Viewpoint

Reflections on Dr. Montagnier's Nobel Prize for the Discovery of HIV-1

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Thomas Kuhn, the late philosopher of science from the University of California at Berkeley, expressed quite eloquently thoughts that we now share regarding periods of transition in science and academia:

"*The transition from a paradigm in crisis to a new one from which a new tradition of normal science can emerge is far from a cumulative process, one achieved by an articulation or extension of the old paradigm. Rather it is a reconstruction of the field from new fundamentals, a reconstruction that changes some of the field's most elementary theoretical generalizations as well as many of its paradigm methods and applications. During the transition period there will be a large but never complete overlap between the problems that can be solved by the old and by the new paradigm. But there will also be a decisive difference in the modes of solution. When the transition is complete, the profession will have changed its view of the field, its methods, and its goals.*" (Kuhn, Thomas [1969] "The Structure of Scientific Revolutions" in the *Foundations of the Unity of Science*, Volume 2, Otto Neurath, editor; University of Chicago Press, Chicago, p. 146-7. Originally published in 1939; a synopsis of this famous essay is now conveniently available on-line at http://www.des.emory.edu/mfp/kuhnsyn.html).

In the early 1980s, the time for a major paradigm shift had arrived. In San Francisco, New York, and many parts of Western Europe, gay men were dying at an alarming rate [1]. The Centers for Disease Control (CDC) in the United States had already reported that a cluster of patients were dying from some mysterious illness that was killing a specific population in the US. The focus was on a new kind of pathogen that was damaging the immune system of these men but no one knew what that was. At that time, very few laboratories around the globe had the means to detect retroviruses. The French team headed by Dr. Luc Montagnier, and the American team headed by Dr. Robert Gallo in the USA, were among the top investigators to discover the unknown virus. Of course, at that time no one knew for certain that the "gay disease" was caused by a new retrovirus [2]. Many suspected that an infectious agent was the root of the mysterious illness, so they decided to test whether it might be a so-called retrovirus. In 1983, Dr. Luc Montagnier (Figure 1) and his team devised a way to grow HIV from lymph node biopsies of an AIDS patient, which enabled them to grow the virus in a cell line [3]. This was a seminal discovery. It facilitated not only the identification of the virus, but also the development of an antibody-based test that could be used to screen HIV-infected individuals [4]. This test saved millions of lives because before that time, over 100,000 hemophiliacs had received HIV-infected blood products. There was no way to detect the virus in the blood banks that supplied blood and blood products to the infirm. The resulting culture methods led to the development of the anti-HIV agents that currently help millions of HIV-1 infected people [4]. The suspicions of Dr. Montagnier's group were correct; their studies revealed retroviral activity in cells taken from a patient's lymph nodes and demonstrated that viruses from these cells could infect and kill CD4+ T cells, leading to acquired immunodeficiency syndrome or AIDS. Soon after the discovery of the virus, several groups contributed to the definitive demonstration of HIV as the cause of AIDS.

Just two years after the first reports of clusters of cases of what we now know as AIDS, Montagnier and Françoise Barré-Sinoussi were the first to discover the virus that later came to be known as human immunodeficiency virus or HIV [5]. The Nobel Prize committee has typically awarded the person or group

who first makes an important discovery. As the French team was the first to find the etiologic agent of AIDS, they were honored with the 2008 Nobel Prize in medicine for their discovery of HIV-1.

Born on 18 August 1932 in Chabris, France, Montagnier studied at the University of Poitiers and the University of Paris, venerable institutions whose origins date to the fifteenth and thirteenth centuries. His award establishes him as one of the most distinguished alumni of these universities. In 1972, at about age forty, he took employment with the Pasteur Institute's Viral Oncology Unit, and in 1985 became a professor of virology. Upon Montagnier's retirement from the Pasteur Institute's leadership, he joined Queen's College in Flushing, New York, where he periodically spoke about possible new ways to prepare an HIV vaccine, and invited Dr. Omar Bagasra to join his teaching team. Dr. Montagnier is currently a professor emeritus and director of the World Foundation for AIDS Research and Prevention in Paris, France.

When the momentous AIDS discovery was made, Montagnier and his associates were searching for a potential relationship between retroviral infection and cancerous growths. In 1970, scientists Howard Temin (1934-1994) and David Baltimore (1938-) described the singular nature of retroviruses, which have RNA genes, unlike the DNA that characterizes other viruses. They also found that retroviruses have the enzyme reverse transcriptase (RT). When, in 1983, the Montagnier team found RT in the blood of a patient with early indications of AIDS, the French scientist focused on specific identification of the virus. He learned that "It was not HTLV-1, a retrovirus recently discovered by Robert Gallo, as serum from the AIDS patient did not react with samples of HTLV-1 provided by Gallo." Rather, he discovered that the virus in question targeted specialized lymphocytes within the immune system known as T-4 (or CD4+) cells [2,6]. Consequently, he used the acronym LAV (lymphadenopathy associated virus), and subsequent subjection of these LAV to electron micrographs demonstrated that the HTLV-1 differed from LAV [2,3,6].

Convinced of LAV's significance, Montagnier led the effort to discover an antibody-based blood test by which LAV's presence could be established [4]. When he learned that AIDS patients had the LAV antibody, and therefore were infected with the lymphadenopathy associated virus, he hopefully and confidently moved forward with his research, which resulted in refining the sensitivity of the LAV blood test [4,6], and confirming an increasing number of AIDS cases [2]. Finally, by October of 1983, he had come to the conclusion that LAV was the virus that caused the immune deficiency condition that later came to be known as HIV [5]. Meanwhile, Robert Gallo had isolated HTLV-3, a retrovirus that he argued caused AIDS [6]. Controversy over who was the real discoverer of the virus that leads to AIDS ensued until a compromise was reached in which LAV and HTLV-3 (T-lymphotropic virus type III) were declared to be essentially similar [7]. In 1986, the name of the AIDS-causing retrovirus was changed to human immunodeficiency virus (5), a name that differed from those used by either Montagnier or Gallo. Moreover, the names of both men were placed on the patent for blood procedures that tested for the presence of HIV.

Late in 1985, Montagnier made another significant advance by establishing the existence of HIV-2, a substantially different strain that he discovered while conducting research in the impoverished West African nation of Guinea-Bissau. While performing blood sample analysis, he found that he could isolate a retrovirus from those "samples which differed from electronmicrographs of HIV-1." The result was the ground-breaking realization that there was an HIV-2 in addition to the earlier type, HIV-1. Montagnier learned that the antibodies that pointed to HIV-2 infection were unusually common in West Africa [8].

A quarter of a century has passed since the French virologist Luc Montagnier and his colleagues discovered the HIV-1 retrovirus. The disease has since traversed the planet and become pandemic [2]. It has proliferated undeterred by social status or geography, and tormented humanity without regard to race, gender, or background. It has forged alliances, albeit unwittingly, with individuals who share needles, engage in unwise intimate behavior, and transmit the virus to newborns who are infected *in utero* or during childbirth [2]. It rarely stems from transfusions of contaminated blood from HIV-infected persons, thanks to a blood test developed by the recent Nobel Laureates, Barré-Sinoussi and Montagnier. Although the means of transmission have been well established, it has been puzzling why viral prevalence is so markedly uneven in different parts of the world, or why it causes significant variance in infection rates among different religious groups within the same region. One explanation is that male circumcision significantly reduces the HIV transmission and prevalence; HIV seropositivity is significantly lower in the regions of the world where circumcision is common [9]. Recent failures and

terminations of potential anti-HIV-1 vaccine trials underscore the challenges of tackling diseases whose heaviest burden falls on developing nations [10-11]. A quarter century after the Montagnier group's landmark discovery, knowledge of how a vaccine might work is distressingly limited [10,11]. Neither the current paradigm nor traditional vaccination protocols seems promising, yet the crisis demands creative ideas, not paralysis [12]. As elusive as reuniting disconnected neurons, the quest for a vaccine is yet ongoing. Efforts to formulate a vaccine based on classical immune responses (both antibody and cell-mediated based) have failed repeatedly [10-12]. Simian immunodeficiency virus (SIV), epidemic among African non-human primates, causes no immunodeficiency, yet we still do not know why. We propose that clues for an HIV vaccine have long been available, but the current paradigm has prevented novel avenues of investigation [12]. Perhaps renewed attention on HIV and the new Nobel Laureates' influence may lead to a new paradigm shift in HIV vaccinology [12].

Dr. Montagnier's last name means "mountain." Anyone who has spent time with him can attest that this is a man to match his surname, a mountain of humility and intelligence that radiate from his demeanor. We cannot imagine a more deserving person to receive the prestigious award. As a promising researcher at the Pasteur Institute, Dr. Montagnier could hardly have dreamed that someday his name would rank among those famous scientists, including Pasteur himself, who would make ground-breaking and lifesaving scientific discoveries. We feel honored to know this man whose name is etched on the map of virology as much as the Pyrenees appear on the geographical map of the land of his birth.

Figure 1. Dr. Omar Bagasra with Professor Luc Montagnier taking a break during his 1993 workshop at Pasteur Institute, Paris.

The Authors

Dr. Bagasra is the director for the South Carolina Center for Biotechnology at Claflin University, where he continues his AIDS research. Bagasra also continues his exploration of novel ideas and presented a new theory in the fight to cure HIV at the 17th International Conference on AIDS in Mexico City in August 2008. Dr. Donald Gene Pace, professor of History (PhD) and Spanish (PhD) at Claflin University, has collaborated with Dr. Bagasra on various HIV-related topics.

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