Lesion Lodgement in Leprosy

The readily observable predominance of lesions on face and extremities as compared with the trunk, together with extensive involvement of skin and peripheral nerves, are characteristics of leprosy which have long stimulated pathogenic speculation. In view of the current common attribution of this singular localization pattern to a presumed low growth temperature preference on the part of *M. leprae,* it seems worthwhile to consider alternate factors which may be contributory. Reliance on single factor hypotheses of biological phenomenon may obfuscate or delay other potentially valuable investigations. This discussion is not designed to disprove an unproven hypothesis but to note some discrepancies and to serve as a reminder that pathologic processes tend to be multifaceted.

Tissue tropism. Neurotropism and dermal tropism have had explanatory vogue for this pattern of lesion lodgement but have little more than semantic interest in view of the long lack of relevant, associated knowledge regarding the biological requirements of *M. leprae.* Nevertheless, these concepts probably cover some present lack of understanding regarding growth preferences of the bacillus, or else the predominant skin involvement would hardly be likely. Likewise, it is possible that these concepts speak to a chameleon-like quality of macrophages (histiocytes), in which cells the bacilli are so proliferative as to have suggested to some that intracellular life is obligate for them ([1]). If it

[1] Suter, E. Some aspects of intracellular parasitism of pathogenic microorganisms. A review. Int. J. Lepr. **22** (1954) 1-11.

is true that *M. leprae* "prefer" life in the skin macrophages as compared to visceral macrophages, then it follows that macrophages probably change their characteristics to some degree by partaking of their environment. Many of these mobile cells, as well as their precursors, arrive at the site of inflammation from other locales. Sensitivity to their environment is attested to by their striking phagocytic and pinocytic activities. Their scavenger functions with resultant changes in their morphology under many conditions suggest that they are probably also subject to alterations in their internal milieu by factors such as tissue oxygen tension, prevailing tissue fluid nutrient content, and many other local factors. These probabilities are so broad and so little understood as to suggest caution in attributing the characteristic skin involvement in leprosy to some single factor.

On the basis of studies of nerves in leprosy, particularly in early lesions, some investigators ([2-4]) have emphasized a postulated affinity of Schwann cells for *M. leprae* or an affinity of the bacillus for these cells. Though there is no questioning the significance and uniqueness of the frequently extensive presence of *M. leprae* in nerves and Schwann cells, there may be some question as to pathogenic interpretation in terms of some special affinity for Schwann cells as compared to macrophages of the reticuloendothelium in general. These cells have phagocytic functions and are associated also with nerves, even of extremities, which are not generally involved in leprosy. Reported studies do not adequately take into account the fixed nature of the Schwann cells as compared to the more mobile, wandering cutaneous macrophages. The use of nerves as markers for finding the Schwann cells, will inevitably disclose more readily the presence of bacilli in the fixed cells than in wandering macrophages not clustered around a fixed marker, especially when the infection is early and mild.

The role of temperature. The characteristic prevalence pattern of skin lesions in leprosy has also given rise to speculation regarding temperature growth requirements of *M. leprae*. Since the predominant dermal localizations, in general, correspond to areas where skin temperature is lower than on the trunk where lesions are less common, it is postulated that *M. leprae* preferentially proliferate at such lower temperatures. Clinical observations have been cited in support of this concept. Thus, Brand ([5,6]), on the basis of observations at many reconstructive surgical procedures on deformed and crippled leprous extremities, when speaking of nerve paralysis stated: "The most constant factor common to all the sites of paralysis is the factor of nearness to the surface of the body.... It so happens that most of the thicker nerve trunks in the body are deeply placed. They are not infiltrated and not paralyzed.... It is only when a nerve is thick and also near the skin that it regularly becomes paralyzed. We suggest that a reason for the increased infiltration in situations near the skin is temperature variation. Superficial structures have a certain range of temperature between body temperature and a few degrees below. It may be necessary for a tissue occasionally to be below body temperature in order that the damaging reaction can take place." Previously he ([6]) related this to growth requirement of the bacillus, stating: "It seems to me that there is probably an optimum temperature for the growth and activity of the lepra bacilli and that this optimum is just below body temperature. It may only be 2 to 3 degrees."

The successful, though limited, growth of *M. leprae* in the mouse foot pad ([7,8]) has lent credence to this concept ([9]) and many current attempts at *in vitro* cultivation of *M. leprae* revolve around this supposed low temperature growth requirement. In fact, the

[2] Khanolkar, V. R. Studies in the histology of early lesions in leprosy. New Delhi, Indian Council of Medical Research, Special Rep. Ser. No. 19, 1951.

[3] Lumsden, C. E. Leprosy and the Schwann cell *in vivo* and *in vitro*. *In:* Leprosy in Theory and Practice, R. G. Cochrane and T. F. Davey, eds., Bristol: John Wright & Sons, 1964, pp 221-250.

[4] Weddell, A. G. M., Jamison, D. G. and Palmer, E. Recent investigations into the sensory and neurohistological changes in leprosy. *Op. cit.*, pp 205-220.

[5] Brand, P. W. Deformity in leprosy. *Op. cit.*, p 451.

[6] Brand, P. W. Temperature variation and leprosy deformity. Trans. VIIth Int. Congr. Leprol., Tokyo, 1958, pp 125-129.

[6] *Ibid.*

[7] Shepard, C. C. The experimental disease that follows the injection of human leprosy bacilli into foot pads of mice. J. Exp. Med. **112** (1960) 445-454.

[8] Shepard, C. C. Multiplication of *M. leprae* in the foot pad of the mouse. Int. J. Lepr. **30** (1962) 291-306.

[9] Shepard, C. C. Temperature optimum of *M. leprae* in mice. J. Bacteriol. **90** (1965) 1271-1275.

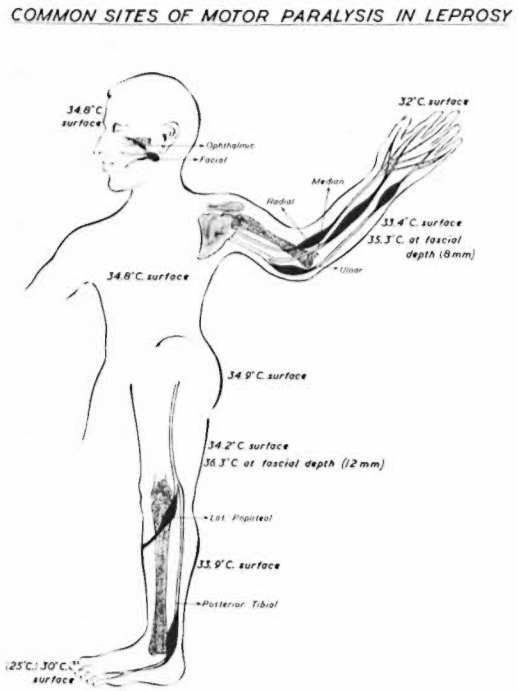

FIG. 1. Common sites of motor paralysis as related to topographical skin temperatures. Adapted from Brand ([3]) with temperatures added.

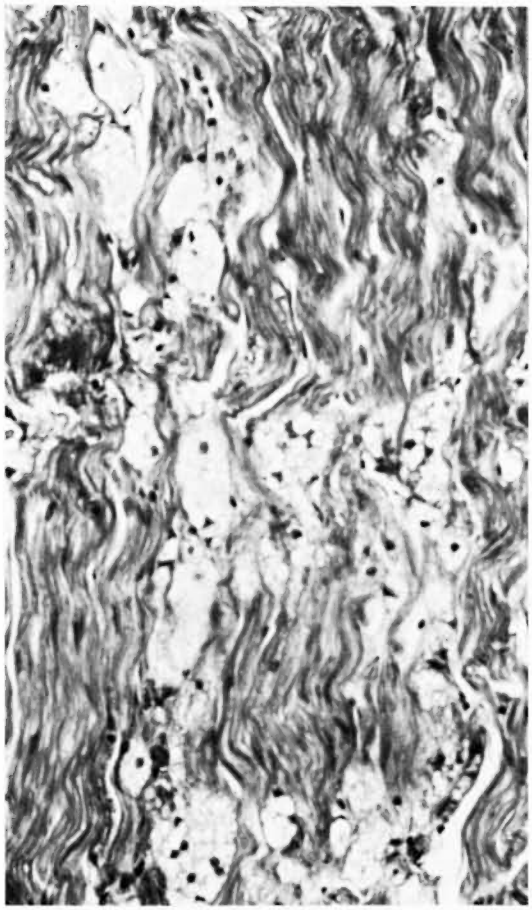

FIG. 2. Lepromatous "foam cells" in ulnar nerve at a point deep under muscle in forearm. Saffron trichrome stain. Orig. mag. × 40.

proliferation of *M. leprae* in the mouse foot pad does not say that the organism will not grow at body temperatures of the host, be that human or mouse. With respect to this question it merely indicates that the bacillus will grow at the lower foot pad temperatures —a fact already attested to by observation of lesions on hands and feet in human patients. In all probability this inoculation technic speaks to unrecognized factors of metabolism and immunity more complex than possible temperature susceptibility alone. Reports of successful inoculation of thymectomized and irradiated mice with considerable resultant growth of *M. leprae* in organs such as the liver ([10, 11]) seem to indicate that this is indeed the case.

It has recently been reported ([12]) that mice inoculated in the abdominal wall with bacillary suspensions derived from human lepromas will develop lesions with marked acid-fast bacillary proliferation if the animals are given weekly injections of hyaluronic acid. The relatively low foot pad temperature is, therefore, perhaps not the prime factor in the success of that model.

A number of considerations speak against the probability of low temperature growth requirement as being of dominant importance in lesion localization.

[10] Rees, R. J. W. Enhanced susceptibility of thymectomized and irradiated mice to infection with *M. leprae*. Nature **211** (1966) 657-658.

[11] Rees, R. J. W. and Weddell, A. G. M. Experimental models for studying leprosy. NY Acad. Sci. Conf. Biology of the Mycobacterioses, Oct. 1967. Published in Ann. NY Acad. Sci. **154** (1968) 214-236.

[12] Matsuo, E., Skinsnes, O. K. and Chang, P. H. C. Acid mucopolysaccharide metabolism in leprosy. 3. Hyaluronic acid mycobacterial growth enhancement, and growth suppression of saccharic acid and vitamin C as inhibitor of β-glucuronidase. Int. J. Lepr. **43** (1975) 1-13.

1. Judging from the range of temperature of common skin areas of bacillary proliferation (Fig. 1), it is evident that this organism will proliferate within a temperature range of at least 10°C, roughly 25° to 35°C. Recent allegations ([13]) of *in vitro* cultivation of *M. leprae* have found that the cultivated organism will grow throughout this range and also at 37°C, though growth may be slightly better at 34°C. If temperature is a critical factor in the growth and localization of *M. leprae*, it is remarkable that this organism, which has apparently parasitized only one host species for centuries and which has such a wide range of temperature tolerance, should be intolerant of about one more degree increase in temperature and should find the normal body temperature of its only known natural worldwide host to be incompatible with survival. It would be equally remarkable that after millenia of association with the human host this microorganism should have been unable, by mutation or adaptation, to adjust itself to such a slight increment in growth temperature requirement.

2. Several observations suggest that the postulated temperature ceiling may be specious.

a. Proliferative leprous lesions containing acid-fast organisms in the liver, spleen, lymph nodes and other tissues in lepromatous leprosy become more impressive the more they are studied at autopsy and biopsy ([14, 16]). Lesions are similarly distributed in the tuberculoid and intermediate (dimorphous, borderline) forms of leprosy but, as would be expected, mycobacteria are there often difficult to demonstrate. Indeed, visceral lesions, especially in lepromatous leprosy, appear to occur as frequently as do the testicular lesions which are often cited as evidence of low temperature growth preference for this organism. The morphology of these lesions in heavy infections suggests bacillary proliferation rather than mere deposition of dead organisms ([15]).

b. *M. leprae* infection of peripheral nerve trunks is, in fact, not limited to areas where these trunks lie close to the skin though the infection may be more prominent in such areas ([17]). In a collection of peripheral nerves studied by serial block sections in our laboratory it has been found that the ulnar nerve, for example, is often severely involved in areas where it lies under thick muscle covering (Fig. 2). Like histiocytes in lepromatous leprosy, Schwann cells in this disease pattern contain considerable amounts of acid mucopolysaccharides. As was demonstrated by Johnson and Helwig ([18]), nerves have considerable associated acid mucopolysaccharide and this can readily be demonstrated in cutaneous and peripheral nerves of armadillos stained by Mowry's colloidal iron stain, counterstained by the PAS reaction.

c. In the general attention given to localization of lesions on the extremities, another nearly as frequently involved area where the temperature is higher, is often ignored; namely the buttocks. This area presents lesions (Fig. 3) far more frequently than the back, chest or abdomen, yet its temperature, as we have determined by measurement, is as high, or higher (especially on sitting) than is that of the skin of the trunk. This lesion localization is so common that in South China local folklore takes note of it. It is believed that leprosy cannot be cured but that therapeutic measures can drive the infection to the buttocks where its manifestations will not be readily evident to society.

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[13] Skinsnes, O. K., Matsuo, E., Chang, P. H. C. and Andersson, B. *In vitro* cultivation of leprosy bacilli on hyaluronic acid based medium. I. Preliminary report. Int. J. Lepr. **43** (1975) 193-203.

[14] Mitsuda, K. *Atlas of Leprosy*. Tokyo: Chotokai Foundation, 1952.

[15] Skinsnes, O. K. The defense mechanism in leprosy as related to the visceral lesion and malnutrition. Trans. VIIth Int. Congr. Leprol. *Op. cit.*, pp 222-229.

[16] Verghese, A. and Job, C. K. Correlation of liver function with the pathology of liver in leprosy. Int. J. Lepr. **33** (1965) 342-348.

[15] Skinsnes, *op. cit.*

[17] Skinsnes, O. K. and Yamashiro, K. M. Morphology and pathogenesis of peripheral nerve involvement in leprosy. Int. J. Lepr. **38** (1970) 351-352.

[18] Johnson, W. C. and Helwig, E. G. Histochemistry of the mucopolysaccharides of skin in normal and in certain pathologic conditions. Am. J. Clin. Pathol. **40** (1963) 123-131.

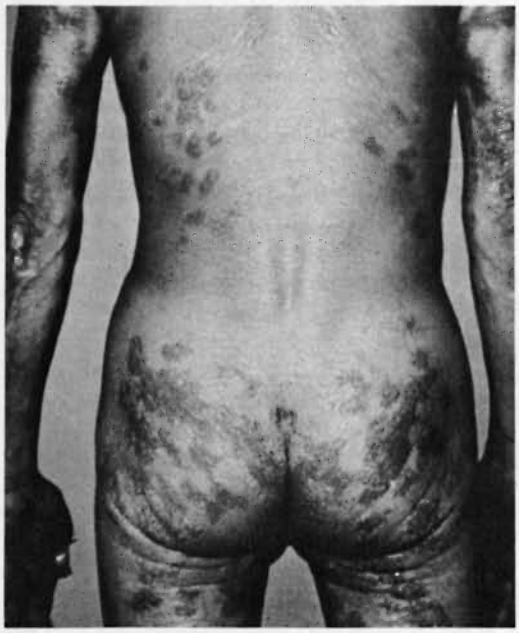

FIG. 3. Prominent lepromatous lesions on buttocks.

d. The generalization that the trunk is comparatively spared from leprous lesions as compared to face and extremities is negated in some patients, as in Figure 4. Likewise, much emphasis has been given to the frequency of testicular involvement as evidence of low temperature growth preference. However, if temperature is the deciding factor there remains a question as to why scrotal involvement, as in Figure 5, is apparently much less common than testicular involvement. Perhaps other factors such as the high testicular content of hyaluronic acid may be relevant to the problem.

Pictures of the Japanese patient, Figure 6, said to have had alopecia from leprous infection, have been shown around the world. The island of remaining hair growth along the course of the temporal artery has been cited as evidence that lack of bacillary growth along this presumably warmer track resulted in the preservation of hair growth. The patient's pate does not reveal any biopsy scars and we have not heard of any detailed pertinent studies of the factors in-

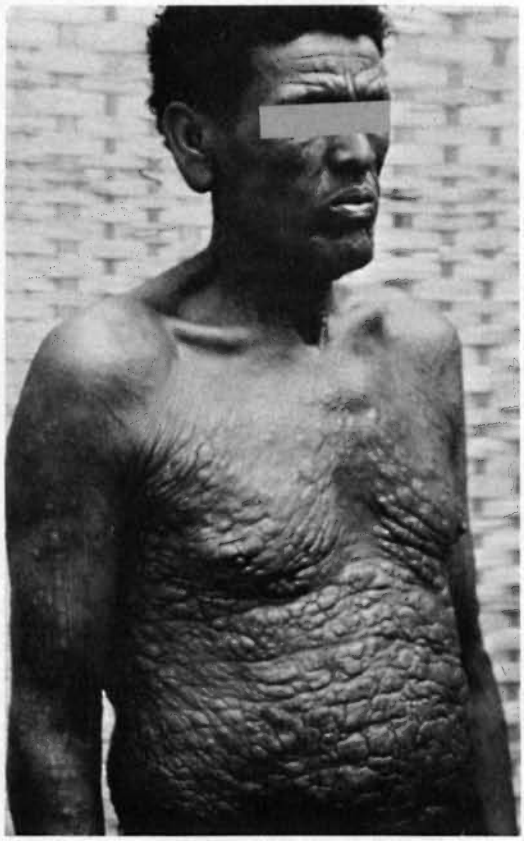

FIG. 4. Predominant leprous lesion localization on trunk and back with relative sparing of extremities. The face showed minimal involvement. Photo: kindness of Dr. Gunnar Bjune, ALERT, Addis Ababa.

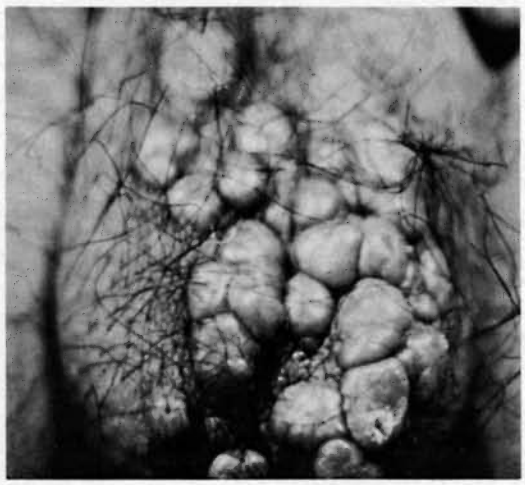

FIG. 5. Nodular lepromatous lesions of scrotum. Photo: kindness of Dr. Kazuo Saikawa, Okinawa.

volved. Possibly other unrecognized factors were involved and the "evidence" may be serendipitous enthusiasm.

Locus minoris resistentiae. The role of *locus minoris resistentiae* ([19]) has not received much recent attention in relation to lesion lodgement in leprosy, though a relationship was suggested in the earlier literature. Yet, many of the observed localizations can be equally well interpreted on this basis.

Often, when the concept is referred to it is considered in terms of "tissue damage." Though tissue necrosis may provide a locus of lower resistance to infection, this is not the only nor is it the dominant feature of the concept as related to the problem of lesion localization in leprosy. *Locus minoris resistentiae* in its conceptualization includes also factors of increased vascular permeability and stasis in areas of minor irritation without actual tissue necrosis or vascular break. Thus it is thought to be a factor in the predominant localization of the vegetations of subacute bacterial endocarditis on the closure contact surfaces of mitral and aortic valves as contrasted with the remarkable scarcity of such vegetations on the nonclosure surfaces. Since in the three score and ten year norm of human life these valves have closure contact in the neighborhood of 2.6×10^9 times, such contact can scarcely be considered as trauma or tissue damage.

It has long been recognized that luetic rashes are apt to crop up in tissue areas which are already occupied by lesions due to some other cause. As long ago as 1843, Cazenave laid down the rule that the locality of a secondary syphilitic lesion is commonly determined by some concomitant irritation or morbid condition. Tarnowsky ([20]) was so impressed by such observations that in 1877 he introduced what was known as the "Tarnowsky test" for syphilis. This consisted in applying mustard plaster to the patient's skin. A positive result was the appearance of an indurated lesion in the treated area after total disappearance of the reaction invoked by the plaster. The test most often yielded positive results if applied just before the secondary rash of syphilis appeared.

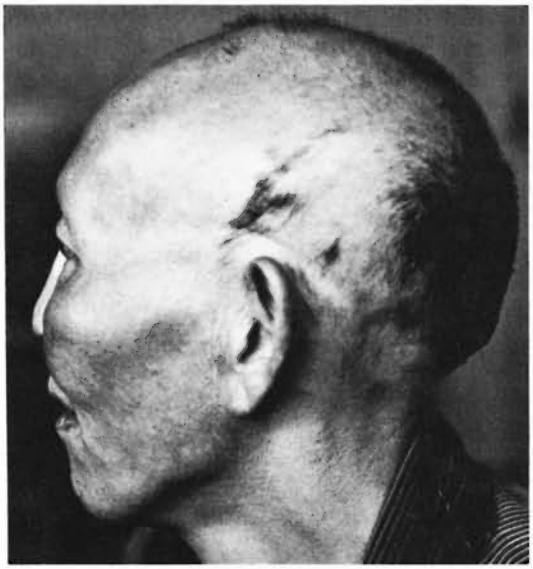

FIG. 6. Presumed leprous alopecia with hair sparing along course of temporal artery.

In 1878, four years before Koch's discovery of the mammalian tubercle bacillus, Jonathan Hutchinson ([21]) noted that skin tuberculosis was often associated with chilblaines and other abnormal conditions of the skin caused by exposure to heat and cold. "The connection of lupus erythematosus," he said, "with the same tendencies which evoke chilblains, is illustrated by the fact that the parts affected are, for the most part, those which suffer most from exposure to cold—for instance the nose, ears, and hands. Lupus erythematosus is very rarely seen in those parts of the surface which are constantly protected by clothes . . . exposure to heat is as injurious to these lupus cases as cold. Sunburn of the nose is a common exciting cause."

Leprosy being a very chronic disease with more slowly developing lesions than either tuberculosis of the skin or secondary lues is, in some respects, a more difficult disease in which to establish the role of *locus minoris resistentiae* since the irritant responsible may have disappeared and been forgotten by the time the lesion appears. On the other hand, the very lack of aggressive invasion

[19] Burrows, H. *Some Factors in the Localization of Disease in the Body*, New York: William Wood & Co., 1932.

[20] Tarnowsky, B. Vrtschr. f. Dermat. u. Syph. **4** (1877) 19.

[21] Hutchinson, J. *Lectures on Clinical Surgery*, London, 1878, part ii, p 275.

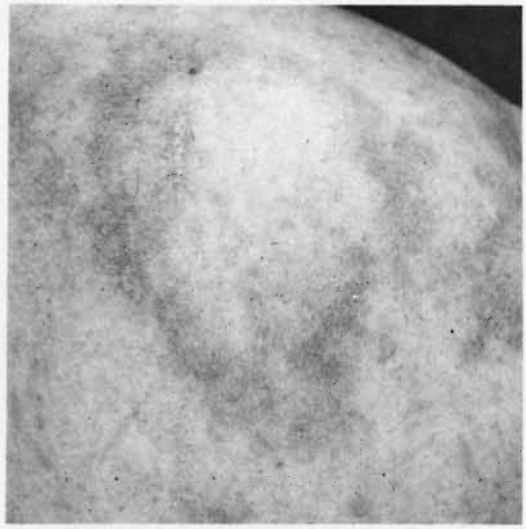

FIG. 7. "Carrying pole" lesion over right shoulder.

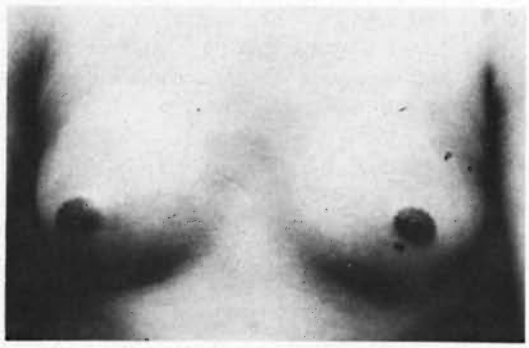

FIG. 8. "Brassiere" type lesion distribution.

characteristics on the part of *M. leprae* may emphasize the importance of any advantage to the organism in gaining a fresh tissue foothold.

Rogers and Muir ([22]) noted that the auricles are perhaps more constantly affected in leprosy than any other part of the body and suggested that this might result from vascular stasis due to pressure at night and from the changes of temperature to which the ears are liable in their prominent and exposed position. Hopkins, Denney and Johansen ([23]) made a careful investigation of the distribution of lesions in cutaneous leprosy. In a survey of 302 patients they noted that there were certain regions where lesions rarely, if ever, occurred. "These areas are among those which are less exposed to irritation from such sources as sunlight, heat, cold, pressure, friction, and other causes." The regions they found to be free of infection were the posterior inferior auricular area, the concha, the orbital side of the nose near the inner canthus of the eye, the lateral palpebral area external to the outer canthus, the axilla, the inframammary fold in women, the interdigital surfaces, and the perineum. This listing alone casts doubt on the appropriateness of regarding low temperature *per se* as a dominant factor in lesion localization except as it serves as an irritant in promoting changes in vascular permeability.

Both common and relatively uncommon lesion localization suggest a significant role of *locus minoris resistentiae* in leprosy.

1. The preponderant distribution of cutaneous lesions on the more exposed areas of face and extremities.

2. Significantly frequent lesion localization on the buttocks. Of added import is the observation that the sitting surface of the buttocks appear more frequently and more intensively involved than the upper area of these eminences (Fig. 3).

3. Occasionally lesion localization is observed over that area of the deltoid which supports the carrying pole in Oriental laborers who employ such poles in their work (Fig. 7).

4. The previously noted predilection for most intense nerve involvement at places such as the elbow, wrist and heel where the nerve trunks are less protected by overlying tissues (Fig. 1).

5. Bilateral localization in the skin of female mammary glands sometimes occurs with a pattern consistent with brassiere irritation (Fig. 8).

6. Bilateral lesion localization in the skin of male mammary eminences have been noted (Fig. 9). This pattern of distribution is compatible with undershirt irritation sometimes especially experienced when living in the warmer climes.

The last two localizations just cited are uncommon as compared to the common use of the garments noted as possibly irritant factors. However, it is to be borne in mind that skin susceptibility to minor irritation is a very

[22] Rogers, L. and Muir, E. *Leprosy*, Bristol: John Wright & Sons, Ltd., 1946, p 191.

[23] Hopkins, R., Denney, O. E. and Johansen, F. A. Arch. F. Dermat. u. Syph. **20** (1929) 767.

TABLE 1.

Comparative Localization of Lesions in Leprosy & Skin Tuberculosis

Body Area	Location First Leprosy Lesion		Distribution of Lupus vulgaris Lesions ①	
o/o	number	o/o	number	o/o
Head & neck	10	172	47	82 ②	55
Upper extremities	19	61	17	34	23
Trunk	33	5	1	11	7
Lower extremities	38	126	35	22	15
		364 lesions		149 lesions	

① Data from Ole Horowitz, Finsen Institute, Copenhagen.

② Excluding lesions in patients with contiguous internal tuberculosis.

variable characteristic. Some persons, for example, are very intolerant of wearing wrist-watch bands of any type of material.

The distribution pattern of tuberculosis of the skin is similar to that of leprous skin lesions (Table 1). The tuberculosis data employed in this table are selected from Tables 62-63 of the report by Horowitz ([24]) from the Finsen Institute, Copenhagen. They were selected to include only those instances of dermal tuberculosis in which the lesions were not contiguous to other possible areas of tuberculosis and therefore possibly only a direct extension of another lesion. The table compares this distribution with that of the stated first lesions in a group of patients with leprosy from our own experience in South China. The latter probably do not represent actual first lesions but rather the first remembered lesions. Their distribution pattern is however, similar to that of the general occurrence of leprous skin lesions. It is noted that the distribution patterns presented for tuberculosis and leprosy are remarkably similar. Since *M. tuberculosis* grows well at the body temperature norm, this comparison suggests that the skin lesion distribution pattern in leprosy does not necessarily witness to a preferential low temperature growth requirement on the part of *M. leprae*. It is not clear what significance there may be in the possibility that for both tuberculosis and leprosy some of these lesions may represent the point of host inoculation. The patterns of distribution, however, with strikingly predominant localization of lesions on the head and neck in both instances, suggest that in both instances the majority of lesions tabulated were not such contact infection localizations. It is concluded that the comparison can reasonably be interpreted as suggesting the importance of common factors of *locus minoris resistentiae* in the siting of lesions.

This conclusion is at variance with the statistical conclusion of Horton and Povey

[24] Horowitz, O. Applied epidemiology. I. Epidemiology and natural history of lupus vulgaris in Denmark, 1895-1954. The Danish TB Index, 1966, pp 114-117.

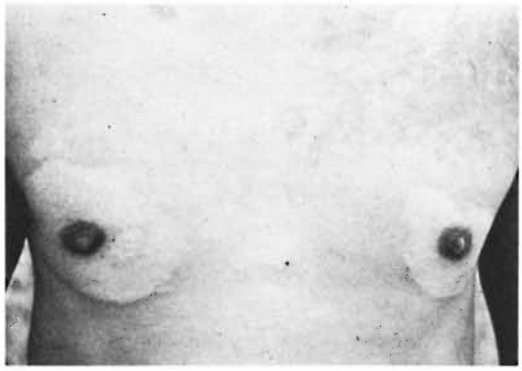

FIG. 9. Bilateral mammary lesion localization in male.

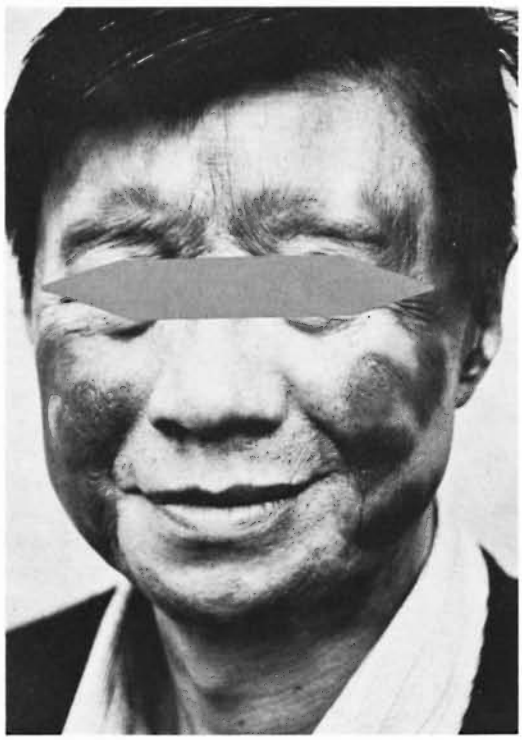

FIG. 10. B663 pigment concentration in leprous lesions.

([25]). Ignoring the possible significance of *locus minoris resistentiae,* they conducted their analysis of "first lesions" in leprosy on the assumption that if the distribution of lesions is random it could be expected that the distribution of lesions in different parts of the body would be proportional to their surface area. Finding that this was not so the investigators concluded that all such "first" lesions represent portals of entry of *M. leprae.* This interpretation may be untenable. The patient's witness as to the location of the "first" lesion in a chronic disease with a long incubation period is not highly reliable, and other operative factors such as *locus minoris resistentiae* preclude single factor statistical analysis. In all probability many first lesions in leprosy do indeed represent portals of entry but the presence of early lesions in areas of lesion predilection does not necessarily prove that this is the case. In any case, the "first" lesion usually merely represents the first remembered lesion.

It is common knowledge that B663 pigment is often most strongly localized in lesions, Figure 10. This may in part be due to its solubility in lipids but may also, in part, be a reflection of increased vascular permeability in the areas of inflammation.

Nasal lesions. Nasal lesions may represent a more striking example of localization of first lesions. The nasal passage, with its high mucus content, has a high level of acid mucopolysaccharides which seem to have a strong relationship to the presence of *M. leprae* in lepromatous lesions ([26, 27]). Children, as well as adults, frequently pick their noses with varying degrees of vigor. Fingernails are abrasive tools and may abrade the mucosa while at the same time repeatedly depositing in the mucosa quantities of leprosy bacilli carried under the fingernails. This is, of course, more likely when the subject is in intimate contact with an "open" case of lepromatous leprosy. We have been a little surprised that we have not found any studies on possible bacillary content in such "dirty fingernails" despite noting that this potential means of infection was noted by several leprosy workers in the 1920's and 1930's. It would seem to be a more likely means of infection than inhalation droplet infection which has recently been again raised in a

[25] Horton, R. J. and Povey, S. The distribution of first lesions in leprosy. Lepr. Rev. **37** (1966) 113-114.

[26] Skinsnes, O. K. and Matsuo, E. Acid mucopolysaccharide metabolism in leprosy. I. Storage of hyaluronic acid and its possible significance in the pathogenesis of leprosy. Int. J. Lepr. **42** (1974) 392-398.

[27] Matsuo, E. and Skinsnes, O. K. Acid mucopolysaccharide metabolism in leprosy. 2. Subcellular localization of hyaluronic acid and β -glucuronidase in leprous infiltrates suggestive of a host—*M. leprae* metabolic relationship. Int. J. Lepr. **42** (1974) 399-411.

number of discussions.

This postulated role of fingernail transmission need not apply to the nose only. Frequent abrasive scratches as in frequent nose picking could probably result in developing an adequate challenge dose of bacilli for lesions to be called forth.

Locus minoris resistentiae and the "isopathic phenomenon" in leprosy. Experimental confirmation of a significant role for *locus minoris resistentiae* in lesion lodgement in human leprosy can perhaps be found in a consideration of the "isopathic phenomenon" in leprosy. As described by Sagher and associates ([28,29]), this phenomenon consists of a profound specific alteration of tissue in the lepromatous host which causes a variety of substances such as tuberculin, peptone, milk, leishmanin, India ink, BCG, etc., to elicit histomorphic changes characteristic of lepromatous lesions at their sites of injection. In response to any of these stimuli, there develops at the site of injection a nodule of foamy reticuloendothelial cells at three to five weeks after injection. These do not have any organizational structure compatible with a "granuloma" ([30]).

In our experience with the "isopathic phenomenon" there is an increasing impression that rather than posing some postulated tissue idiosyncrasy, the "phenomenon" may in considerable measure be a manifestation of *locus minoris resistentiae*. The injection of any of this broad array of substances results in local alteration of vascular permeability or in vascular damage of a more severe and direct form. Either mechanism provides opportunity for the localization of circulating mycobacteria.

In an illustrative instance a lepromatous patient, who presented numerous small, fresh dermal, leprous nodules, was given a deep intradermal injection of 0.1 ml PPD in an area of skin which, though it was surrounded by scattered small lesions, did not appear grossly affected. The site of injection was marked by a surrounding circle made quite vigorously with an indelible pencil by a technician. When the subject returned for biopsy three weeks later, the pencil marking

FIG. 11. "Pencil rim" lesion.

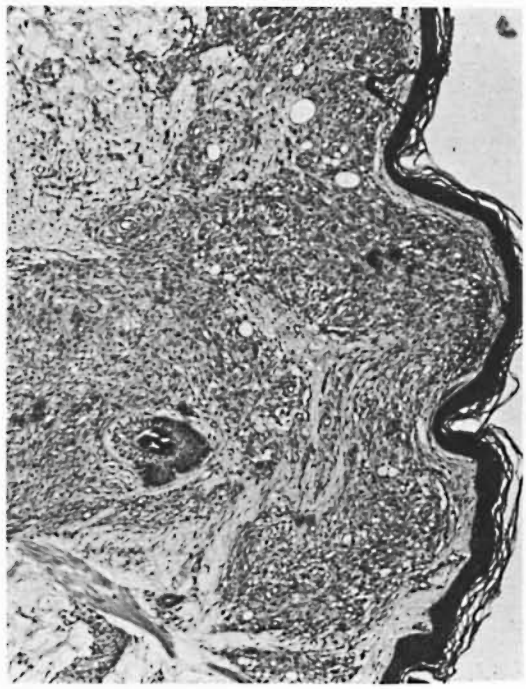

FIG. 12. Lepromatous infiltrate (bacilliferous) under pencil rim of Figure 11. Orig. mag. × 16.

[28] Sagher, F., Kocsard, E. and Liban, E. Specific tissue alteration in leprous skin. I. Transformation of the tuberculin reaction in leprous patients to leproma-like lesions. Int. J. Lepr. **20** (1952) 341-346.

[29] Sagher, F., Liban, E. and Kocsard, E. Specific tissue alteration in leprous skin. III. Specific reaction due to various agents. J. Invest. Dermatol. **20** (1953) 341-352.

[30] Skinsnes, O. K. Leprosy and the concept of granuloma. Int. J. Lepr. **38** (1970) 203-206.

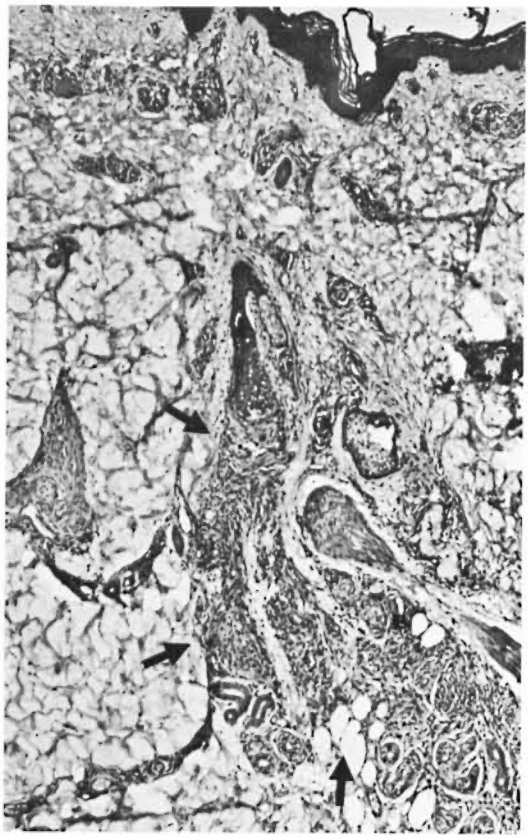

FIG. 13. Lepromatous infiltrate (bacilliferous) at dermal site of PPD deposition. Orig. mag. × 16.

had been washed off but in its place there was a slightly raised, brownish lesion which closely resembled other lepromatous lesions in that general area of skin save that it formed a circle following the track of the marking pencil and had the same width as the "indelible" mark (Fig. 11). Grossly no lesion was evident at the central point of needle injection. Full thickness skin biopsy of the circular, marginal lesion presented a lepromatous infiltrate extending close up under the epidermis underlying the pencil track (Fig. 12). A similar lepromatous infiltrate was found at the site of the PPD injection. Here, however, the inflammation lay deeper in the dermis, corresponding to the level at which the PPD was deposited (Fig. 13). Both lesions presented bacilli on acid-fast staining. Both lesions were localized histopathologically, neither showing any connection with each other.

It is postulated that in this instance both the irritation of PPD injection and the vigorous rimming of the area with a pencil created areas of increased vascular permeability in a patient who gave clinical evidence of having leprous bacillemia. Bacilli, it is postulated, localized in these areas and lesions developed in response to their presence. The time span allowed for lesion development

TABLE 2.

BACILLAEMIA IN LEPROSY

	ALL PATIENTS				LEPROSY <2 YEARS			
Leprosy type	Number patients examined	Acid-fast +	Per cent +	Per cent +	Number patients examined	Acid-fast +	Per cent +	Per cent +
Indeterminate	4	3	75		3	2	67	
Lepromatous	59	26	44	48	14	13	93	64
Intermediate	16	9	56		7	3	43	
Tuberculoid	22	4	18		12	1	8	
Totals	101	42	42		36	19	53	

Adapted from R. Rhodes-Jones (Uganda), 1963

under the conditions of the experiment was fortuitous in that it was short enough not to have permitted significant replication of bacilli and extension of lesions to the point of their merging. The two biopsies produced sufficient area trauma to make further observations on the subsequent course of the lesions meaningless to the experiment.

Clearly one fortuitous instance does not establish the case, and it is likewise evident that there is great biologic variation in degree of vascular reactivity to minor irritation from person to person. In some subjects, therefore, the phenomenon can probably be more readily related to lesion lodgement than in others. This biological variability is part of the total biological variability which influences the differences in lesion distribution in patients. Nevertheless, bacillemia has been shown, Table 2 ([31]), to be common in lepromatous leprosy and demonstrable in the tuberculoid variant, and the experimentally induced lesion lodgement just cited suggests that the concept of *locus minoris resistentiae* as a lesion lodgement mechanism is sujbect to experimental evaluation in the human.

The concept of *locus minoris resistentiae* as an explanation for the "isopathic phenomenon" does not cover all the claimed characteristics of the latter phenomenon as, for example, the claim that it can be elicited in patients who have no active leprosy but whose leprosy was of the lepromatous type. It does suggest, however, that the concept of the "isopathic phenomenon" must be examined critically before being accepted as evidence of tissue idiosyncrasy in leprosy.

Concluding note. The low temperature hypothesis has played a role in leading to some significant advances in experimental leprosy such as the use of the mouse foot pad and the armadillo. On the other hand, perhaps too great enthusiasm for it and virtual acceptance of the hypothesis as fact may have delayed work on other significant factors in leprosy. In either case interesting philosophical considerations seem evident.

—OLAF K. SKINSNES

[31] Rhodes-Jones, R. An investigation into bacillaemia in leprosy. Lepr. Rev. **34** (1963) 26-28.