ABSTRACT

Tuberculosis continues to constitute the principal mycobacterial pulmonary disease. Control measures are known and their effectiveness limited mainly by social and economic factors. Other mycobacterial diseases are not so readily controlled owing to incomplete knowledge of epidemiology, pathogenesis and treatment.

The Runyon classification given in table I developed as cultural characteristics of the "atypical" mycobacteria became known. Groups I and III generally represent pathogenic (significant) species while Groups II and IV are generally saprophytes (not significant) or opportunistic. The occurrence of clinical disease due to atypical mycobacteria is variously estimated as 0.1 to 10 percent of that of tuberculosis. The term mycobacteriosis is commonly applied. The mode of acquisition and transmission of the organisms is not known but man-to-man transmission has not been proved. Atypical mycobacteria generally grow less well on cultures than \textit{M. tuberculosis}. When acid-fast bacilli are found on smears, cultures should be observed for a longer period of time than is usual for \textit{M. tuberculosis}.

Most commonly observed, clinically, are \textit{M. kansasii} (Group I) and \textit{M. intracellulare} (Group III). Mycobacteriosis is more common in males and in advancing age. Other pulmonary disease is commonly present and it is often difficult to distinguish primary from complicating disease. Diagnosis of tuberculosis is commonly made and revised when atypical mycobacteria appear on culture. Clinically, the disease is indolent, tends to wax and wane and responds variably to drugs. Thin-walled cavities give evidence of the breakdown of lung tissue. Disability occurs with some frequency in older males.

Recent experience in 25 cases of unquestioned significance showed 14 in Group I, 2 in Group II and 9 in Group III. By contrast, a group of 30 persons with only bacteriological evidence of mycobacterial infection showed 4 in Group I, 10 in Group II, 10 in Group III and 6 in Group IV. The larger proportion of Group II and IV infections indicated that few among these 30 cases were clinically significant.

Treatment of people with Group I infections is usually similar to that of tuberculosis but ethambutol is especially recommended. Group III bacilli respond poorly to standard drugs and, if progressive, a combination of 4 or 5 anti-mycobacterial agents may be employed. Rifampin is proving useful in
some. Resection is often desirable in localized disease due to Group III pathogens.

Tuberculosis continues to constitute the principal mycobacterial disease of the lungs. With accumulated knowledge of its behavior, epidemiology and treatment, total control of this disease can be envisioned providing social and economic limitations of the application of this knowledge can be overcome. This is not so with the other mycobacterial diseases. The scope of this presentation, therefore, will include those mycobacterial pulmonary diseases which differ in some respects from pulmonary tuberculosis. Major points of difference relate to mode of transmission, epidemiology and treatment.

Several decades ago, the treatment of tuberculosis proceeded without emphasis on cultural identification of the responsible acid-fast organisms, reliance being placed upon smears and concentrates of sputum with the ultimate use of animal inoculation for final confirmation. As culture methods and media improved, laboratories accumulated a number of cultures which differed in their colony morphology from those of M. tuberculosis. The most obvious of these were the chromogens and, for a time, they were regarded with curiosity but little understanding of their significance. Once specific drugs became available for tuberculosis and specificity of diagnosis including drug sensitivity followed, it became evident that people did become ill from the “atypical” mycobacteria. Gradually, the field began to develop both clinically and microbiologically. Although there are now many factors in common, the diseases produced by “atypical” mycobacteria present certain distinctive features. There is still much confusion. Whenever one of these organisms is cultured from clinical material, it is well to decide whether or not it is a pathogen or a saprophyte and whether or not it is the primary cause of the disease process or a secondary invader. It may be noted that mycobacterial diseases affect many organs and systems, but this presentation is limited to pulmonary disease.

The nomenclature of the pulmonary disease is confusing. Many of the patients with mycobacterial diseases are first diagnosed as having tuberculosis and, as such, are included in the count of tuberculous patients for statistical purposes. This is particularly true where data processing equipment is used. In many health departments, on the other hand, the atypical mycobacterial diseases are regarded as distinct from tuberculosis and are removed from the registry upon specific diagnosis and the term mycobacteriosis employed. Clinically, this term is desirable, but it is possible to confuse the morbidity and mortality statistics. This confusion also causes difficulty epidemiologically in knowing what the problem is, whether or not the case rate changes with or differs from that of tuberculosis and how it varies in different parts of the world.

Observations

Terminology of the organisms has been in evolution. Many refer to these organisms as “anonymous,” “unclassified,” or “atypical,” while others take exception to all of these terms. Since these organisms now have names and some semblance of classification, the former two terms are no longer appropriate, but no objection need be raised to the term ‘atypical’ in a clinical sense. Although microbiological details are beyond the scope of this paper, a few observations are in order. In general, these organisms grow less well than M. tuberculosis. When one demonstrates a growth of atypical bacilli, special efforts are needed to clarify the diagnosis and to use microbiological measures appropriate for the suspected species. Patients are frequently
encountered in whom acid-fast bacilli are found on smear, although the same specimen shows no growth on routine culture. This requires the cultures to be observed for a longer period of time and special procedures to be initiated.\textsuperscript{20} Although some regard repeated demonstration of the same organism on culture as a requirement for specific diagnosis, a well documented mycobacterium has been accepted as etiologic on even one culture, provided no other pathogen could be demonstrated.

**Microbiologic Classification**

Atypical mycobacteria are grouped according to the Runyon scheme (table I).\textsuperscript{12} Groups I and III are likely to be primary pathogens while Groups II and IV are commonly secondary ones. There are variations within the groups as to pathogenicity (table II).\textsuperscript{20} In Group I, \textit{M. kansasii} is the major one which is usually significant while there are several significant ones in Group III. Many prefer to use the term Battey-Avium-Swine complex.\textsuperscript{13} The USPHS prefers to refer to all strains pathogenic for birds and swine as \textit{M. avium}. This rarely produces disease in man. The term \textit{M. intracellulare} is then used for strains in this complex which commonly produce disease in man. \textit{M. scrofulaceum} is a Group II organism occasionally of consequence in human disease. \textit{M. fortuitum} is a rapid grower in Group IV which is occasionally implicated in human disease and which has close similarity to \textit{M. abscessus}.

Identification of these organisms frequently requires special procedures including light sensitivity, color production, rapidity of growth, colony characteristics, chemical reactions, biological tests and drug sensitivity.\textsuperscript{21} Phage typing and thin layer chromatography have recently been employed in an effort to characterize these organisms more specifically.\textsuperscript{9} The latter has shown that \textit{M. avium}, \textit{M. intracellulare} and \textit{M. scrofulaceum} correspond closely upon lipid analysis.\textsuperscript{15}

**Epidemiology**

The prevalence of the mycobacterioses is quite variable throughout the world.\textsuperscript{18,21} Estimates are frequently based upon the percentage of \textit{M. tuberculosis} isolates which may be quite inaccurate. From various sources, data are accumulating which suggest that the diseases are quite widespread. From 0.1 percent to 10 percent of the cases of tuberculosis are mycobacterioses, according to various estimates. In the United States, the highest prevalence of disease is in the Southeastern states where Group III (Battey) disease is frequent.\textsuperscript{5,7} In the mid-west and southwest, there are areas where \textit{M. kansasii} is relatively common. In England and Wales, \textit{M. kansasii} is in the lead and \textit{M. xenopi} follows in second place.\textsuperscript{19} In France, Group III bacilli are most frequent both as pathogens and as saprophytes whereas Western Australia notes an occurrence of Group III bacilli with disease about 10 percent that of tuberculosis. Brown et al report a preponderance of Group I organisms among patients from metropolitan New Orleans; at Alexandria, Louisiana Veterans Hospital where most patients reside in rural Louisiana, Group III organisms are more frequent.\textsuperscript{1} The age distribution generally is in the higher decades, and Lincoln has shown that pulmonary mycobacterioses in children are very rare.\textsuperscript{14}

Some epidemiologic data have been developed through tuberculin testing programs in this country.\textsuperscript{5,8} This confirms the
TABLE II

Clinical Classification of Mycobacteria

<table>
<thead>
<tr>
<th>Usually Significant</th>
<th>Usually Not Significant</th>
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</thead>
<tbody>
<tr>
<td>M. tuberculosis</td>
<td>BCG</td>
</tr>
<tr>
<td>M. bovis</td>
<td></td>
</tr>
<tr>
<td>M. kansasii</td>
<td>Low catalase M. kansasii</td>
</tr>
<tr>
<td>M. marinum</td>
<td></td>
</tr>
<tr>
<td>M. scrofulaceum</td>
<td>M. gordoni (&quot;tap water&quot;)</td>
</tr>
<tr>
<td>M. flavescens</td>
<td></td>
</tr>
<tr>
<td>M. avium</td>
<td>M. terrae complex (radish)</td>
</tr>
<tr>
<td>M. intracellulare</td>
<td>M. gastri (&quot;J&quot;)</td>
</tr>
<tr>
<td>M. ulcerans</td>
<td>M. triviale (&quot;V&quot;)</td>
</tr>
<tr>
<td>M. xenopi</td>
<td></td>
</tr>
<tr>
<td>M. fortuitum</td>
<td>M. bovis</td>
</tr>
<tr>
<td>M. abscessus</td>
<td>M. smegmatis</td>
</tr>
<tr>
<td>M. phlei</td>
<td>M. vaccae</td>
</tr>
</tbody>
</table>

high incidence of reaction to PPD-B in naval recruits from the South and Southeastern states, in numerous counties exceeding 70 percent. The area of highest occurrence does not coincide with either the highest occurrence of PPD-S reactions nor with that of reported tuberculosis. The question has arisen whether or not infection with atypical bacilli produces protection against tuberculosis in a manner comparable to that of BCG. From animal observations, this does appear to be the case.

The mode of acquisition and transmission of these mycobacteria is still enigmatic. Tuberculin testing of family contacts of persons with mycobacterioses in non-endemic areas usually shows no infection. Man-to-man transmission has never been proved. Soil and water appear to be the source of many of these organisms, but no details are known. Meissner sees no possibility of eradicating these sources of infection.16

Pathogenesis

The pathogenesis of mycobacteriosis in many respects resembles that of tuberculosis, but there are some differences. Whereas clinical tuberculosis occurs in only a small fraction of persons infected, mycobacteriosis probably occurs in an even smaller fraction of those infected with primarily pathogenic strains. Thus, similar host-agent-environment determinants prevail. Diseases in which mycobacteria are found only in the presence of extensive pulmonary changes may be barely, if at all, influenced by them, the saprophytic nature of the organisms prevailing. Between the two extremes the mycobacteria may act in a manner similar to that of other so-called "opportunistic" microbiological agents, especially fungi and bacteria. It would be a mistake, however, to look upon the atypical mycobacteria as generically "opportunistic" any more than any host-agent relationship implies.

Among the diseases which frequently are implicated in altering host defenses are the pneuamoconioses, obstructive pulmonary disease, bronchiectasis, cystic disease and idiopathic pulmonary fibrosis. Tuberculosis may act in the same manner, since it is not uncommon to find mycobacteriosis some years after treatment of tuberculosis. On occasion, however, the diagnosis of the original tuberculosis may not have been sufficiently well documented bacteriologically. Implicated in general alteration of host defenses which may predispose to mycobacteriosis may be mentioned alcoholism, metabolic factors, hygienic and nutritional deficiencies and corticosteroid therapy.

These diseases commonly occur in males, M. kansasii being especially uncommon in females. In the experience of the authors, this male to female ratio was about ten to one. The age occurrence is generally middle age and beyond.

Diagnostic Considerations

The clinical aspects of mycobacteriosis will be discussed briefly. It is relatively uncommon to make a primary diagnosis of mycobacteriosis. Most commonly, the diagnosis of tuberculosis is made because of
X-ray findings and the presence of acid-fast bacilli on smears. Treatment with drugs is then begun, and only when the response of the patient is unusual or the cultures are reported does one suspect or prove that the process is not tuberculosis. One may suspect something unusual, however, if the tuberculin test is poorly or non-reactive. At times differential tuberculin testing is useful although not conclusive.

It is important to acknowledge that it is not possible to differentiate the mycobacterioses from tuberculosis by X-ray or histological methods. The clinical course of mycobacteriosis is commonly characterized by a waxing and waning of lesions as shown by X-ray. This is especially so if the organisms are resistant to the treatment which was originally instituted. The indolence of the lesions and the lack of communicability also removes some of the urgency about the management. Generally, the patients may work, and it is preferable to permit changes in drug treatment to await results of sensitivity studies. There are exceptions resulting from the degree of clinical illness which may require multiple drug treatment without clear cut in vitro sensitivity results. In general, patients are not seriously symptomatic, but when disease is extensive and cavities thick-walled, hemoptysis in addition to dyspnea, cough and sputum may be troublesome. Where pulmonary disease is already complicated, the total process may be disabling.

Clinical Observations and Treatment

During the past few years, 25 patients have been observed in whom studies were relatively complete (table III). Of these, 14 showed M. kansasii, 2 M. scrofulaceum and 9 showed Group III organisms of which most were M. intracellulare with one classified as M. Terrae (formerly radish). All were regarded as significant. In addition, during the same period, bacteriological data were received regarding 30 more patients in whom cultures showed atypical mycobacteria. Among these were 4 in Group I, 10 in Group II, 10 in Group III and 6 in Group IV. Correlation with patient status suggested that only about one-half of the cultures represented significant disease-producing bacteria. The relative proportions of Group II and IV bacilli, as compared with the clinical group of patients, is noted. In general, treatment was employed for all patients in whom the bacteria were regarded as significant. Results by the authors have been comparable to those reported, although drug treatment has not been aggressive in patients with non-progressive asymptomatic disease.

At times, illness from M. kansasii may respond to standard anti-tuberculous drugs. When this is the case, no change is indicated. Kanssii may also be sensitive to streptomycin. While awaiting sensitivity reports in an individual who is symptomatic, it is thus desirable to use a combination of isoniazid, ethambutol and streptomycin. Rifampin may be added or substituted in this regimen depending on the degree of clinical illness. Evidence is developing that Rifampin is useful in treatment of mycobacterioses, especially M. kansasii.

Group III organisms are generally much less sensitive to drugs than those in Group I. Decision as to whether or not a major effort at drug treatment should be made will thus depend upon the trend of the patient’s illness after a period of observa-
tion. When progressive, one should proceed with a combination of four or five anti-mycobacterial agents under close observation. Davidson et al have reported a moderate degree of success with such a regimen. Where disease is localized to one region, however, there is real merit in advising resection as the most expeditious and definitive measure which has proven successful, especially in Group III infections. Unfortunately, many of these problems occur in patients who are in advanced age groups and who have widespread disease which does not permit a surgical approach.

CASE HISTORIES

Case 1. W. W., Group III, age 63, male. No symptoms. Cavity in left upper lobe discovered by X-ray when left shoulder was dislocated. Indolent course, occasional acid-fast bacilli on smear. Cavity wall thinned out as disease slowly regressed with standard drugs.


Case 3. E. R., Group I, age 42, female. M. kansasi sensitive to streptomycin. Progression of disease during standard drug treatment. Thin-walled cavities. Retreatment with isoniazid, streptomycin, ethambutol and rifampin resulted in clinical improvement. Sputum no longer contains acid-fast bacilli. This patient's symptoms and clinical course were quite similar to those of patients with tuberculosis unresponsive to the usual drug regimen.

Summary

Mycobacterial diseases continue to be a world-wide problem. As tuberculosis is gradually controlled, atypical mycobacteria assume a relatively increasing epidemiologic role. Mode of transmission of the organisms and pathogenesis of the disease are uncertain but man-to-man transmission, characteristic of tuberculosis, is not known to occur in the mycobacterioses.

When atypical mycobacteria are encountered clinically, species identification is needed for estimation of their significance and for guidance in treatment. The intensity of drug treatment will depend upon the presence and nature of underlying bronchopulmonary disease in relation to the identity and drug sensitivity of the bacteria.

References


13. Kubic, M., Kruml, J., Horak, Z., Luvasky, J.,


“Concern for man himself and his fate must always form the chief interest of all technical endeavors.”

Albert Einstein