

Case studies, case series and biological plausibility

As medical students and interns, you learn from patients; so, news of an unusual case spreads rapidly through the hospital. The enthusiastic descend, and if the admission is in a general ward, the nurses can have a difficult time limiting the number of young and eager medical trainees who want to examine the poor patient. In 1986, we were told of a foreigner who was admitted in the Christian Medical College Hospital in Vellore with a condition none of us had ever seen before, Kaposi's sarcoma.

Described by a Hungarian dermatologist more than a century previously, until a few years before, it had been a rare condition, but was now being increasingly reported as pathognomonic of a new immunodeficiency syndrome. Since it was not seen in Indians, the presence of a milliner from New York with purple patches on the skin was not likely to go unnoticed in the relatively small medical community in the hospital. But unusually, for such an interesting case, the medical registrars were not calling students in the evenings to come and take a look. The faculty had decided to limit visitors, and although we did not know it then, decisions were being made about future policies in the hospital, if the contingency arose of needing to treat multiple patients with this condition.

Shortly after that patient was discharged, we heard other news. The virology department, almost completely a research program at the time, had received samples collected in Chennai from commercial sex workers and had identified, for the first time in India, antibodies to the virus called Human T-Lymphotropic Virus III that had recently been described to cause the disease initially called gay related immunodeficiency and now labelled the acquired immunodeficiency syndrome or AIDS. Eric Simoes, a paediatrician in virology, was being sent off to the Centers for Disease Control and Prevention (CDC) in Atlanta with the samples to confirm the testing (Simoes *et al.* 1987). He came back with the confirmation, and the news exploded that India finally had the disease that it believed it would not get, because we were supposed to have higher moral standards than the promiscuous Western world.

Looking back, it seems incredible how far we have come from the days when we knew little or nothing about HIV and AIDS. Starting six years before the disease was finally described in India, Harry Haverkos' book *On the Front Lines of the AIDS Pandemic* begins with a description of his initial encounter with a patient with *Pneumocystis carini* pneumonia (PCP) in Pittsburgh (Haverkos 2012). An opportunistic infection usually leads to a hunt for a source of immune compromise, and in this bath house manager, none was found, although he was to encounter this patient again. Written in a crisp, urgent style, tracking Haverkos's career from 1980 to 1984, the book careens from Pittsburgh to the CDC in Atlanta, where he joined the Epidemic Intelligence Service, and his experience with PCP led to involvement in accumulating data on a case series of Kaposi's sarcoma and other opportunistic infections.

When starting to investigate a disease that is newly arisen or introduced, a great deal can be learned by careful clinical observation. A case series or description of a group of patients meeting a case definition is the first step in being able to measure the extent of a problem, by counting cases meeting the definition, and to formulate a hypothesis of why the disease occurs, by looking for a biologically plausible cause. The book goes on to describe the rapid emergence of evidence of an immunosuppressive disease, initially believed to be restricted to the gay community on both coasts of the US, but soon also identified in injecting drug users and Haitians. However, ascertaining the cause of a disease is not simple, and cytomegalovirus and other herpes viruses, as well as alkyl nitrites, were considered as possible aetiologies, before further evidence emerged from hemophiliacs and other patients who had received blood transfusions, that this was a parentally transmitted agent. This was reinforced by the subsequent description of acquisition of infection by health care workers through needle-sticks and mucosal exposures and women who vertically transmitted the disease to their children. The viral agent was finally identified as a retrovirus that infected immune cells, thus providing a testable hypothesis for causality.

The description of the planning of studies, of the decision-making process for case control designs and for eligibility criteria for inclusion, are classical examples of investigative epidemiology for a disease of unknown aetiology. The drama of chasing cases, of the need for building support systems and collaborations across specializations, of the constant questioning for a biologically plausible cause are told in clear and simple language that creates immediacy and brings the reader into the experience. The politics determining newsworthiness and the competition among academics are frankly described, and the story would not be complete without the discord of human behaviour.

Harry Haverkos left the CDC shortly after the virus was described in France and the US. Although investigators at CDC did not ultimately identify the virus they sought so assiduously, their cumulated data led rapidly to an understanding of this new epidemic and its potential for spread. Thirty years later, there are so many more stories, personal, public and academic, all of which now form a part of collective experience.

In India, despite the documentation of spread of AIDS throughout the world in the early 1980s, the disease was not identified until the mid-1980s. From the beginning, in India, as in other parts of Asia and Africa, heterosexual transmission has been the primary mode of spread, leading to the establishment of screening of antenatal women as an estimate of population based prevalence of disease. Although the National AIDS Control Program was established in 1987 and followed by the setting up of a National AIDS Control Organization in 1992, the disease continued to spread across the country for next 15 years, particularly in high-risk groups, commercial sex workers, truck drivers and injecting drug users, such that India had the second largest number of HIV-infected individuals in the world, and several states had a population prevalence rate of 1%. Intensive efforts to educate young people, the public and high-risk groups through the state AIDS control societies and non-governmental agencies and the introduction of the prevention of parenteral transmission to child therapy and the highly active anti-retroviral therapy programme through the government have led to disease control, resulting in a 50% decrease in the numbers of new cases being identified annually and a prevalence rate of 0.36% (NACO 2011). In the early days of the epidemic, HIV as a chronic disease and AIDS control would have seemed very distant goals. Although HIV/AIDS is a major public health problem and ongoing efforts are needed, there is no longer the widespread level of irrational stigma and the panic that a seropositive report entailed two decades ago. We are now largely past the shock and horror of losing public figures and close friends to a relentless foe.

The description of the start of the AIDS pandemic is a story that needs to be told and retold from many points of view. When facing a problem or a mystery disease, data and as much carefully collected data as possible describing patients, time lines, locations and potential environmental or other risk factors are invaluable. A systematic analysis is then needed to appraise the facts, draw inferences and reach decisions concerning the need for further investigations and for designing interventions based on possible modes of transmission. Overall, to establish causality, formulation of a hypothesis that can be supported or refuted, preferably distinguishing between competing causal mechanisms, without bias or confounding, is needed (Rothman *et al.* 2008).

HIV/AIDS came at a time when for the first time, an infectious disease had just been eradicated by the use of epidemiological principles and we were being told that infectious diseases had been conquered or controlled. Nonetheless, the practice of the principles of surveillance resulted in a rapid understanding of the disease and its spread, even before an aetiology was established. With the amalgamation of epidemiologic principles and modern molecular methods, subsequent investigations of potential epidemics, Nipah virus, severe acute respiratory syndrome coronavirus, avian influenza, H1N1 and now the Middle East Respiratory Syndrome virus have been even faster. Given animal–human interactions and the frequency and intensity of travel today, it is unlikely that we have seen the last infectious disease to become a global problem, but consistent application of defined principles offer our best hope of a rapid understanding of new diseases.

References

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GAGANDEEP KANG
*The Wellcome Trust Research Laboratory,
Division of Gastrointestinal Sciences,
Christian Medical College,
Vellore 632 004, India
(Fax, 0091-416-228-2486; Email, gkang@cmcvellore.ac.in)*