Dermatomic distributions of hypopigmented macular lesions of leprosy: neural dependence of melanocytic functions

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Summary. Dermatomic analysis of the distribution of the hypopigmented patches of leprosy has revealed a pattern wherein patches are most frequent in dermatomes of the brachial plexus, decrease gradually in frequency in succeeding spinal segments and increase again in dermatomes of the lumbar plexus. The predilection of hypopigmented patches for certain dermatomes may be a reflection of easy vulnerability of the neural pigmentary mechanism and/or a reflection of selective multiplication of *M. leprae* in nerves of certain dermatomes, even though the organisms might have been seeded all over the body by hematogenous spread. These preliminary observations are discussed.

Pigmentation of the skin of lower animals, in addition to being under hormonal control, is also under neural control, especially that of the autonomic nervous system[1,2]. Actual synapses between autonomic nerves and dermal melanocytes have been demonstrated in some lower animals[3]. Though a clear-cut relationship between dermal melanocytes and nerves has not been established in higher animals and man, the role of neural influences in the pathogenesis of vitiligo has been strongly advocated[4-6].

In leprosy, it is the universal observation that impairment of sensation is most marked in macular tuberculoid, less marked in dimorphous and least in lepromatous leprosy[7]. Similarly, hypopigmentation is most marked in macular tuberculoid and least in lepromatous leprosy[7]. Further, in all cases of macular tuberculoid and in all the macular hypopigmented lesions of other types of leprosy, where anesthesia is also present, it is observed that the latter does not extend beyond the area of hypopigmentation. This well defined and constant association between anesthesia and hypopigmentation suggests that their concurrent manifestation is due to their being inter-related, and is not just coincidental. Cases of segmental vitiligo are well documented[8,9]. With the above observations strongly pointing towards the role of neural influences on pigmentation, the study of hypopigmented macules in terms of dermatomal involvement was undertaken.

Material and method. A total of 142 untreated cases of leprosy having hypopigmented macular lesions were taken up for study. They were classified on the basis of the clinical, bacteriological and histopathological criteria of Ridley and Jopling[10] into 5 groups: 50 cases of TT, 25 cases each of BT, BB and BL, and 17 cases of LL. The site of each macular lesion was analyzed in terms of the dermatome(s) involved. In each case, the various dermatomes involved in macular lesions, whether bilaterally or unilaterally, were investigated. Finally, the frequency with which each dermatome in leprosy and its groups was involved, was calculated, and the association of hypopigmentation with impairment of sensation was carefully noted.

Observations. In the entire spectrum of leprosy, all macular hypopigmented lesions had impairment of sensations, which did not extend beyond the area of hypopigmentation. Further, hypopigmentation and impairment of sensation were maximum in macular tuberculoid, were less marked in borderline and least marked in lepromatous leprosy.

Thickened and palpable cutaneous (dermal) nerves and nerve trunks were encountered more frequently towards the tuberculoid end of the leprosy spectrum than towards the lepromatous end. They were not encountered in early cases of lepromatous leprosy. The nerves found to be thickened, in their order of frequency were ulnar, lateral popliteal, superficial radial, greater auricular and posterior tibial nerves. The rest of the cutaneous nerves, which supply most of the skin surface, were clinically not found to be thickened. The cutaneous nerve leading from the patch was found to be thickened in only 2 cases of macular tuberculoid leprosy.

In all the 5 major groups of leprosy, the pattern of involvement of dermatomes by leprosy lesions was found to be the same. However, the frequency of involvement of each dermatome increased from the tuberculoid end to the lepromatous end (table). From the cranial end to the caudal end of the dermatomes, a waxing and waning pattern in the frequency of involvement was observed. An increase in frequency was seen in the dermatome supplied by the maxillary branch of the 5th cranial nerve (V_2), between cervical 5-8 dermatomes (C_{5-8}), at lumbar three (L_3) and sacral three (S_3) dermatomes. Frequency of involvement was maximum at C_7 and then at L_3 dermatomes. In all types except the tuberculoid type of leprosy, the dermatomic involvement was more or less bilaterally symmetrical, even though the distribution of patches was clinically not symmetrical. It was also observed that the patches were usually present on the proximal rather than the distal portion of the limbs.

Discussion. The upper extremities are supplied by C_5 to T_1 spinal segments and the lower extremities by L_2 to S_3 spinal segments. Thus from our observations it can be said that the extremities are maximally involved, involvement of upper extremities being greater than of lower limbs. Cochrane[7] observed maximal involvement of uncovered extremities and this has lent support to the contention that leprosy spreads by close physical contact[11,12]. However, our study has revealed a selective increased involvement of some exposed dermatomes namely V_2, $C_{6,7,8}$ and $L_{3,4}$. If close physical contact and cool temperature were the only determinant factors in the clinical localisation of leprosy lesions, then all exposed dermatomes namely $V_{1,2,3}$, $C_{3,5-8}$, T_1, L_3 to S_2 should have had been involved uniformly.

Further, it was found that the lesions were mainly on the shoulder, upper arm and thigh, which are relatively less exposed, whereas the face, which is the most exposed part, showed macular hypopigmented lesions least frequently. Selvapandian et al.[13] in a school survey, in rural leprosy endemic area in Madras State in India also did not find any significant difference in the distribution of patches between covered and uncovered parts of the body.

Only a few cutaneous nerves, namely the superficial radial, greater auricular and posterior tibial, besides the ulnar and lateral popliteal, were clinically found to be thickened. Since other cutaneous nerves, which supply a much larger area of skin and which are equally close to the surface and hence exposed to cold temperature, were not found to be thickened; proximity to skin surface and cool temperature do not appear to be the only determinant factors for clinical involvement of nerves.

Leprosy is primarily a disease of the nerves, and skin lesions are secondary to nerve involvement[14]. Since distribution of leprosy patches is not greater in areas (and their

corresponding dermatomes) supplied by the above thickened nerves, it further appears that the preferential occurrence of skin lesions in some dermatomes, as observed by us, is not a reflection of involvement of particular nerves, but of local nerve endings of the spinal segments concerned.

The preferential bilateral symmetrical involvement of the above dermatomes may indicate that the nerve fibers arising from a particular spinal segment are more susceptible to *M. leprae* than others. As a result of this, the *M. leprae* would multiply selectively in such sites and finally lead to the appearance of clinical lesions, even though they might have had been seeded in other less favourable areas during hematogenous spread. Hematogenous spread of *M. leprae* in early stage of infection has been suggested by several workers[15-18]. We have observed unequivocal histopathological evidence of indeterminate leprosy with nerve involvement and occasional acid-fast bacilli in nerves in biopsies from apparently normal skin taken from the symmetrically opposite site to that having a representative lesion of the disease. This was observed in all the twenty four cases constituting the entire spectrum of leprosy[19].

On the other hand this preferential bilateral symmetrical involvement of the above dermatomes by hypopigmented macules of leprosy may mean that maintenance of normal pigmentation in them is especially dependent upon the integrity of their nerves; in such areas normal pigmentation gets altered much more easily when the nerve fibers concerned are damaged by the onslought of *M. leprae*. This, however, does not mean that hypopigmentation is a result of impairment of sensation. The melanogenetic influence of nerves may be a function, like the neurotrophic function, which is different from the function of sense perception. These functions may get deranged simultaneously or in various combinations when the nerve is damaged at a particular architectural level. This can explain the concurrent occurrence of hypopigmentation and impairment of sensation in the leprosy macule. In areas where nerve involvement is not severe enough, none of the above functions are impaired enough to be evident clinically, that is in the form of hypopigmentation and impairment of sensations.

That epidermal melanocytes are under neurophysiological control has been demonstrated conclusively in fishes and in many other cold blooded vertebrates[2,20-24]. By the technique of histochemical fluorescence, sympathetic innervation of conjunctival and dermal melanophores in teleost fish[1], and iris melanocytes in common laboratory animals[25,26] and in baboons and cats[27] has been established. Actual synaptic contacts between nerves and dermal melanocytes, have also been demonstrated by electron microscope in some lower animals[3]. Uga et al.[28] observed that degeneration of peripapillary pigment epithelial cells occurred when the optic nerve of dogs was afflicted by organophosphates. In humans, Mukuno and Witmer[29] have observed distinct nerve terminals making synaptic contacts with melanocytes in iris stroma. Existence of intraepidermal free axons[30] and of a close relationship between dermal axons and basal cells of epidermis and follicular epithelium, exemplified by the presence of some axons at the level of the dermo-epidermal interface between basal lamina and plasma membrane of basal cells[31] have been reported in human skin. Similar findings have been reported in rat skin[32]. But synaptic connections between the nerve terminals and epidermal melanocytes have not been demonstrated in man[3,33-35]. Still, the possibility of synapses at a distance and hence some sort of functional relationship between them cannot be excluded[3], as it would appear to be strange that all relationships should disappear between the nervous system and the pigmentary system in the course of evolution of animals, especially when the evolutionary evidence indicates that nervous control of pigmentation is of later development and has been superimposed on the more primitive humoral mechanism of control by the melanocyte stimulating hormone of the pituitary[36]. Segmental vitiligo[8,9], decreased pigmentation of the iris occurring after sympathetic denervation in humans[27,37], and the development of repigmentation concomitant with the development of severe diabetic neuropathy along with resultant loss of function of sweat glands in a case of extensive vitiligo[6], further support the neural control of melanocytes. Hence it is quite possible for hypopigmentation to occur when neural control has been deranged by leprosy infection.

This table gives the percentage involvement of various dermatomes by macular hypopigmented lesions in leprosy as a whole and its breakup for different subtypes of leprosy (i.e. TT, BT, BB, BL, LL). V_1, dermatome supplied by opthalmic branch of 5th cranial nerve; V_2, dermatome supplied by maxillary branch of 5th cranial nerve; V_3, dermatome supplied by the mandibular branch of 5th cranial nerve; C, cervical dermatomes; T, thoracic dermatomes; L, lumbar dermatomes; S, sacral dermatomes

Dermatome	Percentage involvement in Subgroups of leprosy					Leprosy as whole
	TT	BT	BB	BL	LL	
V_1	2	4	0	16	0	4
V_2	10	8	4	20	0	8
V_3	4	8	0	12	0	4
C_1	0	0	0	0	0	0
C_2	0	0	0	0	0	0
C_3	2	4	12	28	24	6
C_4	4	28	24	52	54	32
C_5	16	32	64	76	68	51
C_6	20	60	80	52	54	54
C_7	18	72	96	80	70	67
C_8	22	68	76	68	42	56
T_1	12	32	44	64	42	38
T_2	10	8	20	60	66	32
T_3	6	12	4	44	30	20
T_4	4	20	16	56	42	28
T_5	4	4	24	64	42	28
T_6	2	12	20	36	42	22
T_7	2	20	28	60	30	28
T_8	2	8	32	44	28	22
T_9	4	4	14	52	60	30
T_{10}	2	8	16	48	66	32
T_{11}	0	16	24	56	66	32
T_{12}	4	8	12	28	54	22
L_1	4	8	0	28	30	14
L_2	4	12	24	28	54	24
L_3	8	68	78	78	70	60
L_4	28	36	48	48	60	42
L_5	30	32	40	44	42	26
S_1	6	16	16	12	6	12
S_2	4	8	36	24	12	16
S_3	4	20	48	68	48	26

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Comparison of cutaneous hyperemia in cattle elicited by larvae of *Boophilus microplus* and by prostaglandins and other mediators[1]

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Summary. Blood flow has been measured in bovine skin following the injection of tick antigens and a number of pharmacological mediators; including histamine, prostaglandins and slow reacting substance of anaphylaxis. The greatest increase in blood flow (20 times normal) was recorded with tick antigens and with prostaglandin F2. This mediator may therefore influence blood flow during immune reactions to ticks and during the rapid ingestion of blood by the ticks.

An increase in capillary blood flow occurs in cattle *(Bos taurus)* skin at the attachment site of *Boophilus microplus* larvae[2]. On calves without previous tick exposure, an increase was not detected until 24 h post infestation and the peak was not reached until 48 or 72 h post infestation. It was argued that this increase was probably triggered by tick saliva rather than by mechanical damage, since attachments have stabilized[3] and the mouthparts are not found deeply penetrating the dermis at this time[4]. On calves previously exposed to ticks, an increase in cutaneous blood flow was detected as early as 15–30 min after infestation and the flow rate reached a peak at 24 h[2]. The effect of tick feeding on bovine cutaneous blood flow is compared in the present study with the effects of mediators which regulate vascular flow and permeability.

Materials and methods. Cutaneous blood flow was measured using radioactive microspheres (15 µm, diameter, labeled with ^{141}Ce, ^{51}Cr, ^{113}Sn, ^{85}Sr, ^{95}Nb and ^{46}Sc, NEN Co., Boston and 3M Co., St. Paul)[2]. Tick infestation procedures and information on the *B. taurus* cattle used have previously been given[2,5]. All the cattle were 6 months old calves except for animal D (tables 1 and 2) which was 2 years of age. The pharmacological mediators used were prostaglandins (PGE_2 and $PGF_2\alpha$), histamine dihydrochloride, histamine free base, 5-hydroxytryptamine creatinine sulphate (5HT), bradykinin triacetate, dopamine, acetylcholine, (all Sigma), adrenalin tartrate (Evans) and slow reacting substance of anaphylaxis ($SRS\text{-}A^{bov}$). The latter was prepared by Dr J.E. O'Hagan, CSIRO, Division of Entomology, from bovine lung[6]. It was assayed on isolated guinea-pig ileum in the presence of atropine and mepyramine, and 1 unit of $SRS\text{-}A^{bov}$ was equivalent to 5 ng histamine base. A serine esterase, designated antigen I, was prepared from *Boophilus microplus* larvae by Dr P. Willadsen, CSIRO, Division of Tropical Animal Science, as already described[7]. It was injected intradermally in 0.1% bovine serum albumin in phosphate buffered saline (PBS pH 7.5) at a concentration of 10 µg/ml. It was known that injection of 1 µg gave a measurable oedematous reaction in most cattle sensitized to the tick.

The mid-flank of the animals was clipped and marked into 4×4 cm areas and each solution was injected into 3 areas. The various pharmacological agents, the tick antigen and a buffered saline control were injected intradermally in 0.1 ml PBS using a 1 ml syringe and 25 gauge needle. The solutions were kept on ice until used. Blood flow was determined at certain times after injection, and as a gauge of increased vascular permeability, weal diameter was measured after 20–30 min. Skin biopsies of injection sites which were taken for blood flow measurements, were sampled after the oedema caused by injection of the mediators had subsided in order to avoid problems with weight changes in the tissues. Some samples were dried to constant weight at 110 °C to check for this source of error[2].

Results and discussion. The first comparison was made between capillary blood flow stimulation by 1000 *B. microplus* larvae, antigen I and relatively large amounts of the various mediators. There was considerable variation be-