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INFECTIONS CAUSED BY ATYPICAL MYCOBACTERIA

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Proof: n. Evidence having a shade more of plausibility than of unlikelihood. The testimony of two credible witnesses as opposed to that of only one.

The Devil's Dictionary.
Ambrose Bierce, 1906

INFECTIONS DUE TO ATYPICAL MYCOBACTERIA

Despite the fact that the so-called atypical mycobacteria have been known since a very short time after the discovery of the human tubercle bacillus, substantial clinical information concerning the significance of these microorganisms is of relatively recent vintage. A number of problems related to nomenclature have existed and, indeed, a number still exist. Nevertheless, many recent advances in microbiology and in clinical correlations make it seem an approriate time to review the clinical significance of the atypical mycobacteria. The literature on this is burgeoning at present, and a number of good reviews have appeared. I would refer you particularly to Reference 25 entitled Atypical Mycobacteria, Their Clinical, Laboratory and Epidemiologic Significance by Fogan which was published in Medicine in 1970 and to the excellent textbook by Dr. John S. Chapman entitled The Atypical Mycobacteria and Human Mycobacteriosis (11) which was published in 1977. These are very authoritative sources and I will quote so frequently from them in this presentation that I would like to acknowledge this at the outset as it may be difficult to document every reference.

In this discussion the atypical mycobacteria will be considered as those groups of mycobacteria which are biologically distinct from Mycobacterium tuberculosis, Mycobacterium leprae, and Mycobacterium bovis. (11,84,87,99) Although biologically distinct, in some instances these mycobacteria cause infections very similar to those caused by Mycobacterium tuberculosis. At a time when the frequency of clinical tuberculosis continues to decrease steadily, recognition of the infections caused by atypical mycobacteria is

steadily increasing, if one might judge from publications in the medical literature as well as personal experience. In addition, the atypical mycobacteria have a considerable epidemiologic significance as it is now regarded that the majority of reactions to the tuberculin skin test in the United States are not caused by Mycobacterium tuberculosis infections, but are probably latent infections due to atypical mycobacteria.

Only a few years after Robert Koch discovered the human tubercle bacillus, a number of descriptions of other acid fast bacilli from non-human sources appeared. In 1883 Baley (23) described differences of staining between mammalian tubercle bacilli and those of birds. Avian tubercle bacilli were reasonably well characterized in 1889 (65) and it was Theobald Smith who first differentiated bovine from human types of tubercle bacilli in 1898. (97) Over the years microbiologists have sought mycobacteria from various environmental sources and they have been found in various animals such as frogs, fish, voles, as well as from milk and milk products, from hay, water, soil, and manure. (1,5,6,11,24,32,52,54,62,64,70,74) As improved cultural techniques and additional experience added to our knowledge and as clinical microbiologic correlations became more extensive, it was recognized that atypical mycobacteria may have real clinical significance. Pinner in 1935 (79) first referred to these organisms as "atypical" mycobacteria. The drawbacks to this name were immediately apparent and have become more so as the years have passed, especially when such terms as "typical atypical" and "atypical atypical" are used. Other terms such as "anonymous" and "unclassified" have been proposed and perhaps most recently "opportunistic" mycobacteria has been suggested. Despite this confusion, it would appear that in common parlance, the term atypical

mycobacteria has a considerable advantage in usage and we will use that term in this discussion.

The work of a number of investigators was consolidated and systematized by Runyon (86,88) and the Runyon classification represented an important step forward in our understanding of this group of mycobacteria. Runyon's classification was based upon pigment production and rapidity of growth. The first table lists an outline of this classification. (11,25,84,99)

Group I Photochromogen. Slow growing organism which produces a pigment on exposure to light, but is virtually non-pigmented when grown in the dark.
Group II Scotochromogen. Slow growing. Produces pigment either in the light or the dark.
Group III. Slow growing; non-pigmented or only faintly colored and the color is not influenced by light.
Group IV. Rapid growers. Colonies develop after only 5 to 14 days.

In order to give you a visual image of these cultures, I will show a series of slides illustrating their appearance. The next slide shows a culture of Mycobacterium tuberculosis on the usual green colored Lowenstein-Jensen medium. The next slide shows a culture of a photochromogen, the culture on the left grown in the dark and the one on the right grown in the presence of light. The difference in pigment in the light is apparent. The next slide shows a culture of a Group II (scotochromogen) organism as it appears after growing in the dark and the deep pigment is apparent. The next slide shows a Group III Mycobacterium avium which is slightly pigmented and does not change when exposed to light. The next slide shows a Mycobacterium fortuitum, one of the rapid growing organisms, which has a similar type of growth except for the fact that it appears in a short time. This slide

shows all of these cultures side by side, the first being Mycobacterium tuberculosis, the second Mycobacterium kansasii grown in the light and the third one in the dark. The next is a Group II scotochromogen grown in the dark, the next is Mycobacterium avium and the last Mycobacterium fortuitum. These differences may be somewhat more apparent in certain cultures grown on transparent medium, and the next slide shows Mycobacterium kansasii grown in the dark and the one on the right shows the same culture which had been exposed to light for 24 hours. The next shows Mycobacterium scrofulaceum which has this same appearance whether grown in the light or in the dark. The next slide shows Mycobacterium intracellulare, one of the Group III non-chromogenic organisms, and as will be seen, these are the same whether in the dark or not. The next shows again a Group IV rapid growing organism which has very similar cultural characteristics except for growth rate.

A good deal has been said about the difference in appearance of the various atypical mycobacteria on slides stained by the Ziehl-Neelsen method. The next slide shows the characteristic Mycobacterium tuberculosis which is a small organism, relatively regular and uniform. The next is a similar slide of M. kansasii and shows that the forms may be elongated and of quite variable appearance. Indeed, M. kansasii may assume some very bizarre appearances such as is shown in this slide, and in a circumstance like this it would not be difficult to characterize this as atypical. Nevertheless, as is shown in the next slide, they may be virtually identical. On the left is shown a picture of M. kansasii and on the right M. tuberculosis. They appear to be identical. It is true, however, that laboratory workers with considerable experience may frequently be able to recognize atypical mycobacteria on the basis of smears, but confirmation of this with culture methods is always necessary.

The most commonly encountered atypical mycobacteria now may be characterized on the basis of morphology, cultural and biochemical reactions. The next table gives a reasonably complete listing of all of the mycobacteria with an estimate of pathogenicity, the equivalents of Runyon grouping, acceptable common names, and various comments. (98,99)

Table I—Nomenclature of Mycobacteria*

Legitimate name	Relative pathogenicity for man	Equivalent of Runyon Group	Acceptable common name	Names without legitimate standing and comments
M. africanum	+++			Intermediate between *M. bovis* and *M. tuberculosis*
M. asiaticum	++	Group I photochromogen		Similar to *M. simiae* but differs antigentically
M. avium	+++	Group III nonphotochromogens	Avian tubercle bacillus	Closely related to *M. intracellulare*
M. bovis	++++	Bovine tuberculosis	Bovine tubercle bacillus	Causes bovine tuberculosis
M. chelonei	+	Group IV rapid grower		*M. abscessus, M. borstelense* may cause occasional skin disease
M. flavescens	0	Group II scotochromogen		Grows relatively rapidly; should be differentiated from *M. scrofulaceum*
M. fortuitum	+	Group IV rapid grower		*M. ranae; M. minetti* skin infection; may cause disease in immune suppressed host
M. gastri	0	Group III nonphotochromogen		Not known to be pathogenic for man
M. gordonae	0	Group II scotochromogen	"Tap-water" scotochromogens	*M. aquae*—rarely, if ever, pathogenic for man
M. intracellulare	+++	Group III nonphotochromogen	Battey bacillus	*M. batteyi, M. battey*
M. kansasii	+++	Group I photochromogen		Rare, nonpigmented, scotochromogenic, and niacin positive strains
M. marinum	+++	Group I photochromogen		*M. balnei, M. platypeocilus*
M. scrofulaceum	++	Group II scotochromogens		*M. marianum*
M. simiae	++	Group I photochromogen		Facultatively pathogenic; photoreactivity may be unstable
M. szulgai	+++	Group I photochromogen at 25° C Group II scotochromogen at 37° C		Associated with chronic pulmonary and extrapulmonary disease; distinctive lipid composition
M. terrae	Rare	Group III nonphotochromogen	Radish bacillus	May be closely related to *M. triviale*
M. triviale	0	Group III nonphotochromogen	"V" bacillus	Has been called "atypical-atypical" mycobacterium
M. tuberculosis	++++	Human tuberculosis	Human tubercle bacillus	Causes human tuberculosis
M. ulcerans	++++	*M. buruli*		Associated with skin infections in tropics *M. buruli*
M. xenopi	++	Group III nonphotochromogens (scotochromogen)		*M. littorale, M. xenopei* slow growth—best at 42° C

For those who are interested in details of the methods utilized to characterize these mycobacteria, I have reproduced a table from Sommers' article published in February of this year. (99)

Table III—Identification Characteristics of Mycobacteria

Organism	Optimum Isolation Temperature and Rate of Growth	Pigmentation Growth in: Light	Pigmentation Growth in: Dark	Niacin Test	Nitrate Reduction	Catalase: Semi-quantitative[1]	Catalase: pH 7.0 68° C	Tween 80 Hydrolysis 10 Days	Arylsulfatase 3 Days	Urease	Resistance to T_2H 1 μg/ml	Growth on 5% NaCl	Iron Uptake
M. tuberculosis	37° C 12–25 days	Buff	Buff	+	3–5+	<40[2]	–	∓	–	+	+	–	–
M. africanum	37° C 31–42	Buff	Buff	V	V	<20	–	–	–		+	–	–
M. bovis	37° C 24–40	Buff	Buff	V	–	<20	–	–	–	+	–	–	–
M. ulcerans	32° C 28–60	Buff	Buff	–	–	>50	+	–	–		+		
M. kansasii	37° C 10–20	Yellow	Buff	–	1–5+	>50	+	+[3]	–	+	+	–	–
M. marinum	31–32° C 5–14	Yellow	Buff	V	–	<40	∓	+	∓		+	–	–
M. simiae	37° 7–14	Yellow[4]	Buff	+	∓	>50	+	–	–		+		
M. szulgai	37° 12–25	Yellow to orange	Yellow–37° C buff–25° C	–	+	>50	+	∓	∓	+		–	
M. scrofulaceum	37° C 10+	Yellow to orange	Yellow	–	–	>50	+	–	–	+	+	–	–
M. gordonae	37° C 10+	Yellow	Yellow	–	–	>50	+	+	–	–	+	–	–
M. flavescens	37° C 7–10	Yellow	Yellow	–	+	>50	+	+	–	+	+	+	–
M. xenopi	42° C 14–28	Yellow	Yellow	–	–	<40	+	–	±	–	+	–	–
M. intracellulare avium complex	37° C 10–21	Buff to pale yellow	Buff to pale yellow	–	–	<40	+	–	–	–	+	–	–
M. gastri	37° C 10–21	Buff	Buff	–	–	<40	–	+	–	+	+	–	–
M. terrae complex	37° C 10–21	Buff	Buff	–	1–5+	>50	+	+	–	–	+	–	–
M. triviale	37° C 10–21	Buff	Buff	–	1–5+	>50	+	+	∓		+	+	+
M. fortuitum	37° C 3–5	Buff	Buff	–	2–5+	>50	+	±	+	+	+	+	+
M. chelonei sp. *borstelense*	37° C 3–5	Buff	Buff	V	–	>50	+	–	+	+	+	–	–
sp. *abscessus*	37° C 3–5	Buff	Buff	V	–	>50	+	–	+	+	+	+	–
M. smegmatis	37° C 3–5	Buff to yellow	Buff to yellow	–	1–5+	>50	±	+	–		+	+	+

Key to results: + = 84% of strains +; ± = 50–84%; ∓ = 16–49%; – = 16% of strains +; V = variable; blank spaces = little or no data.

[1] Numbers indicate millimeters of bubbles.

[2] INH = resistant strains may be negative.

[3] Positive (most) in 24–48 hours.

[4] Photochromogenicity unstable with repeated subcultures.

For most of us who find this a somewhat bewildering array of details, I have simplified the outline in the next table which includes most of the clinically significant mycobacteria.

CLINICALLY MOST SIGNIFICANT MYCOBACTERIA

Pathogenic Organism	Runyon Group
M. tuberculosis M. bovis M. leprae	Not included in Runyon classification (i.e. "typical" mycobacterium)
M. kansasii M. marinum	Group I (photochromogen)
M. scrofulaceum	Group II (scotochromogen)
M. avium M. intracellulare ("avium-intracellulare group")	Group III (non-chromogen)
M. fortuitum M. chelonei	Group IV (rapid growers)

SOURCE OF MYCOBACTERIA

The atypical mycobacteria which infect man are derived from a variety of sources in the environment. Although there are a very few reports (74) of apparent family transmission of pulmonary disease, there are so few that man to man transmission, for practical purposes, may be disregarded.

In the table on the next page are summarized the major sources which are known for the various microorganisms with which we are concerned. It will be noted that there is no common source from which M. kansasii has been isolated in the environment. (11) Numerous organisms resembling M. kansasii have been isolated from water (32) but are probably only occasionally precisely the same organisms that infect humans. Rarely it has been isolated from animals and the organisms isolated from milk, although similar, are not exactly the same.

ENVIRONMENTAL SOURCES OF ATYPICAL MYCOBACTERIA

SPECIES	COMMON SOURCE	RARE SOURCE
M. KANSASII		WATER ANIMALS MILK (?)
M. MARINUM	WATER, SWIMMING POOLS, FISH, DOLPHINS, AQUARIUMS	
M. SCROFULACEUM	MILK, WATER	
AVIUM-INTRACELLULARE	BIRDS, WATER, MILK DUST	
M. CHELONEI M. FORTUITUM	SOIL, DUST WATER, HUMANS, LOWER ANIMALS	

M. marinum, on the other hand, has been frequently isolated from a variety of aquatic sources. This includes water samples from tap water, water from spring pools, the sides of the swimming pools themselves, from fish, dolphin, and home aquariums. (1,5,7,24)

M. scrofulaceum has been isolated from milk and from water. (11,109)

The avium-intracellulare group has been isolated, obviously from birds, but also from water, milk, and dust samples. The rapid growers, M. chelonei and fortuitum, have been found in a variety of environmental sources including soil, dust, water, and lower animals. A number of strains have been found from human sources in circumstances suggesting that they were saprophytic organisms and not causing disease. (4,6,29,56)

PULMONARY DISEASE

The most common and the most important type of infections due to atypical mycobacteria are those of the lung. It is impossible to estimate the frequency of cases occurring in the general population, but an idea of the frequency of the disease may be obtained from studies as that reported by Gale (29)

who reviewed consecutive admissions to the tuberculosis unit at the Toronto Hospital. In a group of 1667 consecutive admissions to a tuberculosis hospital, 4.8% or 80 patients had sputum cultures from which atypical mycobacteria were isolated. They used four criteria to decide whether these organisms were significant.

1. There must be clinical evidence of disease.
2. There must be radiologic evidence of disease in the lungs or urinary tract.
3. The atypical mycobacteria must be recovered repeatedly.
4. M. tuberculosis must never be recovered.

Utilizing these criteria, only 3% of the patients had disease due to atypical mycobacteria. Such criteria as these are commonly advocated in studying disease due to atypical mycobacteria. Unwillingness to accept a single culture or a culture containing only a few organisms reflects the fact that the organisms are widely distributed in nature and their presence does not necessarily signify disease. Nevertheless, the disadvantages of such criteria are readily apparent.

Whether the repeated isolation of a particular organism in a given patient really constitutes proof of infection or whether reports of a particular type of mycobacterial infection stemming from two different investigators is more plausible than that from one, is open to some question. A number of statements in the literature on atypical mycobacteria make one feel that perhaps Ambrose Bierce's definition of proof, originally published in 1906 and quoted on the title page of the protocol, may not be entirely outdated.

In general, it may be said that most atypical mycobacterial infections of the lung are caused by M. kansasii and M. intracellulare, respectively Runyon Groups I and III. (2,20,22,26,27,29,41,49,80,116,117,118)

Occasionally, cases have been reported as due to M. scrofulaceum (Runyon Group II). (44,109) The disease picture produced by M. kansasii and M. intracellulare is, in general, like that of pulmonary tuberculosis. Underlying pulmonary disease, especially chronic obstructive pulmonary disease, is common, especially in those patients with M. intracellulare infection. The disease tends to progress less rapidly, but it is nonetheless progressive. Silicosis is also a relatively frequent underlying disorder. The disease is more common in males of the older age groups and in a good many series there appears to have been a preponderance of whites as opposed to blacks, especially in the United States. Particularly with M. kansasii infections, certain clinical descriptions have emphasized that there may be some differences in the clinical features, especially the radiologic changes. It is said that thin-walled cavities tend to be more prevalent and that disease tends to be more frequent in the anterior segments of the lung than is tuberculosis. Pleural disease is relatively uncommon.

As previously stated, once the clinical features of pulmonary disease are recognized, it becomes a problem to be certain that the disease is indeed caused by the particular atypical mycobacterium being isolated. It is for this reason that many investigators have recommended, as previously mentioned, that in addition to disease of the lung demonstrated radiographically, one must repeatedly isolate the atypical mycobacteria. Others recommend that not only should they be repeatedly isolated, but they should be present in large numbers. There is little argument that if one of these organisms is isolated occasionally in a patient with a normal chest x-ray, it can readily be disregarded. It is another question, however, to disregard a culture of M. kansasii or M. intracellulare when it is the only organism isolated from a patient with upper lobe disease resembling tuberculosis.

Fortunately, it is generally not difficult to satisfy both of these requirements in such patients.

The extent of the underlying pulmonary disease has been described by Ahn, Nash and Hurst. (2) They studied 232 patients infected with M. kansasii and 120 patients infected with M. intracellulare admitted to the East Texas Chest Hospital. They found an obstructive ventilatory defect present in 69% of the patients with M. kansasii infection, in 57% of the patients with M. tuberculosis infection, and 68% of those with M. intracellulare infection. Whereas these frequencies are not so very different, it was of special interest that the extent of disease as judged by chest x-rays in the M. tuberculosis groups correlated well with the decrease in ventilatory function. In contrast, among the patients infected with the atypical mycobacterium, there was a poor correlation between these values and the extent of disease. That is to say, the values are relatively low even with minimal evidence of infection. Johanson and Nicholson from this department (49) have provided an excellent description of the clinical features of patients with disease due to M. kansasii. They found cavitary disease present in 85% of patients and evidence of prior lung disease in 63%. The most significant factor determining the course of the disease was thought to be the presence of underlying lung disease. They reported that surgical treatment was a safe and effective means of controlling the disease and considered that the indications for such treatment included the persistence of cavitary lesions, failure to eliminate the organisms from the sputum after six months of treatment, isoniazid resistance and drug intolerance.

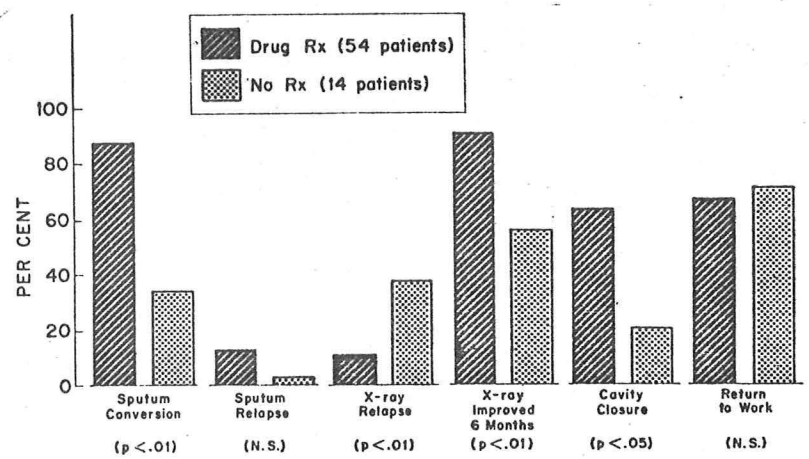


FIG. 1. Comparison of treated and nontreated patients with photochromogen disease.

This figure shows the comparison of treated and non-treated patients with M. kansasii infections and, in essence, shows that the sputum conversion, improvement in x-ray appearance, and cavity closure were better in those patients who received drug therapy. (49)

The next figure shows that in the treated patients having underlying lung disease (indicated in the stippled bars), these same parameters were less favorable.

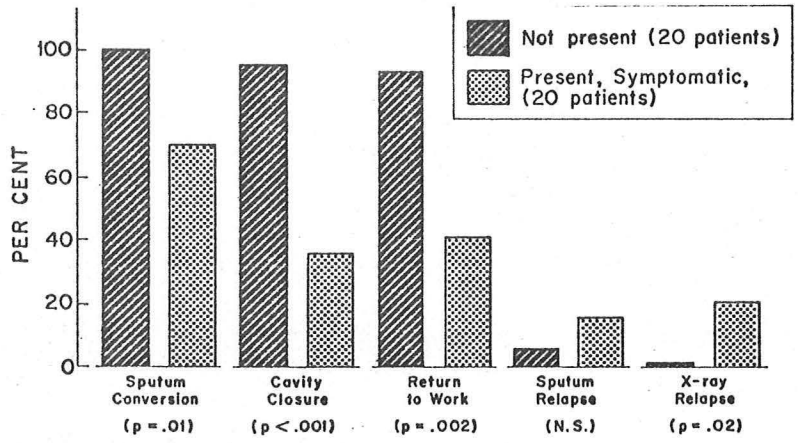


FIG. 2. Influence of underlying lung disease on results of treatment (drug-treated patients only).

In the next figure it is noted that sputum conversions were more rapid and more frequent, cavity closure was more frequent, and x-ray relapse less frequent in those patients who had organisms sensitive to isoniazid.

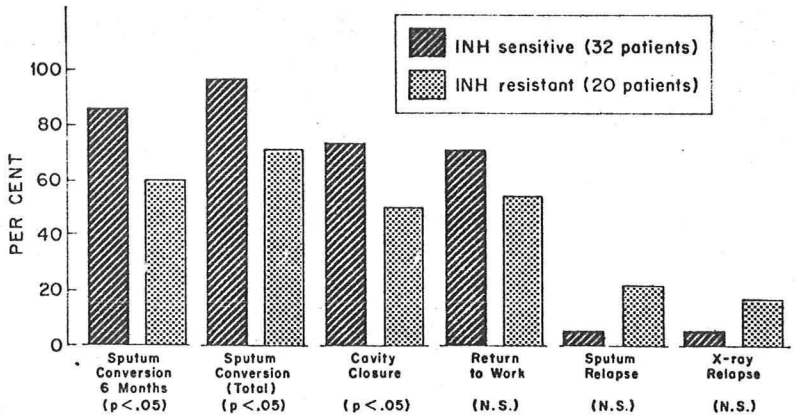
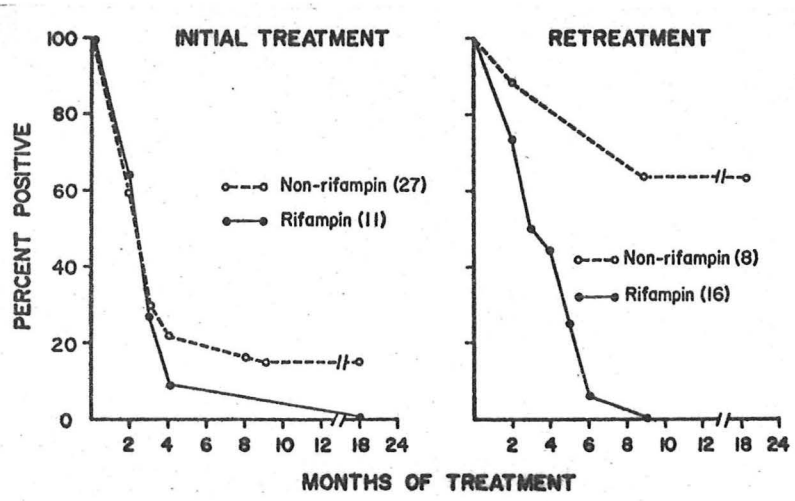


FIG. 3. Influence of susceptibility on results of treatment. Growth equal to one half of control or less with isoniazid concentration of 1.0 μg per ml considered susceptible.

It must be noted that this article was published in 1969 and that in a more recent study published by Harris, Johanson and Nicholson in 1975 (4) the results of drug therapy were in general more favorable. An important addition to drug therapy occurred in the interim, namely the introduction of rifampin and ethambutol into clinical use. In the more recent study designed especially to determine the impact of new antimicrobial agents on the treatment of M. kansasii infection, these authors reviewed 59 patients treated between 1971 and 1974. (41) In all, 92% of the patients converted their sputums while receiving drugs and only one of them had surgery. It was found that drug regimens containing rifampin were very effective in both initial and retreatment cases, but it was felt that rifampin was not of significant advantage for initial treatment. In this study, actual in vitro resistance to isoniazid and ethambutol did not adversely affect the results of treatment with these drugs. Indeed, the effectiveness of this

type of therapy was considered sufficiently good that parameters such as age, underlying lung disease or extent of disease were not really related to the outcome of therapy.



These data from Harris, Johanson and Nicholson clearly show the role of rifampin in initial treatment and retreatment. In the graph on the left there is recorded no statistically significant difference between the groups initially treated as to whether they were treated with rifampin or not, but on the right it is noted that in the retreatment group rifampin resulted in much better sputum conversions than did those in the non-rifampin group.

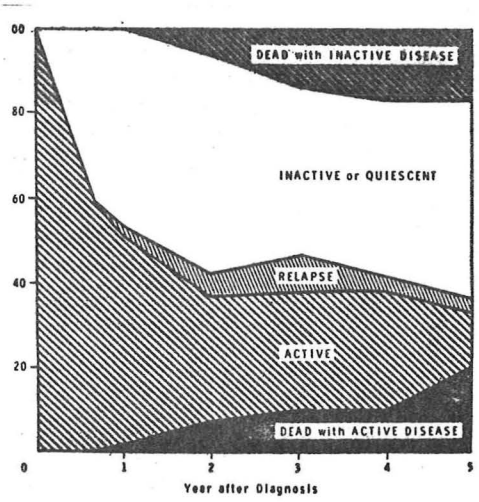
It might be mentioned at this stage that in our usual thinking about antimicrobial therapy, we tend to consider a particular strain of micro-organism which has been designated "resistant" as unlikely to be affected in any way by the particular antimicrobial drug in question. In general, this is a reasonable approach to antimicrobial therapy, but it may not be strictly applicable in the case of mycobacteria and the various antimycobacterial drugs in common use. A theoretical reason for this is that mycobacteria tend to present as a very mixed population of organisms. A given strain considered to be resistant to isoniazid may actually contain 50% or more of sensitive members of the bacterial population. Furthermore, one must be

aware of the fact that the particular levels chosen as the dividing line between sensitivity and resistance may be set at an unrealistically low level.

A good description of pulmonary disease due to M. intracellulare has been published by Yeager and Raleigh in 1973. (113) The data were to some degree biased because of the fact that the patients came from a Veterans Administration Hospital. The disease presented with symptomatology the same as one might expect from tuberculosis itself. Coexisting chronic obstructive lung disease was found in more than half of the patients. They had no patients with significant industrial exposure. More than half of the patients had far advanced disease and 92% had moderately or far advanced disease. A few patients had other underlying disease such as alcoholism and diabetes. Of the organisms isolated, 44% were sensitive to streptomycin and none sensitive to isoniazid. They tested relatively few of their cultures with ethambutol and rifampin because of the time period involved. In this group, age, extent of disease, number of cavities, underlying lung disease, or pretreatment drug susceptibility were not considered to have any significant effect on the outcome. The few patients who were treated surgically had relatively good results over a five year period.

The figure on the following page gives summary data on these 42 patients. It is readily apparent that the outlook for them is not favorable, with only 46% of the patients alive with inactive disease at five years. These authors recommended a combined aggressive medical therapy and surgical resection. Other authors, particularly the group in Colorado headed by Lester and his associates, have adopted an unusually aggressive approach to antimicrobial therapy in this disease. (60,61) Recognizing the fact that most of the strains of M. intracellulare are resistant in vitro to the

majority of antituberculosis drugs, it has nonetheless been their experience that best results are obtained when five or six antituberculosis drugs are given simultaneously. They recommend that the drugs be chosen empirically without strict attention to sensitivity tests. Obviously, any drug to which the strain is sensitive would be included in the therapeutic regimen. It is also clear that any group of six antituberculosis drugs inevitably includes some reasonably toxic drugs and the therapy must be monitored very carefully. If the disease is localized and if the patient is a suitable candidate for surgery, lobectomy is recommended. It is also recommended that the multiple drug therapy be continued after surgery.



g. 1. Yearly status of 42 patients with *Mycocterium intracellulare* pulmonary infection.

The other mycobacteria are uncommon causes of pulmonary disease, but probably can be considered in the nature of opportunistic organisms. Hunsaker, et.al. (44) have reported five cases of pulmonary disease due to scotochromogens. Wolinsky also reported four well documented cases of disease due to these mycobacteria. (109) It is of interest that two patients were arc welders and the other two had significant industrial dust exposure.

Particular care must be taken in considering reports of pulmonary disease due to the rapid growing microorganisms. Nevertheless, despite many disclaimers, it seems reasonably certain that some of these organisms are responsible for such disease. For example, Awe and associates did a retrospective study on 56 patients with sputum cultures containing M. fortuitum. (4) They concluded that in these patients there was no evidence of clinical or radiographic progression of pulmonary disease regardless of whether the patient received any therapy. They also concluded that these organisms generally are innocuous and that repeated isolation of M. fortuitum from a sputum does not warrant incrimination of this organism as the pathogen. Other studies, such as that by Tsukamura and associates, (103) have led to different conclusions. They found M. chelonei in the resected lung lesions of nine patients. These organisms were repeatedly isolated from the lesions, acid fast bacilli were present in the tissues, and the tissues themselves showed fibrocaseous lesions. The clinical followup on these patients indicated a good prognosis after surgery. It is of interest also that in this group of patients the organisms were isolated in small numbers, perhaps due to a peculiar characteristic of M. chelonei on primary isolation, (i.e. on primary isolation it tends to grow slowly, and grows best under microaerophilic conditions).

NON-PULMONARY INFECTIONS

I would like to turn now to discussion of a variety of types of infection due to atypical mycobacteria, all of which are relatively uncommon. In doing this, it is well to recall that a number of different mycobacteria have been clearly implicated in human disease. As a rule, they produce granulomas with giant cells, but at times may show simply abscesses resembling

those produced in an acute pyogenic infection. Because of the fact that the organisms themselves abound in environmental sources, it is axiomatic that simply the isolation of an organism is of questionable value unless it is from a closed lesion. In a sense, they are "opportunistic" organisms - that is, they tend to become invasive in the compromised host. In addition to this, they must be regarded as microorganisms of low virulence which can produce a slowly progressive indolent infection in tissues which generally are considered otherwise normal. In only a few instances is there a relatively characteristic clinical picture which may be suspected at the bedside. Thus, it is necessary to maintain a high index of suspicion in order that when cultures are taken they may be appropriately handled to isolate the organism. If indeed mycobacteria are suspected, careful smears of the lesions should be made looking for acid fast bacilli or for appropriately fluorescent microorganisms. In addition, the special requirements of such organisms as M. marinum and M. chelonei must be considered. Finally, it must be apparent that the last word on the various species of mycobacteria has not been written, and a host of new papers attest to the variety of clinical infections caused by these organisms.

INFECTIONS OF SKIN AND SUBCUTANEOUS TISSUE

Mycobacterium marinum has been recognized as the cause of skin and subcutaneous tissue infections since 1951. (1,5,7,24,45,50,52,54,64,70, 92,93,110) This organism was originally described as the cause of tuberculosis in salt water fish and has been reported as the cause of skin granulomas as well as a disease closely resembling sporotrichosis in which the patients exhibit a series of subcutaneous abscesses extending up the wrist and forearm. It is apparently a characteristic disease in Gulf

fishermen (70) and a number of cases have also been described resulting from manipulations of tropical fish tanks. (1,5,54) These lesions have reportedly responded to rifampin and ethambutol, to trimethoprim-sulfamethoxazole, and to tetracycline compounds. Outbreaks of so-called swimming pool granulomas have been described. (92,93) One case has been reported after the unlikely occurrence of a dolphin bite.

I have not found reports of skin or subcutaneous tissue infections due to M. scrofulaceum although reports of deeper infections certainly have occurred as will be mentioned later. A recent report, for example, describes a patient on long term corticosteroid therapy for sarcoidosis who developed a severe cutaneous infection due to Mycobacterium szulgai, one of the mycobacteria which exhibits characteristics both of Group I and Group II. (102) Cutaneous infections have also been reported, but only very rarely, as due to Group III atypical mycobacteria. (94)

The rapid growing mycobacteria, M. fortuitum and M. chelonei in particular, have been repeatedly found in cutaneous and subcutaneous infections. (40,43,73,85) It is frequently implied or shown that some of these organisms are introduced iatrogenically. For example, (6) an outbreak of fifty abscesses occurred following administration of diphtheria-pertussis-tetanus-polio vaccine to young children at a health clinic in the Netherlands. M. chelonei was identified in these abscesses and the circumstantial evidence strongly supported the suggestion that the infections were due to a break in technique in the administration of the vaccine. Trauma or injections are frequent events leading up to such infections. The Group IV organisms are substantially resistant to all of the common anti-mycobacterial drugs. It is worthy of note that it is possible to test these organisms in the standard Kirby-Bauer or similar sensitivity testing

systems to all of the common antibiotics. (3) A number of these organisms appear to be sensitive to drugs such as erythromycin, cephalothin, and aminoglycoside drugs. How effective the treatment with these drugs will prove to be is uncertain at present.

LYMPH NODES

Early reports of cervical adenitis in children due to atypical mycobacteria from Montreal and from the Mayo Clinic, (81,106) as well as a number of subsequent reports, (66,71,72,82,90,109) describe a reasonably typical syndrome of adenopathy, usually submandibular, but at times involving other nodes and in most of the early cases reported, Group II scotochromogenic mycobacteria were isolated. As this has evolved, the picture of isolated lymphadenopathy has become a relatively well recognized syndrome in children. The histopathology of these lesions (82) in most cases has shown a pattern of tissue reaction similar to that seen in tuberculosis. In the minority of the specimens, however, a dimorphic pattern, that is suppuration and granulomatous inflammation without caseation, either by itself or together with the usual tuberculous reaction, had been found. In a few of the lymph nodes, a truly non-specific diffuse inflammatory reaction has been described. As additional experience has been gained, it has become evident that although this is by far the major site of discovery of Group II microorganisms in humans, it is also true that the same clinical picture is produced by other atypical mycobacteria. (12) An excellent report by Salyer, Vottler, and Dorman (90) gives a detailed description of fifty cases which were observed in Dallas. These authors described fifty patients wbo had had cervical adenitis, the diagnosis being made either by skin testing with antigens from atypical mycobacteria, the presence of mycobacteria in tissue sections or from positive cultures. In the next table it may be seen that of the 21 positive cultures in this group, 6 were in Group I,

6 in Group II, and 9 in Group III.

MYCOBACTERIA ISOLATED FROM
50 CASES OF LYMPHADENITIS

GROUP I	6
GROUP II	6
GROUP III	9

Forty nine of the fifty patients had submandibular lymph node enlargement, either unilateral or bilateral. The ages of the patients included those up to 11 years old, but it was interesting that 40 of the 49 patients were under the age of four. It was noted by these authors that the histologic examination was indistinguishable from that of M. tuberculosis infection. Their recommendation was that the patients be treated with total excision of the disease bearing lymph nodes followed by drug therapy. This has been, and perhaps still is, the best type of therapy although the experience with rifampin and ethambutol to date certainly suggests that they are much more potent drugs than have hitherto been available. Thus, except for biopsy, the role of surgery needs to be re-evaluated. A report published by Mandel and Wright from Boston recently (66) describes four cases which were treated with rifampin with excellent results. Unfortunately, only one of these four patients had a positive culture, but the clinical pictures were relatively characteristic.

At least two cases have been described with cervical adenitis due to M. chelonei. (71,72) In one of these no predisposing cause was noted, but in the other the adenitis followed four months after an injection of a dental anesthetic.

TENDINITIS - SYNOVITIS

A particularly interesting group of patients has been reported to have infections in the deep tissue structures about joints. The cases have been described as carpal tunnel syndrome, (53) tendinitis and fasciitis, (14,77) and infections of the deep structures of the hand. (38,107) Most of these cases have been caused by M. kansasii or M. marinum. In some of these patients the disease presents as a type of "opportunistic infection", discovered at a site in which some operation has already been done or in which injections of steroids have been given. We have had an especially interesting experience with this group of patients. (101) With Dr. Sutker and Dr. Lankford, we have observed a total of 24 patients within the last seven years. These patients presented with reasonably characteristic histories and physical findings. Many of them gave a history of minor trauma to the affected part and in a few, the trauma occurred while they were working or fishing in water. After some latent period, swelling in the course of the tendon sheath or bursa was noted and became painful and tender. In some, the picture was that of the carpal tunnel syndrome. A few patients had previously had synovectomies or biopsies which showed granulomatous synovitis and the symptoms recurred or worsened subsequent to the operative procedure. At operation there has been frequently a reasonably typical gross appearance and on microscopic examination, granulomas were usually seen, although not always. The microbiologic data on these 24 patients are recorded in the table on the following page.

GRANULOMATOUS SYNOVITIS AND BURSITIS

ORGANISM	NUMBER OF CASES
M. TUBERCULOSIS	4
M. KANSASII	6
M. MARINUM	1
M. GORDONAE	1
M. AVIUM	2
M. CHELONEI	1
AFB SEEN BUT NOT GROWN	4
NONE SEEN, NO GROWTH	5

As may be seen in the table, in this group of patients there were four from whom M. tuberculosis was recovered, six with M. kansasii, one with M. marinum, one with M. gordonae, two with M. avium, and one with M. chelonei. In four patients acid fast bacilli were seen in the tissues, but were not grown. In five the microscopic picture was the same as the others - that is, with tissue granulomas - but no organisms were seen and there was no growth on culture. Only three of these patients had some underlying disease which might have predisposed them to infection. One had systemic lupus erythematosus, one had Hodgkin's disease, and one had polymyositis and was on steroid therapy. Most of the patients had involvement of only one site although three were associated with more than one lesion.

The therapy in these patients consisted of some type of surgery, either complete synovectomy or bursectomy when possible, followed by therapy directed against mycobacteria. With the exception of the patient infected with M. chelonei, they have received various combinations of isoniazid, ethambutol, rifampin, and ethionamide. The one patient with M. chelonei infection has been treated with incision and drainage and with erythromycin, to which this particular strain was sensitive. The results of therapy in

general have been good. Two of the patients have had distinct relapses, but have been successfully retreated.

One case of special interest was a 14 year old boy who had Stage IV Hodgkin's disease. During the course of his Hodgkin's disease and while he was receiving steroids and chemotherapy, he developed skin lesions which superficially resembled ecthyma. These were initially negative on culture, but in retrospect it is clear that appropriate cultures were not done. A biopsy of one of the lesions was not diagnostic from a morphologic point of view, but as may be seen in the next slide, presented an unusual picture on Gram stain in which may be seen long microorganisms with multiple gram positive granules. The next slide shows that these were acid fast organisms. At this time the patient was treated with isoniazid, ethambutol and rifampin and the lesions cleared up. Six months after the completion of eighteen months of therapy, he developed granulomatous synovitis in his right hand. The next slide shows a picture of this lesion in the immediate postoperative stage after a biopsy had been done and at a time when the lesion flared up quite strikingly. M. kansasii was isolated from this lesion and he was treated with the same three drugs plus ethionamide and streptomycin. This responded very slowly but ultimately did clear up with some deformity. A photograph of the lesion two months later is shown here, shortly prior to the time when it completely closed over.

Another patient had infection over the dorsum of the hand and the index finger due to M. chelonei. This was a patient with systemic lupus erythematosus who was on steroid therapy and who had multiple other problems. The one most pertinent was an episode of ischemia in the right hand and in this area she

developed multiple subcutaneous abscesses and synovitis. This slide sbows the appearance of her index finger. Diffuse soft tissue involvement is apparent and also a small abscess may be seen. Undoubtedly, some such lesion as this led to the earlier name of this mycobacterium which was M. abscessus.

OSTEOMYELITIS - ARTHRITIS

A number of cases of septic arthritis as well as osteomyelitis have been reported. (10,13,31,46,48,91,96,105) There have been instances of monarticular arthritis or single areas of osteomyelitis. Some cases involved multiple lesions and in some they are simply one of many tissues involved in disseminated disease. They have included infections due to M. kansasii, (91) avium-intracellulare, (13,48) and M. fortuitum. (10,96) Many of the patients have been immunosuppressed although by no means all. One interesting patient with chronic arthritis of the sacroiliac joint and the knee as well as carpal tunnel involvement due to M. intracellulare was reported from the Rheumatic Disease Unit here. (13)

The next slide shows the external appearance of sinus tracts which developed in one of our patients who had infection involving the knee due to M. kansasii. This patient had systemic lupus erythematosus and was on large doses of steroids at the time this developed.

An additional patient had a soft tissue granuloma of the dorsum of the foot which apparently occurred after trauma. This was of particular interest in that the organism was very rapidly growing and the next slide shows a picture of the culture after only three days of incubation. The resemblance to Nocardia is evident here and on microscopic sections there were peculiar collections of acid fast bacilli which probably represented

groups of intracellular organisms as is shown in this slide. This organism was identified as M. fortuitum.

OTHER VISCERAL DISEASE

With the possible exception of the genitourinary tract, other visceral involvement may be considered in large part as that of either disseminated infection or as an opportunistic infection in a patient who is immunosuppressed. For example, (100) a case of M. kansasii infection involving the liver and spleen are reported in a patient with some type of myeloproliferative disorder. A case of granulomatous hepatitis (95) is reported in a patient with leukemic reticuloendotheliosis, the infection being due to Group III (avium-intracellulare.) Other reports detail disease due to a variety of atypical mycobacteria in malignant disease such as were described in Reference 22.

One case of osteomyelitis, pericarditis and mediastinitis due to M. chelonei apparently represented a postoperative wound infection. (46) This patient had coronary bypass surgery and did not have valve surgery. A case of prosthetic valve endocarditis due to M. chelonei has been reported after the placement of a Starr-Edwards prosthesis. (83) These cases are of special interest in that M. chelonei infections of porcine heart valves have also been reported. (9,58,62) This was noted in connection with the recognition that there was at one time a frequent contamination of porcine heart valves with this particular strain of mycobacteria. (9) This was thought to be in some way related to the method of procuring and processing the heart valves from the animals. Nevertheless, it is of special interest in this regard that a similar problem has arisen with implants used in augmentation mammoplasties which in some way have apparently been contaminated

with M. fortuitum. (18) We have seen a case of particular interest in this regard recently and even after the implant has been removed, a protracted low grade infection has persisted.

Although it may be anticipated that infections of the genitourinary tract will be discovered, it is true at present that simply the isolation of a strain of atypical mycobacteria from the urine should be regarded with considerable skepticism as the cause of any disease. One report (78) is a reasonably clear-cut case of disease of the kidney resembling tuberculosis, apparently caused by M. intracellulare. Two other well documented cases of urinary tract infection were described from the Mayo Clinic. (42) A case of granulomatous prostatitis associated with the isolation of both M. kansasii and M. fortuitum was also recently described. (59) Of special interest in this regard is the experience in the Ontario Provincial Laboratory in Toronto. (56)

TABLE I
Ontario Provincial Laboratory
Department of Microbiology
November 1, 1967 to October 31, 1968

55,254 cultures for acid-fast organisms	
1107 *M. tuberculosis*	
1632 atypical acid fast	

As is seen in this table, in 55,254 cultures 1632 atypical acid fast organisms were isolated. As is noted in the next table, 306 of these were isolated from the urine.

TABLE II
Source of atypical organisms

Sputum	1034
Urine	306
Gastric juice	78
Others (Spinal fluid, abscess, bone marrow etc.)	214
Total	**1632**

The next table shows the distribution and, as noted, many of these were Group II microorganisms but there were a few Group I, Group III and Group IV strains.

TABLE IV
Distribution by types in urine

306 cultures — Provincial Laboratory	
Group I	17
Group II	235
Group III	29
Group IV	25

The significance of these remains to be determined.

Relatively few descriptions of infections of the central nervous system have been reported. One case of cauda equina abscess due to M. fortuitum was reported from this institution.(40) Another case of simultaneous infection with cryptococcus and M. intracellulare was reported last year. (30) Two cases of corneal ulcer due to M. fortuitum have also been reported. (108,115)

DISSEMINATED DISEASE

In the next table is presented a relatively complete list of the cases of disseminated atypical mycobacterial infections which have been reported, 31 cases in all. Without going into details about the individual cases, one may make the following generalizations. Most of the cases so far reported have been due to M. kansasii although infections with Runyon Group II and III organisms have also been reported as well as one case due to a rapid growing mycobacterium. Some of the patients clearly have leukemia or other neoplastic disease at the time their infection occurs. Some of the patients have had other causes for immunosuppression such as one patient with a renal transplant and another patient reported from this institution who had primary lymphopenic

DISSEMINATED ATYPICAL MYCOBACTERIAL INFECTION

Year - (Ref #)	Organism	Associated Disease	Anemia	WBC/mm^3	Platelets	Comments
1949 (16)	Rapid grower	----------	+	20,000	------	Died
1953 (8)	Yellow bacillus	----------	+	450-1800	------	Died
1956 (111)	Yellow bacillus	Pregnancy	-----	-------	------	Died
1956 (111)	Yellow bacillus	0	+	850	52,000	Died
1961 (112)	Group III	----------	+	17,000	40,000	Died
1962 (69)	Scotochromogen	Leukemia or leukemoid	+	115,000	-----	Died
1962 (69)	Group III	---------	-----	1,700	low	Also had cryptococcal infection-died
1965 (104)	Group III	---------	+	53,000	-----	Died
1966 (57)	Group III	---------	0	36,000	343,000	Died
1967 (51)	Scotochromogen	---------	-----	Low	Low	Died
1967 (55)	M. kansasii	---------	+	1,000	190,000	Died
1967 (55)	M. kansasii	---------	+	1,400	64,000	Died
1968 (114)	Group II	---------	+	2,200	------	Died
1968 (114)	Group I	---------	+	940	------	Died
1968 (114)	Group I	---------	+	2,500	57,000	Died
1969 (39)	M. kansasii	---------	+	1,900	156,000	Died
1970 (68)	M. kansasii	Primary lymphopenic immunologic deficiency	0	17,500	------	Concomitant pneumocystis disease-died
1970 (33)	M. kansasii	---------	0	20-53,000	350,000	Died
1971 (35)	M. kansasii	Chr.granulocytic leukemia	-----	-------	------	Died
1971 (36)	M. kansasii	Leukemoid reaction	+	15,000	33,000	Died
1972 (21)	M. kansasii	----------	+	1200-3000	84,700	Cured (4 drugs)
1973 (34)	M. kansasii	Lymphoma	+	700	133,000	Died
1973 (31)	M. kansasii	SLE,steroids	0	4,400	-------	Cured (4 drugs)
1974 (89)	M.intracellulare	Exfoliative dermatitis, steroids	+	31,000	141,000	Died
1975 (63)	M. kansasii	----------	+	1,600	99,000	Died
1975 (28)	M. kansasii	Renal transplant,Prednisone, azathiaprine	+	3,700	-------	Cured (3 drugs)
1976 (67)	M. kansasii	Hairy cell leukemia	+	3,000	170,000	Died
1977 (17)	M. kansasii	Ac.gran.leuk. (4 yrs.later)	+	4,100	Normal	Died
1977 (17)	M. avium	Hodgkin's (5 yrs.later)	+	Low	Low	Alive,but doing poorly
1978 (Present)	M. kansasii	Hairy cell leukemia	+	1,800	70,000	Alive
1978 (Present)	M. kansasii	---------	+	2,200	60,000	Alive

immunologic deficiency. Two cases of special interest (17) were those patients recognized to have disseminated M. kansasii or M. avium infections four and five years respectively prior to the development of acute granulocytic leukemia and Hodgkin's disease.

In reviewing these cases one is struck by the fact that a large group of patients who have disseminated atypical mycobacterial disease have various hematologic abnormalities. (114) A summary of these data is given on the next table.

DISSEMINATED ATYPICAL MYCOBACTERIAL INFECTION

RUNYON GROUP	TOTAL CASES	NO RECOGNIZED UNDERLYING DISEASE	ANEMIA	LEUKOPENIA	THROMBO-CYTOPENIA	ALIVE
I	21	13	16	14	8	5
II	3	2	3	1	0	0
III	6	4	4	2	3	1
IV	1	1	1	0	0	0
TOTAL	31	20	24	17	11	6

Of a total of 31 patients, 20 had no recognized underlying disease. Twenty-four were anemic, 17 patients had leukopenia, and 11 had thrombocytopenia. The grave nature of this disease is evident by the fact that only six patients are known to be alive. In addition to these findings, some of the patients appear to have leukemoid reactions without a definite diagnosis of leukemia being possible. There are also two patients with hairy cell leukemia. (Not included here is the patient (95) who had granulomatous hepatitis due to atypical mycobacteria and who also had hairy cell leukemia).

We are currently following two patients who have been treated for disseminated atypical mycobacterial infections. One is a 51 year old man who has leukemic reticuloendotheliosis. He was initially evaluated in January,

1974, for neutropenia, anemia and fever. No definite diagnosis could be made at that time, but in September, 1974, his clinical condition had evolved so that the diagnosis of leukemic reticuloendotheliosis could be made. At this time his leukocyte count was 1800 and his hematocrit 38. In January, 1976, he developed a severe febrile illness and underwent splenectomy as therapy for his disease. His fever continued and he ultimately was found to have a progressive increase in hilar lymph nodes, granulomas in the liver and bone marrow and disseminated hemorrhagic and pustular skin lesions. Cultures of bone marrow, lymph node, liver, and skin all yielded M. kansasii. He has had multiple drug therapy, mostly with isoniazid, ethambutol and rifampin, and slowly responded so that his chest x-ray has been stable, he has been afebrile and his skin lesions have healed. His liver function tests are normal. He was treated for two years. His leukocyte count remains in the neighborhood of 3800 with 22% polymorphonuclear cells.

A second patient became ill at the age of 54 with a very severe illness characterized by high fever, hepatosplenomegaly, enlarged mediastinal lymph nodes, and jaundice. He had multiple granulomas in the liver, bone marrow and mediastinal lymph nodes, the latter showing necrosis with acid fast bacilli. Initially, all of these cultures were negative. The patient responded very slowly to antimycobacterial therapy. Because he was so gravely ill, he was initially given steroid therapy for a short time, but this was soon discontinued. After 1 1/2 years of treatment, his drugs were discontinued and at that time he was apparently well except that he had continued leukopenia and his serum alkaline phosphatase was elevated.

He remained well from June, 1976, until September, 1976, at which time fever recurred, he became anemic, and his white cell count fell to 2200. Bone biopsy and liver biopsy revealed granulomas and the liver biopsy at this time was positive on culture for M. kansasii. Triple drug therapy was resumed and is still being carried on. The patient responded promptly the second time and is symptomatically doing well. His leukocyte count at present is 3900 and his hematocrit is 35. Elevation of the serum alkaline phosphatase persists.

SKIN TESTING

Considerable literature has been published concerning skin testing with a variety of preparations of "PPD" from different mycobacteria. (11,37,47, 75,76) A number of these tuberculins have been prepared and the ones generally recognized are listed in the next table.

TYPES OF PPD

NAME	SOURCE	RUNYON GROUP
PPD-S (SEIBERT)	M. TUBERCULOSIS	--------
PPD-Y (YELLOW BACILLUS)	M. KANSASII	(I)
PPD PLATY	M. MARINUM	(I)
PPD-G (GAUSE)	SCOTOCHROMOGEN	(II)
PPD-B (BATTEY)	M. INTRACELLULARE	(III)
PPD-F (FORTUITUM)	M. FORTUITUM	(IV)

The standard PPD-S is from M. tuberculosis, PPD-Y from M. kansasii, PPD platy from M. marinum, PPD-G is from a scotochromogen, PPD-B is from M. intracellulare, and PPD-F from M. fortuitum. These have been in general prepared like PPD-S, but it should be noted that there is little certainty as to whether the most specific antigens have been preserved in all instances. On the basis of animal experiments, one may say that the reactions to PPD of the various types is relatively specific - that is to say, animals react

more strongly to the tuberculin prepared from the homologous infecting strain. Cross reactions, however, do occur. The skin tests appear to be useful in epidemiologic studies and it is evident that many of the positive reactions to standard PPD are due to contact with mycobacteria of other types. Fogan (25) summarizes the current situation concerning the various tuberculins.

"A reaction of 12 mm. or more (for practical purposes the Public Health Service conservatively retains 10 mm. as the size where the significant reaction range begins) to a 5 TU of PPD-S is, in most instances, a specific response to M. tuberculosis infection no matter how much larger reactions to other mycobacterial antigens may be.....A distinction can be made between most of the cross reactions and most of the specific reactions by using the tuberculin test as a quantitative test to measure the degree of sensitivity. The test need no longer be a qualitative test simply to determine the presence or absence of a reaction. Determining the specific etiology of atypical mycobacterial infections is less certain in human populations because of the uncontrolled influences of their environment and the possibility of multiple infections.....In the case of atypical mycobacterial disease, the largest reaction is usually to the atypical PPD group antigen which is homologous with the organism demonstrated to be the etiology of the disease."

This needs to be taken in the light of Chapman's comments. (11,page 41). 1. Mycobacteria present very similar antigens, so that differential tests for hypersensitivity have very little discriminatory power. 2. Upon retests of the same individual, there is evidence of waxing and waning of response. When populations are retested after an interval, some have acquired

and some have lost hypersensitivity as measured by available sensitins.

The skin test materials are generally not available and as will be indicated by the foregoing, have relatively little diagnostic significance at the present time although that potential remains if better antigens become more readily available.

DRUG THERAPY

Recommendations for antimicrobial therapy of atypical mycobacterial infections must be presented in the most tentative way. In making suggestions, I will rely heavily on the information summarized in Chapman's book (11) in which one may find detailed references as to the literature citations which form the basis for these recommendations. The next table is reproduced from Chapman (11,page 161) and lists a variety of drugs which may be considered in the treatment of atypical mycobacterial infections.

Drug	Symbol	Dose	Frequency
Rifampin	RMP	600 mg/day	Single dose
Isoniazid[a]	INH	300 mg/day	t.i.d.
Ethambutol[b]	EMB	15 mg/kg/day	Single dose
p-Aminosalicylic acid	PAS	200 mg/kg/day	t.i.d.
Streptomycin[c]	SM	1.0 g	Daily or 2–3 times/week
Capreomycin	CM	1.0 g	As for SM
Kanamycin	KM	1.0 g	As for SM
Viomycin	VM	1.09 g	As for SM
Ethionamide	ETH	600 mg/day	b.i.d.
Cycloserine	CS	500 mg/day	b.i.d.
Pyrazinamide	PZA	1.5 g/day	t.i.d.
Erythromycin		1.0 g/day	q.i.d.
Sulfonamides		4.0 g/day	q.i.d.

As mentioned, specific recommendations must be very tentative for several reasons. Experience with many of these infections is relatively limited and because of the fact that over the years new drugs have been added, some of the most promising drugs are those with which we have had the least experience. This is particularly true of ethambutol and rifampin, especially

rifampin, and because of its newness and the fact that it is so expensive, experience is limited. Nevertheless, it may prove to be the most valuable drug we have in treatment of these infections. Clearly, one needs to employ the usual cultural methods with in vitro sensitivity tests as a guide to therapy. Many authors recommend that isoniazid be given regardless of the in vitro sensitivity, for reasons previously discussed. With all of these provisos in mind, we may review briefly suggested drug regimens for the most commonly encountered atypical mycobacteria. These are listed in the next table and I will comment only briefly on this summary.

SUGGESTED DRUGS IN TREATMENT OF ATYPICAL MYCOBACTERIAL INFECTIONS

RUNYON GROUP	ORGANISM	DRUGS
I	M. KANSASII	INH + EMB INH + EMB + RMP
	M. MARINUM	EMB + RMP (?INH) ?TRIMETHOPRIMSULFA ?MINOCYCLINE
II	M. SCROFULACEUM	INH + SM + RMP ?CS ?ETH
III	M. INTRACELLULARE	3-6 DRUGS RMP - EMB - INH PZA - ETH - CM
IV	M. FORTUITUM	KM, ERYTHROMYCIN CEPHALOSPORINS
	M. CHELONEI	? RMP

Infections of the lung due to M. kansasii have, in the most recent series, been reported to respond well to isoniazid and ethambutol. (41) On theoretical grounds, M. marinum infections might be expected to respond to

ethambutol and rifampin with the possible addition of isoniazid, as previously mentioned. Individual case reports of infections treated with trimethoprim-sulfamethoxazole or with minocycline suggest additional possibilities for these drugs.

In the case of M. scrofulaceum,surgery is apparently still considered to be definitive therapy, but drugs are also recommended after surgery. Isoniazid, rifampin, and streptomycin would appear to be reasonable choices although in a report of Salyer, et.al. (90) patients received isoniazid and PAS for eighteen months and did very well. This result, of course, may be attributable to the surgery itself.

A special problem is presented by M. intracellulare infections. Those investigators who have had the widest experience routinely recommend multiple drug therapy although recommendations vary from three to six drugs and the individual drugs themselves also vary. As in indicated in the table on the previous page, rifampin, ethambutol, and isoniazid are generally recommended, even though many strains are resistant to isoniazid. Pyrazinamide, ethambutol and capreomycin are also recommended. On the basis of sensitivity tests, one would think also that cycloserine might be useful. It must be said that, at least until the introduction of rifampin, the results of antimicrobial therapy of pulmonary infections due to these organisms were poor. The combination of this therapy plus surgery, when possible, improves the prospects.

Infections due to M. fortuitum and M. chelonei present quite a different problem and,again, it is very difficult to offer any firm suggestions. In some circumstances, simply surgical therapy has been adequate to treat these

infections. (43,73) In considering drug therapy, it should be recalled that these are rapidly growing organisms and that one may test their in vitro sensitivity quite readily to many of the usual antimicrobial drugs in common use, not generally considered to be antimycobacterial drugs. (3) Among these, kanamycin, erythromycin, and the cephalosporins have been reported to exhibit substantial in vitro activity and,accordingly, these drugs may be tried. Again, rifampin may possibly be a useful drug.

SURGICAL TREATMENT

Surgical therapy has had a distinct place in the treatment of pulmonary disease due to atypical mycobacteria. (15,20,26,80) As was the case at one time with infections due to M. tuberculosis, the role of surgery reflects inadequacy of antimicrobial therapy. In general, surgery has been employed for the following reasons:

1. Failure to influence lesions with suitable chemotherapy.
2. Inability to pursue what appears to be a reasonable regimen of chemotherapy because of toxicity.
3. The presence of localized disease, unresponsive to therapy.
4. The absence of underlying lung disease of sufficient severity to contraindicate the surgery.

SUMMARY

In summary, it may be said that infections with the so-called atypical mycobacteria are being reported with increasing frequency, and considerable experience is being gained concerning their clinical features as well as their therapy. The field is a rapidly evolving one in which one can make only very general statements at the present time and those without too great a degree of certainty. Nevertheless, recognition of the various clinical

syndromes produced by these microorganisms is assuming increasing importance, and a greater awareness of their occurrence promises to provide an area of lively interest in infectious diseases in the future.

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