THE OCCURRENCE OF PRIMARY ATYPICAL PNEUMONIA, AETIOLOGY UNKNOWN, IN SOUTH AUSTRALIA.

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by

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HISTORICAL.

There is no reason to believe Primary Atypical Pneumonia, Aetiology Unknown, is a new disease. Thus it is profitable to consider certain points in the natural history of pneumonia, and to trace the development of present day knowledge of pneumonia. Knowledge of pneumonia has not accrued steadily, but in a series of discoveries which have marked the commencement of an epoch. The early history of pneumonia is of its frequent epidemic character. In the early nineteenth century, morbid anatomy achieved distinction between effusion, lobar and lobular pneumonia. Histopathology soon followed as a result of the previous introduction of the microscope, but was soon overshadowed by the advent of bacteriology toward the end of that century. Refinements in bacteriology, immunology, and the discovery of viruses in the early part of the present century, threw great importance on the aetiological aspect of the acute infectious diseases. This was heightened by the Influenza pandemic in 1918-1919. The more practical nature of X-ray examination and the frequent revelation of unexpected pulmonary disease, has revolutionised conceptions of pneumonia. The discovery of the influenza viruses, and the conquering of pneumonia due to the pyogenic cocci by chemotherapy, have diverted interest to pneumonia caused by viruses. Epidemic respiratory disease in the last War was found, by the use of X-ray diagnosis, to be frequently associated with pneumonia in many known and new conditions. These phases in the history of pneumonia will be elaborated below.

Early History - Pneumonia was known to Hippocrates in approximately 460 B.C., and accurate descriptions of its symptoms were given by Celsus between 25 and 35 A.D. Ruffer (1) examined Egyptian mummies of a dynasty extant from 1500 to 1250 B.C. He obtained histological evidence in some of pneumonia which had advanced to the stage of hepatization. Hirsch, in 1853, wrote of the epidemic character of pneumonia, and in his Geographical and Historical Pathology (2) recorded epidemics as early as the sixteenth century. MacCallum (3), from his perusal of this document and the monographs of Leichtenstein

(3a) and Ripperger (3b), traced such epidemics back to the tenth century, and suggested these world-wide visitations were due to influenza. Boyd (4) noted that it has been suggested the pestilence which attacked the well-greaved Achaians, as narrated in the first book of the Iliad, bears the hallmarks of influenza both in its sudden appearance and disappearance: "For nine days ranged the god's shafts through the host, and the pyres of the dead burned continuously in the multitude."

It is of no small interest that epidemics of pneumonia have occurred through the ages, and it is not doubted that some of these epidemics were due to influenza. Many other aetiological agents were probably responsible for such epidemics, and no doubt diseases like plague in its pneumonic form, measles, typhus, diphtheria and tuberculosis claimed their share.

Morbid Anatomy - Although van Leeuwenhoek discovered the microscope and observed minute organisms as early as 1675, clinical observation and macroscopic pathology, the latter with the aid of the magnifying glass, held sway for many years. Läennec had correlated the pathology, symptoms and the auscultatory signs heard through his stethoscope in 1819. Thomas Addison (5), in his papers written between 1837 and 1843, described the healthy and morbid anatomy of the lungs, and emphasised the variability and the importance of the symptoms in the diagnosis of pneumonia. In a further paper, "Observations on Pneumonia and its Consequences", Addison described simple and lobular pneumonia, corresponding to lobar and bronchopneumonia, as we know them today. Of great interest is the refutation by Addison in this paper of the views of Reissessen and others that the intercellular tissues (that is the walls of the alveoli and interstitial tissues), were the seat of some of the most important inflammatory diseases of the lungs.

Cellular Pathology - Improvements in the microscope in the early part of the nineteenth century, and the discovery by Amici of the oil immersion lens, prepared the way for the study of histology and the recognition of bacteria. The cellular pathologists became familiar with the histopathology of lobar and lobular pneumonia, and Bartels in 1861 (6) described the lesions of interstitial pneumonia

as seen during an epidemic of measles.

Bacteriology - The almost simultaneous isolation of the pneumococcus in 1881 by Pasteur in France and Sternberg in America, was soon followed by definite proof of its association with pneumonia in man. Other organisms, as Friedlander's bacillus, streptococci and staphylococci, and the influenza bacillus, were later found to be associated with acute inflammatory diseases of the lungs. While these discoveries had no great effect on the conception of pneumonia at this time, the advent of immunology, and the demonstration by the Klemperers in 1891 that serum obtained from patients convalescent from pneumococcal pneumonia had a curative effect on experimentally infected rabbits, was of great importance. Refinements in bacteriology indicated all pneumococci were not alike. The serological typing methods of Neufeld, introduced in 1909, made possible the conception that the course and prognosis of pneumococcal pneumonia depended largely on the type of pneumococcus responsible for the illness. Further, the possibility of specific serum therapy became practicable.

The 1914-18 War was remarkable for the use of noxious gases in warfare, for the epidemics of measles in America complicated by pneumonia which was most frequently associated with haemolytic streptococci, and for the pandemic of influenza in the last years of, and the year following the war.

Among those dying in the early stages of these affections, there was evident considerable similarity in the pulmonary lesions at autopsy. Previous to the pandemic, influenza had been regarded as a very mild disease, affecting many with but few deaths: its name "la grippe" is/to have meant originally "the fashion", and said Burnet (7) quotes Creighton "Everybody ill, nobody dying, splendid!" For some reason, in 1918 the disease took on a new quality which has not been explained or repeated since, as it killed not the very young or the aged, but particularly those in the prime of life.

There was great variation in the bacteria associated with the pneumonia in this pandemic. The bacteria isolated were often heterogeneous and differed greatly from time to time and place to place. The confusion created by the absence of a constantly responsible bacterium stressed the need for the isolation of the

common aetiological agent of this obvious pandemic. Despite this, the predominance of certain organisms in different geographical areas yielded valuable information as to the characteristics and range of clinical behaviour of "pure" infection with specific bacteria, and the pathological changes produced by such infections. MacCallum (8) emphasised the occurrence of one peculiar form of bronchopneumonia, Interstitial Bronchopneumonia, which affected mainly the terminal bronchioles, their walls, the surrounding alveoli and the corresponding lobule. The resemblance of this condition to the pulmonary lesions of measles and whooping cough was remarkable, and the nodules formed about the terminal bronchioles were mistaken by many people for miliary tuberculosis. This form of pneumonia was said to be invariably associated with an haemolytic streptococcus.

McCordock and Muckenfuss in 1932 (9), using vaccinia virus, produced experimentally in rabbits an interstitial bronchopneumonia. This closely resembled the pneumonia which so frequently accompanied measles, psittacosis, influenza and whooping cough in man. While measles and psittacosis were known to be caused by viruses, in the case of influenza the red herring of haemophilus influenzae still obscured the trail. These workers, and many before them, considered a virus was the agent responsible for the influenza pandemic. They compared, as Winternitz had done before, the similar effects of the war gases on the lung and the pulmonary lesions of influenza; particularly those persons dying soon after the onset of influenza, when bacteria in the lungs were scarce and confined to exudate within the bronchioles.

Increasing interest in viruses and improvements in technique were not fruitful until 1933, when Laidlaw, Andrewes and Smith isolated the virus of influenza A by transmission to ferrets. To this day it is denied by some that either of the influenza viruses was responsible for the pandemic. The assumption that the new virus of Laidlaw was the aetiological agent led to the analysis of the considerable amount of experimental work already carried out on the production of pneumonia in animals by bacteria, viruses, or both. The results have made clearer knowledge of the pathogenesis and pathology of the acute inflammatory diseases of the lungs.

Subsequent study of minor epidemics of influenza led to the discovery, by Francis in 1940, of influenza B virus. The introduction of an haemagglutination test in 1941 by Hirst provided a useful serological method for the detection of infection among the population by a strain of either virus. Influenza has been given great prominence in this account, because it facilitates the idea of infection of the respiratory tract as a whole, and because of the stimulus the pandemic has provided to later research.

Between the Wars - Improvements in X-ray apparatus and technique have facilitated the examination of the thorax, and encouraged the more general use of this form of examination. Following the 1914-18 War, the interest of physicians and radiologists in the correlation of clinical manifestations with X-ray findings in pulmonary diseases has been heightened by many astonishing discrepancies and discoveries. X-ray examination has revolutionised conceptions of pulmonary disease, and has facilitated the distinction between effusion, consolidation of varying form and extent, atelectasis, lung abscess and cavitation.

In particular the association of transient pulmonary involvement, discovered by X-ray, during minor respiratory tract disease, has been reported with increasing frequence as the use of this method of examination has become more common. Not infrequently such transient pulmonary opacity has caused confusion in the diagnosis of pulmonary tuberculosis. In yet other conditions, many of which are rarely fatal, radiology has provided the opportunity to observe unexpectedly frequent pulmonary involvement: knowledge of the pathological changes in such illnesses are often due to fortuitous death by accident or intercurrent infection.

Immediately prior to the recent War, further improvement in X-ray equipment and technique had made mass surveys for the detection of pulmonary tuberculosis possible, and X-ray examination of the thorax was employed as a routine where there was any suspicion of chest disease. A proportional increase in the number of pulmonary abnormalities, particularly those transient opacities associated with acute upper respiratory tract infections was the natural sequence. The differentiation of such opacities from pulmonary tuberculosis and other illnesses of serious import had become a major problem in

diagnosis.

It is generally agreed that the character of pneumonia has changed perceptibly over the last decade: older members of the medical profession affirm the change has been noticeable for a longer time, even as far back as the beginning of this century. There has been a considerable and real decrease in the incidence of lobar pneumonia. Whether the more recent change was due entirely to the advent of the sulphonamides and later penicillin, which have proved to be specific therapeutic agents for almost all cases of pneumonia due to the pyogenic cocci, is not known. The general success of these drugs has thrown into prominence a group of cases of pneumonia whose illness was not affected by chemotherapy. These included a minority where the bacterium, ordinarily susceptible to these drugs, was shown in vitro to have lost this susceptibility to a varying degree.

Heffron (10) summarised the figures of the bacteria associated with lobar pneumonia in 3,319 patients from several series of cases which had occurred prior to the introduction of sulphonamides: the percentages were as follows - pneumococci 96.1%, Streptococci 2.8%, Friedlander's bacillus 0.5%, Haemophilus influenzae, Staphylococci and mixed infections each 0.2%, making a total of 100%. In the series of cases of primary bronchopneumonia that he quoted, cases of unknown aetiology reach a substantial proportion. His statement "The frequency with which the various types of pneumococci are found in bronchopneumonia approximately parallels the frequency with which they are carried in the mouths of normal persons" is not without significance. For although epidemics of pneumococcal pneumonia undoubtedly occur (11), observers in the last few years have found considerable difficulty in isolating pathogenic bacteria from the sputum of a large proportion of cases which appeared to have acute "bacterial" pneumonia, lobar or bronchopneumonia (12), which apparently responded rapidly to sulphonamides or penicillin. There is some evidence to support this fact not being due to the inhibiting effects of sulphonamides and penicillin in the sputum (13). It is not unknown for the symptoms in such cases of acute "bacterial" pneumonia to subside within forty-eight hours or less when chemotherapy has been withheld!

To continue this digression, minor respiratory illness very frequently precedes the development of "bacterial" pneumonia, either immediately, or a week or a fortnight before. While bacterial sore throat is common, so are virus infections of the upper respiratory tract, which may be so severe as to simulate haemolytic streptococcus infection of the throat. Recent observations have shown that patients contracting "bacterial" pneumonia have concurrently had evidence of infection with influenza virus A or B (14), and the bacteria were apparently present as secondary invaders. There is experimental and clinical evidence however, that epidemics of true bacterial pneumonia do occur.

The 1939-1945 War - Early reports of Primary Atypical Pneumonia have emerged from several sources.

Epidemic respiratory disease associated in a proportion of cases with transient pulmonary involvement, frequently detected only by X-ray examination, is responsible for such reports as those of Arrasmith in 1930 (15), Gallagher in 1934 (16), Bowen in 1935 (17), and a critical evaluation of such manifestations by Scadding and Ramsay in 1939 (18), suggested such pulmonary opacity was due to atelectasis. The aetiological investigations were inadequate, and this has been discussed in the two papers to be presented. By the same token, the "Focal Disseminated Pneumonia" reported by Scadding in 1937 (19) is open to criticism, and like sulphonamide or penicillin resistant pneumonia, is another heterogeneous group. Reviewers of the subject of Primary Atypical Pneumonia have unearthed clinical and pathological descriptions of pneumonia resembling this condition as far back as the early part of the nineteenth century. While this is possible, it is fallacious to make retrospective diagnosis or to extricate such pneumonia with certainty from that accompanying measles, whooping cough, chickenpox, influenza or other diseases.

With the outbreak of the recent War, epidemics of acute respiratory disease were anticipated among recruits, and did follow on the congregation of large numbers of young adults in military camps. Routine chest X-rays revealed unexpectedly frequent pulmonary involvement, and most investigators failed to incriminate either influenza virus. American observers seized the opportunity to study

an unexpectedly high incidence of an unusual type of pneumonia, occurring among the troops at Camp Claiborne, La., in 1941, and the Commission on Acute Respiratory Diseases was set up. This Commission was unable to identify or isolate the causal agent, but placed the clinical, radiological and laboratory characteristics of Primary Atypical Pneumonia on a sound basis (20). The Commission was able to transmit the condition experimentally to human volunteers by the inoculation of filtered throat washings and sputum, indicating the causal agent is a virus or viruses (21). Later experimental transmission to human volunteers, with challenge experiments, has differentiated Primary Atypical Pneumonia from other virus infections of the upper respiratory tract (22).

Another group of observers (23), working in New York on the same condition, had investigated the association of the streptococcus MG with Primary Atypical Pneumonia as the causal agent or as an essential component for the development of this illness. The evidence is slender, and has been largely discounted by the Commission and by Eaton and associates.

Eaton, Meiklejohn and van Herick (24) claimed they were able to transmit to chick embryos, and adapt by passage, a filterable agent from the sputum or lung tissue of certain cases of Primary Atypical Pneumonia. They have evolved a serum neutralization test, as the agent was found to be specifically neutralized by the serum of patients recovered from this illness, but not by acute phase sera. This group of workers have stressed that, in an epidemic of Primary Aytpical Pneumonia, in itself suggesting a single aetiology, a substantial proportion of cases was apparently due to this new virus, but it is unlikely that it is the causal agent of all cases of Primary Atypical Pneumonia.

Summary - This brief survey contains but some of the interesting points in the history of pneumonia, and particularly of that variety now known as Primary Atypical Pneumonia, Aetiology Unknown.

To sum up, epidemics of pneumonia have been recognised since the tenth century. Improvements in clinical diagnosis in the early nineteenth century, followed by the establishment of histopathology, have been overshadowed by the advent of bacteriology and immunology.

The typing of pneumococci and serum therapy emphasised the importance of aetiological diagnosis, and so did the influenza pandemic of 1918-19. The introduction of sulphonamides, and later penicillin, have provided almost a specific therapeutic agent against pneumonia due to the pyogenic cocci. The conquering of the bacterial pneumonias has permitted the direction of attention to pneumonia caused by viruses, which usually have a low mortality. Epidemics of acute respiratory disease among recruits during the 1939-45 War were associated with unexpectedly frequent pulmonary involvement. Accumulating evidence suggests that one such unusual variety of pneumonia is due to a new virus or viruses, and the illness has been transmitted experimentally to humans using filtered material. Challenge transmission experiments have differentiated it from two virus infections, one resembling the common cold, the other resembling the epidemic acute pharyngitis of recruits. Eaton and associates have isolated a new virus from cases of Primary Atypical Pneumonia, and developed a serum neutralization test.

Current opinion inclines to the view that infection with the virus or viruses of Primary Atypical Pneumonia is manifest as an epidemic of acute respiratory disease, in which a proportion of those afflicted develop pneumonia.

VARIETIES OF ACUTE PNEUMONIA.

A shortened classification of the established varieties will at this stage serve to emphasise the complex aetiology of pneumonia. An aetiological classification, by which a pneumonia is designated of a specific organism and its type, is the ideal method of classifying the disease. Such classification promotes clarity of thinking, enables proper evaluation of the results of treatment, and has none of the drawbacks inherent in clinical classifications with their tendency to slipshod diagnosis. Although this is beyond the scope of most hospital services, much can be done along these lines, and such aetiological diagnosis does take cognisance of the virus pneumonias with their tendency to superimposed bacterial infection.

CLASSIFICATION OF THE ACUTE PRIMARY PNEUMONIAS

Bacterial

Pneumococcus (Types I - XXXIII)
Haemolytic streptococcus
Haemolytic staphylococcus, coagulase positive
Friedlander's bacillus
Mycobacterium tuberculosis
Haemophilus pertussis

Less commonly

Haemophilus influenzae
Streptococcus viridans
Bacillus coli
Brucella
Corynebacterium diphtheriae
Bacillus anthracis
Bacillus tularensis
Pasteurella pestis
? Pleuropneumonia

Rickettsia

Rickettsia burneti
Rickettsia of Typhus

Viruses

Influenza A and B
Psittacosis, ornithosis and lymphogranuloma group
Variola
Varicella
Morbilli
Lymphocytic choriomeningitis

Believed to be due to viruses

Primary Atypical Pneumonia, Aetiology Unknown
(Eaton's virus)
Infectious mononucleosis
Primary Virus Pneumonitis with Cytoplasmic
Inclusion Bodies of Adams.
? Pneumonia accompanying Erythema Multiforme
Exuditavum

Higher Bacteria and Fungi

Leptospirosis
Syphilis
Monilia
Blastomycosis
Sporotrichosis
Coccidioidomycosis
Histoplasmosis
Aspergillosis
Actinomycosis
Torulosis

Protozoa

Toxoplasmosis
Malaria
Schistosomiasis

Due to Chemical and Physical Agents.

Noxious vapors
Mineral oils
Foreign material, as food in cardiospasm
X-ray irradiation

"Allergic"

Associated with Asthma (Löeffler)
Tropical Eosinophilia
Sulphonamide Pneumonia
Pneumonia accompanying acute Rheumatic Fever.
? Pneumonia accompanying Erythema Multiforme Exuditavum

PROBLEMS PRESENTING AT COMMENCEMENT OF INVESTIGATION

Two problems presented at the instigation of this investigation. The first was to ascertain the types of bacterial pneumonia occurring in South Australia. The second was to determine if virus pneumonia was present, and its approximate incidence. A large general hospital with reasonable facilities seemed the logical choice for conducting such an enquiry.

Primary Atypical Pneumonia, Aetiology Unknown, is but one condition of the group of cases of pneumonia known or suspected to be caused by viruses.

The subject of the two following papers concerns the confirmation of the recognition of this condition in Australia. This has been the purpose of these investigations which were made possible by a research grant from the National Health and Medical Research Council of Australia, and facilities granted by the Institute of Medical and Veterinary Science and the Royal Adelaide Hospital.

STATEMENT OF WORK PERFORMED BY THE INVESTIGATOR

The method of investigation has been set out below. It was at first intended to study every patient with acute pulmonary disease admitted to the Royal Adelaide Hospital, but it soon became evident that, because of the considerable difficulties in diagnosis, it would be more profitable to confine the study to otherwise healthy adults under the age of sixty years. The routine of investigation consisted of history taking, frequent clinical examination of the patient, treatment, and leucocyte count as soon as possible after admission: these were carried out by the writer.

Examination of direct smears and cultures of the sputum and lung puncture fluid, including aerobic and micro-aerophilic cultures and examination for fungi, were carried out by Mrs. K. Mary Draper of the Institute. Lung punctures were carried out by the

writer. Serial X-ray examination of the thorax was carried out by the technical and honorary staff of the radiological section of the hospital. Specimens of serum were obtained from the patients, and stored in ampoules, by the writer.

Mr. R.W. Sheppard, of the routine bacteriology department of this Institute, carried out cold agglutinin titrations, psittacosis complement fixation titrations, and the routine agglutinations. Miss P.E. Lind of the Walter & Eliza Hall Institute, Melbourne, kindly performed cold agglutination, psittacosis complement fixation and "T" agglutinin titrations. Through the courtesy of Professor F. M. Burnet, Hirst tests were performed at the Walter & Eliza Hall Institute. Through the kindness of Dr. E. H. Derrick, agglutinations for R. burneti were carried out at the Laboratory of Pathology and Microbiology, Queensland.

Extensive use has been made in this investigation of the deep freezing of serum ampoules in an insulated container, the whole being kept at - 20°C. for some four days, then flown to its destination. The interior of such packages was still at temperatures below freezing after five hours. In December, 1947, specimens of sera were flown in an insulated container containing dry ice, to San Francisco. The dry ice was replenished at Honolulu, with appropriate measures en route to avoid a rise in temperature above 4°C. Dr. Gordon Meiklejohn has consented to carry out serum neutralization tests with Eaton's virus, but the results are not available at the time of writing.

Skin testing with old Tuberculin, and with Coccidioidin and Histoplasmin obtained from America, were largely carried out by the writer. A careful system of subsequent examinations of the patients selected for this study was performed by the writer, to guard against the inclusion of unusual forms of pulmonary tuberculosis in these reports.

Post-mortems on the two fatal cases were not carried out by the writer, but post-mortem material and sections have been studied, and I assisted in obtaining the microphotographs and the reproductions of the X-rays. Where other special investigations

have been carried out, by persons other than myself, as attempts to isolate a virus, has been indicated in the papers.