Staff Meeting Bulletin
Hospitals of the » » »
University of Minnesota

Miliary Tuberculosis

Volume XII | Friday, January 10, 1941 | Number 11

STAFF MEETING BULLETIN
HOSPITALS OF THE . . .
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Published for the General Staff Meeting each week during the school year, October to May, inclusive.

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William A. O'Brien, M.D.

I. LAST WEEK

Date: December 20, 1940

Place: Recreation Room
Powell Hall

Time: 12:15 - 1:15 P.M.

Program: Movie: "Sea Scouts"

Staphylococci in Urine
Milton Levine
W. P. Larson

Discussion
Wesley Spink
Gerald Evans

Present: 115

- - - - -

December 27, 1940 - Holiday

January 3, 1941 - Holiday

Gertrude Gunn
Record Librarian

- - -

II. MOVIE

Title: "Mr. Duck Steps Out"

Released by: R-K-O

- - -

III. ANNOUNCEMENTS

1. MARRIED

Evelyn J. Celine (Pediatrics) and Lincoln A. (born on Feb. 12) Thomas, Christmas Day, 1940, at Minneapolis.

Congratulations!

- - - -

2. GUEST FACULTY
Center for Continuation Study.

Ophthalmology - Jan. 20-25, 1941.
Thomas D. Allen, Rush Medical College, University of Chicago.
Ramon Castroviejo, Columbia University College of Physicians and Surgeons, New York City.
Albert D. Ruedemann, Cleveland Clinic.
Derrick T. Vail, Jr., University of Cincinnati College of Medicine.
Robert Von der Heydt, Rush Medical College, University of Chicago.

Hospital Administration - Jan. 27 - Feb. 1, 1941.
Arthur C. Bachmeyer, University of Chicago.
Nellie J. Gorgas, University of Chicago.
Malcolm T. MacEachern, American College of Surgeons, Chicago.
Jos. C. Norby, Columbia Hospital, Milwaukee.
C. Rufus Rorem, American Hospital Association, Chicago.
Stanley S. Seeger, Columbia Hospital, Milwaukee.

Uterine Bleeding - Feb. 3 - 5, 1941.
George W. Bartelmez, University of Chicago.
Ralph A. Reis, Northwestern University.

- - -

3. E. STARR JUDD LECTURE

The eighth E. Starr Judd lecture will be given by Dr. A. C. Ivy, Nathan Smith Davis Professor of Physiology and Pharmacology at Northwestern Medical School, Wednesday evening, January 15, 8:15, in the Medical Science Amphitheater. Subject: "The Mechanisms of Gastric Secretion." Dr. A. C. Ivy will conduct a seminar discussion Thursday morning, January 16, at 9:30 on "Practical Aspects of Applied Physiology of Gastric Secretion" in Eustis Amphitheater. Anyone interested is cordially invited.

Owen H. Wangensteen, M.D.

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IV. MILIARY TUBERCULOSIS

Frank Gratzek

Miliary lesions in the lungs, widely distributed, are most frequently the result of the hematogenous dissemination of tubercle bacilli. While there are other diseases such as capillary pneumonia, obliterative bronchiolitis, carcinomatous metastases, silicosis, and certain fungus infections which also produce widely distributed, numerous small sized nodules in the lung, tuberculosis is the most important etiologic factor. The subject of miliary tuberculosis is ancient but presents certain newer phases which are of interest. A sharp division should be made between the acute and chronic forms as their clinical manifestations, pathogenesis and roentgenologic appearance produce many differences.

1. Acute Miliary Tuberculosis

Definition

An acute infectious disease, excited by the presence and growth of the bacillus of tuberculosis, presenting a characteristic inflammation in the form of miliary tubercles, more or less widely distributed throughout the tissues of the body.

Historical

Franciscus Sylvius (1614-1672) gave the first description which enlightened the basic nature of the disease, clinically long-known as phthisis (the wasting away disease). The condition had been well described clinically in the earliest works of Hippocrates and his co-workers (460-377 B.C.) although other pulmonary diseases were often confused with phthisis or mistaken for it. Galen recognized the contagious nature of tuberculosis, and it is known that many of his patients were given climato and aëro-therapy, when they were sent to the sunny slopes of Vesuvius.

Early Pathology

Sylvius, in doing a number of autopsies, was impressed by the repetition of mostly small, rounded, whitish-gray bodies in the lungs of patients who in life had been diagnosed as having phthisis. He decided that these small spheroids were the underlying anatomical basis of phthisis, and he called them "tubercles," a term used at that time in Latin medicine to represent a small swelling or nodule, and he concluded that the pus in these lesions was the same as that which was expectorated by the patients.

In 1810 Bayle, a French investigator and a co-worker of Laennec, published his "Researches on Pulmonary Phthisis," basing his findings on several hundred autopsies on tuberculous patients whom he had followed during their disease; he described (1) the phthisis tubercle, (2) phthisis granulare, (3) phthisis calcifique, all of which are processes well understood in tuberculosis today. Bayle died in 1816, the year Laennec invented the stethoscope with which he first analyzed and named the various signs of pulmonary tuberculosis.

In 1882 Robert Koch's discovery of the tubercle bacillus clarified many misconceptions as to what actually was the causative agent in pulmonary tuberculosis and eventuated into extensive research and voluminous articles on the various stages and pathological formations in the disease together with a description of the definite actions of the organism and reactions of the host. This also involved the various avenues of dissemination of the disease organisms and today we accept these and understand them to be the bronchogenous, lymphogenous, hematogenous, and direct avenues of spread.

Hematogenous or miliary dissemination

Villemin in 1865 showed that active tuberculosis can develop in animals when they are injected with the blood of tuberculous patients not ill with miliary tuberculosis. Wilson, a British

author, concluded in a 1933 publication, that tuberculous bacillemia is rare in the early stages of pulmonary and in non-pulmonary tuberculosis; it may be present in 5 to 10% of advanced and progressive cases of the disease and in 30 to 40% of cases of miliary tuberculosis. In the postmortem heart blood of patients who have died of tuberculosis, examination may be expected to reveal the presence of tubercle bacilli in about 50% of the cases. In about 3% to 4% of all deaths caused by pulmonary tuberculosis, an acute generalized miliary dissemination is found.

Rubin described three possible routes by which tubercle bacilli may invade the blood stream; (1) by direct extension from a caseous lymph node along efferent lymphatics to the thoracic duct and thence into the venous circulation; (2) by rupture of a caseous focus directly into the lumen of a blood vessel. Arteries are believed to be more often eroded from without, and veins are more apt to harbor intimal tubercles or thrombotic masses containing tubercle bacilli; (3) by settling first in the subintima of a blood vessel and producing an endangitis and then invading the blood stream. Edith Lincoln has stated that "intimal" tubercles are found most commonly at the junction of small pulmonary veins, and localize there when a few bacilli circulating in the blood stream are caught in the eddy at the fork in the blood vessel due to a slowing in the current, where the bacilli may enter the intima and proliferate.

Why in some cases tuberculous lesions, in the lymph nodes or elsewhere, remain entirely dormant during a life time and in others may at intervals discharge tubercle bacilli into the blood stream, is an unsolved question. It appears largely to depend upon the amount of caseation, the opportunity for communication with the blood stream, or the accidental injury or physical strain of an individual which may be factors in producing a rupture of a caseous focus into a vein and cause recurring dissemination.

Ghon, Kudlich and Schmiedl have shown by the study of serial sections that tubercle bacilli pass from the primary focus, which is usually situated in the periphery of the lung just under the pleura, to the regional lymph nodes in the peribronchial and tracheal regions from which regions the thoracic lymph duct is reached and through this the venous circulation. The focus from which dissemination occurs may be found in any organ.

At postmortem examination miliary tubercles are most easily observed on surfaces exposed by cutting in the lungs and in the spleen. In the spleen Malpighian corpuscles are usually very prominent in young persons, and must not be confused with tubercles.

Macroscopically visible tubercles are of fairly uniform size and vary from one to several mm. in diameter. Minute tubercles are not visible macroscopically, the liver usually being the site of microscopic tubercles.

After the tubercle bacillus lodges in the lung tissues, either in the lymphoid spaces, capillaries, or interstitial tissues, a foreign body reaction occurs consisting of epithelioid cells and a few giant cells centrally, and peripherally a few fibroblasts and lymphocytes, forming a nodule seen microscopically.

Four main groups of cases of tuberculous infection due to hematogenous dissemination can be distinguished: (1) the cases of the protracted form of generalized dissemination which when marked becomes a clinical entity; (2) the cases of acute generalized miliary tuberculosis; (3) cases in which, as in those of renal or osseous tuberculosis, the predominant lesion is of hematogenous origin but is not usually thought of in those terms; and (4) cases in which bacillemia may not be evident and in which there may be no changes on physical examination.

Symptoms

In order to study more in detail the symptoms produced by metastatic lesions

of acute general miliary tuberculosis, the cases may be grouped into: (1) the typhoidal infection, (2) the pulmonary form, where the pulmonary symptoms predominate, (3) the cerebral or cerebrospinal form, when tuberculous meningitis is present, and (4) the intermittent form, where the symptoms are more protracted.

The Mantoux test is almost always negative in all types of acute miliary tuberculosis.

The most characteristic lesions of the protracted hematogenous dissemination of tubercle bacilli, when the condition is at its height clinically, are marked panadenitis and penserositis.

Typhoidal Form

In the so-called typhoidal form the disease presents much more clearly the picture of a general infection, since during the course of the disease symptoms indicative of any localized lesion may be entirely lacking. It is more frequently observed in adult life and may develop acutely in persons apparently in normal health or in those recognized as tuberculous. The onset is commonly insidious and protracted and only malaise and progressive weakness, with fever, are notable. As these symptoms become more pronounced, some headache, a slight bronchial cough, and a dull or apathetic mental condition with considerable elevation of temperature and acceleration of pulse are observed. The fever is apt to remain high continuously, 102°-103° F., with slight daily remissions. The spleen is frequently slightly enlarged and there is a leukopenia; the skin sometimes presents pale reddish spots resembling typhoid rose spots. Constipation is noted as a rule, the tongue is dry and coated, and the cheeks are flushed. With continued fever and progressive prostration, active delirium often occurs, the heart action becomes more rapid and feeble, and death occurs in ten days to three weeks.

Pulmonary Form

The primary symptoms in miliary tuberculosis of the lungs may be insignificant. There is usually a slight cough with scanty expectoration from which tubercle bacilli are usually absent, and the physical signs may be limited to the generally distributed, inconstant, subcrepitant rales of a moderate general bronchitis; dyspnea is always pronounced and disproportionate to the apparent involvement of the lung parenchyma. A peculiar dusky pallor is strikingly evident and the patient presents an anxious, distressed appearance which is most characteristic.

The onset in children may be abrupt following pertussis or measles. Rusty sputum, or even pulmonary hemorrhages may occur, confusing the picture with that of a true pneumonia, but the symptoms become progressively more pronounced and the crisis does not occur. Prostration increases, the dyspnea and cyanosis become more severe, the early signs of general bronchitis merge into those of pulmonary edema and death ensues in a few weeks.

Cerebral Form

Tuberculous meningitis may occur as an acute infection ushered in by rigors, nausea and vomiting, with sharp elevation of temperature. Usually, however, there are prodromal symptoms. In adults these may be increasingly obstinate insomnia, or persistent dull headache, frontal in type with some photophobia, or the headache may be occipital or general. Tuberculous meningitis occurs in one-half of the cases of miliary tuberculosis.

In children an insidious onset is marked by restlessness and irritability and there is loss of appetite and weight. 70% of meningitis in the first year of life is said to be tuberculous. The more acute symptoms follow, frequently with convulsions and interrupted sleep. Vomiting often is continuous, and constipation usual. The temperature may be only slightly elevated, the pulse is rapid and there is rarely any respiratory dis-

turbance. Apathy and delirium follow, and strabismus sometimes occurs. Rigidity and retraction of the neck, and tonic spasm or paralysis of groups of muscles, is frequently noted.

Death occurs from exhaustion or respiratory paralysis in from two to four weeks after the time of onset.

Fulminant types of cases, as a rule in adults, occur with sudden acute onset, and terminate fatally in a few days.

Intermittent Form

Here the period of illness is much more protracted, the symptoms are not very marked, and chills and considerable remissions of fever suggest malaria. For none of them can an adequate physical basis be found. Prostration, anemia and emaciation are marked, and finally severe pulmonary or cerebral symptoms develop which are fatal.

The fever, tachycardia, fatigue, loss of appetite, and other such symptoms are probably due to the allergic reaction which requires about ten days to three weeks to develop, and is probably a sign of sensitization to the protein products of the tubercle bacillus. This is proved by the fact that injection of dead tubercle bacilli, or their protein derivatives will produce exactly the same symptoms of toxemia.

Roentgen Findings

The rupture of a tuberculous hilar lymph node into a blood vessel may flood the pulmonary circulation with tubercle bacilli which become lodged in the capillaries of the lung parenchyma where an inflammatory reaction occurs and may become visible on a roentgenogram within seven to ten days. Occasionally several weeks elapse before roentgen signs are visible. This appearance presents usually a symmetrical distribution of innumerable opaque nodules, varying in size from less than one millimeter to three mm. in width, producing on a roentgenogram of the lungs a "snowstorm" appearance. Superimposition of several of these shadows in direct line with the x-ray beam intensifies the densities on the film. The normal lung markings tend to disappear and may become invisible.

Fluoroscopic examination may reveal a uniform diminution in translucency of the lung fields with poor aeration, and diminution of the movements of both diaphragms. At times the fine granular appearance of the tubercles may be visible.

Later the lesions become intensified and may coalesce, and the hilar nodes show definite enlargement. The densities in the lungs may be limited to certain portions only.

The lesions may gradually retrogress on roentgen examinations and no evidence of the disease remain after a few months to a year or the nodules may become fibrosed or calcified and persist throughout life.

While the typical roentgen appearance is well known, there are certain simulants of acute miliary tuberculosis which are difficult to exclude on roentgen examination alone.

Purulent bronchitis, often called capillary pneumonia, may produce numerous small densities widely distributed throughout both lungs. Because such patients may have cyanosis, tachypnea, fever and other symptoms similar to miliary tuberculosis, the differentiation may be difficult. Usually the nodules are larger and more irregular, and there is more tendency toward coalescence. In certain cases, it may be necessary to observe for several weeks with repeated roentgen examinations to determine the final diagnosis.

Miliary carcinomatous metastases may also be confused when they appear rather acutely. Here the lesions are likely to be more discrete, denser and less uniformly distributed.

Silicosis of the nodular type is usually differentiated by the greater density of the lesions, the character-

isticcoalescent patches, and the absence of fever and other acute symptoms.

Other stimulants will be considered with the chronic forms.

The problem of the significance of negative findings is even more pressing. How soon after the onset of miliary tuberculosis should the roentgen findings be diagnostic? Or put in another way, in the presence of symptoms suggestive of acute miliary tuberculosis, do negative roentgen findings tend to exclude the condition as they do in the ordinary chronic lesion? While in most instances, findings appear in a week or ten days, it is readily conceivable that a small number of tubercles of small size may be present in the lungs for weeks without giving clear manifestations of their presence. To obtain some answer to these questions 27 cases of proved acute miliary tuberculosis seen at this hospital during a ten year period were studied.

ANALYSIS OF UNIVERSITY OF MINNESOTA HOSPITALS CASES

In the ten year period from July 1, 1928 to July 1, 1938, of 73,864 admissions, 27 cases of acute miliary tuberculosis were found, either on their first admission or subsequently. This group includes 16 adults between the ages of 22 and 73 years, and 11 children between the ages of 9 months and 16 years. 17 were males and 10 females. 13 of the males were adults and 4 boys, while in the female group 3 were adults and 7 were girls. Only 1 patient, a 25 year old Japanese engineering student, expired from generalized miliary tuberculosis in the Students Health Service Hospital over a 16 year period, 1924 to 1940.

Out of the 27 University Hospital patients 3 were Mexicans, one a male aged 38 years, and two children 18 months of age, one having been exposed to active pulmonary tuberculosis in the mother.

Pathology

Out of the 28 patients, including the Students Health Service case, who had miliary tuberculosis, 26 died in the hospital and 2 were taken home. 20 patients' bodies were examined postmortem and a generalized miliary tuberculosis was found in each instance. 14 died from tuberculous meningitis as a part of a generalized miliary tuberculosis.

Symptoms and Duration

16 of the 28 patients complained of cough as one of the primary symptoms. The duration varied from 5 days up to one year, but the majority of these patients (12 in number) had a cough from 2 to 4 months previous to the time of admission to the hospital. Dyspnea appeared less frequently than cough and occurred predominantly in the adult group. Fever, chills, headache, hemoptysis, loss of weight, weakness and fatigue were symptoms which were mentioned by some of the patients, with the primary complaint of cough.

The number of hospital days in the primary pulmonary group varied. Ten of the patients died within 8 days, two were taken home shortly after admission, one patient had a milder form of miliary tuberculosis for 31 days and developed tuberculous meningitis, succumbing 7 days later. One patient, a 13 year old female was admitted with pleural effusion and succumbed from tuberculous meningitis after 108 days in the hospital; a 49 year old male was admitted with a tuberculous enteritis and died 34 days later from meningitis.

In the remaining 9 patients, one had a tuberculous renal infection, two had a tuberculosis of the knee; one was a diabetic and lateral developed tuberculous meningitis. One patient had severe burns over a great portion of her body and later died of tuberculous pleuritis and effusion, and the remaining 8 were admitted with tuberculous meningitis.

Ten of the patients with generalized miliary tuberculosis had a leucopenia of a moderate degree, their white blood cell counts varying in some cases from

4,500 up to 6,700. Seven had normal white blood counts and 10 showed a moderate to a fairly severe leucocytosis varying between 8,300 and 20,000 white blood cells.

Roentgen Findings

Films were taken of the chests of 26 of the patients; one patient was moribund on admission and expired in a few hours so no roentgen studies of the chest were made. In 17 out of the 26 chests examined roentgenologically, a diagnosis of miliary tuberculosis was made. In 12 patients a definite diagnosis was made and in 5 miliary tuberculosis was mentioned as a probability. Other diagnostic possibilities considered were bronchiolitis, miliary carcinomatosis, pulmonary congestion, capillary pneumonia, pneumoconiosis, and in cases where an effusion or a consolidation was present lobar pneumonia or bronchogenic carcinoma was suggested as a diagnostic possibility.

In those cases where a diagnosis of miliary tuberculosis was made on roentgenographic examination, the time which elapsed from the onset of cough or dyspnea to the time of first chest films varied considerably. The shortest period which elapsed was 11 days in one patient, 14 days in 2 patients, 17 days in 1 patient and in the remaining 12 patients the duration of symptoms varied from one month up to one year before roentgen examination of the chest.

In one patient no films of the chest were made for 2 months before death; the films up to that time were reported negative, autopsy later revealing a generalized miliary tuberculosis. The chest films of 3 patients taken 2 days before expiration were diagnosed as pneumonia; however, these patients were in coma and portable films of the chest were made which were quite unsatisfactory. In one patient a diagnosis of tuberculous pneumonia was made 6 weeks after onset of a tuberculous meningitis, autopsy later revealing a miliary involvement of the lungs.

In the case of the health service patient all films of the chest were made with a portable unit, the final being 17 days before expiration and, outside of enlargement of mediastinal glands, it was thought that the film was probably negative.

It is apparent from this study that in all chests that were examined with the usual technique, a definite or probable diagnosis of miliary tuberculosis was made. The greatest cause for mistaken diagnoses was from inability to cooperate on the part of the patient when the films of the chest were taken, or a masking of the miliary process by an effusion or consolidation. Several obvious difficulties in the roentgen diagnosis of miliary tuberculosis therefore are apparent. Discrete early nodules may be present in a lung but cannot be diagnosed on a film of the chest even with the best cooperation of the patient and under excellent technical supervision, as overlying ribs or other structures may hide the lesions entirely. Usually, however, the patient with acute miliary tuberculosis is extremely ill and unable to cooperate, or films must be made at the bedside for clinical reasons. In the usual instance, the portable bedside unit must necessarily be focused at a short distance (30 to 36 inches target film distance), increasing distortion tremendously, and the time of exposure of the film ordinarily requires two or three times the usual one-tenth (0.1) second which is required for the ordinary upright postero-anterior chest exposure at a six foot focal spot distance. Under such circumstances, the technical factors, added to the patient's inability to cooperate can readily produce unsatisfactory films. Even gross consolidations or effusions are often difficult to determine; minute early miliary lesions usually become obliterated from distortion, or from the respiratory movement of the patient, resulting in the frequent negative or questionably negative reports.

A roentgenogram shows shadows of different densities but does not necessarily determine what produces these shadows. Different lengths of exposure, varying degrees of penetration, different methods of development of the films and

other technical variations may all produce slightly different pictures of the same chest. To attempt to make a diagnosis from a poor film is very dangerous, and the slighter the lesion the better must be the roentgenogram. In the ideal roentgenogram of a chest showing a miliary tuberculous infection, one sees a generalized mottling or speckling extending to the actual periphery of the lungs. When the mottling has hazy cottony borders (a "soft" lesion), activity is suggested; when the shadows are dense and clearly defined there is a suggestion of fibrosis, but in roentgenologic study, as in clinical examination there is no absolute criterion of healing, or on the other hand of activity. The importance of any abnormal roentgen finding lies, just as one evaluates physical signs, not in its mere presence but in the interpretation of its significance when taken in conjunction with the history and clinical symptoms of the patient. A slight change one day may be a gross change at a later date and, conversely, a marked alteration may retrogress and become slight or disappear. Frequent roentgen examinations of the chest, therefore, with stereoscopic films at times, are often necessary to be absolutely certain of diagnoses of pulmonary conditions, and in miliary tuberculosis this is extremely important because of the rapid changes which usually take place in the progress of the disease.

2. Chronic Pulmonary Miliary Tuberculosis

Definition

Chronic pulmonary miliary tuberculosis is a hematogenous dissemination of the tubercle bacillus by way of the lesser circulation mainly, in contradistinction to generalized miliary tuberculosis which is a widespread dissemination of the bacilli by way of both the greater and lesser blood circles.

Historical

Wunderlich, Koenig, Cornet and others have reported cases of healed miliary tuberculosis and Sigg and Burkhardt have made similar reports with autopsy controls. Graw, Muralt, Klingenstein, Diel and others were the earliest observers in the last two decades to report cases of hematogenous tuberculous disseminations with serial roentgenograms showing retrogression. James Alexander Miller, from the Tremont Sanatorium in New York, and Max Pinner, from the Desert Sanatorium at Tucson, Arizona, have contributed much to our knowledge of the disease during the last decade. Nalbant reported thirteen cases of miliary tuberculosis in 253 cases of pulmonary tuberculosis in children in the Maybury Sanatorium at Northville, Mich. in recent years and found that seven of these patients died, three were fully recovered and three were markedly improved after having been hospitalized for one year. Healing took place by calcification of the numerous foci of infection in one instance and by resorption in the others.

Courville and Harrison of California in 1937 reported three cases of tuberculous meningitis which had healed and later disseminated causing a fatal meningitis, and concluded that recovery occurs in tuberculous meningitis only in individuals in whom a relatively small number of tubercles form and in whom invasion of the meninges occurs early in infancy. Healing may take place by complete resolution or calcification.

Borel of France in 1920, Schouermann in 1929 and 1930, and Grethmann of the Bellevue Hospital recently have made studies of hematogenous tuberculous dissemination. Zavod of New York finds that the majority of cases of pulmonary hematogenous tuberculosis occur most frequently in childhood, and in young adults who were heavily exposed to tuberculosis during childhood.

Sweany in a recent report of twenty cases of calcifications in the spleen followed the tuberculous development in other organs of these individuals.

Pathogenesis

In the chronic protracted dissemination

of pulmonary tuberculosis the characteristic finding is extensive caseation of the lymph nodes particularly of the tracheobronchial group, which is usually the result of an acute process developed in childhood. The rupture of a caseous node into a lymphatic vessel and the passage of small numbers of tubercle bacilli into the thoracic duct and then to the pulmonary circulation, or the erosion of a caseous node directly into a pulmonary vein, may deposit enough bacilli in the lung parenchyma to form tuberculous nodules. The infectious organisms, after invading the venous blood channel pass thru the right side of the heart and then by way of the pulmonary arteries thru the lung fields. Few organisms enter the pulmonary venous circulation to be carried to the left side of the heart and to some distant organ by the general circulation. The number of bacilli disseminated in the non-clinical cases is necessarily small and their virulence may be limited by the resistance, allergy, and tissue immunity of the host.

Pathology

The characteristic lesions of chronic hematogenous pulmonary tuberculosis are represented by productive tubercles seeded into the walls of lymph and blood vessels and into the interlobular and alveolar septa. These are the so-called interstitial tubercles which due to their productive character remain covered by unbroken intima or septal membranes. They do not break into communicating channels and generally show but a mild tendency to coalescence and extension. Instead, they tend to absorption and give rise to much fibrosis. Residues of these lesions are usually found in the upper lobes in the form of localized or widespread pulmonary fibrosis associated with calcification.

A very characteristic feature of chronic hematogenous pulmonary tuberculosis is the predisposition of the peripheral subpleural zones to receive most of the repeated crops of lesions. It is in these corticopleural zones where coalescence and extension of the lesions are found most frequently. From here, extension is frequent toward the pleura by involvement of the pleural layers, hence the frequency of pleurisy of hematogenous origin such as tuberculous pleural effusion in absence of pulmonary tuberculosis.

The uninvolved pulmonary parenchyma interposed between the minute fibrosing nodules shows obstructive emphysema going on simultaneously with the fibrosis in the involved areas. The tracheobronchial lymph nodes are either still enlarged and often caseous or they may be infiltrated with calcium salts.

The individual tubercles within the parenchyma of the lung together with the changes which occur in the hilar lymph nodes undergo the series of changes ordinarily found in the progressive stages of healing tuberculous lesions, often with eventual calcification. After implantation of the tubercle bacilli in the tissues of any organ, the first response is a proliferation of the fixed connective tissue cells, or of the endothelial leucocytes (Mallory) or monocytes (Sabin). These multiply and surround the bacilli, and in their growth assume the form of epithelial cells having a large faintly staining protoplasmic structure and a large nucleus. As proliferation of cells continues these large "epithelioid" cells become compressed and elongated.

Leucotytes also accumulate around the tubercle bacilli in the early stages but later give place to lymphocytes. These are scattered thru the tubercle and often form a zone around the periphery

As pressure around the tubercle progresses, coagulation necrosis takes place due to lack of nutrition (Weigert). This is due to the absence of blood vessels in the center of the tubercle and forms the caseous material found in tubercles. These may later undergo liquefaction, the basis of the formation of tuberculous pus.

Replacement of the compressed epithelioid cells by connective tissue cells forms the basis for fibrosis which

may take place throughout the entire tubercle; thus the commonly observed fibrous nodule is developed. However, the fibrosis may only replace the outer layers of the tubercle proper, and encapsulate the tubercle by a fibrous coating.

Another process, however, may enter into the life cycle of the tubercle, whereby healing takes place by calcification. This is due to the deposition of calcium salts in the caseous matter of the tubercle which may eventually become a calcified nodule.

Hematogenous dissemination of pulmonary tuberculosis can resolve without leaving a trace that can be detected on physical or roentgenologic examination, but fibrosed areas can usually be seen on histologic examination postmortem. From this extreme the evolutionary process may gradually lead to the other extreme of conglomeration of tubercles, caseation, softening, liquefaction, excavation, bronchogenic dissemination and eventually open tuberculosis. The disease may become arrested in any of its revolutionary stages and never recur or the patient may suffer repeated attacks of hematogenous dissemination, each succeeding spread involving more pulmonary parenchyma. The emphysema and the interstitial fibrosis are thus increased until a time is reached when, though the tuberculous process may be completely arrested, the patient becomes an invalid because of a state of partial anoxemia. This is owing to marked loss of lung tissue and eventually death may occur from right heart failure.

Incidence

In a study of the control of silicosis among miners by the U. S. Bureau of Mines, in conjunction with the Metropolitan Life Insurance Company and the Tri-State Zinc and Lead Ore Production Association at Picher, Oklahoma, 125 instances of miliary calcifications in the lungs of more than 18,000 individuals were found. These examinations included a roentgenogram of each individual's chest as part of a physical examination prior to employment and at least once yearly thereafter. In only two of these was there a history of a pulmonary disorder. The remaining 123 gave no histories of any pulmonary complaints and were apparently healthy. The most characteristic findings on roentgen examination in this group were the large number of discrete dense, shot-like spots scattered over the lungs, and in 94% of the cases 55% to 95% of the spots were found in the bases. The large spots varied from 4 mm. to 1 cm. in diameter and were mostly in the bases. The small spots varied in size from 1.5 mm. to 5 mm. in diameter and were fairly dense, round and uniform. 88 of these cases were studied intensively and only two were found actively tuberculous with progression; the other 86 remained the same on repeated examinations. In unstained smears 30 of this group showed fungus identified as Aspergillus fumigatus fisheri and Aspergillus niger. Cultures of mine dusts showed none of these organisms and in only one instance the cultures of the oral secretions of a miner were positive. Since the original description, the conception that **Aspergillus** might be the etiologic factor has been abandoned (Lanza).

Sutherland, of the Mayo Clinic, described 38 cases selected from 60,000 roentgenographic examinations, and thought them to be miliary calcium metastases; however, no definite proof of this was given.

Symptoms

The symptoms vary with the acuteness of the disease but are seldom dramatic. The onset may be indefinite as to time and often entirely absent and in many cases the condition is discovered on routine x-ray examination.

The sputum, if present, is usually negative on smear and animal inoculation. The tuberculin test may be negative from the onset, and after several weeks become positive.

Hematogenous pulmonary tuberculous dissemination, according to Pinner, differs from bronchogenic tuberculosis in the fact that it may run the entire

course from seeding to healing with practically no symptoms. Many patients are diagnosed pneumoconiosis until later roentgenograms show complete resorption or multiple calcifications.

Roentgenography

Early hematogenous tuberculosis shows (1) small, fairly evenly distributed foci of slight density 2 to 3 mm. in diameter: (2) single lesions 1 to 2 cm. in diameter also of slight or medium density and these have ill defined borders due to perifocal reaction around the nodules. Both show enlargement and possible caseation or calcification of hilar nodes. The distribution is more or less symmetrical; however the involvement may be limited to certain parts of the lungs and may be denser in certain portions.

The lesions may gradually retrogress as shown on repeated roentgen examinations and no evidence of the disease remain after a few months to a year, or the nodules may become fibrosed or calcified and persist throughout life.

In patients who show roentgenologically the small foci and who die of simple progression of the tuberculosis, the lungs are likely to be more or less densely studded by lesions which are somewhat too large for miliary tubercles. Cavitation in hematogenous tuberculosis is found only on rare occasions but the cavities do not show a distinct wall formation if present.

Involvement of serous surfaces may at times be limited to a clear exudate or to extensive adhesions. In the marked cases, caseation of the serous surfaces may be present and eventually may calcify. This may be the explanation in some of the cases in which calcification of the pleura is seen in the roentgenogram.

Diagnosis

The diagnosis of hematogenous pulmonary tuberculosis is usually made on the history and physical examination but must always be confirmed by a roentgenogram, since the physical signs alone are insufficient for diagnosis.

Prognosis

The prognosis is usually favorable except in the fulminating type which is fatal in most instances.

Differential Diagnosis

1. Hematogenous tuberculosis, in the early stage, is most frequently confused with generalized miliary tuberculosis in which there is usually progression with increased debility and loss of weight, persistence of symptoms and evidence of involvement of other systems than the pulmonary. A period of observation may be necessary to differentiate the condition.

2. Pulmonary congestion, when due to cardiac decompensation, shows the usual loud wet and gurgling rales which decrease in intensity and number from below upward, (the reverse of hematogenous tuberculosis). Signs of cardiac disease may be present and roentgenographic study usually shows cardiac enlargement and clouding of the lower lung fields. The shadows are less discrete and more linear in form.

Congenital heart disease or heart disease that causes long standing passive congestion may offer difficulty in differentiation, since heart failure cells gather into small clumps in the alveoli, which throw a nodular shadow on the roentgenogram resembling hematogenous tuberculosis. The enlargement of the heart, cyanosis in the absence of marked dyspnea, the presence of murmurs and the absence of all evidence of inflammatory pleuritic involvement would be against a diagnosis of tuberculosis.

3. Miliary carcinomatosis is usually found in older persons, dyspnea is progressive and a primary carcinoma is usually found elsewhere.

4. Yeast and fungus infections usually

have increased expectoration which is negative for tubercle bacilli, and the roentgenogram shows ill defined patchy infiltrations much larger in size than is found in hematogenous miliary tuberculosis. The search for yeast and fungi in the sputum helps to verify the diagnosis.

5. Hodgkin's disease of miliary distribution usually shows more discrete nodules and there is no evidence of confluence or cavitation. There is progressive enlargement of the mediastinal lymph glands in Hodgkin's disease.

6. Silicosis shows nodular infiltrations limited to the midportions of the lungs and these tend to become confluent and densely fibrotic. A history of exposure to dusts of free silica or silicates is usually obtained.

7. Sarcoid may show miliary lesions but usually shows bilateral glandular enlargement. Roentgen examination of the bones of the phalanges may show the characteristic changes of cyst-like bone destruction diagnostic of sarcoid. Skin lesions are frequently present.

8. Periarteritis nodosum and disseminated lupus erythematosus with or without skin lesions may appear as miliary nodules on roentgenographic examination.

9. Capillary pneumonia or an interstitial pneumonitis gives a true miliary picture, and may necessitate repeated roentgen examinations and close clinical observation for differentiation from miliary tuberculosis. These are usually acute lesions.

10. Certain pneumonias of an unusual type, as those caused by psittacosis may be confused with miliary tuberculosis.

11. Bronchiectasis of an unusual type may show miliary involvement which is predominantly basilar. Bronchography assists in making a true diagnosis.

12. Bronchiolitis fibrosa obliterans, in the course of measles or influenza, produces a picture of miliary tuberculosis, but the lesions are, as a rule, coarser and less defined and tend to become confluent. The progression or retrogression is usually rapid.

13. Leukemia or lymphadenomatous disseminate foci may have to be differentiated by clinical and laboratory study.

14. Septicemia caused by various organisms may form septic emboli with miliary foci.

15. Bilharziasis of the lungs may simulate miliary tuberculosis.

16. Miliary amyloidosis has been described in the lungs with amyloid disease in other organs.

Multiple Calcified Nodules

As related above in the study of the Picher, Oklahoma miners, patients are frequently encountered with multiple areas of calcification in the lungs. Usually they are symptomless, frequently give no history of any serious illness, the lesion being discovered accidentally.

The problem of the origin of these lesions is difficult to settle. A number of possibilities have been suggested.

1. Calcium metastases usually occur during periods of hypercalcinaemia found in cases of multiple myeloma and metastatic carcinoma (Bell). These calcifications may be found in the lungs, kidneys and spleen. Such instances are very rare.

2. Fungus infections as Aspergillus fumigatus, mucor corymbifer, actinomycosis, streptothricosis and other fungi produce lesions very similar to tuberculosis on roentgenograms. The isolation of the specific mold may occasionally be the only differentiation clinically. There is some doubt as to whether actual calcification may occur.

3. Silicosis produces bilateral nodular lesions confined mostly to the midportions of both lungs. An occupa-

tional history of exposure to silica dust usually is obtained. Here again the question of whether calcification actually occurs in pure silicosis is doubtful but there is good evidence to indicate that this may occur.

4. Calcified chronic miliary tuberculosis occurs in rare cases where the miliary disseminations were of a mild and protracted hematogenous type. The source of such disseminations is usually in the hilar lymph nodes.

5. Childhood dissemination with calcification may occur in cases in which no fulminating infection was present, the spread was confined to one set of organs, as, for example, the lungs, kidneys or spleen, and a small number of tubercle bacilli were implanted in the tissues.

The opportunity to observe the progress of such calcifications is rare but is exemplified in the following case.

, a 16 year old school boy, was admitted to the University Hospital Out-Patient Clinic on August 7, 1935, complaining of repeated colds and congestion in his head since the age of 5 years. Night sweats were noted at times.

A family history of tuberculosis was given, but the patient himself had not been exposed to an open case of the disease.

Physical examination revealed rales at the bases of both lungs. Nourishment of the individual was good. No increase in temperature was noted on several examinations. The Mantoux was positive.

Roentgen examination of the chest on August 20, 1935 revealed multiple fine nodules throughout both lung fields which were interpreted as probable miliary tuberculous nodules but did not appear calcified.

On November 27, 1939 the patient was reexamined as a University student and the nodules had increased in size and had not become calcified. No symptoms of any pulmonary disease were present at any time. The hilar glands were enlarged on the roentgenograms at both examinations.

A study of miliary calcifications in the lungs of patients admitted to the University Hospital Out-Patient Clinic was made, with an attempt to clarify the probable cause of this condition. Several instances of these multiple discrete calcifications were found on roentgenograms of individuals' chests where the symptoms of the patient were variable, and films of the chest were made to exclude some active intrapulmonary disease. In none of these cases were these multiple calcifications suspected clinically, as no symptoms can actually be traced to the presence of these lesions.

Since the institution of routine chest fluoroscopy in the Out-Patient Clinic in February 1939, the finding of these pulmonary calcifications has become more frequent. Up to January 1, 1941, 15 patients were found with multiple miliary calcifications in both lungs. All of them were adults, 9 being males and 6 females. With the exception of the 20-year old University student whose case history was previously given in this paper, all the other patients were past the age of 30 years, 4 being in the third decade of life, 2 in the fourth decade, 6 in the fifth decade, and 2 in the sixth decade. None of these patients complained of chest symptoms at the time of admission to the clinic, nor were there any chest complaints in their past histories. Discovery of the cases was made by the fluoroscopist in practically every instance. Chest roentgenograms revealed these multiple discrete calcifications and there were noted enlarged tracheobronchial lymph nodes in every instance, 13 out of the 15 cases showing definite calcification together with the enlargement of these nodes. In only 2 cases was there a family history of tuberculosis admitted by the patient, the University student being one but he had not been exposed to any active case of the disease, while the other, a female aged 58 years, stated that one of her sisters expired at the age of 57 years from intestinal tuberculosis.

Altho we do not have definite pathological proof of the origin of these calcifications, several authors have made studies of these cases and have stated that the causative agent is the tubercle bacillus. After the invasion of the tracheobronchial lymph nodes by tubercle bacilli and the formation of definite tubercles within these nodes, a rupture of a tubercle into the thoracic duct or one of its smaller lymphatics may take place and several tubercle bacilli enter the lymph. These organisms would then be borne by the lymph stream through the thoracic duct into the pulmonary blood circulation. The bacilli may then become arrested in the interalveolar tissues where tubercles form. However, the number of these bacilli is small, so that clinical symptoms are usually entirely absent. The tubercle undergoes the usual changes and eventually may calcify. The discovery of the calcification is usually accidental at some time thereafter, when the individual is undergoing a complete routine physical examination, which must necessarily include fluoroscopy or roentgenographic examination of the chest. What proportion of the lesions calcify or undergo resolution and fibrosis is not known.

These types of calcification are known to be rare discoveries, even in Tuberculosis Sanatoria where the incidence apparently is even less than in the average Out-Patient Clinic. It is unfortunate that final proof of the origin of these nodules is not at hand. Most of the evidence, especially the constancy of the association of calcified lymph nodes, points to the theory expressed above. It is perfectly clear that they are of little or no clinical significance; the finding of such miliary calcifications should occasion no disturbance in the mind of the physician nor any change in his conduct of the patient's illness.

References

1. Bell, E. T.
Miliary tuberculosis
A. Textbook of Path. 1934, 151-153.

2. Billard, E. W.
Hematogenous tuberculosis
N.Y. State Jr. of Med., Sept. 1939.

3. Courville, C. B., and Evans, H. S.
Residual lesions in healed tuberculous meningitis
H.S. Bull. of Los Angeles Neur. Soc., Sept. 1937, 2, 125-131.

4. Crueze, Aune P., and Kresser, H.
Pulmonary myoses caused by penicillium crustaceum
J.A.M.A., July 1, 1933.

5. Drolet, G. J.
Incidence among children in N. Y. City; survey of 14,699 children tuberculin tested in hospitals or attending clinics 1930-1932
Am. Rev. of Tuberc., July 1934, 30, 1-32.

6. Ernst, E. C.
Roentgenologic aspects of silicosis
Radiology 30, 3-38.

7. Fish, R. H.
Chronic tuberculosis in children
Arch. Dis. of Childhood, Feb. 1937, 12, 1-24.

8. Friedman, Lewis J.
Acute miliary tuberculosis
Text. of Diag. Roent. 1937, 335-341.

9. Ghon, A., Kudlich, H., and Schmiedl, S.
Die veränderungen der lymphnoten in den venenwinkeln bei tuberkulose und ihre bedeutung
Ztschr f. Tuberk. 1926, 46, 1-97.

10. Hickling, R. A.
Tuberculous splenomegaly with miliary tuberculosis of the lungs
Quart. Journ. of Med., 1938, 7, 263-269.

11. Krause, G. K.
Pathology and pathogenesis of pulmonary tuberculosis
Piersols Cyclopedia of Med., Vol. XI, 1934, p. 232.

12. Lanza, A. J.
The present status of silicosis
The Ohio Med. Journ., Sept. 1939

13. Lanza, A. J., and Vane, R. J.
Industrial dusts and the mortality from pulmonary tuberculosis
Am. Rev. of Tuberc. 1939, 419-438.

14. Lincoln, Edith M.
Hematogenous distribution of tuberculosis in children
Am. Jounr. Dis. of Childhood, July 1935, 50-84.

15. Mallory, T. B.
Case record of 53 year old male who died of miliary tuberculosis
New England Journ. of Med. June 11, 1936.

16. Miller, J. A.
Benign hematogenous tuberculosis
Annals of Int. Med. 1934, 8, 243.

17. Nalbout, J. P.
Pulmonary tuberculosis in infancy, childhood and adolescence
Am. Rev. of Tuberc., Oct. 1934, 30, 458.

18. Osler, Sir Wm., and McCrae, Thomas
Pulmonary tuberculosis
The Principles and Practice of Med., 1923, 155-231.

19. Pinner, Max
Hematogenous (non-miliary) pulmonary tuberculosis
Am. Jounr. Roentgen, April 1934, 31.

20. Pomeranz, R.
Chronic nickel poisoning and production of tuberculosis
Am. Rev. Tuberc., Aug. 1938, 38, 252.

21. Rigler, Leo G.
Pulmonary tuberculosis
Outline of Roent. Diag. 1938, 86-94.

22. Rubin, Eli H.
Hematogenous tuberculosis in the adult
Am. Rev. of Tuberc. 39, 557-586.

23. Sayers, R. R., and Meriwether, F. V.
Miliary lung disease due to unknown cause
Am. Journ. of Roent., March 1932.

24. Snicler, S. H.
Tuberculosis of childhood type
Dis. of the Chest, Dec. 1938, 4:20

25. Stewart, C. A., Harrington, F. E., and Myers, J. A.
The Lymanhurst classification of tuberculosis
Am. Rev. of Tuberc., 30, 588-592.

26. Sweany, H. C.
On the nature of calcified lesions,
Am. Journ. of Roent., Aug. 1940.

27. Walton, C. H. A.
Racial incidence in province of Manitoba
Am. Rev. of Tuberc., Aug. 1935, 32, 183-195.

28. Waters, B. H.
Miliary tuberculosis
Tice Practice of Med., Vol. 2, 569-575.

29. Wessler, H., and Jaches, L.
Acute general miliary tuberculosis
Clin. Roentg. of Dis. of the Chest, 1923, 116-126.

30. Wilson, G. S.
Tuberculus bacillaemia
Med. Res. Council Special Report Series, No. 182, London, 1933.

30. Zavod, Wm. A.
Hematogenous pulmonary tuberculosis,
Jour. Am. Med. Ass., Nov. 20, 1937.

V. GOSSIP

The last time I wrote these lines everyone was full of the Christmas Spirit. Christmas is over, but there seems to be a spirit of good feeling around the old place...The New Year started well at the Center for Continuation Study with a highly publicized course for Executive Housekeepers. The average woman is a housekeeper of sorts but these women, and a few men, have actually made a science of it. The executive part of their job consists of training other people to do the job in the simplest, most effective way. They have a variety of duties. They must be able to identify all the common household vermin and know the agents which will do the trick. We had one afternoon program in applied entomology by two representatives of Dr. Riley's division at the Farm School. Another day we concerned ourselves with the purchase of textiles by specification and learned how to clean rugs. Linen control is apparently the most difficult part of a housekeeper's job. In hotels it is simple because the housekeeper knows as soon as you check out what you have stolen. In hospitals linen is used lavishly in some parts and sparingly in others. Painting also comes under the housekeeper's supervision. In regard to training janitors, sometimes called porters, Minneapolis Public School System has the best school in the country. Would-be janitors are first given an intelligence test to see if they can comprehend orders and situations. Next, there is a personal interview to learn the type of individual who is applying for the job. From the standpoint of public relations the janitor may be the most important man in the organization. After the candidate starts to work the training begins. He gets one month on sweeping, one month on cleaning vitreous ware, etc. When he finishes the apprentice training, he then starts to school at Boys' Vocational High School in order to learn the engineering part of his job. A janitor of a high school must have a chief engineer's certificate. We had 42 housekeepers take the course and it looks as if many universities will soon offer the basic training course in executive housekeeping to be followed by an internship in a hotel or hospital. The next course at the Center will be in Ophthalmology, from Jan. 20 to Jan. 25. This will be followed by the course in Hospital Administration and Uterine Bleeding. The February program will also include medical social service and dietetics.....The Bulletin received several Christmas messages, including one from Bacteriologist Milan Novak of the University of Illinois, who expressed pleasure at being able to keep in touch with his associates at Minnesota, and another from Obstetrician and Gynecologist Charles McLennan, of the Deep South, who asks for bigger and better gossip columns and less WPA book reviews.....The program of the Minnesota State Medical Association for January includes a discussion of respiratory subjects. Among others there will be contributions by Dean Diehl and Wesley Spink on the common cold and the treatment of pneumonia. The radio program includes the common cold, influenza and pneumonia. These packets of worthwhile, up-to-the-minute information are supplied without extra charge to the membership of the State Association. Each person must write for a packet and nearly 500 physicians are cooperating in this study program each month.....Health Service Head, Ruth Boynton, was reelected president of the American Student Health Services Association at Ann Arbor, during the Christmas Holidays. Both Drs. Boynton and Diehl have headed this organization and both of them have been re-elected. Ruth Boynton's birthday was also a matter of great elation during the holiday season, which reminds me of a current expression credited to Fanny Brice, who is supposed to have said on her recent birthday, "It's always a great surprise for me to learn how old I am for my age."....In Life Magazine you will soon find a spread on intern training as the reporter and photographer saw it at Minnesota. Most of the scenes were taken at the Minneapolis General Hospital, which, by the way, now has a Superintendent of its own in the person of Dr. Pollard, who has guided the institution during these past few years.

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