

The control of yellow fever: a centennial account

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Just a century ago, yellow fever was shown to be due to a mosquito-borne virus. After another 40 years an effective vaccine became available. Yet large outbreaks of yellow fever still occur and the safety of what was considered to be an excellent vaccine is now in question.

● The historical toll

Up to 1900, yellow fever was greatly feared as a tropical disease. It decimated incomers to Central and South America, whether they were traders, soldiers or settlers, and it gave to West Africa its reputation as the white man's grave. In the Caribbean, yellow fever enfeebled British and French expeditionary armies and it claimed many lives in North American ports on the Eastern seaboard and the Mississippi River. In 1893, together with malaria, it forced the French to abandon their attempt to build a canal across the isthmus of Panama after an estimated 20,000 workers had died. For individuals caught up in a yellow fever outbreak the only protection was through flight, and for an invading army or other large group of incomers the best option was withdrawal. At a time when great strides were being made in other branches of microbiology and immunotherapy, the cause, route of transmission and means of prevention of yellow fever remained enigmatic.

● Enlightenment

The late nineteenth century was a period of colonial expansion, and in 1898 the United States contrived to invade Cuba. Yellow fever outbreaks were feared in the American troops and a US Army team (the Reed Commission), was sent to Havana in the hope of finding and removing the source of yellow fever. This Commission successfully answered three riddles about

the disease. First, it established that yellow fever was transmitted by the peri-domestic mosquito, *Aedes aegypti*; second it showed that there was no other natural route of transmission; third (with knowledge to hand of the recent work of Loeffler & Frosch who had just shown that foot-and-mouth disease could be transmitted with filtrates free of bacteria) it demonstrated that yellow fever was also caused by a filterable agent, i.e. a virus.

The Commission's work, published in the newly founded *Journal of Hygiene*, brought immense benefits. Within a few years mosquito control had made urban yellow fever rare in the Western hemisphere and no outbreaks occurred in the United States after 1905. The confident words spoken by US Surgeon General Gorgas in 1909 reflected the prevailing opinion that yellow fever had been overcome.

'Yellow fever will entirely disappear within this generation and the next generation will look on it as an extinct disease having only an historic interest. They will look on the yellow fever parasites as we do on the three-toed horse – as an animal that existed in the past, without the possibility of reappearing on the earth at any future time.'

However, yellow fever was soon to prove that it had not lost its power to surprise, and the next phase of American research into yellow fever was to have a less fruitful outcome.

● The rise and fall of Hideyo Noguchi

Hideyo (meaning 'gift to the world') Noguchi was an immigrant to the USA who rose from humble origins in Japan to a position of scientific eminence in New York in the early 1920s. Both his energy and the range of his experimental output astonished the American research community. His work on yellow fever, which was just a small part of this achievement, had its origins in investigations of spiral micro-organisms, beginning with attempts to cultivate the agent of syphilis in an artificial medium that bore Noguchi's name.

In 1914 Inada and colleagues, working in Tokyo, had transmitted Weil's Disease to guinea pigs and grown the causative agent in Noguchi's medium. Noguchi was probably piqued that this prize had eluded him, and he quickly sought to turn the discovery to his advantage. If Weil's Disease was caused by a spirochaete that was readily transmitted to guinea pigs and was cultivable, why should it not be the same for the clinically similar yellow fever? Noguchi rushed to establish priority, and he seems to have ignored the Reed Commission's evidence of the filterability, and therefore likely viral nature, of the agent of yellow fever. Generously supported by funds from the newly established International Health Division of the Rockefeller Foundation, Noguchi set off for Ecuador where cases of urban yellow fever were thought still to be available for study. Either as a result of erroneous clinical diagnoses of Weil's disease as yellow



LEFT: Surgeon General William C. Gorgas promoted urban mosquito control. COURTESY WELLCOME LIBRARY, LONDON

fever, or possibly because he was confused by an adventitious leptospiral infection of guinea pigs, Noguchi was soon able to report the isolation of '*Leptospira icteroides*', an organism he considered to be the cause of yellow fever. Noguchi and his followers' subsequent claims of successful treatment with leptospiral antiserum, and vaccine protection from yellow fever shown in trials of a crude leptospiral preparation, now make uncomfortable reading. They demonstrate how readily a group of researchers may race after a false scent.

With the leptospiral aetiology of yellow fever in the New World apparently proven, the Rockefeller Foundation's International Health Division adopted a global strategy for yellow fever eradication. In 1925 it established a field station at Yaba, outside Lagos, specifically to investigate whether the cause of the disease in West Africa was also leptospiral. Repeated attempts to transmit yellow fever to animals and isolate *Leptospira icteroides* followed, but all those animals tried, including African monkeys, proved resistant. Then, in mid-1927, the Yaba researchers (assisted by an Anglo-Irish microbiologist, Adrian Stokes), found a consignment of rhesus macaques to be highly susceptible. At once scientific attention switched to West Africa. Stokes himself very soon died of laboratory-acquired yellow fever, but not before he and his American colleagues had shown that filtrates of infected monkey plasma transmitted yellow fever at very high dilutions, and that leptospira were conspicuously absent from their tissues.

For Noguchi, the West African evidence that the yellow fever agent readily passed through bacteria-proof filters, and that it would not infect guinea pigs, was a direct challenge to the dogma that a leptospira caused yellow fever, and could not be ignored. The story of Noguchi's voyage late in 1927 to Lagos and on to Accra, and of his desperate attempts to vindicate himself in the face of the polite scepticism of the researchers who were his hosts, is a sad one. After several months of lonely work as a guest in the Accra laboratory of the Scottish pathologist, William Young, Noguchi contracted yellow fever and died there on 10 May 1928. Within a fortnight Young, too, had died of the disease.

The deaths of Stokes, Noguchi and Young effectively brought to a close the extensive animal experimentation done in West Africa in 1925–1928, it having shown beyond doubt that leptospira played no part in the aetiology of yellow fever.

● The quest for a vaccine

The discovery of the rhesus monkey as a reliable if risky experimental model of yellow fever opened up several new avenues of investigation. The urgent need to protect researchers began to be met when, in 1929, means were described of maintaining live strains of the virus without constant passage through monkeys. A year later, Theiler described a much more convenient and less hazardous

animal model when he induced a transmissible encephalitis in adult white mice with yellow fever virus. Soon infected mouse brain was used to prepare a vaccine with which to protect laboratory workers. This led, after four more years, to successful trials of the attenuated vaccine strain, 17D, since associated with Theiler's name. Whereas others had simply sought to attenuate strains of yellow fever virus in mouse brain, Theiler and his colleagues used the revolutionary new technique of tissue culture passage to prepare their vaccine.

The trials of the 17D vaccine in Brazil in the late 1930s were to reveal problems both with vaccine stabilization and virus attenuation. At first, the attenuated virus was suspended in human serum to combat the loss of vaccine potency, but this expedient had a spectacularly bad outcome during the Second World War. The serum-stabilized yellow fever vaccine was incautiously given to 2.5 million US troops in 1942, and over 20,000 cases of infectious hepatitis ensued. The reports of the trials in South America also hinted at occasional problems with vaccine reversion to virulence, though this seems to have been overlooked at the time. By freeze-drying the vaccine and not having to stabilize it with human serum it became possible to claim, as was done until very recently, that the 17D vaccine was a potent and protective vaccine, neither icterogenic nor encephalitogenic.

● Yellow fever unvanquished

Both the field work in South America and West Africa in the 1920s and 1930s, and the work in the laboratory in New York throughout the 1930s, were funded by the Rockefeller Foundation. In spite of literally giving the 17D vaccine to the world, however, the Foundation was denied the prize of global eradication for which it strove. The explanation for this lay in the demonstration, by its own scientists, of the forest cycle of yellow fever virus infection. Attempts to immunize tropical populations, such as those in French colonial Africa in the 1940s, were insufficient to protect humans from incidental involvement in that cycle and today, as the encroachment into tropical forests in South America and West Africa continues apace, that danger may actually be increasing. Furthermore, recent reports confirm that the 17D vaccine, like other attenuated live vaccines, carries a remote risk of reversion to virulence. Not only, therefore, is vaccine protection not being afforded to tropical populations who may need it, but its use is now also being questioned among travellers to the Tropics.

Three times yellow fever has been written off as a global threat: first, around 1910 by Surgeon General Gorgas and others, after mosquito control had been achieved in the vulnerable cities of the Americas; second, in the 1920s when Noguchi's work persuaded many that yellow fever was a leptospiral disease for which there was antiserum and a vaccine; and third, in the early 1930s when the true causative organisms had been identified,

Further reading

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an effective vaccine was in prospect and the forest cycle of the virus between monkeys and mosquitoes had not yet been discovered. Each time exaggerated claims encouraged false hopes.

Today, few promises of global eradication are being offered and even though yellow fever attracts less attention than, for instance, the rarer haemorrhagic fevers of Lassa and Ebola, it remains the greater threat. The containment of human yellow fever through effective vector control and the vaccination of all those at risk from the zoonotic threat of the disease, together with travellers to the Tropics, remains an important though frequently neglected goal.

The history of yellow fever research also demonstrates how damaging false and inflated scientific claims can be, a point emphasized by the doyen of 20th century American virology, Tom Rivers.

‘There are times . . . when workers of great scientific repute continue to misconstrue the meaning of their data or will not admit inadequacies in the techniques employed in them. When this happens, progress may be materially impeded and much effort must be expended in tearing down the false edifice before a true one can be built . . . no one has the right to encumber science with premature assertions, for an erroneous affirmation which has taken a day to construct requires sometimes 20 years to overthrow.’

The means exist to keep the global threat of yellow fever under control. However, they carry a large financial and possibly a human cost. Talk of eradication remains specious.

Acknowledgements

I would like to thank Dr Harry Goodall for his advice and Lisa Snowden and Sandra Mackay for their secretarial help.

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Amidst growing concern about the spread of infectious diseases throughout the world, many of which have emerged in the past few years, the UK Department of Health has announced a new strategy to protect human health. The prevention of infectious diseases is to become a major government priority, as described in *Getting Ahead of the Curve*, a report which sets out their proposals. It describes the scope and nature of the threat posed by infectious diseases to health in England, together with the priorities for action.

A new body, the National Infection Control and Health Protection Agency, which will combine the existing functions of the Public Health Laboratory Service, the National Radiological Protection Board, the Centre for Applied Microbiology & Research and the National Focus for Chemical Incidents, will assess the threat of new and emerging infectious diseases, intensify control measures and implement a programme of vaccine development. It will also address the risks posed by chemical and radiation hazards.

Announced by the Chief Medical Officer, Sir Liam Donaldson, on the same day that many of the diseases of concern, such as West Nile fever, Nipah and influenza were being discussed at the SGM/ESCV/ESV conference, the plan will have far reaching effects on microbiologists in the UK.

Included in the strategy for action are:

- A local health protection service to deliver specified functions relating to the prevention, investigation and control of infectious diseases
- A national expert panel to assess the threat from new and emerging diseases
- An expanded system of infectious disease surveillance, integrating information from human and animal infections with environmental monitoring
- New action plans to combat priority diseases – TB, antimicrobial resistance, nosocomial infections, blood-borne and sexually transmitted viruses and chronic conditions caused by micro-organisms
- Rationalization of microbiology laboratories and the introduction of standards for the diagnosis and profiling of micro-organisms
- A new Inspector of Microbiology post
- A programme of new vaccine development
- Strengthened clinical and preventative services for childhood infections
- Enhanced planning to combat biological or chemical attacks
- Better public information
- Stronger professional education and training programmes
- A research programme
- A review of the law on infection control to determine the changes necessary to underpin the strategy.

The report can be downloaded from the web at www.doh.gov.uk/cmo/publications.htm

● Janet Hurst, Deputy Executive Secretary