PATHOGENESIS ASSOCIATED WITH HAIR FOLLICLE MITES (ACARI : DEMODICIDAE) *

BY

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SUMMARY.

In this review of demodicid pathogenesis, information on taxonomic discrimination, gross signs of disease, and histological details of lesions is updated. Particular attention is paid to invasions of the host digestive system, infestations of eccrine glands, subdermal invasions, and formation of the granulomatous response. Techniques used in these studies are discussed, as well as areas in need of further investigation.

RÉSUMÉ.

Dans cet examen de la pathogénie démodécique, nous allons remettre au point nos connaissances sur la discrimination taxonomique, les signes grossiers de la maladie, et les particularités histologiques des lésions. Nous nous attachons surtout à des invasions de l'appareil digestif de l'hôte, des infestations des glandes eccrines, des invasions sous-dermiques, et la formation de la réaction granulome. Nous présentons la méthode employée dans ces études et suggérons des domaines où des enquêtes supplémentaires sont nécessaires.

Several interesting derangements of mammalian tissues due to infestations of hair follicle mites (*Demodex* spp.) have been discovered since our published review (NUTTING, 1965) and report in Washington D. C. in 1970. Valid criteria for species determinations have been established (DESCH and NUTTING, 1971), many cases of synhospitalic species are known (NUTTING, in press), new loci of infestation have been recorded (e.g., NUTTING *et al.*,1973), and several new patterns have been detailed of host cellular reponse to demodicid invasions.

These topics, plus brief notes on gross signs and some unresolved problems of demodicid pathogenesis, form the substance of the following report. Although the major focus is upon pathogenesis, the importance of taxonomic discrimination to this will be developed initially.

TAXONOMIC CONCERNS.

Of all parasitic mites, demodicids seem to be the most host species specific (NUTTING, 1968). Until the proof (NUTTING, 1961) that one host animal housed two species specific demodicids

* Revision of an invited paper presented at the Third International Congress of Parasitology, Munich 1974.

TABLE I. Comparison of measurements used to describe Demodex folliculorum and D. brevis. Data in micrometers ($\bar{x}$ and sd for 20 specimens each measurement) from Desch & Nutting, 1972.

D. folliculorum				D. brevis			
Male		Female			Male	Female	
19.5 ± 0.9		21.3 ± 0.7		Gnathosoma: length	14.5 ± 0.5	16.3 ± 1.1	
24.0 ∓ 0.9		26.5 ∓ 1.0		width	17.1 ∓ 1.4	19.2 ∓ 1.1	
				Podosoma:			
67.7 ± 2.8		75.0 ± 2.8		length	54.4 ± 2.9	65.2 ± 2.3	
45.0 ± 2.0		51.9 ± 3.0		width	46.0 ± 4.2	50.2 ± 3.4	
				Opisthosoma:			
191.0 ± 49.4		197.9 ± 55.7		length	97.1 ± 17.2	126.8 ± 25.0	
32.7 ± 1.7		40.3 ± 3.3		width	39.8 ± 4.6	44.6 ± 7.7	
279.7 ± 52.0		294.0 ± 58.1		Total length	165.8 ± 18.5	208.3 ± 26.5	
24.2 ± 0.9		8.5 ± 0.6		Penis or Vulva	17.6 ± 1.0	6.9 ± 0.4	
Ovum		Larva			Ovum	Larva	
104.7 ± 6.3		282.7 ± 45.1		length	60.1 ± 3.4	105.4 ± 11.5	
41.8 ± 1.8		33.5 ± 2.6		width	34.4 ± 2.2	33.8 ± 4.0	
Protonymph		Nymph			Protonymph	Nymph	
364.9 ± 36.4		392.0 ± 46.8		length	147.6 ± 14.1	165.0 ± 26.3	
36.3 ± 4.4		41.7 ± 6.3		width	34.4 ± 3.5	41.2 ± 5.4	

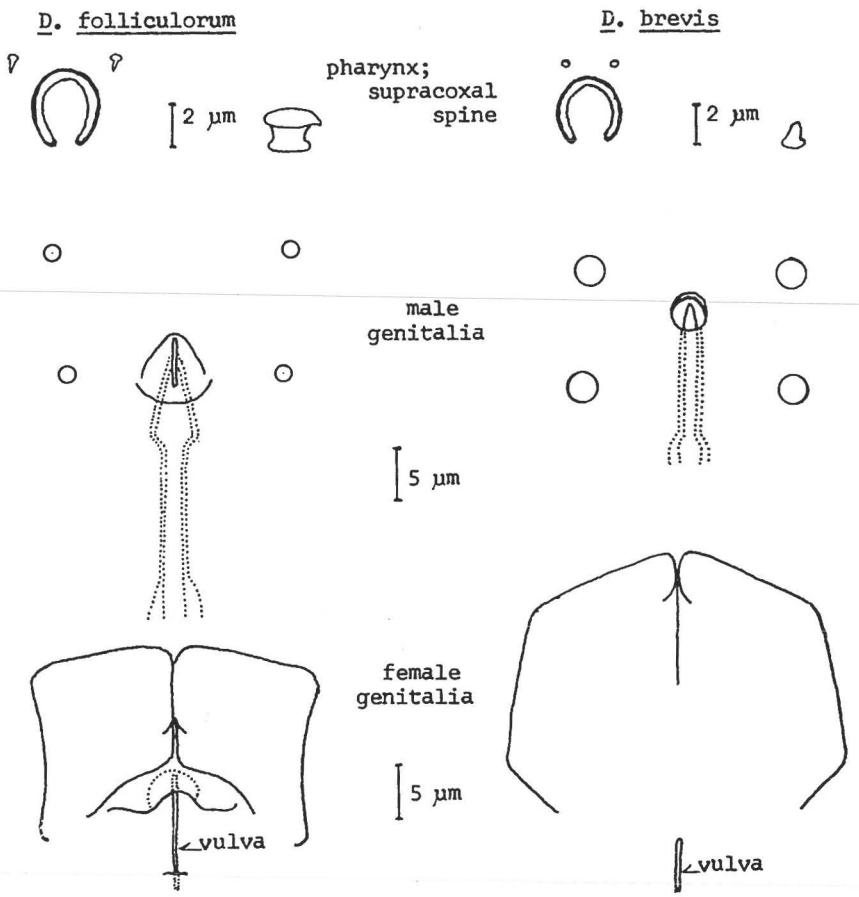


FIG. 1. : Comparison of critical adult structures used in taxonomic discrimination of *Demodex folliculorum* from *D. brevis*. Opisthosomal invagination is present only in female *Demodex folliculorum*. Rearranged and redrawn from Desch and Nutting, 1972.

(= synhospitalic, EICHLER, 1966) and in different habitats, we thought we could assign species designations based solely on the species of host infested. This discovery of synhospitalic species, first proposed by HIRST, 1919 (although on weak criteria) has been followed up by several detailed studies (NUTTING, in press — for review). These studies show that species criteria, such as general body shape and dimensions of adult mites (Table I) are inadequate to separate synhospitalic species. If, on the other hand, ova shape, immatures and certain adult characteristics (Fig. 1) are combined these species are readily separable (DESCH and NUTTING, 1971). A key to the known medical-veterinary species using multiple character couplets will soon be available (NUTTING, in ms.). Although such is adequate for specimens removed from the host and prepared as whole mounts, complications arise in discriminating mites in sectioned material.

Determination of true pathogen status is relatively impossible, especially in synhospitalic cases, without examination of host tissue sections. In some synhospitalic species, as for example *Demodex brevis* and *D. folliculorum*, the mites species may reside within 0.5 mm. of each other, even though in distinct habitats (sebaceous glands and hair follicle respectively). Pathogenesis for these may, also, be quite different (GROSSHANS *et al.*, 1974). Even for those species for which synhospitalic cohorts are unknown, we should note that in view of the marked propensity of this genus to be synhospitalic (nearly 50 % of 134 species examined are synhospitalic — NUTTING in press) these partners may well have been overlooked.

We have tried, therefore, to (1) orient tissues so that suspect mite habitats are cut in longi-section, and (2) obtain serial sections with a few slices at 8-10 μm (for host cells) and others at 20 μm (more than one-half mite width). These last provide adequate characters for mite identification.

In all synhospitalic species studied to date the two, three or four synhospitalic partners seem to utilise different habitats (Table II). Their potential for pathogenesis therefore differs as well as their potential as transfer and inoculating agents for other disease-producing organisms.

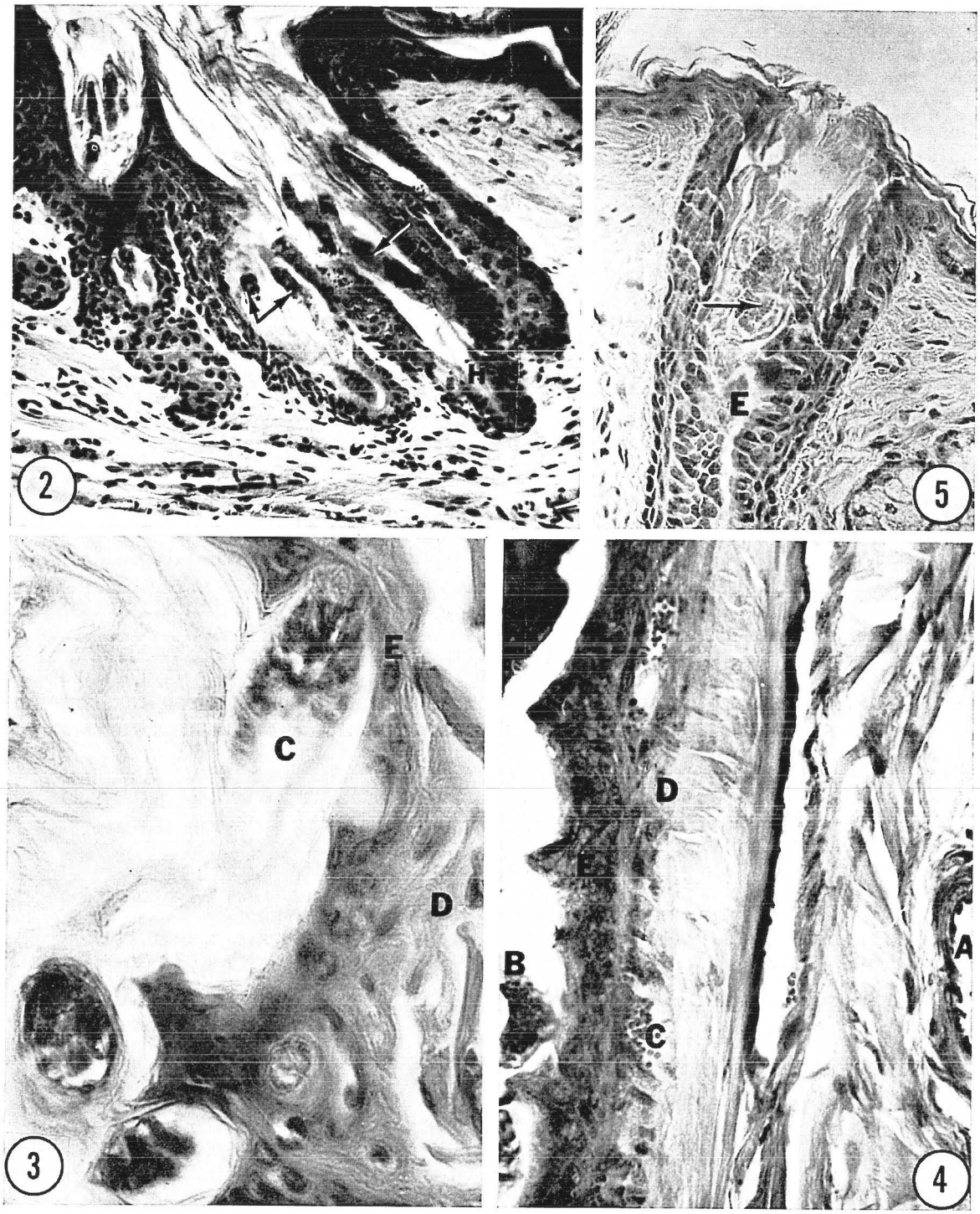
TABLE II. Host species specific "synhospitalic species" of demodicids (Demodex sp.) from selected hosts* with locus of infestation.

Demodex sp.	Host (Order)	Locus	Authority
D. carolliae	Carollia perspicillata	hair follicle	Desch et al, 1971
D. longissimus	" "	Meibomian glands	Desch et al, 1972
	(Chiroptera)		
D. brevis	Homo sapiens	sebaceous glands	Desch & Nutting, 1972
D. folliculorum	" "	hair follicle	Desch & Nutting, 1972
	(Primate)		
D. bovis	Bos taurus	hair follicle or sebaceous gland	Nemeseri & Szeky, 1961
D. sp.	" "	Meibomian glands	Oppong, in press
	(Artiodactyla)		
D. sp.	Equus caballus	Meibomian gland	Desch & Nutting, in ms.
D. equi	" "	elsewhere	Bennison, 1943
	(Perissodactyla)		
D. criceti	Mesocricetus auratus	epidermis	Nutting, 1961
D. aurati	" "	hair follicle	Nutting, 1961
	(Rodentia)		

* of 134 species of mites (Demodex spp.) examined nearly 50% have synhospitalic partners - see Nutting, in press.

GROSS SIGNS OF DEMODICIDOSIS.

The most common gross sign of demodicidisis is the hairless, scruffy condition called " mange ". In view of the plausibility that all mammals have hair follicle mites and the fact that hair



FIGS. 2-5 : 2) Photomicropgrah of stained (HaE) section of Golden hamster skin from animals reported in Estes *et al.*, 1971. Note massive invasion of *D. aurati* (arrows) with displacement of hairs (one bulb at H) ; x 425 ; 3) Photomicrograph of stained (HaE) section of Golden hamster skin from animals reported in Flatt and Kerber, 1968. *D. criceti* (C) numerous and no cellular reaction in epidermis (E) or dermis (D) ; x 1125 ; 4) Photomicrograph of lesion boundaey in infestation of *D. caprae* (B). Note increase in capillaries (C) and arteriole (A.) Epithelium (E) and dermis (D). HaE. x 425 ; 5) Photomicrograph of skin of a bat (*Carollia perspicillata*) showing *D.* sp. (arrow) within eccrine duct (E.). HaE. x 375.

loss can he caused by a variety of chemical, physiological, mechanical and biotic factors, it is difficult without histological examination to ascribe a causative role to demodicids in most instances. Despite this, demodectic mange has been reported in dogs, hamsters, deer, grebils, cats, horses and pigs.

Sections of skin from the mangy hamsters reported by ESTES *et al*, (1971) show that *D. aurati* which lives deep in the hair follicle, has indeed destroyed the epithelium so completely that hairs have been evicted (Fig. 2). In the cases reported by FLATT and KERBER (1968), however, many *D. criceti* but few *D. aurati* are found (Fig. 3). It is hard to see in this latter case, how the epidermis-burrowing *D. criceti* could be responsible for the mange. It seems clear from our examination of many sectioned samples from dogs and white-tailed deer, that *D. canis* and *D. odocoilei*, even without bacteria, are often depilatory agents. In all other instances, and those sure to crop up in the future, careful attention must be paid to histological preparations to establish a pathogenic role for mange conditions.

In similar vein, gross signs such as erythema, skin scurfiness, or vesicle formation as noted in demodicidosis for man (SATO *et al.*, 1965), dogs (many reports) and so on may often be caused not by *Demodex* spp. but by topical drugs, nutritional disturbances, bacterial infections, etc. In these cases, histological studies may be inadequate to show causal connections : long term experimental studies may be needed,preferably with control animals free of demodicids. So far, unfortunately, *Demodex*-free host animals are not available.

Recently, thickened dermal and fascia segments from the whitetailed deer which produced demodicids were sent to us by Dr. F. E. Kellogg, Athens, Georgia. These were discovered on flensing the skin of the neck by a taxidermist. Gross examination showed not only that these were soft nodular thickenings but that mites were most numerous in scattered 1-2 mm. yellow (lipid ?) blebs. This is the first report of such massive subdermal infestations.

Several more cases (see NUTTING *et al.*, 1971) of eyelid sealing in *Clethrionomys gapperi* have been obtained. In all instances examined so far, the eyelids were moderately swollen, slightly

TABLE III. Illustrative cases of gross signs, with histological details, of demodicid pathogenesis.

Host	Demodex spp.	Gross Signs	Histological Detail	Authority
Mesocricetus auratus (Golden hamster)	D. aurati	mange (hair loss and scurfy skin)	mite destruction of epithelium near hair base.	ESTES, pers. comm. Histology - this report.
Antechinus stuartii (marsupial mouse)	D. antechini	benign (to 2.5 cm) tumors	hyperplasia (lobulation) of follicular epithelium	NUTTING & WOOLLEY, 1965; NUTTING & BEERMAN, 1965
Bos taurus (domestic cattle)	D. bovis	nodules (to 3 cm)	mite penetration and granuloma	NEMESERI & SZEKY, 1961; NUTTING et al. in ms.
Capra hircus (domestic goat)	D. caprae	papules (to 4 cm)	marked hyperplasia (mono-lumen lesion)	GRAM, 1925; LEBEL & NUTTING, 1969
Odocoileus virginianus (white-tailed deer)	D. odocoilei	mange with rugosities	hyperplasia and distention of pilo-sebaceous epithelia.	CARPENTER et al, 1972; DESCH & NUTTING, 1974
Clethrionomys gapperi (red-backed vole)	D. gapperi	scaled eyelids	duct plugging (sans bacteria)	NUTTING et al, in ms.
Odocoileus virginianus (white-tailed deer)	D. sp.	papules (1 - 2 mm) in subdermal fascia	mites in fascia and dermis, sans cell response.	NUTTING, this report.

reddened, and the lids were sealed shut. Large numbers of *Demodex gapperi* free of bacteria were found apparently plugging the ducts of the Meibomian glands (see histological details).

On relatively naked or short-haired mammals excrescences such as vesiculo-papules (MISKJIAN, 1951 — for man), benign tumors (NUTTING and WOOLLEY, 1965 — marsupial mice), nodules (NEMESERI and SZEKY, 1961), etc. (see Table III) are readily discernable. The mere presence of demodicids in such is obviously not proof that these protuberances are caused by the mites. Even histological sections, in view of the propensity of these mites to invade tissue, may provide false leads. Some helpful techniques which we have used are :

1. Sterile puncture, contents retrieved and plated for bacteria (NUTTING, 1950).
2. Check sterile puncture contents on cultured cells for virus (SEVOIAN, pers. comm.).
3. Stain central slices of paraffin-embedded biopsies for bacteria (as LILLIE, 1928).
4. Compare histological sections of moderately or non-infested (by *Demodex* sp.) skin with that obtained from the suspect lesion.

In the cases recorded in Table III one or more of these procedures have been used and our assessment is that, in the first five instances, hyperplasia occurs and that these changes are caused by the demodicids. Note that the evidence for a causative role in lid sealing (case 6) is only circumstantial and, further, that (case 7) in the subdermal invasions no host cellular reaction was evident. For many other reports, further study is necessary to incriminate *Demodex* spp. as causative gross-lesion producing organisms.

HISTOLOGICAL DETAILS.

Recent studies (DESCH, 1973) show that demodicids bear two needle-like, chitinous chelicerae which are driven by muscles into host cells. An unguarded mouth opening below the chelicerae leads into a very narrow tube followed by a pulsatile sucking pump, the pharynx. Twin openings in the oral cavity are linked by ducts to the salivary glands. This arrangement of feeding structures reinforces our contention (NUTTING, 1965) that all demodicids are primarily minor pathogens puncturing cells and sucking out the cytoplasm. Further, waste products from the mite are not expelled into the habitat but rather tied up biochemically as crystals (STROMBERG and NUTTING, 1972) in the gut cells (DESCH, 1973) thus reducing the liklihood of host cellular response.

When mite populations increase, the normal replacement mechanism of epithelial cells is somehow stimulated to produce hyperplasia and/or hypertrophy leading to gross signs of demodicidosis as previously described above. Very large populations or moderate populations of aggressive mites over ride the replacement mechanism and penetrate to the dermis. The histological details, reported in keeping with host tissue involved, are as follows :

1. *Hair follicle invasion :* this is the most common route of invasion for demodicids. Many instances (NUTTING, 1965 — and since) are known of undercutting of the follicular epithelium. Increase in mite numbers within the follicle leads to hyperplasia and in at least one case (NUTTING and RAUCH, 1961) to aggregation of melanocytes around the distended follicle. As the follicle increases in size it is apparent that there is an increase in both size and numbers of blood vessels. For very large lesions some increase in the dermis is apparent. Demodicids which penetrate deep in the hair follicle, as *D. aurati*, may displace the hair and, in *D. antechini*, may occasion lobulation leading to " solid core " tumors. Remarkable hyperplasia occurs in infestations of *D. caprae* : here large (to 4 cm) hemi-spherical papules show in section a central mass

of up to several hundred thousand mites encased in a thin 1-3 cell thick epithelium with increased surrounding vascular network (Fig. 4). Penetration of this epithelium by small numbers of mites seem to evoke little tissue response. Massive penetration with rupture of underlying blood vessels produces a typical granulomatous response with mesodermal giant cells which phagocytose and eliminate the mites (for *D. bovis* see NEMESERI and SZEKY, 1961). The tissues then recover as in tumors of the marsupial mouse (NUTTING and WOOLLEY, 1965).

In sections of deer skin (CARPENTER *et al.*, 1972) it is usual to find mite infested follicles adjacent to each other, one with marked leucocyte invasion, the other free of leucocytes. The same observations can be made on sections of demodectic mange in dogs and Golden hamsters (NUTTING, unpublished). The logical interpretation, based in part on the disposition and lack of dermal penetration of the mites in either case, is that the host reactive follicles are bacterially infected. This same situation is found in holocrine gland infestations.

2. *Holocrine gland infestations :* several new records are available for demodicids found exclusively in the Meibomian glands or ducts (NUTTING *et al.*, 1971 ; DESCH and NUTTING, 1972). In the last, species in South America bats, the highly modified hold-fast legs III are occasionally thrust through the epithelial wall into the dermis : some slight massing of lymphocytes and leucocytes is found at this point. Larvae, protonymphs, nymphs and adults undercut the epithelial duct lining or destroy gland cells. For the former account of *Demodex gapperi* resident in the red-backed vole Meibomian ducts, some evidence of epithelial undercutting is found as well as several instances of apparent duct-plugging by the mite bodies which may have reduced the flow of Meibomian secretion leading to eye lid sealing (NUTTING *et al.*, in ms). In this last, mites in all stages of the life cycle are found stranded in the interlid sealed debris.

3. *Epidermis penetration :* although reports of infestations of demodicids in the body epidermis are limited (NUTTING, 1958) we are now sure that there are several species so located. All apparently only excavate body-size pits in the epidermis as in *D. criceti.* Infestations of *D. criceti* in the Golden hamster often reach remarkable population levels with all stages in the life cycle, including ova, in pits against the epidermis. Immatures and adults are found with mouthparts apparently undercutting the epidermis. In the few cases of epidermal penetration, we have found no evidence of foreign body reaction. It is interesting that in the instances in which *D. criceti* invades the epithelium of a distended hair follicle their bodies lie parallel to the skin surface rather than, as with their synhospitalic partner, *D. aurati,* parallel to the hair shaft (NUTTING and RAUCH, 1958).

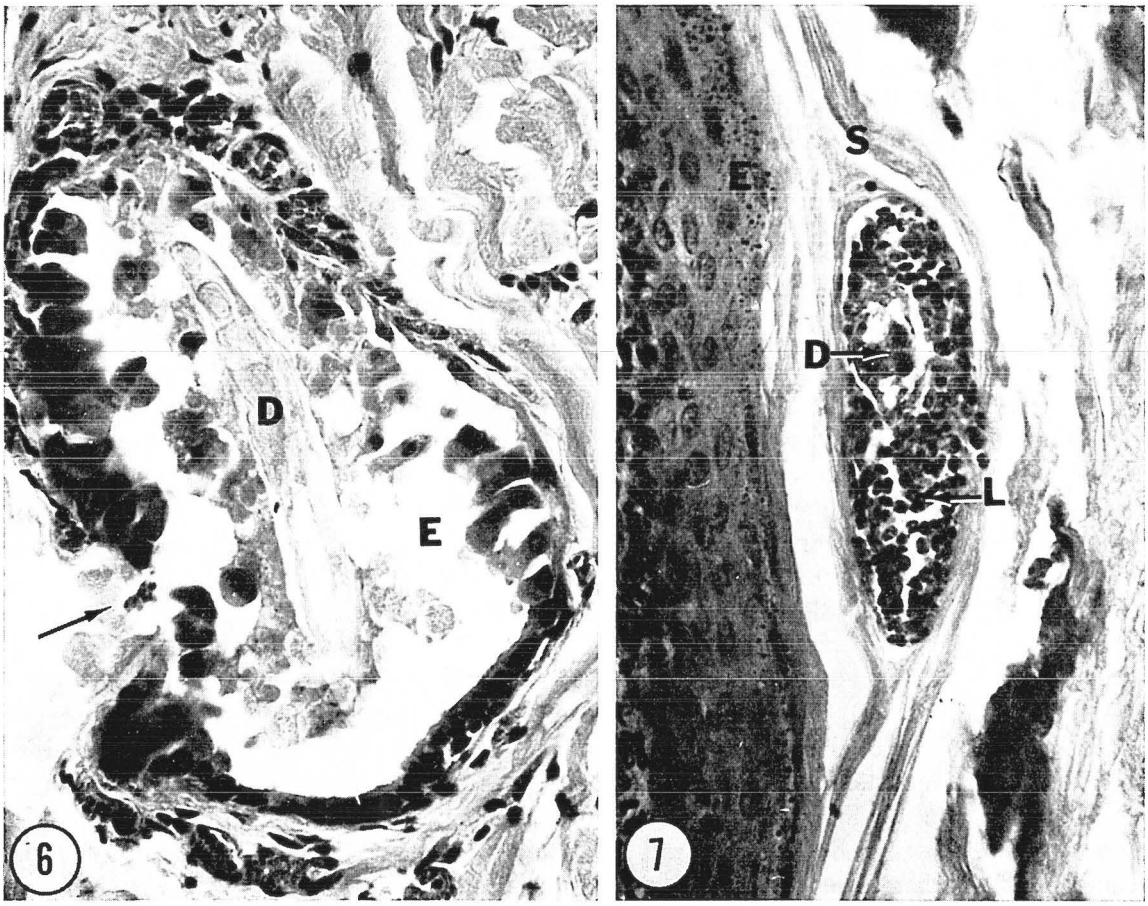
4. *Eccrine gland involvement :* invasion of the eccrine glands are uncommon. MUCCIOLO (1936) reported this for *D. phylloides* of swine. Eccrine glands of the gular papilla were found invaded by demodicids of the bat, *Myotis* sp., with extirpation of the epithelial lining (NUTTING, 1950). Recently an undescribed species has been located in the eccrine gland duct, also in bats, (DESCH, pers. comm. — Fig. 5) and *Demodex odocoilei* found in the lumen of eccrine glands of the white-tailed deer (Fig. 6). In the first, the mites are apparently entering the duct through the ductal orifice, whereas in the latter it appears the mite has entered through the epithelial wall of the gland. Rupture of the gland epithelium has apparently produced no cellular response.

5. *Circulatory system :* in *Demodex antechini* penetration of the vascular wall in degrading tumors (NUTTING and BEERMAN, 1965) is readily demonstrated. That this may be responsible for a granulomatous reaction leading to giant cell phagocytosis followed by reduction of the

benign tumor, is indicated by the relatively low level of perivascular infiltration when mites penetrate the tumor lobules to the dermis in contrast to the high level of cell response occurring in areas in which mites have penetrated blood vessels. Examples of circulatory system involvement have been reported by FRENCH, 1964, for *D. canis* and for *D. odocoilei* by DESCH and NUTTING, 1974. Skin sections just obtained from Dr. M. Dailey show demodicids (an undescribed species from a sea lion) in small dermal veins.

It is now apparent that invasion of the blood vessels by demodicids is of common occurrence.

6. *Anterior digestive tract :* in section, *Demodex* sp. of *Onychomys leucogaster* is found in pits of the esophagus, mouth cavity and tongue with mouthparts against the epithelium (NUTTING *et al.*, 1973) — much as reported for *Demodex musculini* in the tongue of the mouse by TUZDIL (1957). Some slight epithelial undercutting was found in the esophagus, and, on one occasion (Fig. 7), some indication of an inflammatory response of host cells. As noted in our paper, this esophagus infestation is the first clear indication that sebaceous, eccrine or Meibomian gland products are not essential to mite maintenance or reproduction.



FIGS. 6-7 : 6) Photomicrograph of skin of the white-tailed deer (*Odocoileus virginianus*) showing *Demodex odocoilei* (D) within an eccrine gland (E). Plausible point of invasion at arrow. HaE. x 425 ; 7) Photomicrograph of a section of grasshopper mouse esophagus (*Onychomys leucogaster*). Soft keratin (S), epithelium (E) and *D.* sp. (D) surrounded by host cellular response — lymphocytes and leucocytes (L). HaE. x 525.

7. *Subdermal fascia :* the segments of subdermal fascia (see gross signs) show on section that *Demodex* sp. lies in small groups in the fascia directly below the dermis. All stages in the life cycle of this species are present. Examination of several hundred sections failed to reveal any signs of tissue response, although the marked deposits of lipid(?) may be related to mite activity. The remainder of the overlying skin was not obtained with these blebs so no evidence is available as to the route of penetration.

Careful comparison of species characteristics show that this species is quite different from its synhospitalic partner, *D. odocoilei.*

Any epithelial layer or gland (duct) open directly to the exterior of the host animal should be suspect as a demodicid habitat or point of invasion. Under conditions of heavy to massive mite infestations some mites will penetrate the dermis and often subsequently move to other glands, lymph spaces, subdermal fascia and even blood vessels. If the latter are veins of sufficient caliber the mites can be carried in the blood stream throughout the body until stranded in the smaller arterioles or lymph nodes (as FRENCH, 1964). Stranding or penetration of venules, arterioles or capillaries may produce a granuloma with giant cells which phagocytose the mites.

PROBLEMS — DEMODICID PATHOGENESIS.

With an estimated 5,000 new demodicids available for study we anticipate many new interesting cases of pathogenesis. Those here reviewed do present several problems :

1. *Effect of environment, if any, on taxonomic features :* specimens have been maintained or cultures for only 24 days (GRAY, 1968) with no change in taxonomic features. Until culture measures have been perfected and cultivated mites studied, we have only circumstantial evidence as to which features in Table I and Fig. 1 are most valid for species determination. We do feel that a combination of these features establish valid species distinctions at the present time.

2. *Mechanism of transfer :* here again circumstantial evidence, rather than proof, indicates that demodicids are transferred from mother to young early post-partum by physical contact or grooming (NUTTING *et al.*, 1973). We do have new records (see NUTTING, in press) that indicate, as suggested by FISHER, 1973, that the life cycle can be broken. Breaking the cycle of transference seems the most likely way to control mite pathogenesis and the transfer, via these mites, of other pathogens (NUTTING, 1965).

3. *Utilization of host cells and/or cell products :* as noted above, the discovery of demodicids in all life cycle stages in the anterior digestive tract would seem to rule out sebaceous gland products as necessary for mite development and reproduction. Keratin can also be eliminated as food supply in such species as *D.* sp. in horse and *D.* sp. in cattle. In both of these all stages of the mites are found in the Meibomian gland cells far from any area of keratin concentration (see OPPONG, in press). Furthermore *D. criceti* (all stages) and *D. aurati* (adults) were shown to be killed by keratin investment in cases of biotin deficiency (NUTTING and RAUCH, 1961). The conclusion is that most, if not all, demodicids subsist on nutrients abtained from punctured cells, and even here that cytoplasmic components alone may be adequate for mite nutrition. Granular particles are often located in punctured cells near the mite chelicerae : the derivation of these is unknown. The function and derivation of mucopolysaccaride often found near the mite mouthparts is also unclear.

4. *Limiting factors in population increase :* as noted before (NUTTING, 1965), some correlation must obtain between host sex chemistry and mite increase : in Golden hamsters, males are more heavily parasitized than females — in certain bats and rabbits (DI BENEDETTO, 1961 ; MARAVELAS, 1962) the opposite prevails. In Australian cattle a gradient of infestation was discovered along a north (high) south (low) " transect " (NUTTING, unpublished). POLIAKOV (1957 — for cattle) and BENNISON (1943 — for horses) showed seasonal maxima for demodicid infestations. Despite several attempts using castration, sex hormone injections, various temperature and light regimens, seasonal examination studies on Golden hamsters, goats, cattle and man, we have not been able to pinpoint seasonal factors which limit or expand the mite population.

Biotin deficiency did decrease populations of *D. criceti* and *D. aurati* (NUTTING and RAUCH, 1961). Several proprietary drugs, both topical and systemic, do provide some temporary mite reduction (NUTTING, unpublished). For any reported treatment, complete eradication as well as mite population increase has not been conclusively demonstrated or adequately confirmed.

5. *Granulomatous reaction :* we have been puzzled, since 1965 (NUTTING and WOOLLEY), that in many skin sections, and now for at least six host species, small numbers of demodicids have been found in the dermis with little or no inflammatory response or perivascular infiltration. In many instances, adjacent hair follicle epithelia, sebaceous glands or epidermis have apparently been destroyed as mites entered the dermal network.

Under experimental conditions (NUTTING, unpublished) of inserting specimens of *D. caprae* beneath the ankle skin of Golden hamsters, we were able to obtain a typical sequence of (a) lymphocyte invasion, (b) polymorphonuclear leucocyte invasion, (c) histiocyte or plasma cell aggregation, and (d) giant cell formation in 24 days (Figs. 8-11). In a few cases leucocytes were found within the mite exoskeleton indicating tissue invasion and destruction. To our surprise, some 65 day biopsies revealed that intact exoskeletons of the *D. caprae* were stranded in normal-appearing dermis without granuloma, giant cells, or encapsulating connective tissue.

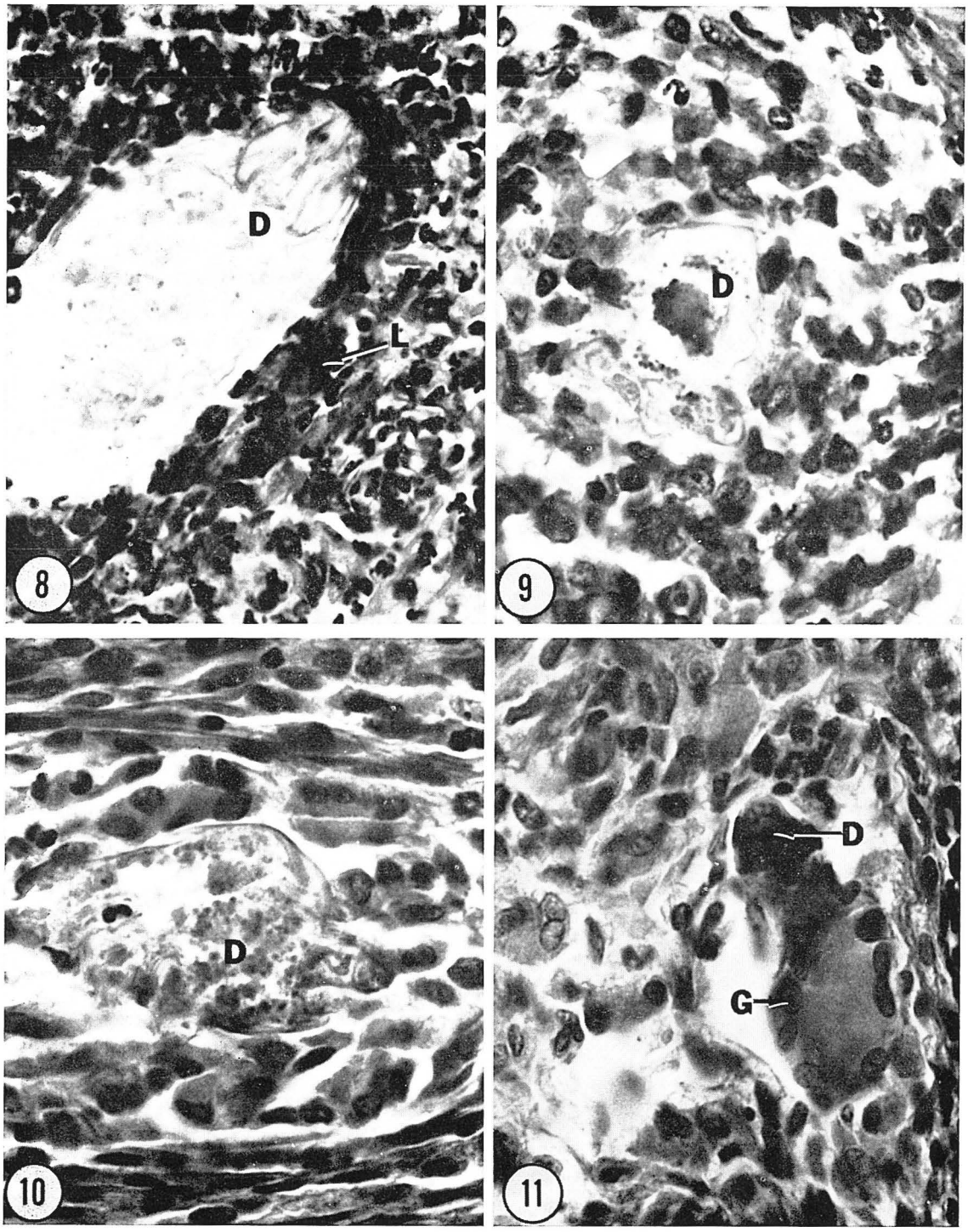
Further, in our lab (GNONG, 1970), we used the above subplant technique to check the host cellular response to small amounts of histamine. *Demodex caprae* exoskeletons were prepared by KOH digestion of live mites. After multiple washes, separate batches of these exoskeletons were soaked in different concentrations of histamine. Subplantation, under ankle skin of Golden hamsters, failed to produce any unusual host reactions.

Further experiments are needed, obviously. We do, however, consider the following as a useful working hypothesis :

If small numbers of bacteria-free mites penetrate to or into the dermis the release of chemicals (as histamine) due to cell destruction and/or disintegration of mite tissues may be inadequate to set up an inflammatory response. On the other hand large numbers of mites which penetrate capillaries, venules or arterioles set up the typical sequence of cellular inflammatory response leading to giant cells which dispose of the mites by phagocytosis.

6. *Giant cell formation, destruction, and metabolism :* so far the formation and destruction of epidermal giant cells by *Demodex antechini* (see NUTTING and BEERMAN, 1965) is apparently unique. Hypertrophy of epidermal cells does occur in infestations of *D. carolliae.* Mesodermal giant cells and demodicids have been found in many species, including man (BERGSTAD, 1925 ; GROSSHANS *et al.*, 1974). It is common to find granuloma and giant cells which have phagocytosed *D. bovis* in sections of cattle hide (NEMESERI and SZEKY, 1961).

In some " subplant " experiments, similar to (in 5) above, using *D. caprae* exoskeletons giant cells were not found. This was surprising in view of several reports that clay particles



FIGS. 8-11 — Sections of subplant reactions to *D. caprae* in the ankle skin of the Golden hamster. HaE x 825 : 8) Day 3 — mite at D and lymphocytes and leucocytes at L ; 9) Day 9 — mite at D with leucocytes and plasma cells dispersed ; 10) Day 18 — mite at D showing aggregation and possible fusion of plasma cells. Note leucocyte within podosoma of mite ; 11) Day 24 — mite opisthosoma at D with adjacent giant cell (G).

and lycopodium spores commonly induce giant cell formation. Even in cases in which giant cells do phagocytose mites (as in *Demodex antechini*), we do not know how they destroy the mites and degrade or eliminate the chitin.

7. *Transfer, introduction, or facilitation of other pathogenic organisms :* it has long been suggested (GMEINER, 1908 ; BORREL, 1909) that demodicids serve as transfer agents of bacteria or virus which cause pathogenetic changes in the mammalian skin. The report by SPICKETT (1961) that *Mycobacterium leprae* was found in the gut of " *Demodex folliculorum* " now seems in part in error — Spickett's mite gut has been shown to be the brain (DESCH, 1973). ENGLISH *et al.* (1971) has shown that bacteria do adhere rather firmly to the exoskeleton of " *D. folliculorum* ". Such observations as these last two should be followed up to prove or disprove a transfer role for demodicids.

Although highly speculative, it does seem plausible that demodicids by invading the pilosebaceous complex and consuming cells may transfer, or mechanically carry organisms extant on the skin to areas of new nutrient supply. In large infestations the mites may also rupture epithelia providing entry for these pathogenic organisms even to the blood stream. Obviously some experimental evidence is needed to settle this important issue.

In conclusion, it is apparent that taxonomic discrimination in demodicids, is important to problems of pathogenesis because they are species specific and commonly synhospitalic : the synhospitalic counterparts occupy different habitats and are differentially pathogenic or may introduce other pathogens to these different loci. In cases with small or initial infestations most well-studied species as larvae, protonymphs, nymphs or adults, puncture host cells, and suck out the contents. Initial infestations or migrants to new loci on the same host may transport other disease organisms. Feeding and/or death of the mites may release these organisms under conditions favorable for their invasion of host tissues. Such invasive infections may provide conditions favorable to mite maintenance and reproduction.

With or without these enhancements, the mites reproduce, producing crowding in the habitat. Host cells respond by increase in numbers (hyperplasia) or dimension (hypertrophy) — not only for epithelial and glandular cells, but also for the adjacent dermis, and elements of the circulatory system. Melanocytes may migrate to the lesion area. Hair loss (mange) may occur at this stage and/or small papular excrescences can be found on gross examination. Histologically several different patterns have been discovered : 1) lobulation as in benign tumors of *Antechinus stuartii*, 2) mono-lumen papules as in *Capra hircus*, 3) dermal nodules, as granulomatous reactions, in *Bos taurus*, and 4) subdermal papules in *Odocoileus virginianus*. Unless the circulatory system is penetrated, small numbers of demodicids penetrate epithelia and invade the dermis without marked host cellular response. Upon penetration of blood vessels a granulomatous reaction is established with either phagocytosis by giant cells and destruction of mites or passage of the mites into the major circulatory system. The final disposition of the mites in either circumstance is unknown. In many instances the infested area regains its normal gross characteristics, although mites may still be present.

Demodicid mites seem remarkably adapted to invade any accessable epithelium including the anterior digestive tract. After invasion, they all seem capable of puncturing cells and removing, by pharyngeal pumping, the cytoplasm. In low level infestations their inroads become a mild sustained yeild of (renewable) epithelial cell contents. When, for reasons unknown, the mite population explodes for numbers, the epithelium becomes hyperplastic or is penetrated.

In many cases, especially in canines, a combination of bacteria and *D. canis* in the absence

of efficaceous controls, become so entrenched and explosive that the host animal dies. In other cases, even if the bacterial infection is controlled, a high level of demodicidosis remains. The continued presence of gross signs of this disease, plus the likelihood that bacterial reinvasion will occur, often suggests euthanasia.

In view of the multitude of new demodicids remaining to be studied each with some potential for pathogenesis, it would seem useful that cooperation among medical practitioners, veterinarians, and zoologist should take place. Under present conditions, small but important observations on demodicid pathogenesis are being made all over the world but remain buried in local veterinary or medical reports, or in the heads of investigators. Without cooperation we are likely to reach the year 2002 without resolving the pressing problems of demodicid pathogenesis, solution of which could provide us with some assuredly efficaceous measures of control.

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