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Non-Bacterial Pneumonias

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BULLETIN OF THE
UNIVERSITY OF MINNESOTA HOSPITALS
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III. MEDICAL SCHOOL NEWS 271

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I.

UNIVERSITY OF MINNESOTA MEDICAL SCHOOL
CALENDAR OF EVENTS

Visitors Welcome

January 17 - 22, 1949

No. 231

Monday, January 17

8:00 - Fracture Rounds; A. A. Zierold and Staff; Ward A, Minneapolis General Hospital.

9:00 - 9:50 Roentgenology-Medicine Conference; L. G. Rigler, C. J. Watson and Staff; Todd Amphitheater, U. H.

9:00 - 10:50 Obstetrics and Gynecology Conference; J. L. McKelvey and Staff; M-109, U. H.

10:00 - 12:00 Neurology Rounds; A. B. Baker and Staff; Station 50, U. H.

11:00 - 11:50 Roentgenology-Medicine Conference; Staff; Veterans Hospital.

11:00 - 11:50 Physical Medicine Seminar; E-101, U. H.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Eustis Amphitheater, U. H.

12:00 - 1:00 Physiology Seminar; Quantitative Histochemical Studies of Urease in the Human Stomach in Relation to Acid Secretion; David Glick; 214 M.H.

12:15 - 1:20 Obstetrics and Gynecology Journal Club; Staff Dining Room, U. H.

12:30 - 1:20 Pathology Seminar; Mammary Tumors in Mice; Louis Thomas; 104 I. A.

12:30 - 1:30 Surgery Problem Case Conference; A. A. Zierold, C. Dennis and Staff; Small Class Room, Minneapolis General Hospital.

1:30 - 2:30 Surgery Grand Rounds; A. A. Zierold, C. Dennis and Staff; Minneapolis General Hospital.

1:30 - 2:30 Pediatric-Neurological Rounds; R. Jensen, A. B. Baker and Staff; U. H.

4:00 - Pediatric Seminar; The Development of the Child; Carl Goebel; 6th Floor, Child Psychiatry, U. H.

4:00 - 6:00 Kellogg Lecture; Carcinoma of the Lung; Bronchiectasis; Alton Ochsner, Tulane University Medical School; Powell Hall Amphitheater.

5:00 - 5:50 Clinical Medical Pathologic Conference; Todd Amphitheater, U. H.

5:00 - 6:00 Urology-Roentgenology Conference; D. Creevy and H. M. Stauffer and Staffs; M-109, U. H.

Tuesday, January 18

8:30 - 10:20 Surgery Reading Conference; Lyle Hay; Small Conference Room, Bldg. I, Veterans Hospital.

9:00 - 9:50 Roentgenology Pediatric Conference; L. G. Rigler, I. McQuarrie and Staff; Todd Amphitheater, U. H.

10:30 - 11:50 Surgical Pathological Conference; Lyle Hay and Robert Hebbel; Veterans Hospital.

12:30 - 1:20 Pathology Conference; Autopsies; Pathology Staff; 102 I. A.

2:00 - 2:50 Dermatology and Syphilology Conference; H. E. Michelson and Staff; Bldg. III, Veterans' Hospital.

2:00 - 4:00 Kellogg Lecture; Nephritis and Nephrosis; E. T. Bell; Todd Amphitheater.

3:15 - 4:20 Gynecology Chart Conference; J. L. McKelvey and Staff; Station 54, U. H.

3:30 - 4:20 Clinical Pathological Conference; Staff; Veterans Hospital.

4:00 - 5:00 Pediatric Rounds on Wards; I. McQuarrie and Staff; U. H.

5:00 - 5:50 Urology-Pathological Conference; C. D. Creevy and Staff; Todd Amphitheater, U. H.

5:00 - 6:00 X-ray Conference; Dr. Lipschultz and Staff; Minneapolis General Hospital

Wednesday, January 19

8:00 - 8:50 Surgery Journal Club; O. H. Wangensteen and Staff; M-515, U. H.

8:30 - 10:00 Orthopedic-Roentgenologic Conference; Edward T. Evans; Room 1AW, Veterans Hospital.

8:30 - 12:00 Neurology Rehabilitation and Ca se Conference; A. B. Baker and Joe R. Brown; Veterans' Hospital.

11:00 - 12:00 Pathology-Medicine-Surgery Conference; O. H. Wangensteen, C. J. Watson and Staff; Todd Amphitheater, U. H.

12:00 - 12:50 Radio Isotope Seminar; Auto-Radiographs; George Moore; Rm. 216, Hospital Court, Temporary Bldg.

4:00 - 5:00 Infectious Disease Rounds; Powell Hall Amphitheater.

4:00 - 5:30 Surgery-Physiology Conference; O. H. Wangensteen and M. B. Visscher; Todd Amphitheater, U. H.

4:00 - 6:00 Public Health Seminar; Missouri River Basin Health Council Organization and Activities; Mr. W. W. Towne, S.D. Department of Health; 113 MeS.

Thursday, January 20

8:15 - 9:00 Roentgenology-Surgical-Pathology Conference; Craig Freeman and H. M. Stauffer; M-109, U. H.

8:30 - 10:20 Surgery Grand Rounds; Lyle Hay and Staff; Veterans Hospital.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; M-109, U. H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:50 Surgery-Radiology Conference; Daniel Fink and Lyle Hay; Veterans Hospital.

11:00 - 12:00 Cancer Clinic; K. Stenstrom and A. Kremen; Todd Amphitheater, U. H.

11:30 - 12:30 Clinical Pathology Conference; Steven Barron, C. Dennis, George Fahr, A. V. Stoesser and Staffs; Large Class Room, Minneapolis General Hospital.

12:00 - 1:00 Physiological Chemistry Seminar; 214 M. H.

1:00 - 1:50 Fracture Conference; A. A. Zierold and Staff; Minneapolis General Hospital.

2:00 - 3:00 Errors Conference; A. A. Zierold, C. Dennis and Staff; Large Class Room, Minneapolis General Hospital.

4:00 - 5:00 Bacteriology and Immunology Seminar; 214 M. H.

4:30 - 5:20 Ophthalmology Ward Rounds; Erling W. Hansen and Staff; E-534, U. H.

5:00 - 6:00 X-ray Seminar; Report of Meeting of Radiological Society of N. A.; Drs. Stauffer, Lipschultz, and Ude; Todd Amphitheater.

Friday, January 21

8:30 - 10:00 Neurology Grand Rounds; A. B. Baker and Staff; Station 50, U. H.

9:00 - 9:50 Medicine Grand Rounds; C. J. Watson and Staff; Todd Amphitheater, U.H.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:30 - 11:20 Medicine Grand Rounds; Staff; Veterans Hospital.

10:30 - 11:50 Otolaryngology Case Studies; L. R. Boies and Staff; Out-Patient Department, U. H.

11:00 - 12:00 Surgery-Pediatric Conference; C. Dennis, O. S. Wyatt, A. V. Stoesser and Staffs; Minneapolis General Hospital.

11:30 - 12:50 University of Minnesota Hospitals General Staff Meeting; Hormone Therapy in Cancer of the Breast; Robert A. Huseby and Stuart W. Arhelger; Powell Hall Amphitheater.

12:00 - 1:00 Surgery Clinical Pathological Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

1:00 - 1:50 Dermatology and Syphilology; Presentation of Selected Cases of the Week; H. E. Michelson and Staff; W-312, U. H.

1:00 - 2:50 Neurosurgery-Roentgenology Conference; W. T. Peyton, Harold O. Peterson and Staff; Todd Amphitheater, U. H.

Saturday, January 22

7:45 - 8:50 Orthopedics Conference; Wallace H. Cole and Staff; Station 21, U. H.

8:00 - 9:00 Pediatric Psychiatric Rounds; Reynold Jensen; 6th Floor, West Wing, U. H.

8:00 - 9:00 Surgery Literature Conference; Clarence Dennis and Staff; Minneapolis General Hospital, Small Classroom.

9:00 - 9:50 Medicine Case Presentation; C. J. Watson and Staff; E-101, U. H.

9:00 - 10:30 Pediatric Grand Rounds; I. McQuarrie and Staff; Eustis Amphitheater, U. H.

9:00 - 12:00 Surgery-Roentgenology Conference; O. H. Wangensteen, L. G. Rigler, H. M. Stauffer, and Staff; Todd Amphitheater, U. H.

9:00 - 12:00 Psychiatry Conference; Powell Hall Amphitheater.

10:00 - 11:50 Medicine Ward Rounds; C. J. Watson and Staff; E-221, U. H.

10:00 - 12:50 Obstetrics and Gynecology Grand Rounds; J. L. McKelvey and Staff; Station 44, U. H.

11:00 - 11:50 Urology Seminar; Hyperparathyroidism; E. N. Cook, Mayo Clinic; E-101, U. H.

11:00 - 12:00 Anatomy Seminar; The Origin of Megaloblasts in Pernicious Anemia and Transformation of Megaloblastic to Normoblastic Bone Marrow Following Specific Therapy, Hal Downey; "L.E. Cells" in Bone Marrow and Blood in Acute Disseminated Lupus Erythematosus, R. Dorothy Sundberg; 226 I. A.

II. NON-BACTERIAL PNEUMONIAS

Jerome T. Syverton

Respiratory infections, inclusive of pneumonia, have long constituted a medical problem of the first order. These afflictions continue to exceed all other diseases in the loss of time from industry and from schools[32]. Despite the means for the therapeutic conquest of pneumococcal infections and of most of the other bacterial pneumonias[44], the complex of pulmonary infections designated clinically and pathologically as pneumonia has remained fairly constant in incidence, and has maintained its role as a major cause of death[29].

The importance of the non-bacterial pneumonias as a component of the group is of recent recognition[1-19,22-28, 30-39,43]. It has been estimated that from 5 to 70 per cent of all pneumonias are non-bacterial. The percental number, of course, depends on the source of patient, i.e., whether from general practice, military service, industrial practice, or hospital practice.

Much of the information concerning non-bacterial pneumonias is recent. It is especially because of the studies reported within the past decade that the causative agents of non-bacterial pneumonia are known to include a wide variety of microbiologic agents and their products, such as viruses, rickettsia, fungi, protozoa, toxins and allergens. A relationship to the pneumonic process of many of these agents is newly recognized. Many factors are responsible for the disentanglement and recognition of successive etiologic entities from the complex. The stimulus for concerted and cooperative effort which was provided by World War II is outstanding. Moreover, the process has been facilitated 1) by the ready availability and common employment of chemotherapeutic and antibiotic agents for treatment, thereby eliminating effecfively most bacterial agents; 2) by the increasingly frequent use of roentgenography for the study of any case of suspected pneumonia; 3) by a realization in hospital practice that the need is for more, rather than less, precise bacteriologic diagnosis, because of the specificity of antibacterial agents and the possibility through adaptation of the appearance of resistant bacteria; and 4) by the development and application of new diagnostic laboratory methods.

It is the purpose of this paper to emphasize the characteristics which make it desirable to consider this wide variety of etiologic entities collectively as non-bacterial "virus-type" or interstitial pneumonias and, secondly, to point out the diagnostic laboratory tests that are available for their separation. The accepted bacteriologic diagnostic measures are inadequate in the study of non-bacterial pneumonias to establish a specific diagnosis, but are essential for the elimination of known bacterial agents.

The range of causative agents, the etiologic entities, and the epidemiologic characteristics of the disease complex are shown in Table I.

It may be seen from this table that many causative agents and etiologic entities are assembled in the category of "non-bacterial pneumonia." However different these infections appear to be, they should be considered collectively, because of essential similarities in their roentgenographic and pathologic pictures. Moreover, the clinical differentiation of any of the entities within the group from each other and from certain bacterial pneumonias is usually difficult or impossible.

CHARACTERISTICS IN COMMON

Pathology

A review of the pathologic alterations which occur in the different types of non-bacterial pneumonias will make readily understandable the basic similarities in the pathologic, roentgenographic and clinical pictures. Such differences in the pathologic picture, as are observed for different entities, are no greater than may be found among cases of the same

Table I

NON-BACTERIAL PNEUMONIAS

Etiologic Agent	Pandemic	Epidemic	Endemic	Sporadic
Virus	Influenza(?)	Influenza A Influenza B	Lymphocytic Choriomeningitis Smallpox Varicella Psittacosis* Ornithosis* Meningopneumonitis* Human SF Pneumonitis* Illinois Pneumonitis*	Inclusion-body Pneumonia Lymphogranuloma Venereum*
Rickettsia			Q Fever	
Fungus			Histoplasmosis Coccidioidomycosis	
Protozoa				Toxoplasmosis
Allergen			Bagassosis	Rheumatic Fever
Unknown, probably virus		Atypical Pneumonia Acute Pneumonitis Grippe Acute Catarrhal Fever "Flu" Viroid	Inclusion Body Pneumonia of Infants (Adams) Infectious mononucleosis	Erythema multiforme

*Basophilic group

entity. Grossly, an infected lung may show little change, except for an increase in weight. The pleural surface may be smooth or show patches of fibrinous exudate. On section, the pneumonic areas vary markedly in size, distribution, and stage of evolution. Areas of atelectasis and emphysema are commonly apparent.

Histologically, the picture is that of an acute interstitial monocytic pneumonitis. The process probably starts as a bronchiolitis to extend locally from the regional interstitial tissues to involve the peribronchiolar tissues, the alveolar walls, and the pulmonary septa. The succession of changes which occur within the process extends peripherally from any given focus and results in the oldest and most advanced lesions being found immediately adjacent to the sites of origin, i.e., the small bronchioles. This succession of changes is about as follows. The alveoli immediately adjacent to the bronchiole fills with edema fluid and occasional polymorphonuclear leucocytes. The edema fluid in such alveoli is replaced by mononuclear leucocytes until the alveoli are distended with mononuclear cells. The mononuclear cells appear to result from desquamation

of the mucosal lining and from proliferation. The result is an interstitial pneumonitis. Ulceration of the mucosal lining of the bronchioles and of alveoli may be quite extensive. For certain types of non-bacterial pneumonia, the application of Mallory's technic for demonstrating connective tissue reveals that proliferative changes are limited to cells lining the alveoli. There is no apparent involvement of the connective tissue elements. The larger bronchi may not escape the inflammatory process. Evidence of involvement of the bronchial mucosa is shown by intense erythema, cellular infiltration by mononuclear leucocytes and a few neutrophiles in the absence of bacteria. Resolution of the pneumonic process within the parenchyma of the lung takes place from the more peripheral portion of the lesion toward the center. During resolution, the alveolar lumina commonly fill with an exudate which is made up of degenerate epithelial cells, mononuclear cells, and a few polymorphonuclear leucccytes. It is at that stage that bacteria of various kinds may be observed. Emphysema and atelectasis occur as sequelae. Desquamation of epithelium from mucosal surfaces to result in ulceration undoubtedly contributes to the bronchiectatic result.

Roentgenological Aspects

Roentgenologic examination[17,33,36] of the chest frequently reveals the first evidence of pulmonary involvement. Lesions are almost regularly demonstrable within the first few days of illness.

A distinctive feature of this pneumonic involvement is the variability in the type and size of the lesion. Characteristically, the inflammatory reaction is not sharply defined, as shown by an opacity which tends to merge imperceptibly with the surrounding pulmonary tissues. This density, which is variable, may remain stationary until resolution occurs, or may act as a focus of spread from which the lesion extends peripherally. Transitory changes are common, as illustrated by mottled densities which appear to disappear within 24 hours. Lesions may be confined in a single lobe or may occur in multiple lobes.

The pneumonic process commonly shows a predilection for the hilar region, either unilaterally or bilaterally, with radial extension outward into the peripheral portion of the lungs. These fan-shaped opacities are accompanied by increased bronchovascular markings. Varying degrees of acute tracheobronchitis are commonly present, as reflected by bilateral increase in the hilar and trunk shadows with indistinct outlines, soft mottling about the hilum, and generally hazy lung fields[17].

Apart from the hilar fan-shaped shadow, which is the more commonly observed lesion, other variations consist of less well defined lesions which may occur in any portion of the lung field. These include such changes as multiple small areas of soft diffuse infiltration that increase in size over a period of days to become irregularly confluent; a diffuse, somewhat coarse mottling, indistinguishable from tuberculosis, especially when it involves the apical regions; and circumscribed foci more commonly in the periphery of the lung field, which are not so dense as the consolidation of lobar pneumonia or the opacity of a neoplastic process.

Atelectasis occurs as a natural alteration in the pathogenesis of pneumonic process and as a complication. As an example, Campbell, et al.,[3] in a study of 200 unselected cases of atypical pneumonia which occurred during an epidemic of this disease at Fort Eustis, Virginia, reported that the impression of atelectasis was substantiated roentgenographically for 19 per cent of these cases by a shift of the mediastinal structures or by an elevation of the diaphragm towards the site of the lung involvement. Exceptionally, an entire lobe becomes atelectatic to suggest lobar pneumonia, but other findings reveal the true atalectatic nature.

Clinical Aspects

The pathogenesis of the pneumonic process makes one suspect wide variation in

Table II

SYMPTOMATOLOGY IN 1833 CASES OF NON-BACTERIAL PNEUMONIA

Authority[33]	1941 Lyght[22]	1942 Green[15]	1943 Campbell[3]	1943 Young[43]	1944 van Ravenswaay[30]	1944 Commission[4]	1945 Curnen[6]	1946 Painton[26]	1946 McCoy[23]
Number of Cases	300	80	200	40	297	69	106	321	420
	%	%	%	%	%	%	%	%	%
Onset gradual			63	most	67	26	73	70	
Cough	80	88	51	100	86	99	98	66	95
Malaise	60	42	25	80	70	77	61	33	34
Headache	55	47		80	48	78	65	20	25
Chills	50	48		50	68	75	59	30	42
Coryza	30			20	49	41		60	3
Sore Throat	30	20	26	70	47	36	30	25	25
Sputum					74	81	82	20	
Bloody Sputum	4	14	6		26	10	25	3	--
Dyspnea	5	9	3	30	21		5		0.5

the clinical manifestations of the non-bacterial pneumonias. Such, indeed, is the case. The symptomatology in 1833 cases of non-bacterial pneumonia, as compiled from reports in the literature[33], are summarized in Table II.

It can be seen from this chart that the onset of illness in approximately two-thirds of patients was gradual and ill defined. Initially, the onset frequently was indistinguishable from that of a cold or grippe. Cough, malaise, headache, and chills were common early complaints which persisted throughout the acute illness. Coryza and sore throat were present less commonly. The cough was frequently accompanied by substernal discomfort or pain and more usually became productive of mucopurulent sputum, which at times was blood tinged. In some series of cases, bloody sputum had been present in as many as a fourth of the cases[6,30].

The physical findings for these same 1833 cases[33] are summarized in Table III.

The ill defined character and obvious overlapping that most of the symptoms and signs which have been selected as outstanding illustrate the hazards of clinical classification and emphasize the impossibility of separating positively on the basis of symptomatology or clinical signs the non-bacterial pneumonias from pyogenic bacterial pneumonias, tuberculosis, tularemia, brucellosis and neoplastic infiltration of the lung, among others.

The variation in clinical manifestations in individual patients with the same disease and among patients suffering from different entities included in the category of non-bacterial pneumonia is understandable, since the disease primarily involves the mucous membrane of the respiratory tract with symptoms and signs in any given case reflecting the predominant site of localization of that involvement. The spectrum of "respiratory" infections that may result is listed in Table IV.

Table III

PHYSICALL FINDINGS IN 1833 CASES OF NON-BACTERIAL PNEUMONIA

Authority[33]	1941 Lyght[22]	1942 Green[15]	1943 Campbell[3]	1943 Young[43]	1944 van Ravenswaay[30]	1944 Commission[4]	1945 Curnen[6]	1946 Painton[26]	1946 McCoy[23]
Number of Cases	300	80	200	40	297	69	106	321	420
	%	%	%	%	%	%	%	%	%
Fever		73		55	97	81	95	90	63
Pharyngitis		65				61	69	60	
Rales		92			56	93	93	60	81
Dullness		58			28	41	54	20	28
Lymphadenitis		5		several			24		

Table IV

SPECTRUM OF "RESPIRATORY" INFECTIONS

Immune carriers
Inapparent infections
Sporadic attacks
Mild URI without systemic involvement
Mild ambulatory forms
Ambulatory forms with pneumonitis
Severe systemic involvement without pneumonia
Systemic involvement with pneumonia

A better understanding of the variation in reaction among hosts can be reached by pointing out, as shown in Table V, that the vehicle for infection consists of minute invisible droplets which are inhaled by way of the nose and mouth to reach the mucous membranes of the respiratory tract. The results of infection are reflected by an inflammatory reaction which subsequently may be categorized as rhinitis, pharyngitis, tonsillitis, laryngitis, tracheitis, bronchitis, bronchiolitis, pneumonitis, or any combination thereof, Moreover, there may result systemic involvement, with or without respiratory symptoms, or intestinal involvement, with or without respiratory symptoms.

Table V

NON-BACTERIAL PNEUMONIAS

Vehicle Minute invisible droplets

Mode of Entry: Inhalation via nose and mouth

Site of Primary Attack: Mucous membrane of the respiratory tract

Dominant localization:
Rhinitis
Pharyngitis
Tonsillitis
Laryngitis
Tracheitis
Bronchitis
Bronchiolitis
Pneumonitis
Systemic involvement with or without RI
Gastrointestinal involvement with or without RI (respiratory infection)

It is apparent from Table V that classification on the basis of dominant anatomic involvement is no more than suggestive insofar as the causative agent is concerned.

It is to be emphasized that a wide spectrum in the clinical, pathologic, and roentgenographic manifestations of an acute respiratory infection may result from a single etiologic agent and that any epidemiologic study involving a causative agent of non-bacterial pneumonia must recognize the complexity of this spectrum. It is only by means of a precise laboratory diagnosis that separation of the many entities which are represented can be brought about. These entities in the past, for the most part, have been conveniently side-tracked by

attaching any of a variety of misdiagnoses, of which a few are listed in Table VI.

Table VI

MISDIAGNOSES OF NON-BACTERIAL PNEUMONIAS

Mild Bacterial Pneumonia	Threatened Pneumonia
Atelectasis	Touch of Pneumonia
	Congestion of Lungs
Broncho Pneumonia	Spot on the Lung
Bronchitis	
Bronchiolitis	Unrecognized

DIFFERENTIAL DIAGNOSIS OF NON-BACTERIAL PNEUMONIAS

The essential similarity in the usual roentgenographic and pathologic pictures of the members of the group of respiratory infections which are manifest as non-bacterial pneumonias has been emphasized. Epidemiologic, clinical, roentgenographic, and pathologic studies may serve for allocation within the group, but differentiation from one another and from certain bacterial pneumonias is usually difficult or impossible. An isolated sporadic case especially demands precise diagnostic measures. It is important, therefore, to learn what criteria can be employed for disentanglement of the group. It can be seen from Table I that the members of this group fall into at least five categories: pandemic influenza, epidemic influenza of types A or B, the psittacosis-lymphogranuloma venereum sub-group, the atypical pneumonia sub-group, and a sub-group which is made up of the remaining entities. Each of these entities will be considered summarily, so as to emphasize the salient characteristics of each.

Influenza

What is meant by the term "influenza"? Any physician when asked this question knows what he means by influenza, but, when pressed for a definitive answer, commonly that answer is inexact and all-inclusive. It is apparent that the term "influenza" is used in clinical medicine with three distinct and frequently confused meanings: First, there is the use of the term in a wide and general sense in which it serves merely as a convenient label for any upper respiratory infection showing systemic involvement, a leucopenia, and being of an unknown or unrecognized etiology, This latter application of the term "influenza" is more commonly applied by older physicians who reflect their experience in the 1918 epidemic by using the term "flu" more commonly than younger physicians who accept and write off the same type of illness as "atypical pneumonia," "viral pneumonia," or "cat fever." The second use of the term "influenza" is in a restricted and specific sense to designate cases which are established as being of known virus etiology by the recovery of the virus of influenza A or the virus of influenza B, or by the demonstration of specific influenzal antibodies. It is common epidemiologic practice today to designate as epidemic influenza any unusual increase in the number of respiratory cases which satisfy the general criteria of

clinical influenza, occur abruptly in numbers, show high communicability, and yield a specific virus type from one or more cases. It is well established that the viruses of influenza, type A and type B, cause disease clinically indistinguishable from each other and from the causative agents of other non-bacterial pneumonias. Specific identification of A or B virus is established by the isolation of the virus or by the demonstration by neutralization test, by complement-fixation test, or by the practical and more commonly applied Hirst hemagglutination test of an increase in antibody titer during convalescence. The third use of the term "influenza" is in reference to pandemic influenza. The single criterion which is available at present for distinguishing pandemic influenza from a host of "imitators" is its capacity for rapidity of spread, i.e., to take a continent or two at each stride. Pandemic influenza is a tremendously important virus disease. Of the three great pestilences of mankind, smallpox, plague and influenza, influenza alone continues to be a constant and immediate threat to man in all parts of the civilized world. - Why? The answer is in the unlimited potentialities of this disease. As an example, let us consider the most recent pandemic, 1918-1919. The final statistics of that pandemic as released by the League of Nations shows that at that time one out of four persons, 500 million out of a population of 2 billion, had the disease and that of these about 15 million died. The mortality rate at the height of the pandemic was one out of fifty persons in the world per month, which is a death rate unsurpassed in history. Influenza killed more in a few months than the first World War in five years or during the entire second World War. In the United States, there were 20 million cases with 450 thousand deaths in six months. Pandemics similar to that of the 1918 pandemic have recurred over the past 425 years at intervals of from 25 to 60 years.

Pandemic influenza is rightfully considered to be a respiratory disease, and yet, in the early stages of the pandemic, there frequently were no symptoms referrable to the respiratory tract. Pandemic influenza is characterized by a short incubation period of from 24 to 48 hours, an abrupt onset, headache, chilly sensations, loss of appetite, sometimes nausea and vomiting, a fever of from 101°F. to 105°F. and commonly limited to three days duration. Muscular pains and leucopenia are characteristically present. Bacterial superinfection, which is common, was assumed to have been responsible for the high mortality rate in the 1918 pandemic. The bacteria implicated were Streptococcus hemolyticus, Staphylococcus aureus, and Hemophilus influenzae. Convalescence is slow and protracted with marked weakness and mental depression being characteristic features.

The cause of pandemic influenza was unknown in 1918 and is unknown today. The 1918 pandemic stimulated many careful bacteriologic investigations. The results of these studies can be summarized by stating that their yield was limited to a better statistical basis for accepting or rejecting subsequent work. It had been assumed following the pandemic of 1892 that Hemophilus influenzae was the causative agent. This microorganism and other bacterial agents were effectively ruled out, except as secondary invaders. The recovery by Shope in 1931 (see reference 38 for a review of the literature) of influenza virus, type A, from an infection of swine closely resembling human influenza led to the isolation by Smith, Andrewes and Laidlaw of a similar virus from cases of human influenza in 1933 and by Francis in 1940 of influenza virus, type B. It was assumed by some that the causative agent of pandemic influenza had been isolated. Influenza virus, types A and B, have been shown in subsequent years to be world-wide in distribution and to be responsible for epidemics at fairly well established intervals. It should be recognized, however, that the relationship to pandemic influenza of existent viruses, even though the latter are called "influenza viruses", is conjectural. On the assumption that among these viruses one may be related to pandemic influenza and to bring about a

better understanding of epidemic influenza, measures for the immediate identification and control of influenza in pandemic form are in existence in this country.[45] A national network of regional laboratories is prepared to isolate and to identify strains of virus from current outbreaks of influenza for supply to other laboratories which are equipped for large-scale vaccine production and for other studies.

Primary Atypical Pneumonia

The clinical syndrome commonly diagnosed as primary atypical pneumonia is a noncommittal designation for acute disease of the respiratory tract which may be manifest as an acute tracheobronchitis or as an interstitial pneumonia. The disease is variable in clinical manifestations and in the severity of the symptoms it provokes, and, therefore, atypical pneumonia as observed in isolated cases is indistinguishable from the other entities that belong in the group of non-bacterial pneumonias.

The many carefully controlled studies which have been carried out with this disease in the past decade have been the subject of numerous reports and reviews. Many reports, such as the outstanding work of Dingle and other members of the Commission on Acute Respiratory Diseases[4,9], of Horsfall[16], and of others make it apparent that primary atypical pneumonia is of common occurrence.

The Commission on Acute Respiratory Diseases reported successful transfer of primary atypical pneumonia to human volunteers by employing bacterial filtrates of sputum and throat washings as source material. It was not established by these workers, however, whether one agent or multiple agents may be concerned in the production of the disease under natural conditions.

Even though evidence for the virus causation of primary atypical pneumonia has been demonstrated, the diagnosis at present rests on the exclusion of other similar diseases. Two serologic tests provide ancillary supportive evidence when positive. These tests are the cold hemagglutinin test[9,22,35] and an agglutination test for Streptococcus MG antibodies[34,35]. The success of each of these tests depends on the demonstration of a rise in the respective titer of either antibody when samples of serum representative of the acute and convalescent phase of the patient's illness are assessed for the presence of agglutinins. The demonstration of cold hemagglutinins utilizes Group O red blood cells as antigen. Agglutination of these erythrocytes takes place at ice-box temperature but not at 37°C. The second test is carried out in essentially the same fashion as other bacterial agglutination tests by employing as antigen Streptococcus MG, which is a serologic type of indifferent streptococcus related antigenically to Streptococcus salivarius. Significant increases in the titer of either antibody, rarely both, occur in about 50 per cent of the cases of primary atypical pneumonia. The presence of agglutinins for these two unrelated antigens occurs independently. It has been suggested that each may possess antigenic components in common with the etiologic agent of primary atypical pneumonia[8].

The Pneumonitis-Psittacosis-LGI Sub-Group

The members of this sub-group are commonly classified as viruses, but they possess common biologic properties which separate them from other viruses and set them apart as intermediate between rickettsiae and viruses[24,25]. Thus, in contrast to other viruses, they are much larger, stain readily with simple basophilic dyes, undergo successive developmental stages to form large basophilic cytoplasmic inclusion bodies in endothelial and epithelial cells, and are sensitive to sulfonamides and antibiotics. The host range includes a wide range of mammals and birds to result in infection characterized by an immunity-infection status.

The best known agents in this group are: A) the pneumonitis viruses, such as

meningopneumonitis, Baker's feline pneumonitis, pneumonia virus of mice (PVM), mouse pneumonitis (SF), Louisiana pneumonitis; B) psittacosis and ornithosis; and C) lymphogranuloma inguinale. Infections in man, excepting lymphogranuloma venereum, are characterized by involvement of the respiratory tract. Pneumonia also occurs in lympho-granuloma venereum.

Diagnosis within this sub-group is established by the isolation and the identification of the causative agents. Mice, cotton rats, hamsters, guinea pigs, pigeons and other birds, and embryonated eggs are readily susceptible to infection. Mice are commonly employed for cross-immunity and cross-neutralization tests. The complement-fixation test is employed as a diagnostic aid, but it is limited in its application because of the possession by members within the group of antigenic components in common. This test, thereby, becomes unreliable as a specific diagnostic aid unless a sharp change in titer during early convalescence supports the clinical findings. Contributory evidence to support a diagnosis in this group sometimes found in the epidemiologic studies which demonstrate factors of contact with natural hosts.

Q Fever

Q fever is a rickettsial infection which was first recognized as a human disease in 1935 in Australia[7] and recovered from naturally infected ticks, Dermacentor anderson,[8] at about the same time in the western United States. The disease has since been found to occur in the Mediterranean area, in North America, and in Central America. Recent reports[17,18] show that Q fever is endemic in California, where from 10 to 20 per cent of the dairy cows in the Los Angeles area were found to possess serum antibodies for Q fever and more than a hundred human cases were diagnosed. The clinical and roentgenographic pictures are essentially similar for what has been outlined for the non-bacterial pneumonias with certain exceptions, i.e., the onset may be more sudden, symptomatic recovery more rapid, and symptoms referrable to the upper respiratory or gastrointestinal tracts are not conspicuous.

Acute Lymphocytic Choriomeningitis

An incubation period of from 7 to 21 days is followed by the primary phase of the disease of from 7 to 20 days duration of an influenza-like syndrome with viremia, sore throat, tonsillitis, cough, bronchitis, and pneumonic changes consistent with what has been described for the other non-bacterial pneumonias. This phase may or may not be followed by involvement of the central nervous system[10,19].

Miscellaneous Group of Pneumonias of Viral Origin

Measles. - Interstitial pneumonia has long been recognized as an integral part in the pathogenesis of measles. Shadows, suggesting infiltration of the lung, are present in from about 10 to 50 per cent of the cases. As in the other non-bacterial pneumonias, the physical signs may be absent in about half of the cases.

Variola and Vaccinia. - Pneumonia may occur in smallpox and generalized vaccinia. Lillie[20] and Lillie and Armstrong[21] have reported that pneumonia in variola and vaccinia results primarily from the virus itself, and, like the dermal lesions, pyogenic bacteria invade secondarily to give rise to the suppurative changes which are commonly accepted as complications.

Other Viral Pneumonias. - Varicella pneumonia and certain pulmonary infections in infants are accepted as being caused by viruses, although the causative agents have not been demonstrated[2,14]. Evidence of virus causation consists of the presence of intranuclear inclusion bodies in the epithelial cells of the respiratory tract.

Adams and his co-workers[2] have studied over a period of about ten years a pneu-

monitis of infants which presumably results from a primary virus infection. This pneumonitis is interstitial in type and is characterized by the presence of cytoplasmic inclusion bodies in epithelial cells. It may occur as a sporadic case and in localized epidemics.

Fungous Pneumonias

Histoplasmosis. - Among the protean clinical manifestations of histoplasmosis is a pulmonary type with cough, sputum, night sweats and chest pain, which may simulate other forms of non-bacterial pneumonia.

Coccidioidomycosis. - Tracheobronchitis and pneumonitis of the interstitial type occur as one of the manifestations of the primary infection with Coccidioides immitus. The concomitant symptoms of headache, general aches and pains, sore throat, and slight fever lead to a diagnosis of non-bacterial pneumonia.

Toxoplasmic Pneumonia

The protozoan parasite, Toxoplasma hominis,[28] gives rise to an infection in adults which may have many features in common with atypical pneumonia, Q fever, and other non-bacterial pneumonias.

Allergic Pneumonias

The causative factors which are responsible for the pneumonias seen in rheumatic fever, bagassosis, tropical eosinophilia, and Loeffler's symdrome are not understood. It is assumed by many that allergens are responsible.

LABORATORY DIAGNOSIS

The diagnosis of an isolated sporadic, mild, or severe, respiratory infection which may manifest itself as a non-bacterial pneumonia is difficult[39], if not impossible, especially when the criteria for diagnosis are delimited by epidemiologic, clinical, and roentgenographic studies. It becomes apparent, therefore, that further progress in the diagnosis and treatment of the non-bacterial pneumonias must be brought about by developing and by utilizing efficient methods for etiologic diagnoses.

The objectives and the criteria to be fulfilled before a virus is acceptable as the causative agent of a given disease are outlined in Table VII.

To better illustrate the laboratory diagnosis of a complex that falls into the category of "non-bacterial pneumonia," a case history and the subsequent laboratory studies will be outlined.

Case 1: ., a 25 year-old colored laborer was brought into the Emergency Division acutely ill. He first noticed aching throughout his body, fatigue and some dryness of his throat 24 hours before admission. About 12 hours later, he felt feverish, had repeated mild chills, and experienced greater general muscular aching. A moderately severe chill 2 hours before admission was followed by anorexia, severe frontal headache, a dry non-productive cough and pain in his right chest. Physical examination revealed that his temperature was 103.5°F., pulse rate 98, respiratory rate 22 and blood pressure 120/80. The patient appeared mildly ill. His skin was clear. The throat was diffusely red; the tonsils were not remarkable; the inguinal and axillary lymph nodes were palpable and shotty. Examination of the lungs revealed over the right middle and left lower lobes slight dullness in the percussion note, decreased fremitus, and many fine rales. The patient was admitted to the hospital with a diagnosis of pneumonia, type undetermined, after samples of sputum, blood, and nose and throat cultures had been obtained.

The laboratory studies which were immediately carried out are listed in Table VIII.

Table VII

THE LABORATORY DIAGNOSIS OF VIRUS DISEASES

Criteria to be fulfilled before a virus is acceptable as the causative agent of a given disease:

I. The virus must be regularly recoverable from cases of the disease and its distribution in the host's tissues must be in accordance with the lesions observed.

II. The virus must reproduce the disease in susceptible hosts.

III. Evidence for multiplication of the virus must be demonstrated by its transfer to susceptible hosts (or cells) in series with successful reproduction of histopathologic changes.

IV. Specific identification of the virus is accomplished by careful study of its:

1) histopathologic changes
2) host range
3) pathogenicity by different routes of infection
4) tissue affinities (cellular tropism)
5) antibodies, as measured by one or more of the following techniques:

a) protection tests (neutralization tests)
b) complement-fixation tests
c) precipitin or flocculation tests
d) chicken red-cell inhibition test (Hirst test)
e) heterophile, etc., tests for related antibodies.

Table VIII

LABORATORY TESTS EMPLOYED ROUTINELY IN THE DIAGNOSIS AND TREATMENT OF BACTERIAL PNEUMONIAS

(I) BACTERIOLOGICAL STUDIES

A. Sputum
1. Record description of:
   a. gross appearance
   b. microscopic appearance of fresh smear preparation
2. Stain smear preparations by Gram and Acid-fast technics
3. If diplococci are abundant, do direct "quellung."
4. Culture on rabbit blood agar plate
5. Inoculate mouse by intraperitoneal route with 0.5 ml. sputum

B. Nose and Throat

For culture on rabbit's blood agar plate, transfer flora from oropharynx and from nasopharynx, utilizing a small cotton swab for each.

C. Blood

Withdraw 40 ml. for bacteriological and chemical studies. Culture a 10 ml. sample of blood, utilizing the pour plate technic for 5 ml. and 5 ml. for transfer to 100 ml. of beef infusion broth.

(II) HEMATOLOGICAL STUDIES

A. Hgb, RBC, WBC, Differential

B. Chemistry	Serum	Citrated Blood
1. Plasma spec. grav.	3 ml.	
2. T. P. A/G	5 ml.	
3. Chlorides)	10 ml.	
4. CO_2)	under	
5. Icteric Index)	oil	
6. NPN		3 ml.
7. SAD (if history of SAD therapy)		5 ml.

(III) OTHER STUDIES

A. Urinalysis

1. Routine
2. Culture of WBC and bacteria are present

B. Radiograph PA Chest

- - - - -

The roentgenograms confirmed the clinical impression of pneumonia. The results of the bacteriologic studies of the blood, sputum, nasopharyngeal specimen and the clinical course ruled out a bacterial pneumonia. The morning after admission, nasopharyngeal washings were obtained immediately on awakening the patient by having the patient gargle with 15 ml. of a 10 per cent inactivated serum-broth mixture. These washings and triturated sputum were treated separately with penicillin to yield a final concentration of 500 units per ml. and streptomycin to yield a final concentration of 100 micrograms per ml.

The resultant mixtures were permitted to stand for 30 minutes at room temperature and then used for the inoculation of white mice and of embryonated eggs by the allantoic sac and yolk sac routes. Samples of blood which were obtained on admission and during convalescence 10 days later were set aside for serologic tests.

The mice showed no effects from inoculation. The allantoic fluid from the eggs when tested three days after inoculation was positive for hemagglutinins. Inhibition tests which were carried out with known type A and type B antisera established the virus as Influenza, type A. This conclusion was substantiated when the hemagglutinin inhibition titer of the sample of serum withdrawn 10 days after the onset of illness was found to have a 16-fold higher titer than the acute phase sample. The pneumonia, therefore, was diagnosed as Influenza, type A. Tests of the serum samples yielded no evidence for cold agglutinins or for agglutinins for Streptococcus MG.

C O M M E N T S

The present status of our knowledge of non-bacterial pneumonias is reviewed. It is pointed out that 1) causative agents include a wide variety of organisms from protozoa to viruses; 2) the more usual pathologic, roengtenologic, and clinical pictures are essentially the same for a wide range of etiologic entities, but that variable differences occur between successive cases of the same entity and of different entities; 3) separation into etiologic entities must be accomplished by laboratory studies. Unfortunately, at present, the facilities of most diagnostic laboratories are inadequate to cope with the problem of the isolation and specific identification of viruses. For this approach, a specialized laboratory and, more particularly, specialized personnel are needed. However, the approach is simple and is in essence that which is applied for the diagnosis of a bacterial disease. Accordingly, attempts should be made to isolate the virus by utilizing materials or tissues derived from the patient, and, secondly, to identify the causative agent, when it is isolated directly or, if that is not possible, the diagnosis can be made in retrospect by assessing the patient's serum for specific antibodies. Evidence in recent years has accumulated of the successful application of present knowledge and of new developments in the field of diagnostic bacteriology and virology by the disentanglement with fair regularity of successive new entities from the "scrap pile" commonly referred to as "virus pneumonia," "interstitial pneumonia," "atypical pneumonia," or "non-bacterial pneumonia."

The general recognition that such widely different biological agents as viruses, fungi, protozoa and allergens may be the causative agent of non-bacterial pneumonia should stimulate the efforts of both the laboratorian and the clinician to direct their efforts toward making a specific diagnosis before antibiotic therapy is undertaken.

FOOTNOTE

Dr. W. S. McCann, Professor of Medicine, University of Rochester School of Medicine, and Chief of the Medical Service, Strong Memorial Hospital, has fostered annually for more than twenty years a comprehensive investigative study of pneumonia. This study has provided for several house officers each year training in the care of patients with acute infectious disease and in the clinical and laboratory development and application of successive therapeutic measures in the treatment of pneumonia. These measures over the period of years have included symptomatic treatment, specific antipneumococcal horse serum therapy, specific antipneumococcal rabbit serum therapy, sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and penicillin. Much of the author's interest and information relating to the pneumonia problem resulted from following this study over a period of twelve years. It, therefore, is a pleasure for the author to make this acknowledgment to Dr. McCann and to the successive participants in the program for the information that resulted

from the study.

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III. MEDICAL SCHOOL NEWS

Coming Events

Jan. 18 - E. Starr Judd Lectureship in Surgery - Dr. Alton Ochsner, Tulane University - "The Treatment of Postphlebitic Sequelae by Vasodilatation and Other Measures" - 8:15 p.m. - Museum of Natural History Auditorium.

Jan. 27 - J.B. Johnston Lecture in Neurology - Dr. Paul C. Bucy - Illinois Neuropsychiatric Institute - "The Cerebral Control of Muscular Activity" - 8:00 p.m. - Museum of Natural History Auditorium.

Jan. 31 - Minnesota Mental Hygiene Society - Dr. Benjamin Spock, Mayo Foundation - "A Pediatrician Looks at Mental Health" - 8:00 p.m. - Museum of Natural History Auditorium.

* * *

Alumni News

Dr. James D. Stephen sent Christmas greetings to his friends at the University on a card received by Dr. Harold S. Diehl. Many of our faculty members will remember Dr. Stephen as a British exchange student who was with us a few years ago. He is at present working in the Department of Pathology at the University of Glasgow and would be happy to hear from any of his friends on our campus.

J.B. Johnston Lectureship in Neurology

Dr. Paul C. Bucy, Professor of Neurology will deliver the J.B. Johnston Lectureship in Neurology on Thursday, January 27, at 8:00 p.m., in the Auditorium of the Museum of Natural History. The subject of Dr. Bucy's presentation will be "The Cerebral Control of Muscular Activity."

During his visit on our campus, Dr. Bucy will also participate in a postgraduate course in Neurology which is given under the direction of Dr. A. B. Baker, Professor and Head of the Division of Neurology. Other visiting physicians who will participate as faculty members in the Neurology Course include Doctors R. Richter, University of Chicago; A. Sahs, University of Iowa; D. Denny-Brown, Harvard University Medical School, and Doctors Lealdes M. Eaton, J. Grafton Love, A. R. MacLean, and Harry L. Parker of the Mayo Foundation, Rochester.

* * *

New Minnesota Foundation Members

Dr. George E. Jacobs, 201½ W. Lincoln Ave., Fergus Falls
Dr. Bernice A. Nelson, Menahga
Dr. N. J. Berkwitz, 1527 Medical Arts Bldg., Minneapolis
Dr. Robert T. Petersen, 427 - 2nd Ave. South, St. Cloud

Kellogg Foundation Lectures

The following lectures will be given during the week of January 17. All medical students, interns, nurses, technicians, dietitians, and physicians are cordially invited to attend these lectures. A special invitation is extended to University Fellows.

Dr. Alton Ochsner (Tulane University)	"Carcinoma of the Lung" and "Bronchiectasis"	Monday, January 17, 4:00-6:00 p.m., Powell Hall Amphitheater
Dr. E. T. Bell	"Nephritis and Nephrosis"	Tuesday, January 18, 2:00-4:00 p.m., Todd Amphitheater