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EDITORIALS

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The Ubiquity of Mycobacteria[1, 2]

Of the multitude of classified microorganisms, few are capable of producing such serious, protracted and potentially lethal disease in human beings and animals as certain organisms belonging to the genus *Mycobacterium*. The two most important and best known species are, of course, *M. leprae* and *M. tuberculosis*, both of which are worldwide in their distribution and affect the lives of countless human beings. The numerous recognized mycobacteria include some species that have been identified but not yet classified. In addition, it seems a valid assumption that other species, as yet unrecognized, exist.

The ubiquity of mycobacteria indicates that they have an extraordinary capacity to survive, even under most unfavorable environmental conditions. Consequently, it is not surprising that, by suitable laboratory methods, mycobacteria of various species have been demonstrated in naturally acquired lesions from mammals, birds, reptiles, fish, frogs, and fresh water snails. In addition, these microorganisms have been isolated from atmospheric air, soil, tap water, milk, and the surface of human skin.

For identification purposes, the most important feature of mycobacteria is their alcohol-acid-fastness, which differentiates them from all other bacillary forms of bacteria. Once they are identified as mycobacteria, subsequent studies *in vitro* and *in vivo* may be necessary. Such studies should be adequate to establish the precise identity of the bacteria associated with, or responsible for, a patient's illness. If the preliminary findings suggest heretofore unidentified mycobacteria, the scheme of the study should be broadened.

A resumé of the distinctive features of the microorganisms constituting the genus *Mycobacterium* reveals the existence of considerable diversity among respective species. For instance, some species require critical temperatures for growth *in vitro*, while others can grow and multiply *in vitro* throughout a fairly wide range of temperatures. Others, including *M. leprae* and *M. lepraemurium*, have not yet been cultivated *in vitro*.

Morphologically, members of the genus grown *in vitro* are capable of marked variations, not only as individual bacilli, but also in colonial characteristics. Impressive and most important are the differences in the pathogenic potentials of the respective species for heterologous hosts, including man.

Of particular significance in the perpetuation of certain pathogenic species of

[1] Received for publication February 28, 1966.
[2] Guest editorial.

the genus *Mycobacterium* is their inherent capacity to infect heterologous, as well as homologous, hosts. For example, domesticated swine are susceptible to natural infection with each of the three types of the tubercle bacillus—human, bovine, and avian. In addition, swine may harbor other species of mycobacteria in various lymphoid tissues, including the tonsils. Most strains of mycobacteria isolated from the tonsils of swine appear to be saprophytic, or at least nonvirulent for the usual laboratory animals. The probable source of the nonvirulent mycobacteria is ingested soil from the animals' environment.

The many saprophytes in this genus may, to the unwary, provide a factor of uncertainty when the possibility of a mycobacterial infection must be considered. That certain mycobacteria have not been proved capable of demonstrable pathogenesis does not necessarily preclude potential mischief from these organisms, if circumstances within the host are propitious.

Several cases in man have been reported in which lipoid pneumonia, related to aspiration of fat as a consequence of cardiospasm, favored the growth and pathogenicity of species of mycobacteria that were not tubercle bacilli ([3]). It has also been shown by *in vivo* experimentation that so-called saprophytic mycobacteria may become capable of pathogenesis in the presence of fatty substances ([4]).

Furthermore, the pathogenic potential of *M. paratuberculosis* (the etiologic agent of Jöhne's disease), was found to be markedly modified when the bacteria were suspended in paraffin oil ([8]). Infection was established in animals of several different species that had resisted infection when the mycobacteria were introduced without the oil.

It should be recognized that not all granulomatus lesions that resemble tuberculosis or leprosy are necessarily due to *M. tuberculosis* or *M. leprae,* even though mycobacteria may be demonstrated microscopically in tissues, exudates, or body fluids. For example, in Australia and Africa, during the past two decades, certain dermal lesions of man were observed that had some resemblance to leprosy. It was eventually established that the infections were due not to *M. leprae,* but to culturable mycobacteria, now designated *M. ulcerans.*

The importance of establishing correctly the true character of mycobacteria associated with clinical entities is further illustrated by certain tuberculosis-like granulomatous pulmonary infections of man associated with several groups of unclassified mycobacteria. When carefully investigated, these organisms have many features that distinguish them from *M. tuberculosis, M. bovis,* and *M. avium.*

Other examples of the ubiquity of mycobacteria are seen in several reports during the past few years of so-called "swimming pool" infections in Sweden and in the United States, including Hawaii. One of the most notable accounts concerned a total of 262 persons who developed a dermal infection referred to as "sore elbow" ([9]). All of those infected had frequented a large public swimming pool in western Colorado. Biopsies confirmed the granulomatous character of the patients' response to the infection, and mycobacteria were demonstrated. It is interesting in this instance that 85 per cent of the persons with a history of dermal abrasions, sustained presumably while in the swimming pool, reacted positively to tuberculin. Conversely, of approximately 1,300 other persons tested who frequented the pool and who did not have dermal lesions, only 4.3 per cent had positive reactions to tuberculin. X-ray examination of the chests of all those with a history of "sore elbow" failed to disclose the presence of pulmonary tuberculosis. The microorganism isolated from the dermal lesions, and presumably responsible for the positive tuberculin reactions, was *M. balnei.* The same organism was also isolated from the water and silt of the swimming pool.

Deserving of mention is a mycobacterial disease of cattle often referred to as "skin tuberculosis." ([2]) The infection, however, is not due to any one of the three species of the tubercle bacillus, consequently, is not tuberculosis. Alcohol-acid-fast bacillary microorganisms occur in the debris of the morbid reaction, which is usually in the subcutaneous tissues. These mycobacteria have not yet been cultivated. Transfer of the infection *in vivo* has been accom-

plished rarely. Cattle infected with this mycobacterium usually become sensitized to tuberculin. This complicates the interpretation of positive skin reactions following the application of tuberculin intradermally. This is another example of sensitization to tuberculin by species of mycobacteria other than tubercle bacilli.

Another example of the ubiquity of mycobacteria is a unique, infectious disease, found only in Indonesia and known as lepra bubalorum ([6]). The infection occurs in the skin of the water buffalo, and is characterized by numerous, firm nodules in the dermis which have a marked tendency to ulcerate. While intracellular, alcohol-acid-fast bacilli are usually abundantly present in the cellular constituents of the granulomatous reaction, the bacilli have resisted artificial cultivation, and the disease has not been transmitted experimentally. The infectious process has many resemblances to lepromatous leprosy of man. Fortunately, the disease is not prevalent, and there is no evidence that this infection of the water buffalo is transmissible to human beings. One significant difference between the pathogenesis of leprosy in man and that of lepra bubalorum is the failure of the mycobacteria in lepra bubalorum to invade and multiply in the peripheral nerves.

Another member of the genus *Mycobacterium* that is infrequently identified as a pathogen is *M. fortuitum*. When conditions are propitious, this organism is capable of serious mammary gland infections of cattle that are sometimes fatal ([10]). A few instances of serious infections of man have also been reported.

During the past three years, two reports have appeared—one from New Zealand ([1]) and one from Australia ([5])—of the occurrence of spontaneous mycobacterial infection in cats. Preliminary studies indicate that the infecting microorganism has characteristics of *M. lepraemurium*.

Some of the diseases caused by species of the genus *Mycobacterium* have been known for many decades. Hansen saw and described *M. leprae* in 1874, and Koch described *M. tuberculosis* in 1882. From time to time, new entities have been reported. One such was the isolation, a few years ago, of a pathogenic mycobacterium from naturally infected fresh water snails ([7]). This was the first reported instance of mycobacterial infection in an invertebrate.

The development of our knowledge concerning the genus *Mycobacterium* suggests that perhaps additional disease-producing species will eventually be observed. With this in mind, it is appropriate to suggest that any unusual granulomatous or ulcerative lesions be carefully examined for the presence of mycobacteria. If preliminary procedures, such as properly stained smears, reveal acid-alcohol-resistant bacillary forms, additional laboratory studies should be made.

The ubiquity of microorganisms of the genus *Mycobacterium* provides a possible complicating factor in interpreting the intradermal tuberculin test. When human or animal subjects are injected intradermally with PPD prepared from *M. tuberculosis*, positive dermal reactions can be accepted, ordinarily, as indicating a previous sensitization to a specific antigen as a consequence of infection with *M. tuberculosis* or *M. bovis*. However, there is evidence that reactions to tuberculin are not necessarily specific. As has been noted previously, persons having proved infection with *M. balnei* and given tuberculin intradermally, reponded positively to the Vollmer patch tuberculin test, even though evidence of infection by *M. tuberculosis* could not be established.

This brief review presents a reiteration of information generally known to microbiologists. Ample evidence establishes the wide distribution of microorganisms belonging to the genus *Mycobacterium*. Many of the species are pathogenic for one to several different hosts, and a few are host-specific. Some are only mildly virulent; others are capable of widespread dissemination within the body of the host, with a fatal termination.

The foregoing suggests the importance of clinical sagacity and knowledgeable laboratory assistance if a correct diagnosis of a mycobacterial infection is to be established. In other words, one should keep in mind that granulomatous lesions contain-

ing acid-fast bacilli do not constitute *prima facie* evidence in support of a diagnosis of a specific mycobacterial disease. In many instances, additional bacterial studies, including animal inoculations, are imperative. Rational therapy for most mycobacterial infections in man should, when possible, be correlated with pertinent information obtained previously by results of experimental studies *in vivo*.

Many voids exist in our knowledge of the diverse microorganisms that make up the genus *Mycobacterium*. Particularly rewarding should be extensive and definitive studies of the pathogenicity of certain species that are commonly considered nonpathogenic. Such studies could embrace many categories of small mammals, preferably those that have not been utilized previously. As a suggestion, use might be made of the numerous species of mammals belonging to the order *Rodentia*.

Also worthy of expediting would be an intensive search for chemical compounds effective *in vivo* against infections caused by the respective species of mycobacteria that presently respond slightly, or not at all, to available chemotherapeutic regimens. Even if only partially successful, such a project might reveal one or more substances that would surpass any of those currently used in mycobacterial therapeutics.

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