Special Communications

ATYPICAL MYCOBACTERIA

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At the time of discovery of tubercle bacilli and their acid fastness by Koch in 1882, it was believed that the disease was caused by only one kind of acid fast organisms. Theobald Smith, sixteen years after, first observed that tubercle bacilli infecting cattle were different than those infecting humans (Dubos and Hirsch, 1965). Thus it was established that there were two types of tubercle bacilli, *M. tuberculosis* variety homines and variety bovis. Later on acid fast bacilli started appearing in the clinical specimens which were found to be quite different from the typical tubercle bacilli. As early as in 1918 Corbett reported repeated isolation of acid fast organisms from a patient with different characteristics. Since then, reports started appearing concerning mycobacteria other than the typical tubercle bacilli. As more and more knowledge was accumulated about atypical mycobacteria, it was established that besides *M. tuberculosis* other different types of acid fast bacteria are capable of causing infection in human beings, although the mechanisms of emergence of these mycobacteria remained in question. Many investigators suggested possible role of mutation, spontaneous or induced, due to chemotherapy, which caused emergence of different types of mycobacteria. Others believed that these were saprophytes as many of these were found in soil and water. These mycobacteria, whenever got an excess in the human system caused the infection. Thus the term of opportunist mycobacteria was adopted by many for these mycobacteria. However, as the present knowledge shows, there is a very thin line between the term pathogenic and saprophytic organisms because many of the saprophytes may become potential pathogens if they get a chance to get into the body and beat the hosts defence mechanisms.

Terminology and Classification:

Like opportunist mycobacteria, there are many other terminologies which appear in the medical literature for mycobacteria other than tubercle bacilli. Many workers started calling these as unclassified or anonymous mycobacteria but this terminology has been dropped after certain system of classification and identification was evolved. The term atypical mycobacteria has established itself in medical literature and is now widely used.

It was early fifties when interest in this subject increased considerably and workers started analyzing the accumulated knowledge. Runyon

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for the first time in 1959 put forward a system of classification of mycobacteria into different groups. Many other systems of classification were also suggested but all are generally based on growth rate and other characteristics, optimum temperature for growth, pigment production and sensitivity to thiosemicarbazone. However, Runyons' classification, with many modifications, is still most widely accepted.

Originally all mycobacteria except human, bovine and avian were classified as atypical mycobacteria. Further studies have excluded a few more bacteria from atypical. Those which are at present excluded from atypical mycobacteria are as follows (Vestal 1975).

M. tuberculosis: This is still the most common species cncountered in human infections, causing pulmonary as well as extra-pulmonary disease. The colonies are rough, non-chromogenic. These bacteria are Niacin producer which is a very prominent characteristic of these mycobacteria. Niacin is a substance which is produced during the growth of these bacteria and is released in the medium and can be checked biochemically. With a few exception all mycobacteria other than *M. tuberculosis* are Niacin negative.

M. bovis: It is found mostly in cattle tuberculosis and rarely in man. Colonies are small, rough to smooth and non-chromogenic. Niacin is not produced or weekly produced.

M. africanum: It is mostly found in Western Africa causing pulmonary tuberculosis and seems to be in between *M. tuberculosis* and *M. bovis*. The colonial characteristics are close to *M. bovis* with Niacin negative.

M. ulceraus: It is isolated from cutaneous or sub-cutaneous ulcerative lesion of men and is never isolated from pulmonary infection. It is generally found in tropical regions and grows slower than *M. tuberculosis*, usually 6-9 weeks. It grows at low temperature (30-32°C) while at 37°C it does not grow. It is Niacin negative.

The rest of mycobacteria, called atypical are classified as follows:-

Modified Key of Runyons Classification:

The Runyons classification separates out all atypical mycobacteria into four groups:

Group I Photochromogens	
Group II Schotochromogens	
Group III Non-chromogens	Slow
Group IV Fast growers	growers

Group I Photochromogenic Mycobacteria: These bacteria produce light sensitive pigment and thus when grown in dark, they are non-chromogenic with buff color, but when exposed to light the colour turns to bright orange. This is why they were originally known as orange bacillus. Originally only *M. kansasii* was included in this group but later studies have included *M. marinum* and *M. simiae*.

M. kansasii: It is one of the commonest atypical mycobacteria causing infection in man in western countries. Generally it causes pulmonary infection but can involve, though rare, renal and other extra-pulmonary sites. It is Niacin negative.

M. marinum: It causes aquatic infection and may be isolated from superficial lesions in men due to swimming pool infection (soar elbows). It is never isolated from pulmonary infection. It grows better at 30-32°C than at 37°C. It is sometime Niacin positive. Previously it was known as *M. balnei*.

M. simiae: It was first isolated from monkeys and was known as *M. habana*. It has also been isolated from pulmonary infection of man in Cuba. It is highly Niacin positive.

This is interesting that all the 2 species in group I are potential pathogens. Some workers have classified catalase negative, *M. kansasii* separately being non-pathogens but actually it is just a different strain of the same *M. kansasii*.

Group II Schotochromogenic Mycobacteria: These are the chromogenic mycobacteria having yellow to orange pigment, when grown in dark as well as in light. Sometimes the pigment gets darker when exposed to light. Usually the growth is smooth and shining. These bacteria do not produce Niacin.

These are commonly encountered in sputum, gasteric aspiration and other extra-pulmonary specimens, sometimes representing contamination from outside. The potential pathogens in this group generally cause extra-pulmonary infection in human beings.

M. scrofulaceum: This is found world-wide, generally causing tubercular lymphadinitis in children although pulmonary infection may also occur.

M. xenopi: It is generally isolated from pulmonary lesion and may be implicated in human disease. Its optimum temperature is 42°C but grows at 37°C. These bacteria are sometimes included in the Group III non-chromogens because of the similar biochemical reaction and pale yellow colour of the growth.

M. zulgai: Little is known about this mycobacterium. It is rarely isolated from human infection. It grows at 37°C but can also grow at 26°C and may be photochromogenic at low temperature.

The other species which are usually non-pathogenic are: *M. gordonae* which was previously known as *M. aquae* or tap-water mycobacteria. These are found in soil and water and are the common contaminating organisms in tuberculosis bacteriology. *M. flavescens* is also a saprophyte from soil and according to the rate of growth it is in between slow and fast growing mycobacteria and thus can be classified in group IV as well.

Group III Non-chromogenic Mycobacteria (Battey-Avian Complex):

These are slow growing mycobacteria which do not produce any pigment or Niacin. These are one of the most commonly encountered mycobacteria in human infection all over the world. This group consists of two very closely related species of potential pathogens.

M. avium and its related organisms are called *M. avium* complex and are causative agent of infection in birds, rarely in man, pigs and some other animals.

M. intracellulare (Battey baccilus): This is the most commonly encountered atypical mycobacteria in human pulmonary and extra-pulmonary infection and is generally grouped together with *M. avium*, known as *M. avium* complex. Because of its similarity many workers consider it as a variety of *M. avium*.

Among non-pathogens in this group, *M. terrae* complex, M. *triviale* and *M. gasteri* are the one which are considered clinically insignificant. These mycobacteria are generally found in soil and soiled water and subsequently gain excess to the clinical specimens. *M. gasteri* has been occasionally isolated from gastric washings but with no clinical significance.

Group IV Rapid Growers: These are the mycobacteria which are grouped separately because of their fast rate of growth. The colonies generally develop within a week and sometime within couple of days. Most of these mycobacteria can grow on ordinary culture media like nutrient agar. The colonies are generally smooth and Niacin negative. These bacteria may be chromogenic or non-chromogenic.

M. fortuitum is the most common pathogen in this group isolated from pulmonary as well as extra-pulmonary infection in man and sometimes in animals. These bacteria are non-chromogenic and show greening of egg medium as malachite green color is absorbed in old cultures.

M. chelonei is also non-chromogenic and has come up recently as a potential pathogen. It has been isolated from well-documented cases of pulmonary infectin.

One of the characteristic difference between these two potential pathogens and other non-pathogens is that *M. fortuitum* and *M. chelonei* can grow on Maconkey medium while others do not.

There are many rapid growing mycobacteria which are grouped as "Group IV and others" without having any established clinical significance. Some of these have been classified as *M. vaccae*, *M. phlei* and *M. smegmatis* while others are yet to be identified and named. Most of these are the common contaminents from soil and water.

All mycobacteria which are known to be clinically significant are summarized in the table along with their potential pathogenicity.

Due to the complexity of the classification and confusion in identifying mycobacteria, in recent years the genes mycobacterium is under intensive studies in order to formulate a definite system of classification. Members of International Working Group of Mycobacterial Texanomy (IWGMT) are investigating various characteristics of mycobacteria following cultural, biochemical and serological analysis, bacteriophage typing and lipid analysis. Final analysis is made by computer in order to establish position of each mycobacterial strain (Wayne and Doubeck, 1968).

More recently Runyon (1974) has suggested another system of identifying these mycobacteria discarding his own grouping system. He suggested ten species or species complexes, each including a number of potential pathogenic mycobacteria. These 10 mycobacterial pathogens are: *M. leprae*, *M. ulcerans*, *M. tuberculosis* complex, *M. kansasii*, *M. marnum*, *M. simiae*, *M. zulgai*, *M. avium-scrofulacium* complex, *M. xenopi* and *M. fortuitum* complex.

There are drastic changes in this system. *M. leprae* which is always dealt with separately is included in this system. *M. ulcerans* is placed second because it causes skin ulcers and is close to *M. leprae* in many respects including very slow rate of growth. *M. tuberculosis* complex includes *M. tuberculosis* as well as *M. bovis* and *M. africanum* all closely related species. *M. avian*, *M. intracellulares* and *M. scrofulaceum* are all included in a complex which means group II and group III mycobacteria are grouped

Table Potential Pathogenic Mycobacteria

Disease	*Runyon's Old Grouping*	*Name of Mycobacterium*	*Pathogenicity*
Tuberculosis :			
	Mammalian tubercle bacilli	*M. tuberculosis*	Chiefly man and monkeys pulmonary and extra-pulmonary infection.
		M. bovis	Chiefly cattle and pigs and also sometimes in man. Extra-pulmonary infection, rarely pulmonary in man.
		M. africanum	Chiefly man in Africa.
		M. ulcerans	Chiefly man, skin ulcers only. (previously included in Group III).
Mycobacterioses :			
	Runyon Group I Photochromogens	*M. kansasii*	In man, pulmonary infection.
		M. marinum	Mostly in fish occasionally skin ulcers in man.
		M. simiae (Habana)	Mostly in monkeys. Rarely in man, pulmonary infection.
	Runyon Group II Scotochromogens	*M. scrofulaceum*	In man occasionally, cervical adenitis and other extra-pulmonary infection. Rarely pulmonary infection.
		M. szulgai	In man, pulmonary infection.
		M. xenopi	In man, pulmonary infection.
	Runyon Group III Non-chromogens	*M. avium*	Mainly birds, also rarely in man.
		M. intracellulare (Battey)	In man, mostly pulmonary but also extra-pulmonary infection.
	Runyon Group IV Rapid growers	*M. fortuitum*	In man, usually extra-pulmonary occasionally skin ulcers and pulmonary.
		M. cheloni	Pulmonary and extra-pulmonary infection in man.

*Adopted from DHEW Publication No. CDC 75-5230, 1975, Bailey and Scott 1974, Selkon 1969 and Wayne and Doubeck 1968.

together. He recommends that diseases caused by mycobacteria other than tubercle bacilli (*M. tuberculosis* complex) should not be called tuberculosis or atypical tuberculosis. It is suggested that mycobacterioses is a more appropriate terminology.

Pathogenisis :

The disease producing capability of any organisms depends mostly on two factors, the virulence of the parasite and the susceptibility of the host. Although the pathogenic mechanism of atypical mycobacteria is similar to tubercle bacilli. It has been established that there is a decreased bacterial virulence and increased native host resistance to atypical mycobacteria (Gentry 1966). This explains the lower incidence of infection due to atypical mycobacteria.

Since, in general, atypical mycobacteria are less pathogenic and less virulent, the infection depends upon large dose of the organism, repeated exposure and the overall decrease in the defense mechanism of the host. Moreover, specific alteration in a particular tissue may make the tissue more susceptible to the atypical mycobacterial infection. These altered conditions ultimately shift the balance of the host parasite relationship making a commensal into a disease producing parasite.

The infection process in case of atypical mycobacteria follows almost the similar pattern as typical tuberculous infection, with basic granulomatous lesion and the immunologic tissue response. However, the disease is generally less progressive because of lower virulence of the parasite. The primary complex, characteristic of tuberculous infection is generally not observed in atypical infection. The organisms do involve the lymphatic tissues and produce, as usual, caseating lesions. Calcified foci have been observed in mycobacterioses but in a lesser degree. This follows the development of tissue medicated hypersensitivity against the particular infecting atypical mycobacteria which can be detected by using purified protein derivative (PPD) prepared from each specific atypical mycobacteria.

There have been reports of generalized infection due to atypical mycobacteria but it is not common (Gentry 1966). No definite information is available concerning type of mycobacteria involved but generally group II and IV may be involved in generalized infection as they are hard to control by chemotherapy and are thus fatal.

The symptoms presented by atypical mycobacterial infection vary to some extent from typical infection. The disease, generally is more chronic and remains chronic even after treatment. However, it presents with lesser symptoms, especially in early stage and thus goes undiagnosed most of the time. The sputum remains positive for longer period. Sometimes even during treatment sputum remains positive for quite some-

time because the bacteria are less susceptible to anti-tubercular drugs.

There is some variation between different atypical mycobacterial infection, like patients with *M. kansasii* infection show greater tendency towards acute inflamatory lesions with caseation, while infection due to group III Battey type is more chronic with usually extensive fibrosis. Usually in mycobacterioses cavities are thin walled and irregular. The lesions are also sometimes more wet. However, in a routine X-ray examination it is difficult to differentiate typical and atypical infection radiologically (Yamamoto et al., 1967; Selkon, 1969). Usually giant cells are less in number in atypical infection with marked non-specific infiltration. Large amounts of free and phagocytosed fats are present. However, most pathologists, feel that it is difficult to differentiate typical and atypical infection histopathologically (Reid and Wolinsky, 1969).

Thus, generally speaking, it is difficult to differentiate between different types of mycobacterial infections depending upon history of the patient, symptoms, clinical findings, radiologically or histopathologically. The only sure way of the differential diagnosis is Acid Fast Bacterial (AFB) culture.

Sometimes, with extensive experience, it is possible to differentiate atypical mycobacteria on Ziehl Neelsen stained smear made from the clinical specimens. There is, often, morphological differences in between different mycobacteria, atypical being larger and thicker or too small and coccobacillary form of acid fast organisms. Moreover atypical mycobacteria are usually more straight rods evenly distributed and with no clumping or chord formation. The culture, however, establishes the final diagnosis because the characteristics of growth of atypical mycobacteria are quite different from *M. tuberculosis*. The smear made out of pure culture also clearly differentiates between many types of mycobacteria. Most of the atypical mycobacteria are easily emulsifyable on a slide smear and thus are more evenly distributed on a smear along with differences in morphology.

Many workers have suggested that just the isolation of a few colonies of atypical mycobacteria does not establish the mycobacterial infection and one has to be more careful in establishing the final diagnosis in case of atypical mycobacteria. Different experts have established different criteria for establishing atypical infection (Fisher et al., 1968; Selkon, 1969; Pellman and Runyon, 1964). Gale (1976) establishing the criteria of causal relationship describes that there must be some clinical evidence of the disease along with radiological evidence in the lung or urinary tract, atypical mycobacteria must be recovered repeatedly and *M. tuberculosis* must never be recovered However, in our experience it is not necessary to have all these conditions fulfilled. Clinical evidence, of course, is necessary, but in many extra-pulmonary infections, it is not possible to have radiological evidence since in our studies, majority of the cases had no indication in the chest X-ray (Siddiqi 1972). In the renal tuberculosis, a good number of patients showed normal intravenous pyelogram but were found culture positive for typical or atypical mycobacteria (Siddiqi and Khan, 1978).

Repeated isolation of atypical mycobacteria is one of the important pre-conditions which has been recommended by many workers. Yamamoto and others (1967) recommended that a strain should be considered significant if the presence of organisms correlated with the disease process or there was response to the treatment, otherwise the organisms should be considered as casual. On the other hand others believe that more than once, twice, or even thrice isolation would confirm the significant etiology of an isolate (Gale 1976; Gentry 1966; Selkon 1969). However, sometimes it is difficult to understand why a clinical specimens yielding heavy growth of atypical mycobacteria should not be considered positive unless it is proved more than once or twice. Many a times it becomes difficult to obtain more than one specimen from a patient, especially in surgical cases. If a single isolation of atypical mycobacteria is disregarded, despite the clinical findings, then it becomes difficult to establish the diagnosis and subsequent line of treatment. This issue is more important in extra-pulmonary infections which unfortunately, has not been dealt with sufficiently in medical literature. In our studies, thus, we established our own criteria that if more than 8-10 colonies of atypical mycobacteria appeared on more than one culture tube or plate, especially in extrapulmonary specimens, and the organisms were those which are considered potential pathogens then we considered the isolation as significant even if it was not confirmed second time. Moreover, if the concentration smear was also positive along with clinical findings, then the diagnosis was established definitely. In our experience, moreover, atypical mycobactrial colonies appearing as a contaminant in AFB cultures are very rare and thus there is less chance of contamination of atypical mycobacteria from outside at least in our laboratory.

The last condition that *M. tuberculosis* must never be recovered in case of atypical infection is again difficult to accept. In our experience simultaneous infection of atypical and typical mycobacterial infection does exist and it has been reported by other workers as well (Gentry 1966; Selkon 1969). The role of atypical mycobacteria in such cases is yet to be determined. However, their presence in large number along

with tubercle bacilli is a sufficient indication of the potential role.

Establishing a strict criteria of atypical mycobacterial infection is due to the fact that many atypical mycobacteria, some even potential pathogens, are frequently found in environment and do appear on the AFB culture as a contaminant. Many studies have indicated that atypical mycobacteria are frequently isolated from patients with chronic cough and bronchitis with no X-ray evidence (Selkon, 1969; Yamamoto et al., 1967a). In such cases the role of atypical mycobacteria becomes doubtful. Moreover, it has been pointed out that atypical mycobacteria may be isolated from healthy persons sputa, gastric washings and urine. Edwards (1959) found 30 positive cultures out of 122 specimens, 17 being mycobacteria and 14 actinomycetes. This seems to be a very high figure and possibility of a source of contamination in the laboratory cannot be ruled out. The presence of these mycobacteria in different studies, however, differ a great deal. In an international investigation, Meisner (1967) reported no atypical mycobacteria in 75000 specimens examined in Budapest, while 6.2% to 2.8% specimens examined in Germany showed atypical mycobacteria. Although no such study is carried out in Pakistan but in our 10 years experience with about 15,000 sputa of tuberculous patients and suspects, contaminating atypical mycobacteria are extremely rare.

In short there is no definite criteria established so far the mycobacterioses is concerned. In general if there is sufficient growth of mycobacteria which are considered significant and the culture results are in agreement with clinical findings then we believe that the diagnosis is safely established. It is very important to identify the organisms and if possible repeat specimen should be checked before giving out report. Presence of fewer organisms with single isolation is generally disregarded because it is possible that the organisms are present as commensals with a host-parasite balance or are contaminant from outside.

Geographic Distribution and Prevalence:

In general, atypical mycobacterial infection, unlike pulmonary infection is less common in a crowded city as compared to rural areas. There is a definite age, sex, racial and geographical distribution pattern as well as the site specifically among different atypical mycobacteria. Negroes and Puerto-Ricans do not have this disease as frequently as tuberculosis (Gentry 1966). Pulmonary mycobacterioses is rare in children while tubercular lymphadinitis in children due to atypicals is frequent. Group I pulmonary infection is relatively more in younger age group than group III infection. Generally pulmonary mycobacterioses is found in males, especially group I infection is rare in females.

One very interesting aspect is the absence of transmission of this disease among contacts. There is no documental evidence that more than one case occurred in any family (Crow et al., 1961). This means that atypical mycobacterial disease is not infectious like tuberculosis. This brings another question that how the disease is transmitted and how a person acquires infection.

So far geographic distribution is concerned the disease due to atypical varies for 0.1% to 10% of the total tuberculosis depending upon the country (Selkon 1969). In countries where there is a high prevalence of tuberculosis like India, Africa and probably Pakistan the relative prevalence of atypical mycobacteria is very low 0.2-0.4%. While in low prevalence areas like western countries, its prevalence is comparatively higher. Thus many people have started believing that if we control tuberculosis in an area, atypical mycobacteria start taking place of *M. tuberculosis*, the reason of which is not very well understood (Klotz 1970). Moreover, the prevalence of different atypical mycobacteria also varies from country to country. Photochromogens are fairly common in the United States but have never been isolated from Pakistan (Siddiqi 1973, 1977). In Australia it has been reported that majority of tubercular lymphadenitis is due to group III type while from Africa no atypical mycobacteria was isolated from lymph glands (Makeller et al., 1967; Sula et al., 1960). In Canada, U.S.A., England and many other countries, generally group II schotochromogens are common, and are on the increase (Keay 1969; Marks 1969). Same variation is found in other mycobacterial infections as well.

Atypical mycobacterial infection is found more common in extra-pulmonary sites than lungs. This is more true in Pakistan as our studies indicate. In the medical literature, most of the data is based on pulmonary tuberculosis and thus there is no comprehensive report concerning extra-pulmonary infections in general in other countries. In Pakistan our studies have revealed that about one fifth of tubercular lymphadenitis is due to atypical mycobacteria, mainly group II schotochromogens (*M. scrofulacium*), while in general urinary tuberculosis about 12-15% of the isolates were atypical, mainly group III type (Siddiqi et al., 1974; Siddiqi and Khan, 1978). Atypical mycobacteria have been isolated from bone, abdomen, pleural fluid, but never from CSF and pericardial fluids (Siddiqi 1975). In pulmonary tuberculosis, out of about 2000 positive cultures 12 were found positive for atypical, mostly group III type (Siddiqi 1977).

Fortunately atypical mycobacterial infection is not a big problem for Pakistan because this country, unfortunately, is rated among one of the few highest prevalence areas for tuberculosis in the world.

The prevalence of atypical mycobacterial infection in a population can be determined by differential tuberculin testing using sensitins prepared from different types of mycobacteria in the same way as standard tuberculin (PPD-S). Although there is always a cross reaction between PPD-S and other sensitins from atypical mycobacteria but it is believed that a person who has been infected with a particular atypical mycobacteria would react predominantly to that mycobacterial antigen. Thus by using differential tuberculin testing, a rough estimate may be made about the prevalence of atypical and typical mycobacterial infection in general. Usually reaction to PPD-S in a low dose (5 TU or less) indicates infection due to *M. tuberculosis*, but if a person reacts only to a higher dose of PPD-S then it is supposed to be due to cross reaction with atypical mycobacterial infection.

One problem, however, exists that the skin reaction to atypical mycobacterial antigen does not differentiate between exposure to potential pathogens and saprophytes commonly found in soil and water. For example PPD-G antigen will indicate exposure to schotochromogenic mycobacteria but does not differentiate between *M. scrofulaceum* infection or other non-pathogens of the same group.

Our studies indicate that reaction to different PPD antigens in patients varied depending upon the site of infection and type of mycobacteria involved (Siddiqi et al., 1974). Overall there was lower tuberculin sensitivity among extra-pulmonary cases. In typical mycobacterial infection there was much lower tissues mediated hypersensitivity giving more tuberculin negative results. Moreover, the differential tuberculin test in culture positive cases did not always correlate well with the type of mycobacteria isolated. This means that differential tuberculin test for diagnostic purpose has got less value in our country. This could be due to the high prevalence of tuberculosis and high infection rate to *M. tuberculosis* in the population.

Our tuberculin sensitivity studies in general population utilizing a battery of different antigens indicate prevalence of infection due to atypical my cobacteria in the population with great variation in allergic responses depending upon the areas tested (Siddiqi 1973). For example in forested areas with lots of water, trees and birds, PPD-A (avian) and PPD-G (schotochromogens) reaction was high. In hilly areas PPD-Y (photochromogens) reaction was comparatively higher than other areas. In crowded city PPD-S was the only predominant reaction. This shows that the disease due to atypical mycobacterial infection may also vary from place to place. However, culture work and typing of mycobacteria in other areas has not been done to establish this assumption.

Drug Sensitivity :

One of the features of atypical mycobacterial infection is the overall low response to antitubercular drugs as most of the organisms are resistant to the major drugs at low levels. Moreover, there is no definite fixed pattern of natural drug sensitivity for different species of mycobacteria. There is variation even among different isolates of the same species. Thus, the treatment of mycobacterioses present manyfold problems and culture sensitivity in-vitro becomes extremely essential in order to have an effective treatment programme. A careful follow-up with periodical check up of drug sensitivity is necessary in the mycobacterioses.

So far the effectiveness of different antitubercular drugs is concerned, different workers have given different reports and thus no fixed pattern can be estimated from the reports in medical literature (Dubos and Hirsch, 1965; David, 1974; Gentry, 1966; Hinshaw, 1969; Hoby et al., 1967; Selkon, 1969). In general, with a few exceptions, all atypical mycobacteria are partially or completely resistant to INH, Pyrazinamide and PAS. Some physicians prefer to use INH any way along with other drugs. One thing for sure that if atypical infection is expected then three and preferably four drugs should be given simultaneously with a very close and constant follow-up. The choice of drug can be made according to the drug sensitivity and a drug can be included even if the infecting organism are partially sensitive to that drug.

In group I mycobacterial infection Ethionamide, Streptomycin and Cycloserine therapy has been reported to be of some value. However, the place of Cycloserine is not definite because of conflicting reports. Thiacetazone, Ethambutol and Rifampicin may also be effective. Group I mycobacteria, in general have greater susceptibility to INH than any other atypical mycobacteria.

Group II mycobacteria are generally sensitive to Streptomycin, Kanamycin, Cycloserin, Ethambutol and Rifampicin, sometimes in higher dose. INH, Ethambutol and Thiacetazone may be effective individually.

Group III mycobacteria are generally more resistant type than those of Group I and II. These organisms generally respond to Streptomycin, Cycloserin, and Rifampicin. Kanamycin and INH may also be effective partially.

Most of the group IV organisms are best treated with Streptomycin, Kanamycin and possibly INH and Ethionamide. Ethambutol has very little value, Rifampicin is doubtful.

With the results in hand at present, it is difficult to call any particular species of atypical mycobacteria resistant or sensitive to any drug because of the variation in the results. Moreover, there is a great margin between degree of sensitivity and resistance and thus each drug has to be evaluated individually and carefully after seeing the degree of sensitivity or resistance of bacterial population. Our experience with in-vitro drug sensitivity indicates vast variation in the drug sensitivity. Ethionamide, Ethambutol and Rifampicin have possible therapeutic role in case of group II, III and IV mycobacteria. Streptomycin had some use in selective strains of group IV mycobacteria. In general we found most of the atypical mycobacteria resistant almost always to PAS, with a few exceptions to INH and to a lesser degree to Streptomycin. In secondary line of drugs, again there was no fixed pattern but Ethionamide, Ethambutol and Rifampicin sensitivity was observed in a few. Cycloserin, Kanamycin, Capreomycin and Pyrezinamide are not being tested in our laboratory.

Some workers have studied sensitivity of atypical mycobacteria to antibiotics as well (Guy and Chapmen, 1961). Mycobacteria for group I, II and III were found sensitive to Erythromycin with varying degree, occasionally sensitive to Chloramphenicol and always resistant to different tetracyclines.

Atypical Mycobecterioses is posing a great problem all over the world. However, so far the identification and classification and criteria for pathogenicity of mycobacteria is concerned, much work is still needed to establish the standards. Knowledge about chemotherapy in mycobacterioses is very limited. Tuberculosis as well as mycobecterioses, has been neglected in those developed countries where most of the research is being carried out because the disease has been brought under control to some extent. On the other hand, in other countries where the disease is highly prevalent, there are no means and facilities to carry out research work, although there is ample opportunity to carry out investigations on the vastly available clinical material. Thus an international joint venture is needed to fight the disease which has been in the roots of mankind from the pre-historic days.

References

Corbett, L. (1918) An acid fast bacillus obtained from a pustule eruption. Br. Med. J., 2:158.

Crow, H.E., Corpe, R.F. and Smith, C.E. (1961) Is serious pulmonary disease caused by non-photochromogenic (Atypical) acid-fast mycobacterial communicable? Dis. Chest, 39:372.

David, H.L. Indications of drug susceptibility testing in tuberculosis and other human mycobacteriosis. Washington, U.S. Dept. of Health, Education and Welfare, Public Health Service, 1974.

Dubos, R.J. and Hirsch, J.G. Bacterial and mycotic infections of man. 4th ed. London, Pitman, p. 965.

Edwards, L.B. and Palmer, C.E. (1959) Isolation of atypical mycobacteria from healthy persons. Am. Rev. Resp. Dis., 80:747.

Fischer, D.A., Lester, W. and Schaeffer, W.B. (1968) Infections with atypical mycobacteria. Five years experience at the National Jewish Hospital. Am. Rev. Resp. Dis., 98:29.

Gale, G.L. (1976) Atypical mycobacterial in a tuberculosis hospital. Can. Med. Assoc. J., 114:612.

Gentry, W.H. (1966) Atypical mycobacterial infections. Pract. of Med., 3:751.

Guy, L.R. and Champman, J.S. (1961) Susceptibility in-vitro of unclassified mycobacteria to commonly used antimicrobials. Am. Rev. Resp. Dis., 84:746.

Hinshaw, H.C. Diseases of the chest. 3rd ed. Philadelphia, Saunders, 1969.

Hobby, G.L., Redmond, W.B., Runyon, E.H., Schaeffer, W.B., Wayne, L.G. and Wichel-hausen, R.H. (1967) A study on pulmonary disease associated with mycobacteria; Characterization of the mycobacteria, other than mycobacterium tuberculosis: Identification and XVIII. A report of the veterans administration. Armed Forces Cooperation study. Am. Rev. Resp. Dis., 95:954.

Keay, A. J. (1969) A typical micobacteria lymphadenitis. Tubercle, 50:85.

Klotz, P.G. (1970) Atypical acid-fast bacteria in urine. Can. Med. Assoc. J., 103:283.

Mackeller, A., Hilton, H.B. and Masters, P.L. (1967) Mycobacterial lymphadenitis in childhood. Arch. Dis. Child., 42:70.

Marks, J. (1969) 'Opportunist' mycobacterial in England and Wales. Tubercle, 50:78.

Meisner, G. (1967) Report to committee on bacteriology and immunology. Bull. Int. Un. Tuberc., 39:17.

Pellman, C.M. and Runyon, E.H. (1964) The significance of mycobacteria other than tubercle bacilli in the urine. A report of forty-two cases. Am. Rev. Resp. Dis., 90:243.

Reid, J.D. and Wolinsky, E. (1969) Histopathology of lymphadenitis caused by atypical mycobacteria. Am. Rev. Resp. Dis., 99:8.

Runyon, E.H. (1959) Anonymous mycobacteria in pulmonary disease. Med. Clin. N. Am., 43:273.

Runyon, E.H. (1974) Ten mycobacterial pathogen. Tubercle, 55:235.

Selkon, J.B. (1969) Atypical mycobacteria: A review. Tubercle, 50:70.

Siddiqi, S.H. Studies on mycobacterial diseases in Pakistan. Final Report, University of Maryland, Karachi, Pakistan Medical Research Center, 1973.

Siddiqi, S.H. (1975) Extra-pulmonary tuberculosis. Prog. Med., 4:1.

Siddiqi, S.H. Annual report 1976. Karachi, Pakistan Medical Research Council, 1977. pp. 64.

Siddiqi, S.H. and Khan, F.A. (1978) Bacteriological study of renal tuberculosis in Pakistan (unpublished).

Siddiqi, S.H. and Stauffer, J.C. (1973) Tuberculin sensitivity to PPD-S and three atypical antigens in Pakistan. Pak. J. Med. Res., 12:11.

Siddiqi, S.H., Stauffer, J.C., Ali., M.A. and Ahmed, B. (1974a) Tuberculin lymphadenitis. A study of mycobacteria isolated from cervical lymph glands. Pak. J. Med. Res., 13:63.

Siddiqi, S.H., Stauffer, J.C., Tariq, F.N. and Baig, S. (1974) Negative tuberculin test in proven cases of pulmonary and extraordinary tuberculosis. Pak. J. Med. Res., 13:7.

Sula, L., Stott, H., Kubin, M. and Kiaer, J. (1960) A study of mycobacteria isolated from cervical lymph glands of African patients in Kenya. Bull. Wld. Hlth. Org., 23:613.

Vestal, A.L. Procedures for the isolation and identification of mycobacteria. Atlate, United States Public Health Publication No. 1995, 1975.

Wayne, L.G. and Doubeck, J.R. (1968) Diagnostic key to mycobacteria encountered in clinical laboratories. App. Microbiol., 16:925.

Yamamoto, M., Ogura, Y., Sudo, K. and Hibino, S. (1967a) Diagnostic criteria for disease caused by atypical mycobacteria. Am. Rev. Resp. Dis., 96:773.

Yamamoto, M., Sudo, K., Taga, M. and Hibino, S. (1967b) A study of diseases caused by atypical mycobacteria in Japan. Am. Rev. Resp. Dis., 96:779.