# A CASE OF PULMONARY INFECTION WITH AN ACIDFAST ACTINOMYCES.*

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THE number of interesting cases reported under the names of *pseudotuberculosis cladothrichica*, *pseudotuberculosis streptothrichica*, *actinomycosis atypica pseudotuberculosa*, together with the attempts of Gasperini, Levy and his pupils, Lachner-Sandoval and Neukirch, to establish the botanical position of the so-called streptothrices on morphological and biological grounds, justifies the report of another similar case. It must be stated in the beginning that owing to the absence of cultures and animal inoculations exact species identification is impossible, yet from the morphology and tinctorial peculiarities, as well as the nature of the lesions produced by the organism, it is highly probable that we have to deal with a pathogenic actinomyces similar to the ones described by Eppinger, Aoyama and Miyamoto, W. G. MacCallum, Schabad, and others.

## CLINICAL HISTORY.

J. C., white male, 19 years of age, was admitted to the Garfield Memorial Hospital, Washington, D. C., in 1901. The clinical diagnosis was diabetes mellitus. The patient was under observation in the hospital for the greater part of the time, although he returned occasionally to his parents, sometimes remaining with them for a month or two. There was very little change in his general condition from his first admission in 1901 to within a few weeks of his death in March 1903. He was extremely emaciated, very feeble, and presented the classical symptoms of diabetes mellitus in the young. During the last six months of his life he complained of pain in the left infraclavicular region. Physical examination of the chest made at intervals by Doctors Claytor, Deale, Cook, and Morgan revealed puerile breathing over both lungs with more harsh breath sounds over the left bronchus. Patient rarely coughed and examination of the scanty sputum three months before death was negative for tubercle bacilli.

*Blood.*—Average red corpuscle count 4,580,000 per c.mm. Hemoglobin 80 per cent. Leucocytes ranged between 7,500 and 12,000 per c.mm. Differential counts disclosed a slight lymphocytosis. Bremer's reaction obtained. Fat not demonstrable with osmic acid.

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*Urine.*—Quantity in 24 hours, 2,500 to 3,500 c.c., clear and pale straw in color; reaction, acid; specific gravity, 1035 to 1040; glucose, 3.5 per cent to 8.0 per cent in samples from urine collected in 24 hours. Acetone and diacetic acid present (November 1901 to March 1903). A faint trace of albumen and hyaline cylinders were frequently found.

The amount of sugar eliminated, the presence of acetone and diacetic acid were not appreciably influenced by rigid diet or medication (codeine, arsenic, etc.). On the evening of March 14, patient became delirious, the delirium passed into coma during which there was a marked odor of acetone upon the breath, and death occurred at 5 A. M., March 15.

AUTOPSY.

The autopsy was held four hours after death.

Body of slender build and extremely emaciated. Rigor absent. Numerous hypostases. Skin dry and glossy. Abdomen distended. Subcutaneous fat scanty and pale yellow; abdominal muscles thin. Peritoneal cavity contains the usual amount of clear serous fluid; layers of peritoneum smooth and glistening. Transverse colon prolapsed.

Costal cartilages and ribs soft and flexible.

Pleurae present no adhesions and cavities contain no excess of fluid.

*Right lung.*—An area of consolidation about the size of a hen's egg is found in the upper lobe. The pleura over this area is dry and lustreless. On section the consolidated portion is grayish yellow in color with scattered whitish opaque nodules. There are central disintegration and softening, with the formation of a small cavity of irregular outline and with shaggy walls, which contains a thin, odorless, grayish-yellow, opaque, pus-like material. The remainder of the lung is pale grayish white, crepitant, with a rather moist cut surface. Well marked carbon deposit.

*Left lung.*—Crepitant throughout, slightly edematous at base.

*Pericardium.*—Smooth and glistening; about five c.c. of clear fluid in cavity.

*Heart.*—Small. Weight 287 gm. Subserous fat abundant. Right side of heart is filled with mixed clot, which is continued into pulmonary artery as a simple red clot. Fluid blood in left heart. Left ventricle wall measures 1.2 cm. Myocardium pale. Mitral valve presents a marked thickening and retraction of posterior leaflet, while on the anterior leaflet there is a yellow, opaque, raised patch about six mm. in diameter. One of the tricuspid flaps presents a similar patch. Aortic and pulmonary valves are normal. Coronaries patulous. Aorta contains numerous yellow, opaque, slightly raised patches of sinuous outline.

*Spleen.*—Slightly enlarged. Weighs 210 gm. On section the Malpighian bodies and trabeculae are easily visible. Pulp is dark red, very little adhering to the knife.

*Kidneys.*—Moderately enlarged. Perirenal fat abundant. Right weighs 230 gm.; left weighs 240 gm. Stellate veins injected. Surface smooth. Sections with moderate resistance. Cortex seven mm., vessels prominent, labyrinth of mottled pale yellow hue. Pyramids, purple red. Capsule strips easily.

*Liver.*—Uniformly enlarged and weighs 2750 gm. Surface smooth and mottled with large areas of a deep yellow color. Section: consistence not increased; similar yellow patches seen on cut surface. Gall bladder distended with brownish yellow bile; biliary channels patulous.

*Stomach.*—Enlarged and distended. Colon enormously enlarged and slightly thickened. Caliber of small intestines equal to that of normal adult colon. Mesenteric glands enlarged, white, and soft.

*Pancreas.*—Small, soft, and flabby. In the substance of the tail there is a soft hemorrhagic area, 1.5 cm. in diameter. The parenchyma is moderately atrophic. Interstitial tissue not increased. Weight 67 gm.

*Bladder* distended, containing 1056 c.c. of urine. Wall extremely thin.

*Brain and membranes.*—Excess of subarachnoid fluid. Blood vessels of pia injected; arachnoid opacities well developed. Substance of brain and medulla everywhere normal in appearance.

*Microscopical examination of the pus from the cavity in the right lung.*—Smears were fixed by heat, stained with Ziehl's carbolfuchsin heated to the point at which steam was given off and kept there for five minutes, followed with Gabbet's solution. On examining with $\frac{1}{12}$-inch oil immersion, numerous large masses of tangled bright red threads are seen on a background consisting of moderately numerous polymorphonuclear leucocytes, large and small mononuclear cells with sky blue nuclei and colorless or very light blue protoplasm. The individual threads vary in width from two to three or four times the width of the tubercle bacillus; they possess true branches which are given off at right or acute angles. No clubs or bulbous extremities are observed. While the filaments are usually interwoven into a colony of indefinite shape and outline, quite frequently a decided radiate arrangement is demonstrable. The protoplasm of the filaments stains a clear red, but is frequently interrupted by clear spaces, and the free ends of some filaments are almost colorless. On the other hand a tinge of blue is almost never found in any of the filaments. The colonies are so large that they can be seen easily with a $\frac{2}{3}$-inch objective, and the beading of the filaments is so clean cut that it can be seen without any effort through a $\frac{1}{6}$-inch lens.

HISTOLOGICAL EXAMINATION.

Brain and medulla apparently normal. There are numerous small and large vacuoles in the epithelial cells of the kidney and liver; otherwise these organs are normal. Mesenteric lymph nodes hyperplastic. Slightly enlarged Malpighian bodies in the spleen. The pancreas shows marked atrophy of the glandular lobules, but no appreciable changes in the epithelial cells. Interlobular fibrous tissue not excessive. The islands of Langerhans are apparently normal in size, number, and architecture. Sclerosis and hyaline degeneration are wholly absent.

*Wall of cavity in right lung.*—On examining a large section stained with hematoxylin and eosin and taken from the lung surrounding the cavity, there are seen with the naked eye deep blue roughly circular areas, about four mm. in diameter, surrounded by a zone of bright pink airless tissue. Around this the lung is porous and of a more delicate pink hue. The blue areas correspond to collections of cells, largely polymorphonuclear leucocytes, among

which a few alveoli plugged with fibrin are seen. In general the alveolar outline is indistinct, yet in sections treated by Weigert's method for elastic tissue the alveolar scaffolding is present, although very greatly fragmented. While many of the polymorphous nuclei are well preserved, there is a marked tendency to karyorrhexis, and fine chromatin droplets are sprinkled throughout the nodule. Larger cells with more faintly staining, single nuclei and a thin rim of pink protoplasm are not infrequent. By the confluence of such areas, large irregular patches measuring 1.5 cm. to 2 cm. are formed in which groups of aveoli filled with fibrin and leucocytes alternate with large dense collections of polymorphonuclear leucocytes. In sections stained by Weigert's fibrin method numerous tangled masses of branched and sometimes beaded organisms are found in the cellular areas. In fact, wherever a dense collection of polymorphonuclear cells is found one can almost invariably demonstrate the delicate filaments of the actinomyces. Other organisms are not present. Numerous attempts to stain the organisms by methods employed for the tubercle bacillus were unsuccessful and genuine tubercle bacilli were absent. Controls made at the same time with the tuberculous tissues in the laboratory offered no especial difficulty in staining or finding the bacilli.

In the consolidated lung surrounding the nodules the fibrinous exudate is very abundant. Some alveoli contain chiefly fibrin in which a few leucocytes and large mononuclear cells are entangled. Many contain moderately numerous leucocytes and few mononuclear cells intermingled with less fibrin, and in a few alveoli leucocytes predominate, only a few small fragments of fibrin remaining. Strands of fibrin passing from one alveolus to another through the pores of Kohn are frequently encountered. There is no trace of organization of the exudate.

In the adjacent air-containing tissue, the alveoli are partially filled with a finely granular, sometimes homogeneous, albuminous material, a few polymorphous leucocytes, and a varying number of large mononuclear cells. The albumen stains light pink with eosin and does not stain by Weigert's method for fibrin. The leucocytes are fairly numerous in some alveoli, very scarce in others. The mononuclear cells present a great diversity of appearances. Some are clearly derived from the alveolar epithelium, for in many alveoli the lining epithelium is distinctly cuboidal or polygonal in outline, and similar polygonal cells possessing a nucleus fairly rich in chromatin surrounded by a moderate amount of pink protoplasm with just a suggestion of violet are found lying free near the center of the alveolus. Others have a smaller, eccentric, deep blue nucleus and clear, relatively abundant, almost colorless, protoplasm. A third variety is represented by a much larger cell with a large vesicular nucleus, frequently situated at one side and surrounded by abundant, faintly staining protoplasm, which contains a few or sometimes many small round brownish black pigment masses. Potassium ferrocyanide followed by hydrochloric acid has no effect upon this pigment. Occasionally large cells with two or three nuclei are found, but Langhans' giant cells are never encountered. Except when bounded by an interlobular septum, there is no sharp demarcation of the nodular consolidated areas from the edematous air-containing lung, the leucocytic infiltration passing gradually into the fibrinous zone, and the latter insensibly giving place to inflammatory edema.

The small bronchi and the bronchioles are the seat of intense inflammation. Desquamated epithelial cells, leucocytes, and fibrin occupy the lumen. The bronchioles are usually plugged with leucocytes and frequently only vestiges of a bronchiole remain—a strip of columnar epithelium and a few muscle fibers embedded in collections of leucocytes. The filaments of the actinomyces are usually present within these structures, the number of colonies bearing a direct relation to the amount of destruction in the bronchial walls. While it is not possible to demonstrate bronchioles within many of the nodules composed of leucocytes, the occasional presence of a row of epithelial cells and remnants of muscle fibers together with the intimate relation to the colonies of the actinomyces reveals the bronchogenic nature of the process.

The alveolar capillaries contain an excess of polymorphonuclear leucocytes but are not engorged with red corpuscles. In the areas of leucocytic infiltration and fibrinous exudation, many of the capillaries are filled with hyaline thrombi. Save for the presence of an increased number of leucocytes, small amount of fibrin, and an adventitial mantle of small mononuclear cells, the vessels of medium and large caliber present no striking changes. Filaments of actinomyces are not demonstrable in any of the vessels.

The lymphatic vessels in the perivascular and peribronchial tissues and in the interlobular septa are markedly dilated and contain numerous polymorphonuclear leucocytes, large and small mononuclear cells with varying quantities of fibrin. The actinomyces is not present.

Although the interlobular septa and the alveolar walls are much thickened, careful staining after the methods of Van Gieson and Mallory fails to show any increase in the fibrillar connective tissue. The septa are widened by the presence of fluid and fibrin, and by the dilated lymphatics. The apparent thickening of the alveolar walls is due solely to the distended capillaries.

On the pleural surface there is a thin fibrinous exudate. The subpleural connective tissue is edematous. There is very slight carbon deposit.

Sections taken from other portions of the right lung and from the left lung show a slight degree of edema, but are otherwise normal, no organisms being demonstrable. The bronchial glands contain a small amount of carbon. Neither the actinomyces nor the tubercle bacillus can be found in them.

*Distribution of the organisms.**—The filaments of the actinomyces are found only in the pus in the cavity, and in the bronchopneumonic tissue constituting the walls of the cavity. In the latter the organism is present in the small bronchi, in the bronchioles, and in the air-sacs filled with leucocytes. In the alveoli containing fibrin or serous fluid the filaments are rarely found, and in the blood vessels and lymphatics they are never seen. The best method of demonstrating them in the tissues in this case is some modification of Gram's method, preferably Weigert's. Concerning the morphology of the fungus in the tissues, there is no deviation from its appearance in the pus. Tangled masses of branching threads, sometimes in a distinct radiate

* As far as we know neither the pus nor the tissues contained any organisms besides the actinomyces. For this reason the tissue changes can hardly be ascribed to mixed infection.

arrangement with beaded filaments in the more central portions are the usual forms encountered. In a painstaking examination of hundreds of such colonies no clubbed forms were observed. The fragmentation or plasmolysis is never so extreme as to suggest micrococci. Sections stained with the usual nuclear and combination stains, as well as with methylene blue, bismarck brown, sudan III, safranin, or the various methods for the tubercle bacillus give no clue to the presence of the actinomyces.

## SUMMARY.

From the foregoing description it will be seen that the pathogenesis of the process is about as follows: entrance of the actinomyces into the respiratory passages and lodgment in the bronchioles where an active emigration of leucocytes into the lumen of bronchioles and especially into the adjacent alveoli is incited; farther removed from the organisms the inflammation is less intense and is expressed by a fibrinous exudate; still less is the stimulus felt in the more distant portions of the lung and an inflammatory edema results; by the confluence of the nodules composed largely of leucocytes, and subsequent softening of the resulting mass, cavity formation ensues. This coincides in essentials with Ribbert's investigations and views on bronchopneumonia in general.

## COMPARISON WITH SOME SIMILAR CASES.

While information as to the biological characters of this organism is wanting, the close agreement in morphology and staining properties with the organisms of Aoyama and Miyamoto, Schabad, and others, and especially the similarity in the lesions make the relationship or even identity highly probable. A peculiarity in the acid-resisting properties of this organism is the failure to demonstrate it in sections of the hardened tissue by methods designed for the tubercle bacillus. This is entirely in accord with the experience of Berestnew, working with *Actinomyces asteroides Eppingeri*, *Actinomyces farcinica*, as well as with an acidfast actinomyces isolated by him. Flexner and Schabad record parallel experiences.

## AS TO NOMENCLATURE.

Savaugeau and Radais have shown that the word "streptothrix" was first used by Corda, in 1839, for a mould wholly

different from the organisms now designated as streptothrices. Having this in mind Gasperini and Lachner-Sandoval have urged the adoption of the group name "actinomycetes" (actinomyces, Harz 1877) on the grounds of priority. Lachner-Sandoval also pointed out that the true *Oospora* differ essentially from the actinomycetes, and, therefore, the latter cannot be included in the genus "oospora." It is hardly necessary to consider the designation "Nocardia," since the permanent adoption of a man's name for a group of microorganisms is without a precedent in the history of bacteriology. There is certainly little desirable in a nomenclature which is historically inaccurate, etymologically meaningless, and of no descriptive value. Actinomyces, consequently, has priority in its favor, and it is also to be noted that it is etymologically preferable since the radiate development of the colonies is a constant and striking feature. Schabad, following Berestnew, erects a subgroup *Actinomyces atypica* for those organisms which do not develop clubbed ends and consequently do not form "Drusen;" are not present as sulphur granules in the pus; and which are acidfast. He affixes *pseudotuberculosa* to those which produce a tubercle-like disease in the lower animals (Eppinger, Aoyama and Miyamoto, MacCallum, Schabad, Horst, and Stokes). While "pseudotuberculosa" is descriptive of the pathological changes, and also implies the relation of the organism to the tubercle bacillus, it has already been used for so many diverse processes that its omission would be in the interest of simplicity in terminology. Although in the majority of instances clubs have not been encountered in the study of these particular organisms, MacCallum has shown that even typical "Drusen" may be a part of the life cycle of some members of the group.

While the pathological picture is not a uniform one, in the majority of instances there is an accumlation of grayish pus in a pulmonary cavity of extremely irregular outline, and with shaggy walls. The proliferation of fixed connective tissue cells frequently does not occur (Aoyama, Schabad, Buchholz), and consequently encapsulation by a comparatively smooth, thick, fibrous wall as in the usual form of tuberculosis is absent. It may be said that the gross appearance stands between a nodular broncho-

pneumonia on the one hand and caseous pneumonia on the other, the bronchopneumonic nature of the condition being expressed by the opaque grayish nodules surrounding the pus collection, while the tendency of the nodules to coalesce, soften and break down leaving an excavation with ragged walls and accompanied by fibrinous and gelatinous pneumonia in the contiguous tissue resembles more or less closely the caseous pneumonic type of acute tuberculosis. The absence of true caseation and the failure to find tubercle bacilli are, of course, the distinctive features. There is almost always an accompanying pleurisy of varying degree. The two extremes are probably the empyema encountered by Birt and Leishman, and the slight dryness and opacity of a small area of the visceral layer in the case here reported.

Turning for a moment to the historically older form of actinomyces, we find a miliary "pseudotuberculosis" caused by a club-bearing actinomyces, described by Pflug in 1882. In Boström's classical work on human actinomycosis reference is made to an autopsy on a man dead of phthisis, at which pneumothorax, pleurisy, and a small cavity in the right lung were found. The cavity was lined by a necrotic villous wall and contained a gray-red turbid fluid. In this fluid and in the necrotic tags of tissue projecting into the excavation grayish white granules were present. On microscopical examination the granules were seen to be composed of densely packed, long, usually spiral, genuinely branched filaments of radial arrangement and without thickening of the free ends. Boström regarded this as a very recent invasion of the lung by an actinomyces, and yet many such cases have been reported in following years under the head of pulmonary streptothricosis. Orth in his textbook, describing pulmonary actinomycosis and having in mind the organisms of the *Actinomyces bovis* group, gives as characteristics the formation of confluent abscesses with a tendency to involvement of the pleura, vertebral column, pericardium, diaphragm and peritoneum. The majority of these lesions are reproduced by the acidfast actinomycetes and by those which do not under ordinary conditions form clubs. Thus Birt and Leishman found empyema and pericarditis. An excellent example of the burrowing character of the

lesions is found in Schabad's case, where in addition to the pulmonary cavity, there were pleurisy, caries of the adjacent ribs, and an intermuscular abscess. Quite recently Sanfelice in a work on streptothrix-tuberculosis, draws the closest analogy in the biology of certain actinomycetes and the tubercle bacillus, and in the histology of the lesions produced by them. Employing intravenous injection of some air actinomycetes, he produces in dogs cavity formation in the right lung without a generally disseminated "streptothricosis." The histogenesis of the lesions is almost identical with that of true tubercles; giant cells, epithelioid cells, a mantle of wandering cells, and acidfast bacillary forms of the fungus being found on microscopical examination. This is somewhat different from the results obtained by other investigators, many of whom place the process among the inflammatory necrotic conditions rather than among those of the productive or granulation type. In the cases of Aoyama and Miyamoto, Norris and Larkin, and in the present case the lesions were essentially acute inflammatory and necrotic in nature.

There is, therefore, a large group of acidfast actinomycetes without clubbed extremities, many of the individual organisms differing fundamentally in their cultural characters and comparative pathogenesis for the laboratory animals, nevertheless producing similar or almost identical lesions in the human lung. On the other hand two actinomycetes with the closest possible biological relationship may produce widely different pathological pictures. It is needless to refer to the possible variation in the virulence of the organisms and the resistance of the host. The similarity in the pulmonary lesions produced by the many acidfast actinomycetes as well as the imitation of the pathological anatomy and course of the conditions due to the ordinary club-bearing varieties is certainly more than a coincidence.

The interest in this group of cases lies in the extremely wide geographical distribution and in the possibility of diagnosis during life (Lubimow, Birt and Leishman, Aoyama and Miyamoto, Schabad, and Warthin). The case in hand claims attention in being an exception to the rule that all diabetic phthisis is tuberculous. To what extent the glycemia predisposed to or affected

the course of the disease is not known. At the same time the especially luxuriant growth of the pathogenic actinomycetes in media containing two per cent of glucose is very suggestive.

Finally, it remains for me to express my indebtedness to Dr. J. B. Nichols for the control of the material, and especially to thank Dr. MacCallum for stimulating and guiding my interest in this group of cases.

## REFERENCES TO RECENT CASES.

(The literature can be collected so easily from the writings of Schabad and Horst, that it is only necessary to mention new works bearing upon the subject.)

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## EXPLANATION OF PLATE 15.

A young colony of the organism from one of the bronchopneumonic nodules. The radiation, branching, and slight beading of the filaments is clearly shown. The predominating cells are polymorphonuclear leukocytes; large mononuclear cells are figured, and to the left there is a row of alveolar epithelial cells. Section is stained with carmine and Weigert's method for fibrin. Magnification about 1500.

PLATE 15.