Mycobacteria and the Skin

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Leprosy is one of the most serious of the skin diseases afflicting humans, but many other members of the genus Mycobacterium also cause skin lesions. In this review the nature of these other mycobacteria and the types of disease they cause are described.

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The Mycobacteria

The genus Mycobacterium, by causing tuberculosis and leprosy, probably causes more suffering for humans than all other bacterial genera combined. It is hardly surprising, therefore, that most attention has been given to Mycobacterium tuberculosis, while other culturable strains have been grouped together under such derogatory terms as "atypical," "unclassified," "anonymous," "pseudotubercle," and "tuberculoid." From the biologic point of view, however, M. tuberculosis is not the most central nor most typical member of the genus. It may indeed be said that M. tuberculosis and Mycobacterium leprae, by devolving to a state of obligate pathogenicity, are the atypical mycobacterial species.

The mycobacteria are the ducks of the microbial world. They have thick, water-repellant coats and are found at water/air interfaces. Indeed, the name Mycobacterium was given to this genus because the strains grow as mould-like pellicles on the surface of liquid media. The saprophytic strains therefore are found in soil, marshes, ponds, rivers, swimming pools, and estuaries. Sphagnum bogs are particularly rich in mycobacteria. They have also been isolated on several occasions from domestic and industrial water supplies, water storage tanks, and taps.[1] There are therefore many opportunities for contact between mycobacteria and animals or humans, and such contact, particularly through dermal abrasions, probably has played an im-

portant role in the evolution of immune response to this group of bacteria.

Contrary to popular belief, this genus is probably the best classified of all bacterial genera. This is due to a number of excellent individual taxonomic studies and also to the cooperative investigations of the International Working Group for Mycobacterial Taxonomy. The genus can be divided into two distinct subgenera—the rapid growers and the slow growers. Antigenic analysis and DNA studies show that these two groups of species are quite distinct and are probably due to a major evolutionary split occurring very early in the evolution of the genus. The rapid growers show a considerable antigenic overlap with the genus Nocardia.

There are, at present, 41 approved mycobacterial species names.[2] Two of these species, as mentioned above, are obligate human pathogens, some others occasionally cause disease when given the opportunity, while others, almost without exception, never cause disease in humans.

Many of the slow-growing species cause infections in humans while only two of the rapid-growing species have been implicated as pathogens. These two are Mycobacterium chelonei and Mycobacterium fortuitum, which include the turtle and frog tubercle bacilli, respectively. Of these, M. chelonei is the more important pathogen, although this has been obscured by the frequent practice of grouping these species together in a so-called "Fortuitum complex." M. chelonei can be divided into two major types: M. chelonei abscessus, which is the most common variant in Africa and the USA, and M. chelonei chelonei, which occurs prinici-

pally in Europe. These variants do not appear to differ in their virulence for humans. Strains of M. fortuitum can be divided into three biotypes, A, B, and C, of which type A is the most common pathogen. These types are easily distinguished from each other and from all other rapid growers.[3] Although these species produce good growth in less than a week on subculture, they may not appear for many weeks or months on primary isolation.

The slow-growing species that cause disease in humans are listed in Table 1. These species are traditionally grouped according to Runyon's[4] classification into group 1: photochromogens (yellow pigment formed after exposure to light); group 2: scotochromogens (yellow pigment formed in the dark); and group 3: nonchromogens. The rapid growers, irrespective of their pigmentation, comprise group 4. This classification is not entirely satisfactory as pigmentary variants occur in many of the species.

The species M. avium and M. intracellulare are now regarded by many mycobacteriologists as being members of the same species which also includes M. lepraemurium and M. paratuberculosis, the causative agents of rat leprosy and Johne's disease, respectively. Although M. scrofulaceum is a distinct species, it is often included with the above in the so-called MAIS (Mycobacterium avium-intracellulare-scrofulaceum) complex.[5]

Two species listed in Table 1, M. marinum and M. ulcerans, cause specific skin diseases in humans, ie, Swimming Pool or Fish Tank Granuloma and Buruli Ulcer. The others, in common with M. tuberculosis, cause a wide range of pulmonary and extrapulmonary lesions, including skin infections.

There are a number of important epidemiologic differences between disease due to the obligate pathogen M. tuberculosis and the environmental mycobacteria.[1,6] Infections by the latter are very rarely due to person-to-person spread. The incidence of such infections is governed by the occurrence and distribution of the

TABLE 1. *Slow-growing Mycobacteria Causing Human Disease*

Runyon's Group	Species
1	M. kansasii
1	M. marinum
2	M. scrofulaceum
2	M. szulgai
3	M. avium
3	M. avium-intracellulare
3	M. malmoense
3	M. ulcerans
3	M. xenopi

mycobacteria in the environment and by the opportunities afforded for contact with susceptible individuals. Opportunities include breakage of the skin by accidents, injections, and surgery; and natural or iatrogenic immunosuppression including autoimmune diseases, malignancies, and post-homograft immunosuppressive therapy.[5] Industrial dust-induced lung disease is a predisposing factor, especially if individuals are exposed to aerosol of water contaminated with mycobacteria in shower-houses.[1] The incidence and distribution of these mycobacterial diseases are quite independent of tuberculosis: as the incidence of the latter decreases, the relative incidence of the former increases.

A further important difference is that the isolation of an environmental mycobacterium from a clinical specimen does not necessarily indicate that it is the cause of the patient's disease. This is a particular problem with sputum specimens, but mycobacteria may also contaminate the skin. Several supposedly successful attempts to culture M. leprae were due to the presence of such contaminants.

The environmental mycobacterial flora is only rarely a cause of overt disease in humans. On the other hand, recent evidence, outlined below, indicates that contact with this flora is of great importance in determining the nature of the immune response to subsequently encountered pathogenic species.

Immunologic Characteristics of Mycobacterial Skin Lesions

Robert Koch,[7] in his description of what we now term the Koch Phenomenon, observed that an injection of viable M. tuberculosis in the skin of a guinea pig induced a small local lesion followed by a systemic spread of the disease. A second injection a few weeks later induced, within 48 hours, a strong necrotic reaction which led to a total elimination of the injected bacilli. The animals, nevertheless, died eventually as a result of the systemic disease. Subsequently, Koch elicited a similar reaction by means of killed bacilli and even concentrated bacteria-free culture filtrates (tuberculin). The erroneous assumption that the induction of a systemic tuberculin reaction would have a similar beneficial effect as the local dermal reaction led Koch to advocate tuberculin as a remedy for tuberculosis. The failure of this remedy almost ruined Koch's high reputation.

During the ensuing years a belief arose, and is still prevalent today, that hypersensitivity to M. tuberculosis was a direct correlate of protective cell-mediated immunity which is associated with macrophage activation.[8] Although both phenomena are cell-mediated and are transferable by lymphocytes, it is now widely recognized that these cells can be grouped into several subsets with quite different functions. There is also a considera-

ble amount of evidence from experimental and clinical studies showing that the two phenomena are dissociable and that a high degree of tuberculin hypersensitivity is antagonistic to protection in a systemic disease.[9] Rook and Stanford[10] noted that strains of mice that develop low levels of tuberculin hypersensitivity are relatively resistant to intravenous inoculations of M. tuberculosis but are susceptible to intradermal challenges. The reverse is true for animals that develop high levels of tuberculin hypersensitivity. The same authors also demonstrated that mycobacterial infections in mice elicited at least two distinct immunologic reactions, both of which produced positive tuberculin tests. One of these reactions is the result of macrophage activation and is protective in systemic mycobacterial disease, while the other is a necrotic Koch-type reaction.

There is, therefore, considerable evidence for two major cell-mediated immune responses in mycobacterial disease which vary in their protective efficacy depending on the site of infection. It has been postulated[11] that the Koch-type of response is a fairly primitive reaction that developed when the genus Mycobacterium consisted of environmental saprophytes which contaminated skin abrasions. The evolution of a successful immune reaction to the more recently evolved pathogens causing systemic infections may not be complete, accounting for the very high incidence of mycobacterial disease in humans.

Other immune reactions also affect and modify mycobacterial skin lesions. Antigen-antibody complexes lead to dermal reactions of the Arthus type, thus the size of the tuberculin reaction at 6 to 8 hours correlated with the levels of circulating antimycobacterial antibody.[11] The type 4 delayed hypersensitivity reaction is enhanced by a lymphokine termed *skin-reactive factor*, released by lymphocytes in the presence of IgG-containing immune complexes.[12] A low but significant correlation between the size of the tuberculin reaction at 48 hours and antimycobacterial antibody levels in the IgG class only has been demonstrated.[11] The relationship between the Arthus reaction and delayed cutaneous hypersensitivity may be relevant to the pathogenesis of the poorly understood tuberculides (see below).

Mycobacterial Skin Lesions

Skin lesions caused by mycobacteria are classified according to the causative organism and according to the clinical characteristics. In addition to tuberculosis and leprosy, there are two distinct mycobacterial skin diseases, namely Buruli Ulcer and Swimming Pool Granuloma which are caused by M. ulcerans and M. marinum, respectively. Other mycobacteria cause a wide range of lesions, including skin lesions, which are usually similar to those occurring in tuberculosis. Such infections do not, therefore, bear specific clinical names.

A number of clinical classifications which are applicable to tuberculosis and the other mycobacterioses have been described.[13] The older ones in particular are unnecessarily complex and are based on picturesque but outmoded terminology. The following classification is probably adequate for most purposes.

Mycobacteria Detectable in the Lesions

Primary Lesions. (1) Inoculation into the dermis, eg, M. marinum infection, verrucose tuberculosis. (2) Inoculation into subcutaneous tissues, eg, post-injection abscesses.

Secondary Lesions. (1) Inoculation into skin from an endogenous source, eg, tuberculosis orificialis cutis. (2) Lesions due to hematogenous dissemination, eg, miliary nodules, widespread cutaneous abscesses. (3) Lesions due to lymphatic spread, eg, satellite lesions in lupus and M. marinum infection. (4) Lesions secondary to involvement of underlying structures with sinus formation, eg, scrofuloderma.

Mycobacteria not Detectable in the Lesion

Classifications for this category include (1) the tuberculides and (2) erythema nodosum.

Tuberculosis of the Skin

The incidence of both pulmonary and non-pulmonary forms of tuberculosis decreased markedly in the industrially developed countries during this century, but there has been a recent increase in non-pulmonary forms, in some countries, among immigrant groups.[6] Among these non-pulmonary cases have been a number of unusual tuberculous skin manifestations. Kounis and Constantinidis[14] described and illustrated four such cases among Asian immigrants in Great Britain: tuberculous erythematous nodules, tuberculous ulceration of the skin, warty tuberculosis, and tuberculous dactylitis. Miliary tuberculosis presenting with skin lesions also has been observed in the same immigrant population, although it is rare.[15]

In other parts of the world the incidence and predominant type of cutaneous tuberculosis appears to vary considerably. Although it has been claimed that this form of tuberculosis is rare in the tropics, reports from India suggest that it may not be so uncommon.[16,17] The three major types of cutaneous tuberculosis reported in India are scrofuloderma, lupus vulgaris, and tuberculosis verrucosa cutis.

The Tuberculides

This term, introduced by Darier in 1896, covers a number of poorly understood and ill-defined skin lesions occurring in tuberculosis but which are supposedly not a direct result of the bacilli.

Many different names have been given to tuberculides. The three most commonly referred to are: (1) papulonecrotic tuberculide, (2) lichen scrofulosorum; and (3) erythema induratum (Bazin's disease).

The etiology of the tuberculides is unknown. In 1913 Bandelier and Roepke[18] suggested that they might be due to the soluble bacterial toxins, immune reactions, weakened or dead bacilli or their remains, cell-wall-free forms of tubercle bacilli, scanty bacilli in the presence of copious amounts of antibody or a form of skin tuberculosis in which the bacilli rapidly perished. These authors remarked that "a complete explanation of all these detailed questions may be expected shortly." The decline in the incidence of tuberculosis in the industrially developed countries had led to a virtual disappearance of tuberculides: indeed their very existence has been doubted. In less prosperous countries such lesions do occur, however.

Papulonecrotic Tuberculide

This condition is characterized by eruptions of necrotizing papules usually affecting the limbs symmetrically. Although each lesion only lasts a few weeks, successive crops of papules often occur. Initially, each papule is pink or flesh-colored; later, a central black discoloration occurs due to necrosis. The tuberculin test is usually strongly positive and the condition responds rapidly to antituberculous chemotherapy.

In a review of 91 cases of papulonecrotic tuberculide seen during a 17-year period in South Africa,[19] seven of the cases were associated with so-called idiopathic gangrene of the extremities and about one-third were associated with a deep focus of tuberculosis, most commonly cervical lymphadenopathy. Both the tuberculides and the gangrene responded rapidly to antituberculous chemotherapy. In four cases, the tuberculides progressed to patches of lupus vulgaris and M. tuberculosis was cultured from two of these. Early tuberculide lesions showed the features of an Arthus-type of reaction; later, a cone of necrotic tissue formed and this was eventually cast off. It was postulated that papulonecrotic tuberculides were due to the trapping of blood-borne tubercle bacilli, coated with large quantities of antibody and complement, in capillaries leading to an Arthus-type of reaction followed by delayed hypersensitivity. It was suggested that the delayed hypersensitivity reaction destroyed the bacilli, except in those few cases in which survival of the organism led to the development of lupus vulgaris. It was also suggested that erythema induratum (Bazin's disease) was due to a similar phenomenon occurring in larger blood vessels.

A case of papulonecrotic tuberculide secondary to involvement of cervical nodes by M. tuberculosis var. bovis has been reported.[20] The histologic features of the lesions were illustrated and discussed, with reference to the differentiation of this condition from granulomatous vasculitis and allergic granulomatosis (Churg-Strauss syndrome).

Lichen Scrofulosorum

In this tuberculide, symptomless papules 0.5–3 mm in diameter occur principally on the abdomen, chest, and back. They are follicular in distribution and often occur in groups. The tuberculin test is often strongly positive.[21] The papules contain granulomas situated around hair follicles and sweat ducts. These granulomas are composed of epithelioid cells with some Langhans giant cells. Caseous necrosis, although usually absent, has been observed in one recent case.[22] The etiology of lichen scrofulosorum is unknown, but it has been postulated that it was due to hematogenous disseminations of tubercle bacilli from a primary focus in individuals with a high degree of cutaneous hypersensitivity to the bacilli.[21]

A similar condition, termed lichenoid tuberculid, has been described,[23] but these cases differed from those of lichen scrofulosorum in that caseous necrosis was seen in most biopsy specimens and the tuberculin test was frequently negative. The relationship between these two entities is unknown.

Erythema Nodosum

This was classified as a tuberculide in some early publications before it was realized that this hypersensitivity vasculitis could occur in a wide range of infections and other diseases.

At present, in industrially developed countries, tuberculosis is a rare cause of erythema nodosum, but prior to the introduction of antituberculous chemotherapy it was the most common cause of this condition in children.[24] It usually made its appearance at the time of development of tuberculin hypersensitivity, three to eight weeks after primary infection. In some individuals, phlyctenular keratoconjunctivitis occurred at the same time.

Buruli Ulcer

Mycobacterium ulcerans infection is the most recently described of the major mycobacterial diseases. It was first described in the Bairnsdale district of Australia in 1948.[25] In 1958, a similar disease was observed in the Buruli district of Uganda[26] and was found to be caused

by a mycobacterium which, although very similar to *M. ulcerans,* differed in certain biochemical properties, and was therefore regarded as a separate species—*M. buruli.*[27] The two mycobacteria are now both recognized as being *M. ulcerans.* This species grows very slowly on Lowenstein Jensen medium and is negative in most of the biochemical tests used to identify mycobacteria. It is non-chromogenic, although a light yellow color sometimes is seen. Characteristically, strains show a very restricted temperature range of growth—between 32 and 34 C. Although this species has not yet been isolated from the environment, epidemiologic evidence strongly suggests that infections are, in fact, due to environmental contact.[28] It has been suggested that the organism is introduced into the skin by the spines of a tall prickly grass *Echinocloa pyrimidalis.*[29]

In addition to Australia and Uganda, the disease has been found in Malaya, Mexico, New Guinea, Nigeria, and Zaire. The exact incidence of the disease is unknown but it may, after tuberculosis and leprosy, be the most common mycobacterial infection of humans. The disease is not distributed evenly, but tends to occur in a number of "hot spots" characterized by low-lying marshy ground subject to periodic flooding.

The disease affects all age groups but is more prevalent in children and young adults. Any part of the skin may be involved, but exposed parts, such as the elbows, are involved most frequently. In a few cases metastatic bone lesions which may lead to sinus formation are encountered. The disease commences as a hard, sometimes itchy, nodule attached to the skin but mobile over deeper structures. In Zaire, this form of the disease is termed "mputa matadi" (the itching stone). In some patients the disease resolves at this stage, while in others it progresses to the ulcerative form. The infection involves principally the interlobular septa in the subcutaneous adipose tissue and leads to an area of fat necrosis followed by overlying necrosis of the skin. The lesion is seen as a deeply undermined ulcer from which necrotic fat is discharged. The lesion may be enormous, sometimes involving a whole limb. At this stage, numerous acid-fast bacilli are found at the progressing edge of the lesion but there is little or no histologic evidence of a cellular immune response. In addition, the dermal response to Burulin, a skin test reagent prepared from *M. ulcerans,*[30] is negative. This apparent anergy has been ascribed to a trapping of the antigen-specific lymphocytes in the lymphoid tissue.[31]

Usually, a stage is reached in the disease when this anergy is replaced by a reactive phase. A cellular infiltrate with granuloma formation is seen in the lesion, the number of bacilli decrease considerably, and a positive dermal response to Burulin occurs. Healing takes place, often with massive fibrosis leading to crippling contractures. The mechanism of this immunologic turnabout remains a mystery. The answer to this mystery could be of great practical importance, as the therapeutic induction of such a change in reactivity could be of benefit in this and other mycobacterial infections in which anergic forms are encountered. Even more mysterious is the occasional simultaneous occurrence of anergic and reactive forms of the disease in the same patient and even in the same lesion.

Mycobacterium marinum Infection

This condition is usually called Swimming Pool Granuloma or Fish Tank Granuloma, emphasizing the fact that swimmers and tropical fish fanciers are particularly at risk. The causative organism, *M. marinum,* originally was isolated from diseased fish in 1926; a strain termed *M. balnei,* isolated from cases of Swimming Pool Granuloma[32] was found to be the same as *M. marinum.* This species is a slow-growing photochromogen and is distinguishable from the other important member of this group, *M. kansasii,* biochemically, serologically, and by its poor growth at 37 C.

The disease usually presents as one or more verrucoid lesions at the site of inoculation, usually the elbows and knees of swimmers and the hands of aquarists. In a minority of cases, proximal secondary lesions develop, as occur in sporotrichosis, and such cases are referred to as "sporotrichoid." Most patients react to tuberculin. The lesions usually undergo spontaneous healing after 1 to 3 years, but some cases persist for much longer.

Skin lesions due to *M. marinum* were first described by Linell and Norden[32] in 1954 following the occurrence of 80 cases in users of a swimming pool. Several other epidemics of this disease have been traced to infected swimming pools, including a series of 290 cases in Colorado.[33] Infections have also occurred in persons bathing in brackish estuarine water[34] or following prolonged immersion in sea water.[35]

The term Fish Tank Granuloma is applied to cases occurring in aquarists, and a number of such cases have been reviewed briefly.[35,36] One unusual case occurred after a dolphin trainer was bitten on the hand while swimming with the animal in an attempt to improve teacher/pupil relationships.[37]

It now appears very likely that many cases of so-called inoculation lupus vulgaris, which were thought to be a form of skin tuberculosis,[38] were in fact due to *M. marinum.* Many similar cases of "swimmer's lupus" have been reviewed.[39]

The histologic appearance of the lesion depends on its age.[40] Lesions of less than six months duration show a chronic granulomatous infiltration of lymphocytes and epitheliod cells. In some cases noncaseating tubercle-like granulomas with Langhans giant cells are seen, while in others the infiltrate is more diffuse. Acid-fast

bacilli are very scanty but occasionally are seen within epitheliod cells. In older lesions, in the resolving stage, nonspecific aggregates of lymphocytes and fibrous tissue are present. Lesions show parakeratosis or hyperkeratosis, and in some cases ulceration and secondary infection is evident. Ultrastructural studies have shown that the granulomas are of the high-turnover type of immunogenic origin.[41]

Nonspecific Skin Infections by 'Environmental' Mycobacteria

This group of infections may be due to local implantation of the organisms or due to local or hematogenous dissemination from lesions in deeper structures. Localized lesions are either cutaneous granulomas or, more often, post-injection or post-traumatic abscesses.

Superficial Granulomas

Although these are most frequently caused by M. marinum, other species also have been implicated. Four cases of such infections due to M. kansasii have been described.[42] One patient had widespread lesions which had been present for 22 years, and two patients had lesions appearing on the hand in an ascending proximal or "sporotrichoid" fashion. The fourth patient had a crusted lesion with central ulceration on the right nasolabial fold. Unlike the other cases, this patient also had involvement of the mediastinal lymph nodes.

Two cases of superficial granulomatous lesions due to unidentified slow-growing scotochromogens have been reported. One case[43] occurred after the patient abraded his arm on a storage crate, and the other[44] followed an abrasion acquired while removing barnacles from a boat.

Post-injection Abscesses

There have been several examples of outbreaks of "tuberculous" abscesses following vaccinations and also individual cases following injections of penicillin.[4] It was suggested that the latter cases were due to the carriage of tubercle bacilli to the injection site by macrophages in persons who were already infected, leading to so-called fixation abscesses. It now seems likely that many of these cases were due to contamination of the injectable material by environmental mycobacteria, particularly M. chelonei and M. fortuitum.[46] It is also evident that some cases of cold "sterile" post-injection abscesses, especially those occurring in the tropics, are caused by these organisms.

Secondary Involvement of the Skin

Sinus formation, with or without scrofuloderma, may follow lymph node involvement, usually due to M.

avium (including the intracellulare variant) or M. scrofulaceum. Most cases occur in childhood and the cervical nodes are most frequently involved. The clinical features are essentially the same as those of tuberculous lymphadenitis, and the diagnosis is usually made bacteriologically.

Skin abscesses and nodules associated with disseminated disease are usually due to M. avium or M. chelonei.[5,47] Such infections may occur at any age, and the patients often show evidence of a deficiency in cell-mediated immune responses. Some such infections have followed renal transplantation. Unless the immune defect can be corrected, the prognosis is poor.

Therapy of Cutaneous Mycobacterial Disease

Any form of tuberculosis is treatable by one of the modern curative standard or short-course chemotherapeutic regimens. The treatment of the other mycobacterioses has, because of infrequent occurrence of such infections, not been carefully evaluated.

Buruli Ulcer

The therapy depends on which of the three stages—pre-ulcerative, anergic, or reactive—the disease is in. Small pre-ulcerative lesions usually are curable by excision and primary closure. It is therefore important to educate people in endemic areas to present early for treatment. In the reactive or resolving stage it is important to promote healing with as little deformity or loss of function as possible. This is achieved by skin grafting, excision of fibrous tissue, splinting, and physiotherapy. Treatment of the anergic progressive lesions is the most difficult as it is necessary to destroy or remove the bacilli.

Antimicrobial chemotherapy is, at present, of secondary importance in the management of this disease. Clofazimine has been shown to be effective.[48] Several other drugs, including rifampicin, are active in vitro but it is uncertain whether they affect the disease in humans.

M. marinum Infection

The self-limiting nature of this infection renders the assessment of therapy difficult. Solitary lesions may be removed by surgical techniques. More widespread lesions are susceptible to rifampicin with ethambutol, and there is also evidence that therapy with trimethoprim with sulphamethoxazole or with minocycline or doxycycline is effective.

Other Mycobacterioses

Localized lesions, such as post-injection abscesses, in patients with normal cell-mediated immunity are usually treatable by local surgical procedures. Widespread in-

fections with skin involvement are much more difficult to treat because of the resistance of the organisms to many microbicidal agents and the frequent suppression of the immune response. Infections due to *M. kansasii* can be treated with a regimen containing rifampicin, isoniazid, and ethambutol, while those due to *M. avium* require long periods of therapy with five antituberculous agents.[49] *M. chelonei* is also resistant to many agents, but very limited evidence suggests that erythromycin with amikacin is a suitable regimen. The ideal therapy for such infections would be a correction of the underlying immunologic defect.

Drug Names

amikacin: Amikin
clofazimine: Not available in USA
doxycycline: Vibramycin
minocycline: Minocin
rifampicin: Rifadin, Rifomycin, Rimactane
trimethoprim with sulphamethoxazole: Bactrim, Septra

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