar-Ilan University in Ramat-Gan, Israel, and the head of the Laboratory for Modeling In-vivo Clinical Kinetics there. But the work he did in New Mexico—and his love of the landscape—led him to a position of external professor at the Institute. Over the years, he has often collaborated with SFI faculty and continues to make the long trip to Santa Fe about once a year.



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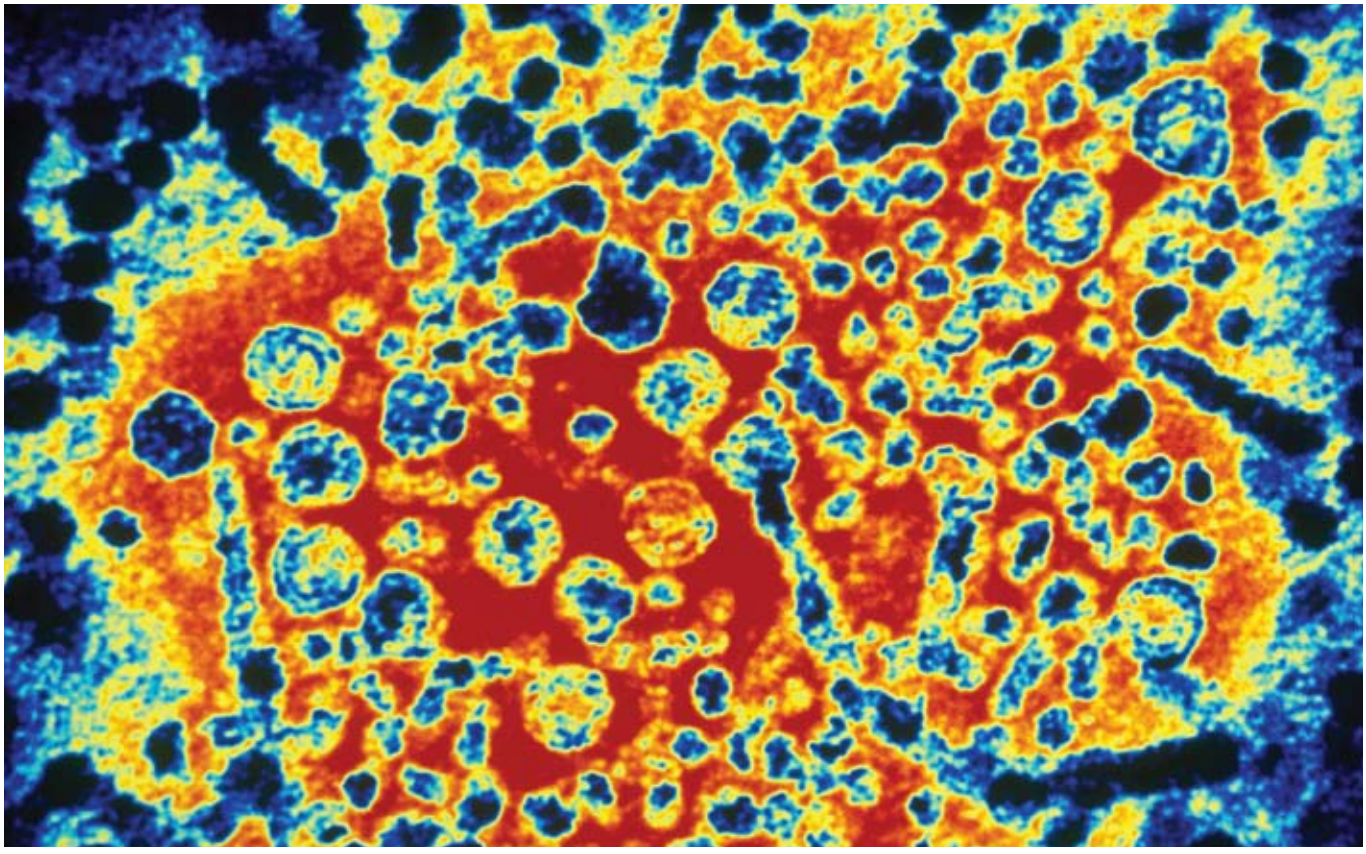

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This color-enhanced transmission electron micrograph shows the Hepatitis B virus, which infects the liver of humans, causing inflammation, vomiting, jaundice and, rarely, death.

He did so last fall to give a talk at the 2008 Annual Business Network and Board of Trustees' Symposium on the topic of individualized medicine. Often this term, also known as personalized medicine, is used in the context of genome science as researchers continue to build links between diseases, drugs, and genes. Neumann's idea for individualized medicine is different in two ways: he wants to personalize drug therapy based on each patient's response, rather than simply considering the mean response to the drug; and he wants to take into account the health history of individual patients, their "clinical kinetics," to allow timely diagnostics of a developing disease.

Battling Mediocrity

Neumann's research focuses on how individualized medicine will affect the future of medicine, but of course the future was shaped by the past. "Until the 20th century, an individual's health was often worsened after a visit from a physician," he says. "For the simple reason that doctors in the 19th century did not wash their hands before seeing a patient."

The 20th century, Neumann points out, brought major advancements in medicine and a steep increase in life expectancy. He attributes this to four factors: the introduction of antibiotics; mass vaccinations which eradicated many diseases; the ability to screen large numbers of drugs by trial and error; and the introduction of sizable clinical trials, which have helped differentiate good therapies from bad.

"The 20th century really helped the average patient," he says. "I like to call it the century of statistical medicine, the medicine of large numbers." For most of the world, particularly the West, this was a good thing. But in Neumann's opinion, it is no longer good enough. He uses results from a

clinical trial of the drug Adefovir to explain.

For background, Adefovir is an anti-viral drug used to treat Hepatitis B. Neumann studied a trial of 340 patients, with a control arm in which 170 received a placebo and an active arm where 170 received the drug. The trial lasted 48 weeks.

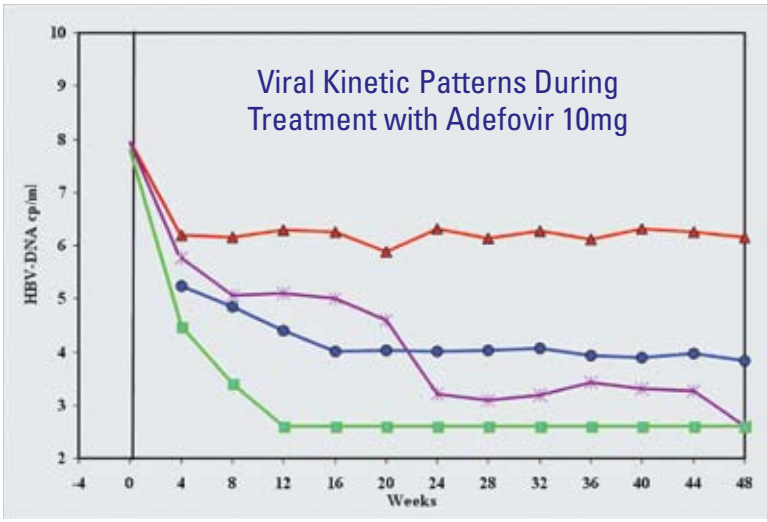
Looking at the median response of each group as a whole, the patients on placebo showed very little change in viral load over time, whereas the patients who received the drug showed a significant decline in the virus. Statistically, this outcome was very unlikely to be chance, Neumann explains, so the FDA approved the drug for Hepatitis B treatment. "This is a median viral kinetics analysis," he says. What drives Neumann is the nagging question: "Is the median kinetics the correct thing to look at?"

Neumann took a closer look, analyzing the individual data to verify if it was indeed accurately reflected in the median results. "If you look at the individual kinetic profiles," he says, "we see several distinct kinetic patterns, rather than only one median pattern."

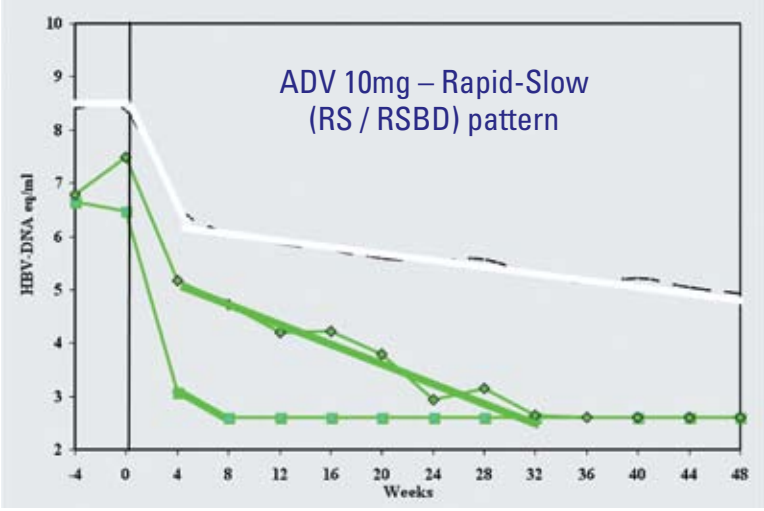
Indeed, about a quarter of the patients that took the placebo had no response at all, similar to the median. However, more than half of the placebo patients had major oscillations in their viral load. "What is clear is that the pattern generated by the median is incorrect," Neumann says. "We really have to look at individual kinetics to understand what is happening here." He further points out that many patients had "flares" in ALT, which is a marker of liver damage, indicating the immune system is killing infected liver cells, just before the decline in the virus.

For those that received the drug treatment, Neumann found that upon closer individual inspection, the first phase of treatment matched the median line. However, after the initial decline, many patients stopped responding. Other patients' viral load continued to decline in a slow second phase and stopped responding after a few months. Still others had a continuous decline of the virus, until the viral load was undetectable. But theirs was a rapid decline, not the slow average decline shown by the median.

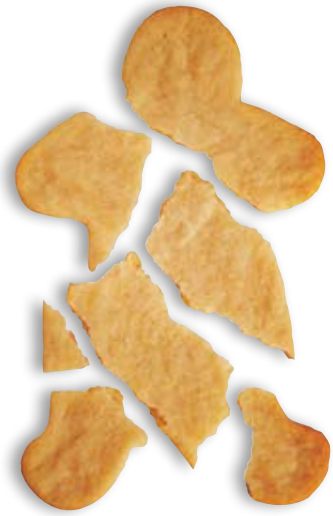
"In general, if we look at the distribution of the individuals' decline instead of the median, we can actually see four different patterns," Neumann says. His previous work helped measure the median response, but now he's moved



The FDA approved the drug Adefovir based on the median effect on patients. However, when Neumann looked closely, he saw that, after an initial rapid decline, four different patterns of response to the drug emerged.



In this graph, though the disease in both patients (green) showed an initial rapid decline with the Adefovir, one continued to respond in a slow second phase, while the other stopped responding. Both patients' responses differed from the median (white)



"You remember when people just died of old age?" he asks. "That's not allowed to be put on a death certificate anymore. It's illegal."

beyond it. "I believe the median analysis is a mediocre approach to medicine. Can we optimize treatment based on those individual patterns of kinetics?"

Further analysis of the patients who received the placebo in the first year of the trial, but received Adefovir in the second year, revealed that the individual kinetic patterns during the first year—flat versus oscillatory—predicted which patients would respond to treatment and which not. Even more important, it was possible to identify a number of points—the beginning of a flare, for example—at which starting therapy allowed for highly successful treatment.

Redefining Health

According to Neumann, in the 21st century and beyond, medicine will redefine sickness and health. He points out that lifespan in the Western world is now more than double what it was in Medieval Britain: 66 years, rather than 30. In the U.S. the average lifespan is 77, with estimates it will rise to 85 by 2050. "You remember when people just died of old age?" he asks. "That's not allowed to be put on a death certificate anymore. It's illegal."

Neumann suggests we start to look at lifespan, not beginning at birth, but when people reach 65. "If people live to 65, they are expected to live another 20 years," he says. "We no longer expect to die of old age. This has to change the way we look at medicine."

When people do reach old age, Neumann points out, most are dealing with multiple ailments. What's more, some have chronic diseases which become drastic at some point. "We have to ask: Is 'healthy' a person with no symptoms or is 'healthy' a person who does not need therapy?"

His solution is to use individualized medicine for early diagnostics. The use of genomics-based personalized medicine poses a problem in this regard. Diagnostics based on the sequence of a patient's genes can be done early, but they only give a probability for the disease to occur sometime in their life. For example, you might find that you have an 80% chance of developing cancer sometime in the next 30 years. "What can you do with such information?" he asks.

Instead Neumann suggests using what he calls clinical kinetics to allow for timely diagnosis of diseases as they develop. "We need to look at how various clinical markers change over time for each patient, and based on that—possibly including genomic data as well—be able to make a specific, individualized diagnostic at real-time," he says. "That will allow us to find out when a patient is developing a disease and treat it before it becomes serious."

Treatment, he adds, will have to remain fluid and responsive, finding a starting point, but then tweaking therapy based on the patient's response. In addition, he explains, the example of Adefovir shows that *when* to start a therapy is as important as what drugs to give.

Neumann warns against physicians relying too much on genomics. "There are limitations," he says, "because of the confounding effects of multiple genetic factors. Moreover, a patient's history—immunological and metabolic—is important. We are more than just the sum of our genes." ◀

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