Indian plague poses enigma to investigators

New Delhi. Doubts are emerging about the precise nature of the apparent outbreak of pneumonic plague in the Indian town of Surat. The World Health Organization (WHO) has launched an investigation into what it describes as a "very baffling and mysterious" outbreak, while there is scepticism among some Indian microbiologists about whether the disease is in fact pneumonic plague.

After a visit to India last week by Hiroshi Nakajima, director general of WHO, the organization formally announced on 10 October that a team of experts from the United States, Russia and WHO would investigate the outbreaks of both bubonic and pneumonic plague. The team, which includes epidemiologists, clinicians, a veterinary scientist and experts in communicable diseases, is expected to report within the next few weeks.

After visiting Surat and the laboratories of the National Institute of Communicable Diseases (NICD) in Delhi, Nakajima confirmed that there was pneumonic plague in Surat. But he added: "How it started, why all cases are pneumonic, and how it spared family contacts are just some of its features that are baffling."

But the unusual features of the outbreak have led some Indian microbiologists to question whether it really is pneumonic plague. N. P. Gupta, for example, a former director of the National Institute of Virology (NIV) in Pune, points out that pneumonic plague is a disease of cold climates, whereas the temperature in Surat was 35 °C.

Furthermore, contrary to experience elsewhere in the world, the alleged outbreak of pneumonic plague was not preceded by an outbreak of bubonic plague. Indeed, Bombay escaped without a single case, despite the influx of 50,000 panic-stricken migrants from Surat.

Enver Akhmedov, an epidemiologist at the Russian embassy in Delhi, is one of the foreign experts who admit to being surprised at the small number of confirmed positive cases in Surat, pointing out that "pneumonic plague is the most infectious of all known diseases".

Despite these doubts, WHO is convinced that no other disease is involved. "It is 100 per cent plague," said Nakajima.

Nakajima said his team agreed fully with NICD's identification of *Yersinia pestis*, the plague bacillus, as the organism involved in the Surat outbreak. "However, with only 196 out of 1.8 million population being positive for plague, I am hesitant to call it an epidemic," he added.

The fact that WHO's judgement is based on data presented to it by the NICD, the national centre for plague surveillance and control, has also upset the sceptics, some of whom have criticized the centre's techniques for identifying the bacillus. But specific identification for *Y. pestis*, using fluorescent antibody test, was made by NICD on the day Nakajima visited its laboratory.

N. K. Shah, an expert adviser to WHO, says that the inquiry team is keeping an open mind, and will investigate all plausible explanations for the outbreak. The team will also look at the role of rats in the outbreak of bubonic plague in Beed in the state of Maharashtra, and the later outbreak of pneumonic plague in Surat in the neighbouring state of Gujarat. "We are 100 per cent sure of the involvement of rats in Beed," said Guneael Rodier, an epidemiologist with WHO. "But Surat is the big question mark."

The Indian government is confident that both epidemics are now under control, and claim that the number of suspected new cases is continuing to decline. But the outbreak cannot be declared officially over until 12 days after the last case of pneumonic plague.

Subash Arya, a former deputy director of NICD, says that much of the confusion over the cause of the outbreak is the result of the concentration of all plague-related work at NICD. But he also predicts an end to the dispute, as scientists at the All India Institute of Medical Sciences in Delhi have developed a DNA probe that can detect *Y. pestis* not only in humans, but also in samples from rodents and fleas.

The Indian Council of Medical Research (ICMR), which has no plague expert among its staff, has called for a meeting of all microbiologists — both retired or serving — who have worked with *Y. pestis* or handled a plague case. It has also directed the NIV to make an independent analysis of samples from Beed and Surat. ICMR's laboratory in Ahmedabad, the National Institute of Occupational Health, has taken air samples from Surat to detect any bacilli in aerosols, but has not announced its findings yet. **K.S. Jayaraman**

Nobel honours pursuit of G proteins

London. This year's Nobel prize for physiology or medicine throws cell signalling into the limelight. The prize has been awarded jointly to Alfred G. Gilman and Martin Rodbell to honour their discovery of the role played by G proteins in cellular signal transduction, a decision greeted as "tremendous news" by many scientists.

AP/Ron Heflin

Gilman: analysed role in cell signalling

In 1971, Earl Sutherland received the Nobel Prize for discovering cAMP and the enzyme that creates it — adenylyl cyclase. At the time, it was assumed that when a hormone bound to its receptor at the cell surface, the receptor signalled directly to enzymes such as adenylyl cyclase in the interior of the cell.

As a result, when Martin Rodbell, then at the National Institutes of Health (NIH) (and now at the National Institute of Environmental Health Sciences), proposed in the early 1970s that there were intermediates between hormone receptors and the cell's interior, most researchers ignored their possible existence.

But in a series of ingenious experiments, Rodbell and Lutz Birnbaumer, his first postdoctoral fellow, demonstrated that the step between the hormone receptor and adenylyl cyclase was dependent on GTP (hence the name G protein). "Martin wrote out the protocol and I did the pipetting" remembers Birnbaumer.

The intermediate step had previously been missed simply because most scientists had unwittingly added GTP to their experiments when using 'dirty' preparations, according to Robert Lefkowitz, professor of medicine and biochemistry at Duke University, who was then at the NIH.

Stephen Nahorski of the University of Leicester in Britain describes Rodbell as a bright and generous scientist, always willing to discuss unpublished data, and keen to help younger colleagues. But Rodbell's observations also inspired Alfred Gilman, a young pharmacologist with a keen eye for important issues in pharmacology, to hunt for a GTP-dependent protein.

The isolation of the first G protein by Gilman (and independently by Thomas Pfeufer) confirmed Rodbell and Birnbaumer's suspicions. It also left Gilman, now professor of pharmacology at the University of Texas Southwestern Medical Center, leading the field, as he has since done for many years. With relentless commitment, he has purified, cloned, and even crystallized G proteins, revealing the molecular basis of the way in which they transduce signals.

Rodbell's continuous production of ideas, combined with his infectious enthusiasm, have complemented Gilman's prolific experimentation and total commitment to his subject. Several hundred receptors that signal by this route are now known, and altered G-protein signalling plays a pivotal role in conditions like whooping cough and cholera, as well as various genetic conditions (see, for example, *Nature* **371**, 164; 1994). **Harriet Coles**