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YELLOW FEVER—THE SARASWATI OF VIROLOGY

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Saraswati is the Hindu Goddess of Wisdom and Learning and is the consort of Brahma the Creator. Saraswati is usually portrayed with four arms, which provide a convenient framework within which to discuss yellow fever virus and its relationship to the development of techniques for the study of viruses in general, and the acquisition of knowledge relative to other viruses. This subject can be discussed conveniently under four headings: virology; immunology; zoology; and ecology. With apologies for any liberties I may take, I am going to assign one of Saraswati's arms to each of the four disciplines I have mentioned.

Before I do that I should like to pay my personal tribute to Carlos Finlay. I would stress the fact that the acceptance of the validity of his theory that yellow fever was transmitted by *Aedes aegypti* made it possible to eradicate yellow fever from Havana, from Cuba, from the Panama Canal Zone and from the rest of the Caribbean littoral.

The demonstration in 1901 by the U. S. Army Commission that yellow fever was due to a virus had little practical importance until the virus was captured alive and brought into the laboratory for study. This was first accomplished in 1927 and the period of eight years from then to 1935 has been described as the golden age of virology.

Virology is the first of the major disciplines to which Saraswati may be said to devote her arms. The isolation of yellow fever virus in Indian monkeys at the Rockefeller Foundation Laboratory in West Africa is one of the principal milestones of microbiology. This event, involving as it did one of the great pestilential diseases of mankind, captured the attention of investigators everywhere and greatly hastened the isolation of many new viruses in a very few years.

If one lists all the virus diseases of man, a list which is now of quite considerable length, he finds that the only human viruses which were already in captivity before the isolation of yellow fever virus were rabies, poliomyelitis and herpes simplex. Though not really a human disease, vaccinia must be added to this list because of its relationship to smallpox. Of the animal
viruses only foot-and-mouth disease had been adapted to a small laboratory animal prior to 1928.

Consider some of the viruses which have been discovered, in addition to influenza, mumps, and chicken pox, since 1927. There is a host of arthropod-borne viruses starting with those most unfortunately named “equine encephalomyelitides.” These three viruses are all American; they are known as Eastern, Western and Venezuelan equine encephalomyelitis. Philadelphia is well within the region in which the Eastern virus is periodically epizootic and epidemic.

Then there is the group of five antigenically related viruses each from a different continent, all of which appear to be transmitted by one or another species of Culex mosquito: Japanese B, St. Louis, West Nile, Ilheus, and Murray Valley. Japanese B is as common as measles in most of Japan and in many other parts of the Orient, and West Nile is equally ubiquitous in parts of Egypt, as well as being periodically epidemic elsewhere in Africa. Nor can St. Louis encephalitis virus be relied upon always to stay west of the Mississippi River.

Mention must be made of a number of viruses isolated in Africa and South America as a by-product of the studies of yellow fever. These viruses, to a total of about eleven different species, were isolated from men, mosquitoes and monkeys over a period of about ten years in the course of yellow fever studies.

The virus of Bwamba Fever was the first to be isolated by Dr. Mahaffy in Bwamba Forest. It was my very good fortune to visit Uganda for the first time last month and drive down the road at the base of Mount Ruwenzori where in 1937 Dr. Mahaffy found African road workers suffering from a febrile disease which, greatly to his disappointment, proved to be not yellow fever. He inoculated blood serum from patients into the brains of mice which he kept in a field laboratory in tents by the roadside.

Semliki Forest, Bunyamwera, Zika, Ntaya, and West Nile viruses were isolated during the next few years from either mosquitoes, monkeys or man. West Nile is perhaps the most interesting because it represents a new phenomenon: the isolation of a micro-organism before the disease it caused was recognized.

West Nile virus was isolated in 1940 in Uganda from the blood of a native woman who had a low fever and was never seen again, but it was not until 1950-51 that the disease West Nile Fever was described clinically. Two thousand miles away, in Israel, recently arrived Europeans were laid low by an epidemic of non-fatal dengue-like fever which was identified as West Nile Fever. The infection is highly endemic in the rural population of the Nile Delta in Egypt but it is so mild there that it is not identifiable clinically.
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Most of these viruses are still scientific curiosities, but there is no knowing when one or another of them may become of importance as to the cause of an important new epidemic disease.

If we accept the theory that man evolved from tree shrews, lemurs, monkeys and anthropoid apes, all of which have an arboreal habitat, it seems probable that he has also inherited some virus diseases transmitted by blood-sucking arthropods. Jungle yellow fever is in this group of parasitic diseases and perhaps if we could find enough fossil mosquitoes it would be worth while looking for fossil virus particles.

Following the isolation of yellow fever virus, there was a rather intense search for animals which were highly and usefully susceptible to important viruses. This led to the discovery that the ferret—of all animals—was susceptible to influenza virus. The great usefulness of the rhesus monkey protection test in yellow fever, expensive and cumbersome though it was, stimulated the development and use of the same test in poliomyelitis, resulting in the acquisition of much information about the extent and degree of immunity to the disease which was not immediately credible.

These are two examples of the diversity of the stimulus which yellow fever gave to virology.

Both the ferret and the rhesus monkey tests are now obsolete, having been replaced almost completely by simpler and better tests, but only after they had served to unearth much basic information. The thing that made obsolete the monkey protection test for yellow fever was the discovery that yellow fever virus could be cultured in the albino mouse if one inoculated the virus directly into the brain of the mouse. The demonstration that yellow fever virus—which attacked the liver, kidney, and heart of man and the rhesus monkey—also had a neurotropic component that produced a fatal encephalitis in mice, really jarred the laboratory Brahmins of 1930.

This finding made possible the mouse protection test for yellow fever, tens of thousands of which have been done in the search for neutralizing antibody in the blood serum of man, monkeys, and other vertebrates.

Once the albino mouse was known to be susceptible to yellow fever virus, it was not very long before ways and means were found to culture other viruses, including poliomyelitis and influenza, in the mouse. Nowadays the mouse has become largely obsolete in these two diseases, but it is still the most useful of all laboratory animals in the virology laboratory.

We come next to immunology, Saraswati's second arm. Long before Carlos Finlay entered Jefferson Medical College it was generally recognized that one attack of yellow fever protected a person against the disease for the rest of his life. This belief received great support from the laboratory finding that the blood serum of a person convalescent from the disease contained large
amounts of neutralizing antibodies. Such antibodies were detected in the blood serum of persons who had suffered their attacks as many as 50 years previously, and had subsequently lived in areas in which the disease did not occur.

The original monkey protection test was used to demonstrate that the yellow fever of the Americas was immunologically as well as clinically and pathologically identical with the yellow fever in Africa—a demonstration of fundamental importance.

Mention has already been made of the fact that the development of usable protection, or neutralization, tests for yellow fever led to an intensive search for neutralizing antibodies in other virus diseases. There was a considerable degree of success in this search, and the identity of several viruses was thus established.

Early in the work with yellow fever considerable attention was given to the use of the complement-fixation test. One of the most potent yellow fever antigens is the blood serum of rhesus monkeys that are acutely ill with the disease; another excellent source is the brain tissue of mice inoculated with the virus. The complement-fixation test has proved very useful, not only in distinguishing between different viruses but also, at different levels of sensitivity, for showing relationships of viruses.

Finally, I must mention the hemagglutinating antigens of yellow fever and a number of neurotropic viruses, in which there is much interest at present. With these hemagglutinins it is possible to set up a hemagglutination-inhibition test quite similar to that of influenza, and to show that yellow fever is closely related not only to dengue virus but also to Japanese B and St. Louis viruses, among others.

I mention this matter because yellow fever is the recipient in this instance, rather than the donor. Things have come full circle, and now a phenomenon which was perfected with a very different virus is shown to be of value with yellow fever virus.

Saraswati’s third arm, to continue the analogy, is the broad science of zoology with its two important branches: entomology and mammalogy. Studies of the reservoir of jungle yellow fever in the forests of tropical America and Africa led to a consideration of all the bloodsucking arthropods—ticks and mites as well as insects—and of all the warm-blooded vertebrates in the forests. Knowledge was scanty on many counts and the taxonomic problems were numerous both in entomology and in mammalogy. The taxonomists who performed the absolutely essential service of putting labels on insects and mammals, so that less erudite persons like doctors interested in yellow fever could be sure that they, and everybody else, knew what species they were dealing with, inherited from their predecessors much that was useful, but there were many important lacunae to be filled.
The taxonomists of today are paying off our indebtedness to Linnaeus and his contemporaries and successors by putting the taxonomy of many groups of mosquitoes and mammals into definitive order—or at least so they think. Our grandchildren will know better about this than we do.

The fourth arm of Saraswati may be said to represent the science of ecology, of which epidemiology is really only a minor subdivision. When I was a premedical student, ecology was something that girls who were majoring in botany had to take. I fear that we rather looked down on them. What the deal is today, I must confess that I do not know, but I sincerely hope that the discipline is receiving the attention which it richly deserves.

Ecology is the science which deals with the relations of organisms to their environment. The organisms may be plant, animal, or viral—giant sequoia trees, whales, or yellow fever virus. And environment means all aspects of the environment—physical and biological.

Now as far as Saraswati is concerned, all species have equal rank before her throne: yellow fever virus is just as important as *Homo sapiens*.

Ecological studies are often oriented around a single species. The epidemiologist orients his studies around man, whereas the ecologist could just as logically orient his work around a parasite that was causing trouble.

As long as there was only urban yellow fever to consider, ecological studies were rather crude. Things like the lowest temperature at which *Aedes aegypti* could over-winter were about the upper limit of scientific elegance. But once it became evident, in South America, that jungle yellow fever was contracted in places in which there were no *Aedes aegypti*, then ecological studies became more and more necessary, and more highly refined.

The ecological studies on jungle yellow fever revealed very conclusively that though that disease was identical with *aegypti*-transmitted urban yellow fever in all ways, except its manner of transmission, there were several different epidemiological types of the infection. Once this fact was clearly recognized in regard to yellow fever—a disease which forced itself upon everybody's attention because of its ability to kill, and to kill in horrible fashion—it served to alert the people who were working on other virus infections to the possibility that similar or equivalent factors were operative in connection with other virus diseases. Truly, yellow fever has been a model for the study of arthropod-borne virus infections.

In summary, the acceptance of the fact that yellow fever was transmitted by *Aedes aegypti* made it possible to eradicate the disease from the Caribbean littoral. Twenty-five years later the isolation of yellow fever virus inaugurated the golden age of virology. First there was the direct stimulus to pure virology—the isolation and identification of the viruses that caused a number of important human diseases. Then the results with yellow fever led directly to
a variety of important studies in a variety of other disciplines: in immunology; in zoology; and perhaps most important of all, in ecology. These studies had to do with yellow fever, and they also had to do with other virus diseases, more or less distantly related to yellow fever. Perhaps the most important of all these contributions were those in ecology because they spurred medical investigators to get away from the classical viewpoint of man as the point of departure in their thinking. They underlined a refreshingly new point of departure: the virus, into whose orbit man was wont to wander, sometimes with very unpleasant results.

The simpler problems have been solved, in virology, in epidemiology, in ecology; the more difficult ones remain to be solved, in yellow fever as well as in general. Yellow fever virus cannot lead the pack forever. Some fine day, some other virus will provide the clue which will solve one or more of the many interesting and important questions about yellow fever which still remain to be answered. When this occurs it will be more than poetic justice; it will be scientific justice of the highest order.