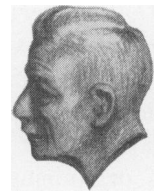
The R. E. Dyer Lecture



The Natural History of Plague and Psittacosis

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THE invitation to deliver the sixth R. E. Dyer Lecture is interpreted as an opportunity to appraise the past, present, and future of bacteriology and epidemiology in their relation to medicine. As the investigator honored by these lectures has so eminently shown, the study of infectious diseases still promises exciting discoveries, despite the advances of recent decades.

Immunization and antimicrobial therapy have certainly expanded man's control over many infections. Few who entered the fields of pathology and bacteriology 50 years ago could foresee the imminent reduction in the number of deaths from diphtheria, pneumococcal pneumonia, streptococcal infections, yellow fever, typhus, and plague. One keeps in mind the intelligence and devotion of those whose work made this reduction possible. Some of their work was brilliant; much more of it was simply intelligent. It was all invariably persistent.

The triumphant results of these efforts have led to the prevalent misapprehension that no one should now die of or even suffer inconvenience from an infection. The origin and consequences of this attitude are readily traceable from the success of chemotherapy of spirochetal and protozoan infection to the more dramatic experiences with sulfonamides and antimicrobial drugs. In many cases, chemotherapy has unquestionably eliminated the infector from the infected, allowing the infected to survive where once he would have perished. If a measure can preserve life, it may be unfair to point out its shortcomings, even its faults.

To comprehend the whole nature of the relationships of the new chemotherapeutic agents, the micro-organisms, and the infected human being is not so simple. Misleading simplifications abound in the minds of laymen and of physicians. But among microbiologists there is still much conjecture about the mode of action of these drugs.

The exceptional nature of the host-drug-parasite relationship is not always understood. Infectious agents do not characteristically submit to unconditional surrender. Throwing great quantities of every drug against every infection will insure only a steady decrease of satisfactory responses and a steady increase in toxic reactions, sensitized patients, and re-

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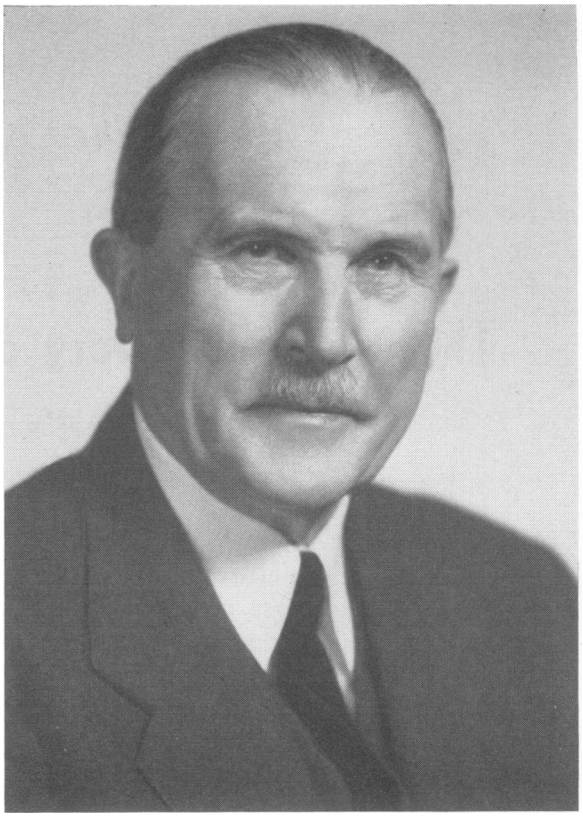
sistant bacteria. It is now fairly well understood that insufficient amounts of the drugs may allow bacteria to survive treatment and that later the bacteria may multiply and cause a relapse. But it is not always understood that the organisms may not be easily reached by the drug and may therefore not be subjected to its adverse effects. Adequate elimination of the organisms may depend on continued administration of powerful drugs in large doses or on combined chemotherapy.

Use of the antimicrobials is not without dangers. To overlook or even deny the toxicity of some of the drugs leads to carelessness, misplaced enthusiasm, inevitable disappointment, and abuse of a useful tool. In order to use the extraordinary powers of the drugs to greatest advantage, one must recognize that some of the drugs are toxic, that they may lose their effect, and that they may even do harm unless those who administer them have a thorough understanding of bacteriology.

The dramatic early results of chemotherapy were not matters of chance. Fundamental research in bacteriology made the miracles possible, and day-to-day study has been necessary to keep them miraculous. When the new drugs were scarce, each patient to be treated was chosen with care and treatment was carefully controlled. This is an important reason why failures were few. Knowledge and understanding of the natural history and pathogenesis of infections must correct some of the grosser mistakes now being made. Adequately trained workers in good laboratories open to physicians in hospitals, in public health agencies, and in private practice are and will continue to be needed.

Other factors refute the prevailing view that infectious diseases have been conquered. These diseases have been significant through centuries, and they will continue to be so. The human race is condemned to coexistence with parasites. If they are underestimated they may regain their lost ground. The advances called to mind by the names Jenner, Pasteur, Lister, Koch, Roux, and Theobald Smith have altered the course of the infectious diseases quantitatively with respect to location and time. But the suppression of certain epidemic diseases in relatively small areas has in no way



Dr. Karl F. Meyer

influenced parasitism in general. The everlasting question, what forces create, maintain, and suppress epidemic diseases of man and animals? has never been fully answered.

From 1857 on, the work of Pasteur and those who followed him turned bacteriology from a conjectural into a scientific discipline. The impact on medicine was immediate, and it was with few exceptions one sided. The pathologist analyzed the gross and microscopic changes in the cadaver and interpreted these end results of the infection. The study of the causative agents as living creatures, rather than the disease process itself, created the field of microbiology, a field already so broad that no single scientist can hope to deal with it competently. Experimental methods have brought bacteriology and pathology together. This left another area to be explored by the epidemiologist. Field investigations, clinical records, and laboratory researches on individual patients were correlated in an effort to understand the mass phenomenon of infection and disease

manifested in epidemics. The development of methods of investigating epidemics has made it possible to analyze newly discovered infections more efficaciously.

Initially, epidemiology was concerned with learning what maintained epidemic diseases. Medical bacteriology, fascinated by the rich rewards granted the unilateral search for new causes, at first failed to realize that infectious diseases are biological manifestations of parasitism. By placing the parasite in the foreground of the inquiry and by failing to consider as equally important the receptivity of the host to the parasite, the pioneers remained unaware of the full natural history of infection. Once it was recognized that most infectious diseases are characteristically asymptomatic, the strictly utilitarian concepts changed.

Today, the epidemiologist is less concerned with etiological specificity than with reactions between the infector and the infected. Study of the prime incitant of disease and tracing it to its natural environment share importance with appraisal of the spectrum-like individual, clinical, and immune variations within an infected group. Furthermore, the epidemiologist recognizes that knowledge of an infection in an individual patient is basic to comprehension of an epidemic. The broad field inquiries and experimental studies of the biology of infections indicate that the tragedy of individual events and the course of an epidemic are ultimately conditioned by innumerable variables in the constitution of the host and in the characteristics of the parasite. Study of both components of an infection must continue.

From this point of view, the contributions, even with respect to the parasite, which is more accessible to study than the host, seem modest. Bacteria and probably viruses are infinitely adaptable and versatile. Studies of bacteria and viruses have increased knowledge of their anatomy and physiology to the extent that the subject of bacterial heredity is topical. When it is argued whether bacteria have nuclei or reproduce sexually, difficulties arise about the precise use of these terms. This is not the place to enter into this controversy, but it can be said that bacteria contain material chemically akin to the constituents of the nuclei of plant or animal cells. This material is partitioned among the dividing bacterial cells, but, more important, identifiable components of one bacterium can be assimilated by another and transmitted to the descendants of that other, producing a race with a structure and properties different from those of the parent organism. These facts are in full harmony with what has long been known: Bacteria vary and mutate.

Successive generations of bacteria may differ fundamentally from those that preceded them, and the physical and chemical effects expressed as virulence produced by a bacterial population, even in a defined environment, cannot necessarily be predicted on the basis of previous experience. This fact may be irritating to the pure scientist who has studied bacterial chemistry. He does not know what to make of fugitive micro-organisms that differ from one another even when they originate from a single cell in a chemically defined medium. Allowing for variation, mutation, such sexual activities as transduction and transformation, and the appearance of a new generation every 20 to 30 minutes, change in infectious agents in so inconstant an environment as man and animals should surprise no one. But physicians and patients are bewildered about why epidemics wax and wane, and about why this person is stricken and his neighbor is not.

No one can say whether knowledge of present epidemics can be used to explain the ebb and flow of past epidemics. Changes in the state and circumstances of the host alone certainly cannot explain the great cyclic variations in virulence over the centuries. Mutation of the parasite as conceived in very general terms is, at least in the modern view, a decisive factor. Mutation of the parasite toward greater invasiveness and virulence along with favorable conditions in the host opens the way to rapid proliferation and transfer for a time. But as the host is reduced in number, the parasite tends to be subdued because its field of action is narrowed. Natural selection apparently acts in favor of a more balanced relationship in which host and parasite survive with minor damage to either. The epidemic explosive phase is relatively short; the stabilized endemic, symptomless phase, relatively long. This may or may not explain fluctua-

tions in epidemic patterns. Since infection is a natural phenomenon, infectious agents are likely to take new forms, and milder or deadlier infections may arise from the usual pathogenic agents or from nature's vast reservoir of feebly pathogenic or nonpathogenic creatures.

Infections do cross into regions where they were previously unknown, and they also may exist in unexplored areas. Man's entrance into uninhabited territories in quest of natural resources or land for agricultural development has led to the discovery of natural foci of zoonoses transmissible to man. These remain unrecognized until human beings come in contact with them. They constitute a potential danger, and their existence and localization should be anticipated.

How can a thoughtful student accept the view that the infectious diseases are losing their importance and that they will probably be conquered within a decade? Bacteriology and virology, with their important components microbiology and immunology, as cornerstones of epidemiology have made great contributions to medicine, public health, and preventive medicine. There are still challenges to the younger generation to apply effectively what is already known and in an adventurous spirit to decline acceptance of all prevailing views and incline to exploration of the remaining unknown. It has always yielded to determined, qualified investigators.

The laboratory worker observes that the number of specimens being received is growing and that the methods and the interpretation of results are becoming more complex. There is an unsatisfied need for diagnostic work and for the kind of assistance that can be furnished only by a qualified bacteriologist and epidemiologist receptive to problems in infectious diseases.

It seems appropriate on this occasion to discuss the natural history of two infections on which the predecessor of the National Institutes of Health—the Hygienic Laboratory—did pioneer work in the United States. My friendship with Dr. Dyer stimulated my continuation of plague studies during the past 15 years. Earlier counsel of Dr. George McCoy led the way. And without the studies on psittacosis in 1930 by McCoy, R. D. Lillie, H. E. Hasseltine, V. M. Hoge, and others, and the encouragement offered by the late Surgeon General Hugh S. Cumming, it is doubtful whether so extensive an effort would have been made to solve problems in California. In addition to the support given by the officers of the Public Health Service, perhaps sentimental ties with the country of my birth fostered my interest in these two infections. The cause of plague was first conclusively demonstrated by A. Yersin, a Swiss. Psittacosis was first described as a specific clinical entity by J. Ritter, another Swiss.

PLAGUE

Black Death claimed 14,000 inhabitants of the city of Basel between 1347 and 1353 and left its mark on many permanent records. Historical documents, religious ceremonies, and art treasures reminded later generations in that ancient city that plague was its worst visitation, surpassing war and famine in its impact. Family chronicles described the scourge and listed the medicaments that the head physician of the city hospital compounded by mixing 23 different herbs into what was called *aqua theriacalis*. This I well remember because translation of one of these documents from Latin into German was one of my assignments in the gymnasium in Basel.

At the time of that translation, the cause of plague had just been discovered, and the infection was embarking on its pandemic march out of Hong Kong. Perhaps nothing among the reminders left a greater imprint on my mind than a canvas by Boecklin, the famous Swiss painter, shown in the Basel gallery in 1897. Here the horrible feeling of the epidemic is conveyed by grotesque, triumphant Death, astride a monster, hurtling through a street.

While a graduate student at the Institute for Infectious Diseases in Bern, I assisted in the active immunization of horses with virulent plague bacilli. This experience provided ample opportunity to become acquainted with the plague cell and with procedures for guarding against infection. Efforts to develop a test on rats that would reveal the protective and, to a lesser degree, the curative properties of the

unpurified antiplague horse serum were disappointing.

Later, during a visit to Ann Arbor, Mich., Prof. F. G. Novy described the dramatic experiences in San Francisco in 1901, where he had been a member of an expert commission on plague. Subsequently, a worker in his laboratory had contracted pneumonic plague. From 1913 on, I followed eagerly the plague investigations conducted by the Public Health Service first in California and later throughout the 15 western States. Opportunities for studying plague developed slowly, but since 1920 the disease has been one of my main interests.

Epidemics in California

The urban murine phase of plague in San Francisco, with at least 159 cases and 77 deaths, terminated in 1908, and the subsequently discovered reservoir in wild rodents of rural areas yielded few specimens for study. In fact, by 1914 optimists contended that all discernible plague had been eradicated. But official records after 1915 continued to report that plague-infected squirrels were being found around the bay area. Human infections apparently did not occur, and for a time a feeling of security prevailed.

Then, like a thunderbolt, rapidly fatal pneumonic plague struck in Oakland, between August 15 and September 11, 1919. The circumstances of the outbreak, in which 13 persons died, including 2 physicians and 2 nurses, were described and interpreted by Force and Kelly (*1*). The first patient, who had secondary plague pneumonia after incision of a bubo in the right axilla, had hunted and shot squirrels in the Alameda foothills. The customary search for squirrels with gross anatomical lesions led to a small reservoir.

It was necessary then to look into the intrinsic and extrinsic factors that conditioned the episode.

With respect to the causative organism, this outbreak was compared with the earlier devastating epidemic of pneumonic plague in Manchuria. Because of the violence of both, it was thought that the plague bacillus involved differed from the ordinary strains, that it was specific, highly virulent, and pneumotropic. In both, lung lesions had been found in the responsible reservoir of wild rodents. It was believed that the respiratory infection was a mixed infection. Carefully planned experiments later showed the oneness of the plague bacillus, irrespective of host origin or symptoms. The strain isolated in the Oakland epidemic was not pneumotropic and differed neither biochemically nor serologically from the other continental strains.

Influenza interjected further diagnostic doubt. This disease had not entirely disappeared in August 1919, and the cause of death of one plague victim had been reported to be influenzal pneumonia. Methods of studying this virus had not then been developed, and the usual bacteriological tests on the lung specimen available did not answer the question.

The extrinsic factors in the Oakland outbreak had to be reconstructed from data collected after the epidemic. The temperature had been around 60° to 68° F. and the humidity low. Such climatic conditions would not favor the transfer of infected droplets carrying plague bacilli from one person to another, a fact suggesting that contact with the patients was probably close.

The climate was similar during October and November 1924 in another outbreak, this time in Los Angeles. There were 40 cases—29 pneumonic, 3 tonsillar, and 8 bubonic—and 35 deaths. Appearing in a few households, the infection was carried by visiting relatives or friends to other households, and these then became subsidiary centers for spread. An autopsy was performed in 9 of the 29 cases of pneumonic plague, and in 3 the evidence suggested contact infection through the oral or faucial mucosa. The significance of this type of infection was not known then. In 1926, Wu Lien-Teh reviewed 250 reported cases of pulmonary plague from various epidemics and mentioned tonsillar plague with primary cervical buboes in only 3 cases (*2*).

The epidemiology of the Los Angeles outbreak has never been critically analyzed, nor has an epidemiological report of it ever been published. On epidemiological grounds it is believed that secondary pulmonary invasion developing from bubonic plague of rat flea origin

started the epidemic. The recrudescence of rat plague in that area was a great surprise. Surveys begun in 1908, when an infected squirrel caused a human infection, and carried through until 1915 had revealed no infected rodents. Two possible sources of the infection in Los Angeles rats in 1924 were investigated: (*a*) infection in rats brought in from foreign ports through San Pedro, the port of Los Angeles, and (*b*) infection in ground squirrels in the area.

The first possibility was dismissed because plague-infected rats could not be located in the port. The second possibility seemed to fit the circumstances. The rats in that area did have contact with squirrels; infected squirrels were found in the urban section of the city; and squirrel fleas were found on the rats. The interchange of fleas between wild rodents and commensal rats had been recorded earlier (*3-5*) and has been observed since (*6*).

Wild Rodent Reservoirs

An ecologic study in 1946 on a ranch near Santa Paula, roughly 50 miles northwest of Los Angeles, established for the first time the simultaneous occurrence of plague in rats, ground squirrels, a cottontail rabbit, and their ectoparasites (*7*). One-fourth of the fleas taken from the rats were ground squirrel fleas carrying *Pasteurella pestis*. Plague was probably also transmitted from wild to commensal rodents in the rat epizootic in Tacoma, Wash., in 1942 and 1943.

Interestingly, rat plague has never been recorded inland in the western States. Not only are there fewer rats inland, but also there is no evidence that ectoparasites from other wild rodent reservoirs are transferred to the rat.

Recurrence of plague in commensal rats in countries where the principal natural reservoirs are squirrels and gerbils without notable repercussions in nearby human populations has not been adequately explained. The idea that commensal rats are the sole reservoir was based on observations that without exception domestic rats and the classic plague-bearing flea were abundant where bubonic plague was epidemic. Whether this combination is responsible for epidemics in India, Madagascar, Egypt, Senegal, Peru, Brazil, and elsewhere now requires thorough reevaluation.

As late as 1940, investigators familiar with plague in South America believed that natural infection of wild rodents was confined to Argentina. Then wild rodent foci were found in Venezuela, Bolivia, Peru, and Ecuador (*8*, *9*, and personal communications from Macchiavello). At first the investigators believed that the infection was not entrenched in smoldering wild rodent foci, but more recent observations indicate that it is.

In the brilliant investigation of the epidemiology of plague in Kurdistan Province in Iran, Baltazard and his associates discovered two pockets in which the reservoir included three species of sand rats (*10*). These rats were the most numerous rodents near the foci where there had been two explosive outbreaks of pneumonic plague. Since some of these rats were resistant to plague, they would not be likely to be wiped out by epizootics, but they could serve as reservoirs of enzootic plague. It is becoming apparent that the highly susceptible rodents, such as the marmot, the squirrel, and the rat, are not the permanent reservoirs of the plague bacillus. In his picturesque description, Baltazard states that if the rat has made the fortune of plague, it is not the original, probably not even the actual, proprietor of the disease, but only the disseminator.

It was once assumed that whenever a parasite brings about its host's death in a short time, the host is not the natural one or that it is a natural one in some unnatural environment. Now Baltazard's findings suggest that that concept may have to be modified: In Kurdistan some sand rats were quite resistant while others were highly susceptible to plague. Only analysis of the chromosomes, not of gross zoological characteristics, would permit the necessary distinction in susceptibility. As Baltazard has pointed out (in a personal communication), it now seems that maintenance of plague in focal areas requires resistant wild rodents capable of surviving the epizootics and thus of perpetuating the infection, as well as susceptible species capable of rekindling the infection. The ecologic factors in the focal habitual niches filled with hosts, parasites, and

vectors are obviously far more complex than they were once thought to be.

Influenced by the work of Baltazard, other workers have proceeded to find centers of wild rodent plague in Kenya, central Africa, and the United Provinces (Uttar Pradesh) in India. Heisch, while studying plague near Rongai in the Rift Valley of Kenya, found a focus in three different species of wild mice in a certain field (*11*). *P. pestis* was isolated from these rodents long after the widespread epizootic had died down and the animals in adjacent fields were proved by animal tests to be free from infection. After the field was ploughed up, infected rodents could no longer be found, but "permanent foci" persisted in the escarpments where rodent burrows were relatively undisturbed. The ecologically unstable plains are ideal for dissemination of *P. pestis* when conditions are suitable, but the infection retreats to the foothills between epizootics among the highly susceptible domestic rats.

According to studies supervised by Baltazard at the recommendation of the Expert Committee on Plague of the World Health Organization, the endemicity of plague in India is similar to that in Kurdistan, Kenya, and other parts of the world. It is due to an effective disease reservoir, not in rats, but in certain wild rodents, in particular in bandicoots (*Tatera indica*).

The geographic origin of plague has given rise to much speculation and much argument, and it has been hoped that bacteriology would eventually settle the issues. The glycerol reaction of a large collection of *P. pestis* strains has recently been restudied, and some interesting differences have been observed. The glycerol-positive strains, designated continental, are perpetuated in wild rodents in the old pestilence centers: southeast Russia, central Asia, Mongolia, Manchuria, Transbaikalia, and central Africa. The strains that apparently originated in the pandemic in Yunnan, China, in 1894 are glycerol negative and have been designated oceanic. These have been found in Kenya and in certain parts of the United States. One would expect the strains in the ports of Texas to be the pandemic glycerol-negative strains, but 3 of 29 strains isolated there from rats and 2 from patients were glycerol positive. Whether the glycerol reaction solves the nosographical problems is a question to be answered by further critical studies and interpretations.

Pathogenesis of the Infection

Nothing can happen in an epizootic or an epidemic that has not already been founded in a single infection. It is always important to understand the pathogenesis of bubonic, or zootic, and pulmonary, or demic, plague in experimental models, usually the mouse or the guinea pig. The pathogenesis of the infection after the introduction of *P. pestis* through the bite of a blocked infectious flea can be readily followed in these animals. It follows a standard pattern: afferent lymphatics to regional lymph nodes, to efferent lymphatics, to thoracic duct, to blood stream, to liver and spleen. When the bacteria multiply to such an extent that the liver and spleen can no longer filter them out, they appear again in the circulating blood. Active multiplication of *P. pestis* in the bloodstream, so essential to infection of the flea, is always terminal.

In this connection, the nature of septicemic plague should be clarified. As commonly defined, septicemic plague is a form of the disease in which, owing to the magnitude of the infection or to the low resistance of the host, the regional lymph nodes are overrun and the blood stream is immediately invaded. Because the infection is progressing so rapidly, the reactions taking place in the lymph nodes are overshadowed by the general condition of the patient or animal. What is considered primary septicemic plague is really bubonic plague in which the buboes are inconspicuous.

For these reasons it seems preferable to distinguish between two main types of human plague: the primary bubonic, or zootic, form and the primary pulmonary, or demic, form.

The spread of the infection in the immunized animal is similar to that in the unimmunized animal, differing from it only quantitatively. The organisms reach the bloodstream early, but they are destroyed so effectively that only isolation of the bacilli from the bone marrow testifies to the transient hematogenous spread.

The marked lung involvement regularly found in the absence of spleen or liver lesions in partly resistant or immune animals and in man dying after prolonged illness has not been satisfactorily explained.

This lacuna in our knowledge should be filled. Secondary lung involvement leads to cough and copious expectoration and often to pneumonic plague epidemics. Without knowing exactly what the mechanism is, one has to depend on epidemiological observations. Travelers who fall ill with bubonic plague before leaving an infected locality or en route therefrom are particularly prone to secondary lung involvement. Muscle efforts made by such people may cause detachment of infected thrombi from blood vessels around the buboes and may lead to lung embolism. Malnutrition and such extrinsic factors as cold and rainy weather may all contribute to impairment of resistance. Guinea pigs or squirrels surviving acute experimental plague for at least 6 to 10 days invariably have extensive secondary lung involvement.

At first it was believed that circulating toxin reduces the resistance of the lung tissue, just as staphylococcal toxin does (*12*). But guinea pigs and squirrels are quite resistant to the toxin. Mice and rats rarely have secondary pulmonary plague lesions. It is unlikely that the scattered foci of necrosis result solely from lowered resistance induced by toxin. Their location beneath the pleura suggests that they are initiated by bacterial emboli arrested in the arterioles and capillaries. In partially immune guinea pigs and naturally resistant ground squirrels, rapid mobilization of agglutinins favors embolus formation; agglutination promotes clumping of plague bacilli in the vascular beds. It is always striking that in the animals with secondary lung involvement the spleen and liver are singularly free from necrosis. Why neither the microphage nor the lymphoid-macrophage defense system is functioning effectively in the lung while it operates in the spleen and liver remains unanswered.

Discussion of secondary pulmonary plague recalls observations in the Los Angeles epidemics. Three plague infections described as tonsillar by experienced pathologists, Dr. George D. Maner and Dr. Lawrence Parsons, aroused no particular interest at the time because in the days of the Anglo-Indian Commission, in 1898 and 1899, it had been made clear that the plague bacillus can enter the host by channels other than the skin. An opportunity to investigate the portal of entry in tonsillar infection came quite accidentally.

Transmission of Pneumonic Plague

During studies on immunization of monkeys against pulmonary plague, healthy animals were exposed to cage mates with frank primary pneumonic plague in order to learn something about the contagiousness of the disease. A monkey (*Macaca mulatta*) infected by the intratracheal route and reacting with fever and definite roentgenologic evidence of pneumonia was placed in a cage with a healthy monkey. To learn whether *P. pestis* was being exhaled from the nasal passages of the infected animal, blood plates were held before its nose for ½ to 2 minutes at the time the healthy animal was put in the cage. In this interval, from 2 to 66 organisms were exhaled onto the plates. The healthy monkeys were left in the cages until the infected ones died: for from 2 to 72 hours. Of the 18 exposed, 9 contracted septicemic and 3 bubonic infection.

The procedure was then refined by confining the 2 monkeys in a large cage divided into 2 separate compartments by a coarse wire barrier. Bodily contact was thus eliminated, and a situation was created in which any exchange of *P. pestis* was through airborne droplets alone. Of the 8 exposed in this manner, 4 contracted septicemic infection.

Clinical and X-ray examinations and blood cultures demonstrated that primates exposed, with or without body contact, to cage mates suffering from primary pulmonary plague may contract plague and die. The rapidity of the course of the infection, the negative X-ray findings, and the early positive blood cultures in 13 of 16 successful transmissions left no doubt that the exposed animals died of "septicemic" plague. There was very little visible involvement of the lymph nodes. Systematic autopsies confirmed the clinical findings, but careful dissections invariably showed that the

superficial and deep cervical lymph nodes were slightly enlarged, hemorrhagic, and imbedded in edema. The lungs showed no consolidation; congestion and edema were at first glance interpreted as patches of pneumonia. Only 3 of the 26 exposed monkeys had pulmonary plague in the form of lobular foci extending to lobar involvement. Two of the animals with septicemic plague and no involvement of the lungs had ulcerations in the stomach and jejunum and buboes in the adjacent lymph nodes.

The gross anatomical lesions of the lymph nodes incriminated the upper part of the respiratory tract as the portal of entry of the plague bacillus, but generally there were no characteristic changes of the oral or faucial mucosa. Some congestion and swelling of the tonsillar region were noted in some animals. Examination of serial sections of the entire nasopharynx of six animals disclosed that the lymphatic tissues forming the ring of Waldeyer surrounding the oropharynx were the likely portal of entry of the organisms. Enormous masses of plague bacilli were embedded in the severely altered lymphoid tissue on one side, rarely on both sides, of the tonsillar sinus. The so-called tonsillar lymph nodes adjacent to the diseased lymphoid tissue invariably had the characteristics of primary plague buboes. As a rule, the palatine and faucial tonsils were not markedly involved. Clumps of plague bacilli were numerous and scattered through the epithelial layers of the pharynx. It is not unlikely that swallowing these clumps of bacilli led to the gastrointestinal lesions.

Two observations from these studies are of particular significance: Plague was transmitted through infectious droplets from primates with pulmonary plague; the apparent septicemic plague was bubonic tonsillar plague with cervical buboes. Most epidemiologists have believed that primary pulmonary plague is caused by an infection entering through the deeper portions of the respiratory tract, but a few, especially Kulescha (*13*), have considered the possibility that the organisms enter through the tonsils or other parts of the upper part of the respiratory tract and are then carried to the lungs by the blood stream. This idea was dismissed at one time with the statement that experimental observations did not support it.

Recent experiments by Druett and his associates (*14*) in which infection was introduced by means of bacterial clouds are most instructive. Two forms of plague, both originating in the respiratory tract of the guinea pig, developed, the form depending on the size of the particle conveying *P. pestis* to the host. Particles no larger than 1 micron initiated a bronchopneumonia that terminated in septicemia and death. Larger particles, 12 microns in diameter, deposited in the region of the head penetrated local epithelium and through the afferent lymphatics led to septicemia much earlier than occurs with organisms deposited on the bronchial or alveolar wall.

The monkeys infected by their sick cage mates suffered from the form of disease found in animals exposed to large-particle clouds, namely, septicemia arising from a primary focus of infection in the cervical lymph nodes with infarction, but no pneumonia. Attempts to establish an epizootic by cross-respiratory infection were abortive, probably because of the nature of the disease developing in the first cross infection.

Thus certain epidemiological observations are now partly clarified. What has been seen in man has been reproduced in animals.

Chemotherapy

The value of the antimicrobial drugs in treatment of plague has been soundly documented (*15*). In fact, one is justified in stating that it should be possible to cure any plague infection without complications if it is treated soon enough. Light and moderately severe bubonic plague infections have been cured in India with sulfathiazole, sulfadiazine, and sulfamerazine. The most spectacular effect of antiplague chemotherapy was that observed in Madagascar where pneumonic plague was treated with streptomycin, chloramphenicol, and tetracycline drugs (*16*). The overall curative effects were so impressive that failures in treatment, particularly in modern hospitals, were not anticipated.

A recent experience with a patient suffering from bubonic plague clearly teaches, however,

that there was still something to be learned. The patient had hunted in an area where a wild-rodent epizootic had been in progress. A plague pustule developed on his right ankle, and a corresponding inguinal bubo appeared. Other symptoms arose on the third day after exposure. He was then treated with penicillin, and the diagnosis was established and bacteriologically proved by lymph node puncture and blood culture on the fourth day after onset. Treatment consisted of administration of 2 gm. of streptomycin and dihydrostreptomycin, 2 gm. of terramycin, 4 gm. of sulfadiazine, and 600,000 units of penicillin every 24 hours. One week after onset, 3 days after specific treatment had been instituted, the patient died. The autopsy, conducted by two pathologists, one an expert in plague, proved all the tissues to be free from *P. pestis*; *Candida albicans* was present in the right and left lungs. Microscopic examination furnished evidence of activity of a potent toxin: edema of the myocardium, liver, and lungs, and nephrosis associated with hemorrhagic nephritis. It is well known, for instance, in diphtheria, that "serous inflammation" is entirely due to toxin of the causative organism.

The investigator of experimental plague is continuously impressed with the fact that the most effective drugs may kill the bacilli in the blood, liver, spleen, and bone marrow and reduce the number of viable bacilli in the focal lesions of the lymph nodes or lungs. Despite this remarkable therapeutic feat, however, the animals ultimately succumb, probably because of the damage done by the plague toxin (*15*). During the chemotherapy studies in Madagascar, a patient with pulmonary plague was not treated until the 48th hour of disease and died after 40 hours of therapy with chloramphenicol. At post mortem her tissues were free of *P. pestis*, and the death was ascribed to toxin.

Efforts to understand this intoxication and its treatment have been only partly rewarding. Potent antiserums containing antibodies against both infection and toxin have ameliorated this damage in mice, but not in monkeys. In more recent preliminary studies on mice with the *P. pestis* strain isolated from the California patient, streptomycin was indeed highly bactericidal; in fact, this strain was more rapidly lyzed by a combination of streptomycin and penicillin than was the control strain. When treatment with doses comparable to those used on the patient was begun late in the infection, animals died even though their tissues were completely free of *P. pestis*. That the deaths were probably attributable to the toxin was indicated by the observations that the effectiveness of the antimicrobial drugs was increased by from 15 to 50 percent when one dose of purely antitoxic serum was administered. This serum had a very high toxin-neutralization index and was completely devoid of demonstrable antibodies against infection.

Some of the basic knowledge essential to production of such an antiserum is available. Experiences in the United States with production of antiplague rabbit gamma globulin can readily be used to manufacture the amounts that might be required as an adjunct in treatment of the relatively few cases recognized in enzootic foci.

This leads back to some of the general thoughts expressed at the beginning of this lecture: Throwing great quantities of every drug against every infection without proper guidance by the laboratory will insure only the type of complications described here. As long as there are places where infections are spread to man, fundamental research in infectious diseases, efficient diagnostic services, and cooperation between the physician and the laboratory are essential to advances.

PSITTACOSIS

It once would have been said with confidence that the largest reservoir of psittacosis is the wild psittacine birds of the tropics: Australia, New Zealand, Mexico, and South America. But the list of wild birds in which the infection has been found has lengthened almost every time the virus is sought, and the continuing revelation of ornithosis in domestic poultry—pigeons, chickens, ducks, and turkeys—raises the question of its origin. Right now it is impossible to fit the fragments of information together. The answers cannot be found in sample serum surveys or virus isolation studies carried out in a single group of wild birds in a small area in a single season.

The stabilized association of birds with the basophilic elementary body psittacosis agent extends over such a wide geographic area and involves so many species of birds that it is hard to imagine that it has existed only as long as it has been known. Maintenance and transfer of the virus is assured by the flocking and nesting of birds. Fulmars, petrels, domestic and wild pigeons, chickens, ducks, and turkeys, birds that congregate and nest together, are hosts of viruses related to, but immunologically distinct from, the psittacine serotypes. The virus is rarely if ever found in species of more solitary habits. Under ordinary circumstances few birds die of the disease.

All observations on psittacine infections are consistent with the hypothesis that low-grade psittacosis has been enzootic for many years among Australian budgerigars, or shell parakeets, and among the more common wild South American and Australian parrots. Psittacosis was undoubtedly imported with the original breeding stock first into England and then into nearly every country of the world. The enzootic infection in parakeets bred in Europe and America in all probability derives from the natural infection of the Australian budgerigar from which these parakeets are descended. However, this does not necessarily mean that the virus did not exist elsewhere in the world at that time.

Course of the Infection in Birds

The course of the infection in the wild bird population has not been studied extensively. This focus has rarely given rise to known human infections; man does not ordinarily associate with wild birds closely enough to endanger his health. It is necessary to resort to analogy to describe what may be the natural course. Under stress of egg laying and hatching, the hen with latent infection excretes virus through the alimentary canal. Susceptible nestlings contract the infection; most of them recover and some become carriers. It seems likely, too, that the virus goes through periodic phases of increased virulence, and if an adequate number of birds is susceptible, an epizootic may result. The uncertainties of an outdoor climate may contribute to spread of the infection. This leaves unexplained the occurrence of the infection in widely separated areas in birds that do not migrate. It may be found eventually that the virus is not so exotic or so tropical as it once seemed.

It is not surprising that the best known segment of the natural history of psittacosis is the infection in an unnatural niche: the parakeet-breeding aviary. When the parakeet is bred and raised in captivity in large numbers under conditions that differ radically from those of the Australian bush, the host-parasite relationship undergoes some changes. The parasite itself apparently behaves differently. The virus strains isolated from acutely infected cage birds have been distinctly more virulent than most isolates from acutely infected Australian parakeets. Occasionally, epizootics have killed 5 to 10 percent, sometimes an even higher proportion, of flocks in aviaries or pet shops.

During the acute infection the organism abounds in the diarrheal droppings and nasal secretions, and through these the parasite is conveyed to young birds. Some latently infected hens under stress of egg laying and hatching have excreted the virus more frequently and possibly in higher concentration than have latently infected hens not under this stress. Birds less than 6 months old are then the likely victims of the disease. The greater susceptibility of immature parakeets under experimental conditions and in aviaries is conclusively proved. The outcome of the infection in some maturing birds is asymptomatic infection grossly evident only in an enlarged infected spleen. This enlargement probably indicates that the parakeets have been infected but have suppressed or completely eliminated the infector. The latent infection rates have ranged from 5 to 80 percent in aviaries and pet shops.

Factors in Resistance

Resistance is an important factor in the natural history of psittacosis, and most of what is known of it has been learned through experimental studies and observations on the course of the infection in aviaries. Here again no single factor can be given credit; heredity, age, and previous infection all participate.

Certain birds have an innate resistance to

psittacosis and do not become infected. The proportion of naturally immune birds varies from flock to flock. It may be low, for example, in parakeet-breeding flocks that are being inbred for certain feather coloring.

Age seems to condition resistance to some extent. Liability to fatal infection declines with age, but susceptibility remains fairly constant. Highly toxic isolates induce symptoms in only a few adult parakeets; less toxic ones induce only transient symptoms or latent infection. Within 30 days about 25 percent of infected adult birds have eliminated the invading parasite from their tissues.

In the early days, when symptomatic disease was the only criterion of infection, it was thought that parakeets that had been experimentally infected and had then recovered had a strong immunity to infection. This is supported by the apparent immunity of a large proportion of the adult population of aviaries in endemic areas. It is further supported by the high susceptibility of flocks that have been successfully kept infection free and by the resistance of treated birds a month after artificial infection. Accidental introduction of infected birds into aviaries, cages, or zoological gardens may be followed by fatal, but more frequently by latent, infections. How long the resistance manifested in a small group of treated birds would persist one cannot say. Infection unquestionably does provoke immunity; there is a specific acquired antigen-antibody immunity. It is the duration of the immunity that varies from bird to bird.

And the effectiveness of any of these factors varies according to the vigor of the infector.

Control Methods

When latent infection becomes epizootic in an aviary, usually some departure from good husbandry and cage hygiene has taken place. Formerly, only destruction of diseased birds brought the epizootics under control. A great deal can be said in favor of attempting to control the disease, despite its infrequent occurrence in man, and with the knowledge available it should be possible to eliminate the infection from aviary breeding stock. Until this major undertaking can be achieved, the proper handling of shipments and distribution of birds in the retail trade would reduce and possibly eliminate some major sources of human psittacosis. Chemotherapy will serve as one of the most effective instruments.

That drugs inhibit multiplication of large viruses of the psittacosis-lymphogranuloma venereum group was first demonstrated with the lymphogranuloma venereum virus and the sulfonamides (*17*). Not all strains are equally sensitive, and it is the exceptional strain of the psittacosis agent that is susceptible. Aureomycin and terramycin are effective against the psittacosis virus because they prevent initial-body formation and almost completely inhibit growth, but they do not destroy the virus. Since 1950 the curative effect of these antibiotic drugs has been well established.

If adequate amounts of the drugs are given for an adequate time, at least 10 days, the mortality rate is less than 1 percent. If the disease is not treated, the rate is 20 to 40 percent. The lifesaving ability of the tetracycline drugs is spectacular in comparison with that of penicillin (*18*). The difference can be readily explained. Penicillin arrests cell division, but the organisms continue to grow and abnormally large forms develop (*19, 20*). The effect of the tetracycline compounds is more profound, for it includes inhibition of growth.

In large-scale field trials acute infections have been suppressed within 4 to 8 days, and 98 to 100 percent of latent infections have been cured with daily doses of 1.0 to 1.5 mg. of oxytetracycline, chlortetracycline, or tetracycline (a total of 15 to 30 mg. per bird). Intramuscular administration of the antimicrobial drugs is laborious and, if carried out on infected birds, exposes the injector to the risk of infection. The successful impregnation of hulled millet, sunflower seeds, or peanuts with tetracycline now allows administration of the drug in a uniformly acceptable and stable feed. This method is the most convenient way of suppressing the reservoir of human infections.

It must be remembered, however, that birds free from infection are still susceptible. Offspring from an aviary stock free from psittacosis are highly susceptible to acute psittacosis, and the infection, of course, may become latent. Treated flocks and their offspring must be pro-

tected against infection by chemotherapy whenever exposure is suspected. A program aiming at the distribution of psittacosis-free birds, readily identifiable by characteristic leg bands, may be achieved if the bird-breeding and bird-distributing groups cooperate wholeheartedly.

The Disease in Nonpsittacine Birds

With respect to psittacosis arising from nonpsittacine birds, epidemiological histories invariably report that the patient handled sick or visibly diseased carcasses of birds or was exposed to a flock that at the time of exposure or shortly before contained sick birds. The pathogenicity and virulence of the strains isolated from pigeons, chickens, and ducks and from the patients who have contracted the infection from them have been low for mammals and highly susceptible avian species. Most infections caused by these strains are inapparent. Despite the extent of the avian reservoir, the human infections are mild and infrequent. Few of numerous attempts to convert these distinct serotypes into more virulent strains by repeated passage through mice or ricebirds have been successful.

In pigeon lofts and poultry yards exchange of the parasite is similar to that in parakeet aviaries, but the balance is disturbed in favor of the parasite less frequently than it is among crowded cage birds in aviaries. It has occurred in young birds and in flocks that have been inadequately fed, poorly housed, or crowded (*21*).

Now a new ecologic problem has arisen. Infections among poultry workers and rendering plant employees comprise 398 (nearly a fourth) of the 1,687 human psittacosis cases reported in the United States in the past 5 years. These have been due to exposure to anatomically diseased poultry, principally turkeys. Enough isolations have now been made from diseased and apparently healthy turkeys raised in different parts of the United States to warrant consideration of the ecology of this phase.

Certain virus isolates from the fibrin-coated air sacs, peritoneal lining, pericardium, and blood of turkeys that had succumbed to natural infection have been exceptionally virulent for mice and guinea pigs. Sometimes they have induced fatal infection within 48 hours, and when injected intravenously in the high dilution of 1:1,000, they have formed a highly potent toxin that kills white mice. Only 2 virus isolations have been made in the 398 human cases. These were identical to the turkey strains in their intense virulence. In outbreaks in Texas, New Jersey, and Oregon highly virulent isolates from the viscera of poultry have been identical to those isolated from these two plant workers in Texas and Oregon.

Random examination of spleens of apparently healthy turkeys not involved in human outbreaks in Texas, California, and Michigan have yielded seven isolates belonging to the psittacosis group. On primary isolation they were of low virulence for mice and guinea pigs. Two became virulent after repeated mouse passage, and in dilutions not exceeding 10^{-5} they fatally infected mice. However, they retained their low toxicity and did not fatally infect guinea pigs. Despite numerous passages the remaining five isolates retained their low virulence for mammals.

Several isolates were derived from a flock of turkeys in California in which mortality had not been undue. When the first part of the flock was processed, the hearts and livers of some birds were condemned because they were visibly diseased. The remainder of the flock was serologically tested, and 83.5 percent were positive. Of 88 employees who had handled the diseased poultry, the serums of 3 gave complement fixation reactions indicative of previous exposure to agents of the psittacosis group. None of the employees gave a history of illness. The serums of residents and employees on the turkey ranch where the infected flock was raised did not react in the complement fixation test.

This single observation does not justify the conclusion that the turkey ornithosis serotypes of low mammalian virulence are equally harmless to man.

Results of indirect complement fixation tests indicate that many flocks have been infected, but since the infections were mainly latent little is known of them. At this preliminary stage of the inquiries, it seems that natural infection of low virulence in turkeys resembles that in Australian parakeets and some pigeon flocks.

The gross anatomical lesions observed in the processing of the flock of subclinically infected birds mentioned above suggest that this strain was more virulent than the usual strains of low virulence.

There has been little opportunity to study the natural history of ornithosis in the turkey flocks responsible for the explosive outbreaks of human illness in processing plants. In only a few instances is there opportunity to follow the course of epizootics. The epidemiologist encounters the end result of the epizootic on the processing line. Naturally, he speculates on possible sources of infection.

Since the droppings of the acutely diseased birds contain the parasite in abundance, it is no surprise to find 50 to 80 percent of a flock are seropositive within a few weeks. However, while knowledge of the pathogenesis and course of the infection in the turkey is still so sketchy, one has few leads to what initiates and promotes the epizootic. The parasite may be introduced into the flock by wild birds, by other turkeys, through eggs, contaminated feed, or biologics, or even by visitors to the ranch. For incubator-hatched and artificially brooded poultry, the nest infection chain does not exist. Ecologic investigations such as those made in the parakeet-breeding establishments must be undertaken and extended over several years before the natural history of the disease in turkeys will be understood.

Ornithosis in turkeys is of growing interest to large groups: consumers, flock owners, poultry industries, agricultural agencies, poultry processors, labor unions, insurance companies, health agencies, and biologists. Each component has something to gain if methods of control can be worked out. If control were to be approached by all concerned in an investigative and determined spirit, it seems credible that something could be done. No one can predict at this time how serious the problem may become.

Summary

The age of the biological phenomenon of parasitism is at least that of recorded history. For centuries, man's survival has been chaotically interferred with by the infectious diseases, in pandemic form dramatically. In the last half century, man, through his intelligence and diligence, has begun to control this chaos effectively for the first time. The host's reaction against certain parasites is being fortified by immunization, and the life of certain parasites is being destroyed by antimicrobial drugs. These advances are good cause for great rejoicing. They are not cause for believing that parasitism holds no further challenge to man's ingenuity.

Very few parasites depend solely on man for their survival. Even if all the people of the world could be immunized, it would be an oversight of the characteristics of biological processes to hope that the infection concerned would thereby be banished from the earth. Immunization, which in some infections protects even the eagerly susceptible, usually must be repeated in the individual and certainly with each new generation. Effective chemotherapy must wait until the host is manifestly affected adversely by the parasite. Both of these defenses, magnificent but temporary, leave the parasite free to carry on its usual latent existence untouched: to multiply, to adapt, and to exert its capricious effects on the host.

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Johns Hopkins University to Revise Medical Curriculum

A revised program of medical education, which will reduce the period of study and emphasize the humanities, is scheduled to begin at the Johns Hopkins University School of Medicine in the fall of 1959. The plan cuts 2 years from the training period for a carefully selected group of students and shortens the course for others by 1 year.

A total of $10 million was granted by the Public Health Service, the Ford Foundation, the Rockefeller Foundation, the Commonwealth Fund, and by other private sources for the construction of a new basic science building and for additional faculty.

Program objectives are to shorten formal medical education without sacrifice of quality; to overcome the barrier between the liberal arts and the medical sciences; and to encourage students to follow careers in the basic medical sciences, such as physiology, anatomy, and pharmacology, in which there is the greatest shortage of teachers and research workers.

Candidates with adequate "motivation and maturity" who have completed 2 years of college will be permitted to enter medical school, where they will pursue a 5-year course. During the first 3 years of medical school, they will continue studies in the liberal arts, at the end of which they will receive the bachelor of arts degree.

Students accepted after 3 or 4 years of college will begin medical school with the second year of the 5-year program.

For all students the last year of medical school will be combined with the first year of internship at the Johns Hopkins Hospital. In addition to 24-hour responsibility for patients, the student will have a 2-month elective period for work in the basic sciences or further clinical training in any of the hospital departments.

Although the years of medical training are reduced, with a consequent cut in medical education costs, the actual period of training is shortened relatively little. The academic year is increased from the present 32 weeks to 40 weeks; the fifth year covers 50 weeks.