PRACTICAL MEDICAL MYCOLOGY

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Practical Medical Mycology

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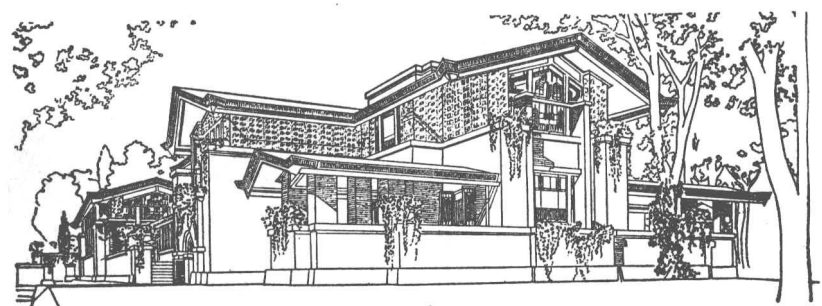

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Chapter 1

INTRODUCTION

THERE ARE MANY fungi capable of provoking disease in the human. Some of these fungi are purely saprophytic; therefore they are referred to as nonpathogenic. These fungi are capable of producing disease in man even though they do not invade the tissues of the host. Some saprophytes are poisonous; others produce airborne spores that are capable of acting as allergenic substances in a manner similar to pollens. There are other fungi that are parasitic; hence they are spoken of as pathogenic, because they invade and destroy tissue.

The very nature of a mycotic infection to proceed slowly at first and then become accelerated would suggest that the causative fungi at first rely on dead or injured tissue to grow, that they have a slight inherent invasive power, and that they are able to spread only after some change has taken place in themselves or in their environment. There has not been any evidence to date that fungi increase in virulence with the progress of an infection. It is reasonable to assume, therefore, that during the course of a mycotic infection the tissues of the host become altered. This alteration in the tissues may be due to the liberation of fungus toxins, or to the development of hypersensitivity on the part of the host to the fungi or their breakdown products.

There are four classes of fungi: the Basidiomycetes, the Ascomycetes, the Phycomycetes, and the Fungi Imperfecti. The class, Basidiomycetes, comprise in part the large, fleshy fungi with compact mycelium; for example:

the mushrooms and the puffballs. There are, however, more minute forms included in this class; these are the plant parasites, the smuts, and the rusts. The Ascomycetes, the largest class of fungi, include many plant pathogens as well as molds that are of interest and importance to the bacteriologist. This class is characterized by spores that are formed in a membrane or sac called an ascus. The Fungi Imperfecti possess the characteristic mycelium of Ascomycetes; they produce spores similar to those formed by the Ascomycetes but they do not form ascospores, or at least ascospores have not been observed. The Phycomycetes are the most primitive class of fungi. They develop loose, non-septate mycelium. Common examples of this class are the species of the genera of *Mucor* and *Rhizopus*.

The molds of interest to the clinician and the bacteriologist reside, for the most part, in the class of Fungi Imperfecti. The rusts, the smuts, and the poisonous fungi of the class Basidiomycetes, the ergot fungus of the class Ascomycetes, and the species of *Mucor* and *Rhizopus* of the class Phycomycetes, are the exceptions.

Diseases caused by fungi are no longer an unimportant and remote problem in medicine and public health. Data obtained from the latest Vital Statistics Reports show that in the United States mycoses accounted for 0.56 per cent of the total deaths from infectious diseases in 1949. The number of deaths attributed to fungous infections in 1949 exceeded the total of all deaths from infections by protozoa, rickettsiae, and helminths. This trend, if not reversed, will undoubtedly assume greater importance.

Chapter 2

HUMAN INFECTIONS FROM ACTINOMYCETES

AN UNDERSTANDING of the classification of microorganisms according to their natural relationships (taxonomy) is not just an academic nicety. It gives a depth of knowledge which allows the clinician to appreciate more fully the genesis of the disease that each closely or remotely related microorganism creates. Herein has been included a key (Table 1) to the family and the genera of the order of Actinomycetales.[1] The term actinomycete is not used in a taxonomic sense, but is employed in the same manner as the terms yeast or molds might be used, and includes all of the Actinomycetales except the family of Mycobacteriaceae.

TABLE 1

THE FAMILY AND THE GENERA OF THE ORDER ACTINOMYCETALES

A. Family MYCOBACTERIACEAE. Mycelium absent or rudimentary.
   1. Genus *Mycobacterium.*
B. Family ACTINOMYCETACEAE. Mycelium produced. There is disarticulation of filaments of septate mycelium into spores (arthrospores) resembling bacilli and cocci. Conidia not produced.
   1. Genus *Actinomyces.* Anaerobic. Not acid-fast.
   2. Genus *Nocardia.* Aerobic. Partially or not acid-fast.
C. Family STREPTOMYCETACEAE. Mycelium not disarticulated. Conidia develop on proper media.
   1. Genus *Streptomyces.* Conidia in chains from aerial mycelium.
   2. Genus *Micromonospora.* Conidia not in chains; formed terminally, singly or in clusters on conidiophores.

Careful study of the classification of the order of

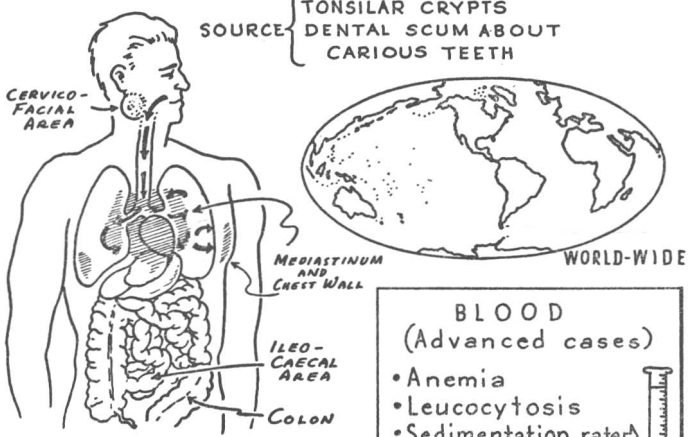
Actinomycetales reveals that there is a close resemblance of the acid-fast actinomycetes (*Nocardia*) to the tubercle bacilli in morphology, pathogenicity, and cultural characteristics.[2] Of the pathogenic actinomycetes the genera of *Actinomyces* and *Nocardia* are of interest to the physician. Strictly speaking the term actinomycosis should refer only to the infections that are caused by the anaerobes *Actinomyces Israeli* and *Actinomyces bovis.* A mycosis caused by a species of *Nocardia* (aerobic and in some instances acid-fast), in the narrow sense, should be referred to as nocardiosis.

Until the appearances of the studies of Erickson,[3] of England, and later Thompson,[4] of the Mayo Clinic, it was the opinion of the majority of investigators that human and bovine actinomycosis were caused by the same aerobic microorganism, and, depending upon the investigator, the organism was referred to either as *Actinomyces bovis* or *Actinomyces Israeli.* However, since the appearance of the sixth edition of Bergey's *Manual of Determinative Bacteriology* in 1948, *Actinomyces Israeli* has been catalogued as the cause of actinomycosis in human beings and *Actinomyces bovis* as the etiologic microorganism of the bovine infection. The cultural differences of these two anaerobic actinomyces, originally described by Erickson in 1940, were subsequently supported by the findings of Thompson in 1950. Herein dogma must not be followed because it seems probable that a small number of human infections have been produced by *Actinomyces bovis* and Thompson himself, recovered one strain of *Actinomyces Israeli* from a bovine source. With the cognizance of these possible exceptions, the discussion of actinomycosis, as the disease occurs in the human, will be limited to the manifestations brought about by the invasion of the organism *Actinomyces Israeli.* A separate section under the heading of nocardiosis will deal

ACTINOMYCOSIS

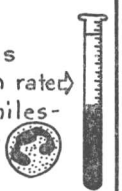
ORGANISM: *Actinomyces Israeli*

SOURCE { TONSILAR CRYPTS
DENTAL SCUM ABOUT CARIOUS TEETH



BLOOD
(Advanced cases)

- Anemia
- Leucocytosis
- Sedimentation rate ⇧
- Pmn. neutrophiles - % increase ⇧



SPUTUM OR PUS

CULTURE	DIRECT MICROSCOPIC
BREWER'S MEDIA (ANAEROBIC)	

"*SULFUR GRANULES*"
gram-positive
(*ANAEROBIC*)
NOT ACID-FAST

TEMPERATURE

- Irregular, spiking.

DIFFERENTIAL DIAGNOSIS

1. Tuberculosis
2. Syphilis
3. Neoplasm
4. Tularemia
5. Osteomyelitis
6. Other mycoses:
   (a) Nocardiosis
   (b) Coccidioidomycosis
   (c) Blastomycosis (N. & S. American)
   (d) Sporotrichosis

with infections produced by various species of the genus *Nocardia.*

ACTINOMYCOSIS

Actinomyces Israeli commonly exists as a saprophyte in the oral cavity and has never been isolated from soil or vegetation. In the mouth the organism is commonly present in and about carious teeth, dental scum, and the crypts of tonsils. From such strategic positions the organism may spread locally, giving rise to the cervico-facial type of actinomycosis, or to be swallowed to infect eventually intestines and abdominal organs, or to be inhaled or aspirated into the lungs to incite a pulmonary infection. The primary lesion of actinomycosis in man occurs most frequently in the region of the face and neck. Second and third in frequency are the primary lesions that involve, respectively, the abdominal cavity and the lungs.

Diagnosis

Clinical Picture: ***Cervico-facial actinomycosis*** is the commonest form of the disease and ordinarily follows neglect of carious teeth, dental extractions, fractures of the mandible, or injury to the face. From these sites the organism, that was formerly present as a saprophyte in the buccal cavity, is introduced into the tissues. The jaw bone that is so frequently involved in cattle is not as commonly affected in the human. The infection may spread to the paranasal sinuses, the salivary glands, the orbit, the neck, or the mediastinum. The skin and subcutaneous tissues of the involved site assume a swollen, woody hardness with a dusky red hue. Eventually from this chronically inflamed mass, which is riddled with intercommunicating sinuses, appear fistulous, suppurating ulcerations.

In the ***abdominal type of actinomycosis*** the primary

lesion frequently has its origin in the neighborhood of the appendix or cecum; consequently the symptoms of acute or subacute appendicitis are produced. From the ileocecal region the infection spreads to invade the neighboring structures, and in the female a large number of cases involving the fallopian tubes and ovaries have been reported. When the colon becomes infected the clinical picture closely resembles that of carcinoma. The primary abdominal lesions frequently are responsible for the development of secondary liver abscesses, but actinomycotic hepatic abscesses have been reported in patients without a demonstrable primary intestinal infection. Most cases of the abdominal type are eventually accompanied by chronically draining sinuses with local involvement of the abdominal muscles and subcutaneous tissues.

The primary lesions in ***pulmonary actinomycosis*** are usually bilateral and basal, but may occur unilaterally in any portion of the lung. From the primary site a granulomatous process is induced which usually extends to the mediastinum, pericardium and heart, and/or to the pleura producing pleural pain and occasionally pleural effusion. Eventually the organism invades directly through the pleura to the chest wall giving rise to numerous draining sinuses. Infrequently the pulmonary infection will be the result of a spread from a primary focus in one or more of the ribs. Rarely in any instance of pulmonary actinomycosis is there a spread to the regional lymph nodes, but metastasis by the blood stream does occur.

In both the abdominal and pulmonary types of actinomycosis, as the disease progresses, the patient becomes anemic, presents a leucocytosis and an elevated sedimentation rate, loses weight and strength, and has a spiking temperature with night sweats.

It has been emphasized that actinomycosis primarily

involves the cervico-facial region, the abdominal cavity, and the lungs, and that the infection spreads by continuity affecting contiguous structures. Occasionally spread occurs via the blood stream, and on such occasions any part of the body may become involved. Although skin lesions are usually secondary, a few cases of primary actinomycosis involving the subcutaneous tissues have been reported. The same may be said for the endocardium.

Mycology: The diagnosis is established by isolating, from the sputum or pus, the organism in the form of characteristic "sulphur granules." These granules vary in size and shape and have a radiating lobulated structure, and are usually, though not always, yellow in color. They are best observed with a low power microscope lens; yet they are occasionally large enough to be identified with the naked eye or with a hand lens. The interior of the granule does not stand out sharply, but the clubs of the periphery are very refractile and appear as irregular lines marking the borders of the lobules. By crushing the granule between two slides and then staining with Gram's stain, the Gram positive branched filaments can be demonstrated. These branched filaments make up the interior of the "sulphur granules."

Actinomyces Israeli is difficult to culture. The pus or sputum should be washed several times with sterile normal salt solution. Suspected granules should be recovered with a bacteriological loop, washed again in sterile normal salt solution, and then placed in Brewer's thioglycollate media and incubated at 37° C. The colonies that gradually develop appear as fluffy discrete masses of variable size suspended in the media. These colonies, as they increase in size, appear dense with a finely pebbled surface. Mycelia do not project from the surface.

Skin and Serological Tests: A satisfactory antigenic

substance prepared from the organism or from the broth in which the organism has been grown has never been isolated. Therefore, diagnostic skin tests and serological tests, which would be of doubtful value any way for this infection, do not exist.

Treatment

The specific measures of therapy are identical regardless of the location of the lesions. Since any therapeutic schedule must persist for months, if success is to be obtained, the choice of a drug or a combination of drugs must take into account the patient's ability to accept these medicines without concomitant allergic or noxious reactions.

Crystalline procaine penicillin [5, 6] in aqueous suspension, in doses of 600,000 units, should be administered intramuscularly once or twice daily depending upon the severity of the infection.

For those patients who do not respond well to penicillin therapy, sulfadiazine [7] alone or in combination with sulfamerazine, in doses of 1.0 to 1.5 grams every six hours, should be added. As soon as improvement is evident the sulfonamide dosage may be reduced to 1.0 gram, twice daily, and the penicillin discontinued.

If the infection does not respond to penicillin and/or the penicillin and sulfonamide therapy, then aureomycin,[8, 9] 2.0 to 4.0 grams daily, or chloramphenicol,[10, 11, 12] 750 mg. every four to six hours, should be prescribed.

The iodides which apparently hasten the resorption of inflammatory tissue should be administered along with the antibacterial and antibiotic drugs. The official solution of potassium iodide should be used beginning with five drops, three times daily. This dose should be increased by two drops, a dose, a day, until the largest dosage that the patient can receive with tolerance is attained. This

dose should be maintained throughout the period of treatment.

Roentgen irradiation in semi-intensive dosages, administered only by a specialist, should accompany antibacterial, antibiotic, and iodide therapy.

The wisdom of surgical incision and/or excision must be left to the judgment of the attending physician and surgeon, either after or before adequate medical treatment has been given a trial. If there are incised lesions or sinus tracts, they should be irrigated daily with half-strength Lugol's solution, or 1 per cent aqueous solution of gentian violet.

Non-specific measures of treatment are as important for the patient with actinomycosis as they are for the patient with any other chronic infection. There must be prolonged bed rest; long-headedness in the administrations for restlessness and insomnia; provision of a simple, nutritious diet adequate in calories and vitamins; prevention of dehydration by supplying an adequate fluid intake; and vigilance to the care of the mouth, bowels, urinary bladder and skin.

NOCARDIOSIS

In this section the term nocardiosis has been reserved to define infections in man caused by one or several of the species of actinomycetes included under the genus of *Nocardia.* The discussion will be divided into two subheadings: (1) infections caused by the acid-fast actinomycetes; (2) infections caused by the species of *Nocardia* that are responsible for the clinical picture, mycetoma pedis.

1. Infections from Acid-fast Actinomycetes

Although infections caused by these organisms are not common in man, they are of considerable interest scien-

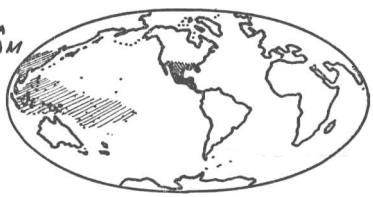
NOCARDIOSIS

ORGANISMS:

1 *Nocardia asteroides* - lung infection

2 *Nocardia madurae* } mycetoma

3 *Nocardia mexicana* }



SOURCE { Organisms present in soil, probably inhaled into lung; may enter foot or hand through injury.

} MYCETOMA; general health good.

BLOOD (ADVANCED CASES)

- Anemia
- Leucocytosis
- Sedimentation rate ⇨
- Pmn. Neutrophiles - % increase ⇨

TEMPERATURE

Irregular-spiking

SPUTUM OR PUS

CULTURE (WASHED GRANULES) VEAL INFUSION AGAR - 1% GLUCOSE

DIRECT MICROSCOPIC

Mycelia

Granules

Aerobe; usually acid fast; gram positive.

DIFFERENTIAL DIAGNOSIS (Pulmonary nocardiosis.)

1. Tuberculosis
2. Other mycoses:
   (a) Actinomycosis
   (b) Coccidioidomycosis
   (c) Blastomycosis (N. & S. American)
   (d) Sporotrichosis
   (e) Cryptococcosis