

Studies on the role of Fe in the blast disease of rice indicated the importance of lipoxygenase in disease resistance and that resistance is likely to be mediated by Fe. Active monogenic resistance to blast seems to be mediated by pre- and post-infectionally formed antifungal compounds and development of resistance to such natural antifungals may be a key to evolution of physiologic race in blast fungi.

Suryanarayanan was always keen on employing the latest techniques in laboratory bioassay of plant products. In this quest for excellence he had brought

to the CAS in Botany at Madras many such techniques as he worked at the International Rice Research Institute, Philippines; Departments of Biological Sciences, University of Dundee; Imperial College, London; Long Ashton Research Station, Bristol and the Prairie Regional Laboratory, Saskatoon, Canada. More than using these techniques he had trained all his research associates to handle and maintain the many sophisticated instruments they had gathered together.

In the sudden passing away of Suryanarayanan on 18 June 1994 when

his scientific productivity was still high, even in retirement, we have lost an able investigator in the modern field of Physiological Plant Pathology. He was a much respected academic. He leaves behind his wife and son and a host of scientific colleagues to mourn the loss.

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## HISTORICAL COMMENTARY AND NOTES

### From the annals of plague

C. C. Kartha and E. Jeetendra

Giovanni Boccaccio, a contemporary of Dante and Geoffrey Chaucer is the father of Italian prose. His masterpiece the *Decameron* is a collection of tales, told to one another by ten friends who terrified of an epidemic of plague, fled to an isolated villa.

#### A memorable description

The prologue to the *Decameron* contains a vivid portrayal of the Black Death, an epidemic of bubonic plague, worst of all times, which ravaged Europe during Boccaccio's life time<sup>1</sup>.

In the year of our lord 1348, in Florence, in the finest city of all Italy, there occurred a most terrible plague: either because of the influence of the planets or sent from God as a just punishment for our sins, it had broken out some years earlier in the East, and after passing from place to place and reeking incredible havoc along the way had now reached the West where, in spite of all the means that the art and human foresight could suggest, such as keeping the city clear from filth, and excluding all suspected people.... Different from what it had been in the East, where bleeding from the nose suggests a fatal outcome, here there appeared tumors in the groins or under the

armpits, some as big as a small apple, others like an egg. Afterwards purple spots appeared in most parts of the body... the usual messengers of death. To the cure of this disease, neither the knowledge of medicine nor the power of drugs was of any effect, whether because the disease was itself fatal or because the physicians, whose number was increased by quacks and woman pretenders, could discover neither cause nor cure, and so few escaped. They generally died the third day after the appearance without fever.... The disease grew daily by being communicated from the sick to the well.... Nor was it (necessary) to converse or even to come near the sick; even touching their clothes or anything they had touched was sufficient.... The events and similar others caused various fears among those people who survived, all tending to the same cruel and uncharitable end which was to avoid the sick and everything that had been near them.... Some felt it best to live temporarily.... but others maintained free living and would deny no passion or appetite they wish to gratify.... And the public distress was such that all laws, whether human or divine, were ignored....

The outbreak was first noticed in Sicily by early 1348, the infection carried from Asia Minor by sailors in merchant vessels which plied across the Mediterranean. Then it struck the Dorset ports and spread across Europe. Within a decade about 33,000,000 people, approximately one third of the population of Europe, were estimated to have succumbed to the disease. Men wore masks with pointed beaks containing vinegar and sweet smelling potions to counteract the fetid smell of dead bodies. Clerics convinced the people that the plague was a divine retribution for their sins. Crusaders in Germany took upon the sins and flagellated themselves to drive off the plague. Jews were tortured to confess that they had poisoned the wells and then persecuted.

However, sensible ways to contain the epidemic were established towards the end of the middle ages. Venice, the chief port of trade established observation centres where immigrants were made to stay for forty days, the period of quarantine (from 'quarantina', Italian for forty). The choice of this period is said to be based on the period Christ and Moses spent in isolation in the desert). A sanitary code which provided for isolation of patients, burial of the dead with their personal effects, fumigation of the place where they had

died, street cleaning and garbage disposal by the local authorities came into existence.

### The aftermath

'The year of the Black Death was the year of the conception of modern man' wrote Friedell<sup>2</sup>.

When the plague struck, Europe had basically an agrarian economy. A series of bad harvests and a decade of war (the hundred years war between England and France) had resulted in economic recession. Epidemics of plague in subsequent years aggravated the economic decline. The marked reduction in the population and the consequent scarcity of available labour force caused a change in the relationship between employer and employee and landlord and tenant. The rents had to be reduced and the wages were pushed up. Landless labourers were suddenly well off. Some believe that the altered social structure created by the Black Death contributed to the Peasants's Revolt of 1381 which ushered in the doom of the feudal structure in Europe<sup>2,3</sup>.

Another victim was the Church. The disillusion and despair that set in during the decades of plague probably eroded the moral stamina of the people. There was spiritual unrest which gave birth to an aggressive anti-Church movement, leading to a decline in the authority of the Church. As the death toll of the priests went up, the reputation of the Church also fell. Conscientious priests rarely survived thus divesting the Church of its able men. In short, the Black Death created an environment conducive for the Protestant Reformation<sup>2</sup>.

Over the ages there were two other outbreaks of plague which consumed large numbers of people. The great plague of London during 1664-1665 resulted in more than 70,000 deaths. Another epidemic in Hong Kong in 1894 left 80-110,000 dead. Within twenty years the disease spread from the Southern Chinese ports throughout the whole world resulting in more than 10,000,000 deaths.

### Ancient times

Pestilence identical to plague have occurred in epidemic proportions in

ancient times but with lesser consequences. Around 430 BC was the great plague of Athens. Later an Ethiopian plague threatened Greece. Hippocrates is supposed to have driven it off with fires in which flowers, unguents and perfumes were burnt. A century after the death of Hippocrates, the plague struck Rome. The elders decided to bring the image of Asklepios, the patron God of physicians, from his shrine in Epidauros in Greece and despatched a trireme. The envoys brought back a serpent which crawled into their ship. They believed that the God was present in the snake and when it went ashore on the island of Tiber, a temple was built there. The plague is reported to have abated!<sup>4</sup>

### Eureka! The plague bacillus

Two centuries after the Black Death, Fracastoro, a fellow student of Nicholas Copernicus at the University of Padua proposed the germ theory of disease in a book he published<sup>5</sup> in 1546. He wrote: 'Contagion is an infection that passes from one thing to another'. Three types of contagions were mentioned: (i) by contact, (ii) by fomites (articles used by the patients), and (iii) from a distance. Fracastoro's ideas derived support from a German Jesuit Athanasius Kircher a hundred years later. Kircher in his book entitled *Physico-Medical Scrutiny of the Contagious Pestilence, which is called the Plague* reported of seeing 'small worms' in victims of an epidemic plague which occurred in Rome in 1656. This was probably the first time a microscope was used in the investigation of a disease<sup>5</sup>.

The next two centuries witnessed the universal acceptance of the germ theory of diseases. Microbial basis of a number of diseases were detected. The Pasteur Institute which opened in 1888 at Paris exerted a profound influence in the further development of microbiology. It was here that Alexander Yersin who isolated the bacillus of plague was trained<sup>6</sup>. (Shibasabura Kitasato of Japan also independently discovered the bacillus.)

Yersin was born in Aubonne in 1863 and had his medical training in Lusanne, Marburg and Paris. A shy and introverted person, he chose pathology so that contact with people would be minimum. Before joining the Pasteur Institute Yersin went to Robert Koch's

laboratory and equipped himself with Koch's methods in pathogenic bacteriology. Back in Paris he collaborated with Emile Roux and discovered the diphtheritic toxin. A man with varied interests and irresistible desire for adventure, one day when Roux was absent, Yersin left Paris to explore the tropical jungles. He was fascinated by Indochina and settled there to collect data on flora and fauna as well as anthropological and sociological information on the natives.

What brought Yersin back to bacteriology was the epidemic of bubonic plague in Hong Kong. In a short period of time after he was summoned there, he published a report of his studies on plague. Yersin demonstrated that pulp of the enlarged glands (buboes) contained 'masses of short stubby bacilli rather easy to stain with aniline dyes but not stained by the method of Gram'<sup>6</sup>. The pulp when seeded on agar gave rise to transparent white colonies consisting of chains of short bacilli interspersed with larger spherical bodies. Mice, rats and guinea pigs were inoculated with pulp from buboes and at autopsy he saw characteristic changes of plague as well as numerous bacilli in the lymph nodes, spleen and blood. He observed that dead rats in houses and in the streets harboured large quantities of the microbe in the organs. The transmission of the disease from infected to healthy mice was also demonstrated by him. He suggested that rats may be major vectors for the propagation of the disease and flies may be agents in its transmission. He also predicted that inoculation of non-virulent strains would give protection against plague.

Yersin was 31 years old when he discovered the plague bacillus which was named after him as *Yersinia*. A year after the discovery he established an Indochinese Pasteur Institute at Nhatrang dedicated to the manufacture of sera and vaccines against the diseases of the Far East. Later however, conscious of the importance of developing agriculture in the region, he turned to agronomy.

### The carrier traced

Even though many had observed the death of rats at the time of a plague epidemic the link between rat and man was not recognized till P. L. Simond's

studies. Simond, during his missions in French Indochina in 1894 and in India later, had seen that the disease in rats preceded the epidemic in man. He considered that rat was a much more important agent of transmission than man. By carrying out feeding experiments he showed that rats were not usually infected by eating infected tissues of other dead rats. He also noticed blisters containing plague bacilli on the feet and legs of some patients which he considered were probably at the site of a transmitting insect's bite. He looked for rat parasites, the flea and the louse. The fleas on an infected rat had numerous plague bacilli in their intestinal tract. The crushed infected material when injected into rats produced the disease. When a healthy rat was kept in a cage along with infected rat infested with parasites the healthy rat developed the disease. However, a plague-infected rat free from parasites could not transmit the disease. Based on these observations the rat-flea theory was propounded in 1898 (ref 7). Simond went on to study the actual mechanism of transmission. He found that the infected fleas while feeding, excreted the bacilli introducing them into the bite site. He also reported that the fleas detach themselves from a dead rat and quickly attach themselves to any animal or man coming in contact with the dead rat.

Six years later, W. Glen Liston independently put forward the rat-flea theory based on his own experiments<sup>8</sup>. He was probably unaware of Simond's earlier work. Liston's findings were similar to those of Simond. Yet, the cynics were unconvinced of the rat-flea theory. E. F. Gordon Tucker commented: 'A recent theory which appears to have taken the fancy of the public is the flea theory. Sanitary authorities have made use of the subsidized rat catchers and now I suppose we shall see the utilization of subsidized flea catchers'<sup>9</sup>.

During the first quarter of the twentieth century more information on the fleas was gathered thanks to the investigations of L. F. Hirst, W. H. Webster and G. D. Chitre<sup>10, 11</sup>. Hirst found that *Xenopsylla cheopis* is the more efficient transmitter of plague than *X. astia* or *X. braziliensis*. Webster and Chitre described the 'blocked flea' dangerous to the spread of plague. A blocked flea has its proventriculus blocked by bacillary multiplication. Such a flea eventually would face

## Facts about plague

- ◆ It is a rapidly fatal infection with a mortality of 60 – 90% without treatment.
- ◆ The causative agent *Pasteurella pestis* or *Yersinia pestis* is a pleomorphic small gram-negative coccobacillus that presents with polar bodies and is often encapsulated.
- ◆ The organism can be cultured in ordinary nutrient agar or blood agar. Blood cultures are positive in approximately 50% of the cases. Guinea pig or white rat can be inoculated by rubbing the infected material onto shaved skin on the anterior abdominal wall. The animal will die in 3 – 5 days with symptoms and organ changes of plague if the material contains the bacilli.
- ◆ Primarily a disease of rodents, it is transmitted to man in two ways: (i) the common bubonic form of the disease results from the bite of infected fleas (*Xenopsylla cheopis*, *X. astia* and *X. braziliensis*) with a taste for both human and rat blood and (ii) the pneumonic form is spread by inhalation of infected droplets of sputum or bacilli entering through cuts and abrasions or through transfusion of infected blood.
- ◆ The incubation period is two to four days.
- ◆ All ages and both sexes are susceptible to plague.
- ◆ An attack of plague gives life-long immunity.
- ◆ Plague season usually starts in September and lasts until May.

starvation and death if it cannot obtain a blood meal. In its frantic efforts to bite and suck blood it would regurgitate plague bacilli each time it bites. A partially blocked flea may live even up to one year. Webster and Chitre also characterized the climatic conditions which influenced the spread of plague.

With the campaign against rat and rat fleas and concomitant improvement in hygiene and sanitation plague came to be controlled. A cure was yet to be found.

## Haffkine and the vaccine

During the great epidemics of plague effective treatment was not available. Various antiseptics were tried but were not found adequate. Antibiotics were yet to be discovered. It was then that the idea of developing antiplague serum was advanced. A pioneer in the pursuit of the plague vaccine was W. M. W. Haffkine.

Haffkine, the son of a Jewish school master, was born in 1860 at Odessa. He was a student of the Nobel laureate Elie

Metchnikoff. Like many of his Jewish colleagues, he migrated to Switzerland fearing torture by the Russians. Then in 1889 he shifted to Paris to work with Louis Pasteur on cholera. Seven years later he was appointed to investigate the outbreak of plague in Bombay and suggest preventive measures for the disease<sup>12</sup>.

Soon after his arrival in Bombay he set up his laboratory in one of the rooms of Grant Medical College. Within three months of the outbreak he began to make two preparations, (i) for curative treatment, and (ii) for prophylaxis. He had only one clerk and three peons to assist him at that time. Haffkine tried antitoxin for the plague victims. Concurrently he investigated in animals the protective role of killed plague bacilli. The initial success gave him confidence to inoculate himself with the killed plague bacilli. Convinced of the beneficial effects of this form of prophylaxis, he tried the injection on volunteer inmates of the House of Correction when the plague broke out at Byculla. In his report to the Secretary, Home Department he wrote: 'The experience gained by the observation in

## Prevention and control of plague

### ◆ Control source of infection

Antirodent measures such as sound environmental sanitation (proper storage, collection and disposal of garbage, proper storage of foodstuffs), elimination of rat burrows by blocking them with concrete, trapping of rats, and use of rodenticides (zinc phosphide, sodium fluoroacetate, warfarin, pindone, etc.), or fumigation (using calcium cyanide, carbon disulphide, methyl bromide and sulphur dioxide) may be employed.

### ◆ Block channels of transmission

Control fleas of houses, pets, bedding, and clothing by spraying with DDT, benzene hexachloride, gammexane, pyrethrins, phosmet, cythioate, lindane, etc.

### ◆ Immunization

Plague inoculation confers roughly fourfold protection against attack, and sixfold against death. It should only be used for prevention and not control of plague. Two doses with an interval of 7 – 14 days is to be administered. Immunity starts 5 – 7 days after inoculation and lasts for about 6 months.

### ◆ Chemoprophylaxis

Advised to all contacts and personnel exposed to the risk of infection.

### ◆ Disinfection

Sputum, discharges and articles soiled by the patient should be disinfected. Dead bodies should be handled with aseptic precautions. Dead rats found should not be handled with naked hands. They should be buried or preferably burned.

### ◆ Dead rats and suspected human cases should be promptly reported

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this jail tends to show that injection of 3 cc of the prophylactic seems to be sufficient to effect the desired protection, no repetition of inoculation being necessary to arrest the disease during an existing epidemic. The prophylactic is powerless to arrest the symptoms of plague already started or which developed within a few hours. But there is the possibility of influencing the disease in the incubation period in individuals infected three or four days previously.<sup>12</sup> Haffkine administered the prophylactic injection to 7905 persons during a six month

period from January to July 1897. The results were more than optimistic. Only two persons who were already unwell at the time of inoculations died

In 1896 the Government of India appointed a Plague Commission to objectively assess the value of Haffkine's vaccine. The commission found that the injection diminishes the death rate among the inoculated population, but does not provide absolute protection against attacks. It also suggested that an accurate standardization of inoculation techniques be done. Soon after the report was submitted in

1900, a laboratory was set up for the preparation of the inoculation material and plague inoculation teams were appointed in all major cities of India. Years later, B. P. B Naidu and colleagues at the Haffkine institute standardized Haffkine's prophylactic and went on to prepare a potent antiplague serum<sup>12</sup>. A live vaccine against plague was developed by L. Otten of Pasteur Institute in Bandoeng<sup>13</sup>. Thousands of human lives were saved from plague thanks to the efforts of Haffkine and his successors

Queen Victoria decorated Haffkine with the Order of the British Empire. He was soon made the Director of the Plague Research Laboratory (which was later designated as Bombay Bacteriology Laboratory in 1904, and then rechristened as Haffkine Institute in 1925). Unfortunately he became the target of victimization by military medical personnel who were jealous of the success of a Jewish non-medical man. When in November 1902, a segment of inoculated people in Punjab developed tetanus and died, a commission of enquiry held Haffkine guilty of the charge that he had stopped using carbolic acid, an antiseptic, in the preparation of the vaccine. Haffkine was relieved of his post and with great disappointment, he returned to Europe. Later when the commission report was referred to scientists at the Lister Institute, Haffkine was exonerated. He was reinstated at Calcutta, where he worked till his retirement in 1914.

## Outbreaks in India

The first recorded outbreak of plague in India was in Agra during the reign of Emperor Jehangir. Since then the disease was present in endemic form in different parts of the country, particularly in the northern regions. Plague became a serious problem in early nineteenth century and the situation worsened when the pandemic of 1894-1896 involved India. The epidemic from Hong Kong first spread

to Bombay and paralysed life in the city by one description Bombay reminded of the desolate streets of London during the plague of 1665 (ref. 12). From Bombay the disease extended to other cities resulting in heavy casualty. During the year of 1897, it was estimated that 57,965 people died of plague. The figure rose to 950,863 in 1905. Then slowly the incidence began to decline. In 1968 no deaths from plague were reported<sup>14</sup>. Nearly three decades later now there is a resurgence at Surat.

## A point to ponder

Sir McFarlane Burnet wrote: 'The great plagues of history were biologically unimportant accidents, the result of human entanglement with a self-contained triangular interaction of rodent, flea and plague bacillus.'<sup>15</sup> How did we get ensnared at Surat, is it by chance or through acts of omission?

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