Demodicidiasis and Leprosy
(Review and Proposal)

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Despite a wealth of speculation there is no proof that any arthropod serves as transmission agent for human leprosy (Dungal, 1961). As a suspect vector the acarine *Demodex folliculorum* is in some respects unique since it is (1) apparently ubiquitous with an incidence of 100 per cent (Fuss, 1933), (2) found in intimate association with *Mycobacterium leprae* in the skin complex (Borrel, 1908), and (3) probably passed from mother to young during the nursing process. Furthermore, Spickett (1961b) reported the presence of acid-fast bacteria in the gut of *D. folliculorum* and that the gut contents of the mite can be regurgitated. These observations point up the need for continuing re-evaluation and for further studies on the possible causal relationship between demodicidiasis and leprosy.

The present paper represents an attempt to examine all facets of our knowledge of the association of *D. folliculorum* and leprosy, to present information on the biology of other demodicids pertinent to an evaluation of this relationship, and to indicate a programme of study which could materially advance our understanding of the role, if any, of demodicidiasis in the initiation of leprosy.

Demodex folliculorum

Borrel (1908) was apparently the first to suggest an association between *D. folliculorum* and *M. leprae*. He found, in sections of skin from leprosy patients, that the bacteria were investing, i.e. closely surrounding, the mite (1909a). From this he speculated (1909b, p. 126) 'Le transport et l'inoculation dans le système pilaire peut certainement se faire au moment de la migration des parasites d'un nez lépreux à un nez sain.' He suggested (1909c) that *Demodex* as it fed on sebum could take up the bacillus and so transfer the organism to another host. His reports thus associated demodicid mites with sebaceous gland activity and leprosy transmission.

In some respects as pointed out by Spickett (1961b) the careful work of Gmeiner (1908) retarded investigation based upon the speculations of Borrel. He reported that in twelve different skin diseases demodicids were no more common than in normal skin. On this basis and from examination of skin sections which showed no inflammatory reaction associated with *D. folliculorum* he concluded that this demodicid was non-pathogenic (see Beerman and Stokes, 1934) and held no causal or cooperative position with respect to any disease. In a later paper (1909), however, Gmeiner discussed a consistent relationship in red mange of dogs wherein *D. canis* is associated with *Staphylococcus albus*. He stated that here the demodicids had prepared the way for the bacterial infection. He assumed that a like situation may well prevail in blepharitis associated with *D. folliculorum*. The analogy here with *M. leprae* is obvious and had this latter work been better known it undoubtedly would have served as a spur to leprosy-demodicid studies.

In 1910 LeFebvre, familiar with the work of Borrel, reported on studies of leprosy and *D. folliculorum*. He found a 25 per cent incidence of this mite in his examination of 100 patients with leprosy. He stated that this figure was nearly identical to that obtained from an examination of 'healthy' individuals. Although he found both the mite and *M. leprae* in the same hair follicle he could not find bacilli within the mites. He noted that demodicids are not found on the

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appendages of man, a predilection site for leprosy[sic], and also that in his studies no children were *Demodex* positive. His conclusion was that *D. folliculorum* was not a likely transfer agent of leprosy.

The work of Bertarelli and Paranhos (1910) was based also on the findings and speculations of Borrel. They examined 60 patients from the leprosarium at Guapira. According to their report only 15 of these [only 59 listed!] were positive for *D. folliculorum*. Furthermore, in their sample patients with abundant 'comedoni' (indicative of involvement and hyperactivity of the sebaceous glands) were rarely positive for *Demodex* (only 3 of the 59). They stated that many leprosy cases with advanced facial lesions had an abundance of the mite. This led them to the interesting idea that *Demodex* is a secondary invader of an area in which skin defences had been reduced by the leprosy bacillus. In a remark unfortunately not documented by data they noted that demodicids are scarce in negroes even though facial lesions of leprosy were present. Bertarelli and Paranhos concluded that their study gave no information in favour of the transmission of leprosy by *Demodex*.

Majocchi (1914) reported on some observations similar to those of Borrel. He suggested that the fusion of leprous nodules was responsible for placing the leprosy bacteria in contiguity with *D. folliculorum*. These last could then spread the disease either over the body of the infected host or to healthy individuals.

In two papers A. Serra (1912, 1921) reported the results of his examination of patients with leprosy for *D. folliculorum*. In brief his data show 32 of 80 positive for *D. folliculorum*. He found a higher incidence in 'tuberculoid' and 'mixed' (63+ per cent) when compared to 'anaesthetic' leprosy (36+ per cent). This mite abundance does, however, seem to correlate not so much with the kind of leprosy but rather with the presence or absence of comedones. His figures (1921) show that of 28 patients with abundant comedones 22 (or 78 per cent) were *Demodex* positive. Also in his study of 1921 he found 15 of 58 patients with *Demodex* and bacilli together in the examination samples. Serra smeared a mixture of *Demodex* and leprosy bacilli on a patient assessed negative for both but showing symptoms of 'anaesthetic' leprosy. Mites and bacilli

were recovered in two months. He also experimented with applications of like material on dogs (no positive results) and inoculated a glucose preparation of the same material into the anterior chamber of the eye in rabbits (negative results). His attempts at demonstrating *Demodex* and bacilli in the hair follicle of man or bacilli in *Demodex* failed. Serra notes the difficulty of establishing *Demodex* as a vector if the bacilli are rarely found within the hair follicle or sebaceous gland. He also suggests that *Demodex* could produce an irritant which would induce mobile elements of the connective tissue to act as mediators between mite and bacilli.

In assessing the value of all of these survey accounts (Borrel through Serra) one should bear in mind that Gmeiner (1908) found normal people 97 per cent positive for *Demodex*. It is also true as noted by Serra (1921), and others since his report, that mites may readily be missed on one examination; subsequent study will often reveal their presence.

Since the work of Serra (1921), with the exception of Spickett (below), accounts of the *Demodex*-leprosy problem are either text-book allusions (e.g. Neveau-Lemaire, 193 papers commenting on the work of Borrel, Majocchi, or LeFebvre (e.g., Hirst, 1919; Dungal, 1961).

Included in his review of the possibility that *D. folliculorum* is a vector of leprosy bacilli Spickett (1961b) reported the following information:

1. *D. folliculorum* will ingest minute bits of plastic and resin.
2. These ingested particles are regurgitated by the mite.
3. Acid-fast bacteria are occasionally (in two ovigerous females) found in the gut of *D. folliculorum*.
4. *D. folliculorum* does penetrate the sebaceous gland to the dermis.

He also suggested that *D. folliculorum* might transport bacteria between hair follicles. This, however, is open to question since Spickett's assumption is based on very circumstantial evidence (Spickett, 1961a) that ovigerous females must have recently entered a hair follicle. This is certainly not assured as is indicated by such studies as Nicholas (1943) who

found large numbers of *D. folliculorum* in hypertrophied sebaceous glands and from studies of other demodicids as *D. caprae* where marked populations build up in one locale. There is certainly the added possibility that the bacteria within the mites as reported by Spickett were obtained from within the same hair follicle.

Spickett's (1961a) account of the biology of *D. folliculorum* which might be useful to studies of the *Demodex*-leprosy relationship does not take into account many interesting observations in older publications. Fuss (1933) in a very careful study of 104 individuals in age groups from children to 70 years found 100 per cent infestation with *D. folliculorum*. This mite has been found in man from all major areas of the world and in Caucasoid, Negroid and Mongoloid races (see LeFebvre, 1910; Yokayama, 1941; G. Serra, 1942). *Demodex* would, therefore, seem to qualify under Spickett's criteria that a transfer agent be ubiquitous, and be found in areas endemic for leprosy.

Hirst, in 1919, provided excellent figures to show that the mouth parts of *D. folliculorum* are stylet-like chelicerae admirably suited to cell penetration. He also noted the absence of an anus and the sac-like nature of the digestive tract. These two features plus the obvious undercutting and destruction of cells by this and other species led Nutting and Rauch (1963) to contend that all demodicids are primarily cell feeders. The implication or statement that *D. folliculorum* feeds only on sebum (Gmeiner, 1908; Spickett, 1961a – although revised 1961b) would appear unfounded. Several accounts are in existence of the occurrence of *D. folliculorum* in loci other than sebaceous glands (see Nutting, 1965). It has been noted (Nutting, 1964) that because of its low nitrogen content sebum is an unlikely product to sustain mite development.

It should be further borne in mind that the details of the life cycle of *D. folliculorum* (Spickett, 1961a) are based on short-term *in vitro* studies (6 + days on sebum) coupled with limited and circumstantial *in vivo* evidence. We need confirmation of the suggested mechanism and stage of transference (direct contact during the nymphal stage?), span of the life cycle ($14\frac{1}{2}$ days?), and movement between hair follicles (adults or nymphal stage?) as postulated by Spickett. As

yet no complete study of the anatomy of any demodicid has been published although certain systems and a review account of our current position in this regard may be found in Nutting, 1950 and Nutting, 1964.

To date no attempt has been made to examine critically the physiology of any demodicid. Spickett (1961a) using *D. folliculorum* maintained on sebum or lanolin reported negative phototaxy for all stages, positive stereotaxy for larvae, protonymphs, and females with shifting stereotaxy for deutonymphs and males, no reaction in any stage to gravity, and that larvae feed continuously, males rarely and deutonymphs not at all. Although no survival studies for this species have been attempted Daniel *et al.* (1959) did find one mite viable in dry cerumen after four months.

Until we have more secure observational or experimental information on the biology of *D. folliculorum* we are in a weak position to assess the *Demodex*-leprosy problem.

Demodicids would seem to have access to *M. leprae* in the lumina of the hair follicles or sebaceous canals or even from within the cells of the pilo-sebaceous complex. They would, furthermore, appear capable of opening the pilo-sebaceous apparatus both by enlargement of the canals (distension and undercutting) and by actual penetration of the cells. Bacteria could be held in the sac-like gut and upon regurgitation or on death of the mite be liberated to the host tissue. In this last circumstance the problem of elimination from the exoskeleton is discussed below. Unlike many arthropods, demodicid salivary glands are solid (holocrine) cell masses (Nutting, unpublished) so that here only the hollow salivary duct could house bacteria unless these are able to survive intracellularly in the mite tissues.

Entry of *M. leprae* bacilli to the host cells from *D. folliculorum* could conceivably come about not only through regurgitation but also through phagocytosis of the infected mites by mesodermal giant cells (see Nutting and Beerman, 1965). Khanolkar (1959) has noted that *M. leprae* multiplies within phagocytic monocytes in silent cases of leprosy. These last are noteworthy for the fact that giant cells are also present both free in the dermis and associated with the nerves (Lever, 1961). Giant cells were found

in man by Bergstad (1925) in a tumour infested with *Demodex*. Similar cells have been reported in cattle (Nemeseri and Szeky, 1961) and dogs (French, 1964) as phagocytic for demodicids. In sections of skin infested with *D. bovis* which were recently examined in the laboratory of the senior author it appears that the chitinous exoskeleton is rapidly degraded even before degeneration of the internal cells of the mite. Definite lacunae are found in the exoskeletal wall sufficient in size to permit passage of bacteria to the cytoplasm of the giant cell. It would seem logical to presume that one should search here for a likely mechanism of bacterial inoculation. Infected mites could be the source for seeding giant cells with bacteria which could then multiply and spread from the giant cells to the surrounding tissue.

Fuss (1935) has discussed and depicted the marked polymorphism present in *D. folliculorum*. Specimens obtained by one of the authors of the present report (Pfaltzgraff) in North-east Nigeria are in several respects different from her account. The specimens from Nigeria are very similar to a human demodicid photographed but not discussed in taxonomic terms by Daniel *et al.* (1959). A recent paper (Akbulatova, 1964) states that two distinct subspecies of *Demodex* (*D. f. longus* and *D. f. brevis*) do occur in man.

With few exceptions due to the limitations of the host organism the studies on *D. folliculorum* are restricted to superficial examinations or study of biopsy material. Incidence surveys of cadavers (Gmeiner, 1908) have been few and have been carried out on carcasses available rather than on selected specimens with heavy demodicid infestations.

Demodex spp.

Since all 38 species and subspecies (Nutting, 1964) of the genus *Demodex* are remarkably alike in structure (see Hirst, 1919) and niche requirements (Nutting, 1965), it would seem profitable to examine facets of their biology which may be useful in studies of the *Demodex*-leprosy association.

Of all demodicids, *D. canis*, of *Canis familiaris* is the most thoroughly known. It is also of more direct interest to our problem in that it shares a relationship with a bacterium. Although normally an inhabitant of the hair follicle it has been reported free in the dermis (Krulikovskii, 1878), in the lymph nodes (Canepa and da Grana, 1941) and in most other viscera (Koutz, 1957; French, 1964). Canepa and daGrana found all stages of the mite life cycle in the lymph nodes which may indicate mite reproduction in this location. French stated that he could find no evidence of bacterial infection in the invaded lymph nodes. This is, however, not usually the case in the above mentioned dermal invasions which are associated with *Staphylococcus albus*. Apparently for this relationship no attempt has been made to locate bacteria within the mites. Bacteria and debris do adhere externally to *D. canis* as they move *in vitro* (Nutting, unpublished).

Several papers on *D. canis* purport to have discovered the mechanism of mite transference (Enigk, 1949; French *et al.*, 1964; Sako, 1965). This is reputedly not by an *in utero* route (see Unsworth, 1946) but rather by direct contact between bitch and pup during nursing. As suggested elsewhere (Nutting, 1965) the observational and experimental measures used by these investigators are not sufficiently critical to settle this issue.

Demodex caprae of *Capra hircus* have been found in papular lesions which may be either infected with or free of bacteria. Nutting (1950) reported that the contents, mites in all stages and an ether soluble product, of unruptured papules were commonly sterile. A suspect relationship in the goat between demodicids and lymphadenitis due to *Staphylococcus* spp. has been noted (Nutting, unpublished). Durant (1944, and personal communication) does not believe that a vector relationship is present in this association. The nodular lesions due to *D. bovis* in *Bos taurus* are said to be bacteria free (Nemeseri and Szeky, 1961) but as in French's account for *D. canis* no procedure for ascertaining this is given. Open nodular lesions are, however, often markedly suppurating in bovine demodectic mange. Lesions due to *D. caprae* represent the only assured source of large numbers of bacteria-free mites useful for vector studies.

Other than the dog, most laboratory animals so far examined in our University of Massachusetts laboratory (rabbit, guinea pig, rat, mouse, cat), have been either negative for demodicids or harboured very small mite

populations. The Golden Hamster, *Mesocricetus auratus*, is an exception to this. In these a remarkable host-sex difference in parasite load is apparent with low populations in females and high populations in males (Nutting and Rauch, 1963). In the latter populations are occasionally so high that one or more mites may be found in nearly every hair follicle! Mites have not been found in internal tissues including the uterus or in foetuses (Nutting, 1965). They have been recovered from the muzzle of suckling young at five days postpartum from mothers isolated in screened and sterilized cages (Nutting, 1950). The transference mechanism here seems to be by way of direct contact which in our studies proved 100 per cent effective. Both species of *Demodex* in the hamster have been shown to be low grade pathogens which harvest cells of the epidermis (*D. criceti*) or of the follicular epithelium (*D. aurati*) (Nutting, 1961). As noted elsewhere (Nutting, 1964) the hamster is an ideal laboratory animal for work on demodicidiasis, and may under improved experimental conditions prove to be a choice subject for *Demodex*-leprosy studies.

As far as we can discover no attempt has been made to see whether populations of *D. folliculorum* fluctuate with time of year. Such changes have been reported for *D. equi* (Bennison, 1943) and *D. bovis* (Poliakov, 1958). In these papers no experimental evidence is available to indicate the mechanism of population fluctuation. So far we have not been able to find any seasonal differences in *D. aurati* of the Golden Hamster under controlled laboratory conditions.

It should be mentioned here that other associations between demodicids and disease organisms have been suggested (Table I). We have yet to obtain any proof of a causal or cooperative connection between the mites and any disease entity. The work of Magnusson (1929) would seem to rule out a transfer role for *D. bovis* in hoof and mouth disease of cattle. As a working hypothesis demodicids should be held suspect as cooperative agents for any disease organism of the skin.

Facets of Investigation

From considerations of our knowledge of the biology of demodicid mites and the information on the association of *D. folliculorum* and leprosy certain fertile facets for investigation become apparent.

In laboratories associated with leprosaria it would be relatively easy to determine:

1. The incidence of *D. folliculorum* in leprosy patients *versus* 'controls' with attention to race, sex, drug regimen, age of the host and time of year.
2. Distribution of *D. folliculorum* in body areas and with respect to lesions of leprosy.
3. Whether or not *M. leprae* is found in the gut of *D. folliculorum* and confirmation of Spickett's observation on mite regurgitation.
4. If *D. folliculorum* commonly invades the dermis with especial attention to infections or degenerative changes in the skin.
5. Whether or not *D. folliculorum* is found in internal organs in man.

Other problems such as (1) if offspring delivered by Caesarean section with no history of nursing, which may negate Demodex transfer, develop

TABLE I

Suspect cooperative relationships, with some degree of circumstantial evidence, between demodicids and disease organisms.*

Disease	Demodicid	Authority	Date
Acne	D. folliculorum	Simon	1842
Pustulous mange	D. canis	Nunn	1878
Blepharitis	D. folliculorum	Stcherbatchoff	1903
Cancer	D. folliculorum	Borrel	1909d
Red mange	D. canis	Gmeiner	1909
Hoof and mouth	D. bovis	Magnusson	1929
Lymphadenitis (?)	D. caprae	Aynaud	1931
Nodulous mange	D. bovis	Momberg-Jorgensen	1943

*demodicids have been found in most skin diseases (see Gmeiner, 1908).

leprosy, and (2) if siblings from parents arthropod-free (i.e. other than *Demodex*) develop leprosy, could be resolved in long term studies.

Techniques for incidence studies of *Demodex* are simple and quickly performed. Mites are most readily recovered by examination of expressed sebaceous material from the facial naso-labial area. Lawrence (1916) recommends expression with a small silver spoon. One could also use a comedo expressor although this is relatively tedious. Expressed material may be examined under the microscope (mites are under 0·5 mm.) in the living condition by simply adding a drop of mineral oil. Permanent mounts can be made with Hoyer's solution (may be purchased from Wards Natural Science Establishment, Inc., Rochester, New York).

Biopsy or necropsy material should be fixed in 4 per cent formaldehyde. Sections, 10 microns thick, should be cut from paraffin blocks and stained with hematoxylin and eosin (HE). By noting their morphological and tinctorial characteristics it also is possible now to examine for presumably viable *M. leprae* on, in, or around demodicids *in situ* (Rees and Valentine, 1962). A further refinement could be made using carefully washed and crushed demodicids injected into the foot pads of mice (Shepard, 1960).

Sako and Yamane (1962) found that internal structures, especially lymph nodes, which were adjacent to skin areas with the greatest parasite (*D. canis*) loads were most heavily infested. It would, therefore, appear most profitable to examine cervical or axillary lymph nodes in cadavers with high populations of *D. folliculorum*. Lymph nodes may either be digested in KOH (5 per cent), centrifuged and examined for mite exoskeletons or they may be sectioned (10 μ), stained (HE) and examined under the microscope.

Three ideal experimental animals are currently available for *Demodex* studies, the dog (*Canis familiaris*), Golden Hamster (*Mesocricetus auratus*) and the goat (*Capra hircus*), all of these with large populations of demodicids.

As noted above *D. canis* of the dog is easily obtained and should be re-investigated in order to resolve (1) the mechanism of mite transference, (2) the relationship of *D. Canis* to *S. albus*, and (3) the origin and function of giant cells. Such information could offer some valuable leads to studies of the leprosy problem.

The large populations of demodicids in the male Golden Hamster seem ideal for experimental purposes. Not only are two species present, *D. criceti* and *D. aurati*, but these inhabit distinct niches in the skin complex and are rather generally distributed over the body of the host. Furthermore, in *D. aurati* a differential position in the hair follicle is apparent for the stages of the mite life cycle. Since moderate infections of *M. leprae* have been obtained in the ear and testis of the hamster (Binford, 1959) it would seem feasible to concentrate on this animal in studies of *Demodex*-leprosy relationships.

Hamsters are the present host of choice in screening drugs for the control of *Demodex*. So far no absolutely dependable measure is available to extirpate demodicids (see Koutz, 1957; Nutting, 1964). Should such measures be devised massive prevention or treatment in endemic leprosy areas would answer our major question. Whether or not these mites transmit leprosy we still need an effective control procedure to prevent other demodectic diseases (see Nutting, 1965).

Only in the goat do we have massive populations of demodicids (*D. caprae*) and these free of bacteria. The mites are found in large (to 32 mm.) papules from which they are easily obtained by sterile puncture. The University of Massachusetts laboratory is currently attempting to find whether or not *D. caprae* will ingest bacteria and if these are transported or regurgitated. We are also concerned with the possible vector role of this species in lymphadenitis. Goat demodicids are also well suited for studies of the *in vitro* effects of chemicals which might be useful in control.

Giant cells are reputedly obtained from preparations of whole blood (Lewis, 1925). It would be instructive to examine with the Lewis technique the response of giant cells to demodicid mites, *M. leprae* and if possible the result of giant cell phagocytosis of *Demodex* which contain *M. leprae*. As has been shown for *Trichomonas vaginalis* (Honigberg, personal communication) in man, it seems plausible that *M. leprae* may subvert or destroy giant cells and thus be in a position to cause further damage to the host. It is certainly possible that destruction by phagocytosis of demodicids with an internal flora of bacteria would liberate these to the detriment

of the phagocytic cell and subsequently to surrounding cells.

We should not overlook the suggestion of Gmeiner (1909) that demodicids may pave the way for the establishment of bacterial infections. Their activity which enlarges the lumen of the hair follicle and their ability to penetrate cell membranes may well be necessary features in leprosy invasion. Such factors coupled with the apparent ubiquity and sure mechanism of mite transfer from mother to young could account for the long term close contact which may be necessary for leprosy transmission. It could also explain the baffling and spotty results of such studies as Worth's (1960) where various rearing procedures for children from mothers with leprosy gave conflicting results for incidence of the disease.

Undoubtedly most of the suggestions above will be studied and the questions resolved in the next few years. A large laboratory could conceivably undertake the entire programme but it is more likely that independent workers will attack one or more of the separate facets of the problem. In either case it would seem profitable to pool our thinking and our experimental programmes along these lines so that cooperative timing or the benefits of new perspective may reduce the period necessary to determine whether or not demodicids are in any way causally related to human leprosy.

Summary

1. The literature on *Demodex folliculorum* pertinent to the problem of the possible transmission of *Mycobacterium leprae* and the initiation of leprosy is reviewed.

2. Information on other demodicids (esp. *D. canis D. caprae* and *D. aurati*) is also presented with an eye to its use in resolving the suspect relationship of *D. folliculorum* and *M. leprae*.

3. A number of suggestions are made which would materially aid an attempt to settle the problem of whether or not there is any causal relationship between *D. folliculorum* and leprosy.

IN MEMORIAM

Dr Edgar B. Johnwick, Medical Officer in Charge, Public Health Service Hospital, Carville, La. passed away on October 14, 1965. His pleasant, helpful and catalytic personality will be missed deeply by all of his friends and by his associates in problems of leprosy.

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