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Vicious Chronicles of Virology

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Abstract : Presented in this article, aimed at both the virologists and non-virologists among the readers, are the dark episodes of virology. These anecdotes overshadow, in comparison, the effects of Hiroshima and Nagasaki atomic bomb explosions, both in impact and magnitude. Needless-to-say, the episodes listed here involve viruses and may represent re-recording of largest outbreaks of some viral infections. The article concludes with a cautious approach to the on-going global Rubella vaccine program.

Keywords : Bacteriophages, Cholera, Yellow fever vaccine, Hepatitis B virus, Hepatitis C virus, Rubella, Cataract.

I. **Introduction**.

History abounds with anecdotes that overshadow the effects of atomic bomb explosions on Hiroshima and Nagasaki, both in magnitude and impact. Whereas the atomic bombs were chemical weapons, the biological incidents are silent, involve the entire global population, continue to exert their effects even as I write this article, and involve viruses. Honestly speaking, these events were originally intended to help the humans overcome other pathogenic infections but went unwittingly out of control. Perhaps as a consequence of these events that took place in the backdrop of the two world wars and the cold war, stringent laws to test newer therapeutic agents and laboratory practices to maintain absolute sterility of medical equipment came into effect. We shall look into the details of these events, but first…

… Viruses are unique obligate parasitic entities that invade living cells of all types - animal, human, plant, bacterial and fungal. Outside the living cells, they are inanimate objects waiting to invade the next cell. The study of viruses is termed Virology. Viruses can be seen only with the aid of an electron microscope, and viruses that attack bacterial cells are referred to as Bacteriophages or simply as phages. Because viruses invade cells of all types, they are the first items of choice for biological pest control, be it in humans, animals or plants.

II. **Phage Therapeutics**.

Antibiotic resistance in bacteria is a well documented phenomenon. In fact, it was known to the medical fraternity as early as in 1919. Felix d'Herelle was one among the first persons to identify the pest control potential of phages. He observed that an alternative to antibiotic resistance in bacteria lies in the usage of phages against bacteria. Thomas Häusler in his treatise on phage therapy titled 'Viruses vs Superbugs – A solution to the antibiotics crisis?' mentions that the first phage therapy was performed on 2 August 1919 when Felix d'Herelle treated one Robert K for severe dysentery [1]. Inspired by the success of this treatment, d'Herelle advocated, conducted large scale studies and treated patients literally all over the world including India. Success word spreads like wild fire in scientific and medical communities. Häusler says that many countries like Russia, The Americas and Britain conducted systemic studies on phage therapy in humans. In the backdrop of the two world wars antibiotics were indiscriminately used to treat the wounded soldiers. However, as it happens during the wars, shortage of antibiotics was acute. This shortage clubbed with antibiotics resistance made scientists look for alternative. d'Herelles' phage therapy was God's gift.

In a series of experiments, perhaps reminiscent of the award winning graphic 'V for Vendetta', wherein the protagonist survives a series of experiments conducted on him by the British authorities, doctors in Britain tested phage therapy on German prisoners of war (POWs) during the Second World War. Around the same time cholera was a major problem in the North East India and the (now) neighbouring Bangladesh. Thomas Häusler mentions that Lt. Col. Morison, F d'Herelle and Major Reginald Malone carried out large scale studies in Tea gardens of Assam, early reports of which appeared in the Indian Medical Gazette, 1930. Based on the success of pilot studies, Morison, d'Herelle and Malone mixed phages in water wells and in rivers to avoid cholera epidemics…

…And all that shines is not gold. In 1950s, Scientists discovered two types of phages – the temperate and the lytic phages [2]. Temperate phages integrate their nucleic acids into the genomes of bacteria. Lytic phages just kill the bacteria. How the earlier researchers avoided temperate phages in their therapeutic regimen is anybody's' guess. In 1996, US researchers Waldor and Mekalanos discovered that the cholera toxin, one of the two lethal diarrhoea causing elements of the Cholera pathogen, *Vibrio cholerae*, is transmitted by a temperate phage in the intestines [3]. In 2005, in a series of articles, Shah Faruque and colleagues from Bangladesh observed a see-saw effect between *Vibrio cholera*e and the phages that are active against the cholera pathogen. When *Vibrio cholerae* are more in the rivers, there were cholera epidemics. These epidemics subsided with an increase in the population of phages in the waters [4, 5]. Incidentally, d'Herelle hinted at this see-saw effect in one of his publications as early as in 1930 [6]. More recently, Sheetal R Modi *et al* found evidence for the expanded interactions between phage and bacterial network for gene exchange in gut microbiota during antibiotic treatment [7]. Furthermore, Sheetal R Modi and colleagues implicate phages in emergance of multidrug resistance. Taken together, the observations of Waldor and Mekalanos, Shah Faruque and

colleagues, d'Herelle, and Sheetal R Modi *et al*, history is waiting to unfold itself… Whether it will be beneficial to humans or antagonistic to the public at large is beyond the realm of anybody's imagination…

III. **Regularly irregular vaccine**.

At least two types of vaccines for preventing yellow fever viral (YFV) infection are available – the 17D live attenuated vaccine developed in 1936, and the French Neurotropic Vaccine (FNV), which of course is no longer in use, as per CDC-MMWR [8]. Scientists were trying to produce the already tested and successful vaccine by alternative means on a large scale in an environment of a planet preparing for war. Large scale production started in chicken eggs and included pooled normal human sera. Serum (*pl*. sera) is the straw coloured liquid that exudates upon clotting of the blood. Serum, yet to be completely characterised even today, is the main ingredient in a number of biological experiments, preparations and vaccines. For some unknown reason, sera, either from animal or human sources, when used in concoctions have a stabilising effect on a number of bio-molecules and viruses.

By 1939, apart from numerous neurological complications associated with YF vaccine in the form of encephalitis, viscerotropic associated disease and multi-organ failure, large outbreaks of hepatitis B was observed in Brazil. Owing to this, all the components included in the vaccine manufacture were changed and in 1942 in US servicemen, whence as per Gordon Frierson [9], a whopping 7 million doses have been dispensed. Yet the adverse effects, particularly hepatitis B virus (HBV) showed up its ugly head in the new vaccinees. Estimates vary, as to how many actually died of the ensuing hepatitis B infection, from 3 to 50 per 1000 vaccinees. In 1966, the then available YF-17D vaccine was found to be contaminated with avian leukosis virus (ALV). Although no adverse effect was reported, suspicions of incidences of cancer, perhaps not attributable to vaccine, did cause a stir in scientific circles. Thomas Monath further questions the safety of the presently available YF-17D vaccine, with the discovery of a new syndrome - The Yellow fever vaccine associated viscerotropic adverse events (YEL-AVD) [10]. The earliest of the YEL-AVD was first reported in 1973, and subsequent cases after 1995.

IV. **Beyond Schistosoma**.

Egyptian Ministry of Health (MoH) undertook large campaigns between 1950s and 1980s to control Schistosomiasis, the traditionally most important health problem in Egypt. Schistosomiasis is a disease caused by parasitic worms. These control campaigns involved intravenous administration of tartar emetic, the then available standard treatment for schistosomiasis. In fact, this standard treatment was used to control schistosomiasis as early as 1921 [11]. By 1995, Frank and colleagues observed a direct relationship between parenteral treatment of schistosomiasis and prevalence of antibodies to Hepatitis C virus (HCV) [12, 13]. Presence of antibodies in an individual to a particular pathogen is indicative of the persons' exposure to that particular pathogen at some point in that persons' life. Today, 8 to 10 million Egyptians are having HCV antibodies; among these 5 – 7 million have active viral infection. Egypt, therefore, now serves as a reservoir of HCV. This makes exposure to blood and related products one dangerous medical option.

Thomas Strickland reports in Hepatology, that people with co-infections of HCV and Schistosomiasis respond poorly to the standard treatments in comparison to those who are infected with HCV alone [13]. Note that HCV, unlike hepatitis B virus (HBV) has no vaccine, and the response to treatment with interferon, the standard treatment option, a very costly option even for the developed world standards, is far from satisfactory. Strickland concludes his article with the observation that the control measures of MoH against schistosoma made HCV the most important public health problem in Egypt than schistosomiasis.

As per WHO factsheets, 950 000 people die every year globally as a consequence of either HBV or HCV infections [14, 15]. Whether these two episodes of YF vaccine and control measures against schistosomiasis, contribute directly to the above numbers is anybody's guess. Club this with increased international travel, health problems that originally are restricted to one geographic location, now become global.

V. **Towards a blind planet**.

World Health Organisation (WHO) says that as on 2010, 20 million people worldwide are blinded as a consequence of cataract [16]. Cataract, *per se*, is not a transmissible disease, but human actions ensure that it can be made transmissible. One of the various forms of cataract is the 'congenital cataract'. If the mother is infected, during pregnancy, with either Rubella virus or Varicella Zoster virus or herpes virus, congenital cataract sets in. This is important in the light of WHO's global Rubella vaccination and its implementation [17]. Given these observations, the question that promptly arises is the global vaccination programs one contributory factor for cataract? Reports are already trickling in with instances of cataract post vaccination [18, 19]. Perhaps this article comes at the right time.

VI. **Rider**.

The observations mentioned in the preceding sections are important in view of the findings of various scientists on phage therapy and associated biological pest control measures on Cholera in India. Note that scientists argued against the usage of phage therapy as early as 1922 [20 - 22], discovered the presence of two types of phages 30 years after the first episode of phage treatment. Also, 77 years later, researchers identified transmission of cholera toxin in intestines by phages. Seasonal dynamics between phages and the cholera pathogen a full 85 years after d'Herelle cured his patient of dysentery… And this world did not have an electron microscope until 1939… In the backdrop of all these, Hiroshima and Nagasaki episodes are just glorified tear drops in the sands of time…

Endnote.

This is a self-financed study.

Abbreviations used.

ALV – Avian Leukosis Virus; CDC-MMWR – Centers for Disease control and prevention – Morbidity and Mortality Weekly Report; FNV – French Neurotropic vaccine; HBV – Hepatitis B virus; HCV – Hepatitis C virus; MoH – Ministry of Health; *pl*. – plural; POW – Prisoners of War; WHO – World Health Organization; YEL-AVD – Yellow fever vaccine

associated viscerotropic adverse events; YF – Yellow fever; YFV – Yellow fever virus; Other abbreviations carry their usual significance.

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