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EDITORIALS

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Nutrition in Leprosy: A Review

Hansen's disease, ignorance of its causes and cure, and the fear of it have been associated as a terrible triad since earliest times. In the last half of the 1800s, scientific schools disputed the evidence for contagion versus heredity. In the light of our present understanding the full etiopathogenesis of leprosy appears to be multifactorial. But we also have our unknowns. Why, if the multiplication of *Mycobacterium leprae* alone is the cause of leprosy, has it not responded to treatment which kills the organism, as has tuberculosis? Why do not all individuals from whom the organism can be isolated develop clinical disease? Why does every successive WHO Global Survey show increase in the number of registered cases far exceeding the increase in world population (Table 1)? In the face of failure of bactericidal therapy to eradicate the disease, and of the development of drug resistance of *M. leprae,* it seems appropriate to re-examine the basic biological defenses against Hansen's disease. In this context, we have reviewed the literature regarding the influence of nutrition in the overall etiopathogenesis of *M. leprae* infection.

Our search of the literature revealed that most articles appeared in the half-century between 1910 and 1960, peaking around 1940 (The Figure). Diet was considered important in the prophylaxis and pathogenesis of leprosy in the first half of this century.[1] Relatively few articles have appeared since that period, while knowledge of other facets of the disease has been advancing. Our review attempts to place the nutritional literature since 1900 into the context of our present understanding of Hansen's disease.

METHODS

Literature search

We identified 115 references to diet or nutrition in the leprosy literature for the years 1900–1967. After 1967, literature in computer data bases became available. A search of 9581 citations identified six references on diet in relation to leprosy for the years 1967 to October 1985. The United States National Medical Library data bases were searched using the MEDLARS retrieval program and the MESH headings:

[1] Report (Leprosy Commission). The principles of the prophylaxis of leprosy. League of Nations P III Health 1931; CH 970 III 2:12 pp.

TABLE 1. *WHO global report on leprosy, 1966–1985.*[a]

Survey year[b]	No. countries or territories reporting	No. registered cases	Increase over 1966 survey	
			No.	%
1966	151	2,831,775		
1972	124	2,887,481	+55,706	2%
1976	148	3,598,167	+766,392	27%
1982	155	5.327,346	+2,495,571	88%
1985	162	5,368,202	+2,536,427	89%

[a] Data based on two reports: Sansarricq[143] and Noordeen and Bravo[144].
[b] In 1966 the prevalence rate of registered cases was 0.84 per 1000 population; in 1976, 0.88; in 1985, 1.2.[144]

Leprosy
- *Mycobacterium leprae*
- *M. lepraemurium*
- leprostatic agents
- diet and nutrition in combination with infections and immunological factors

The articles were categorized into: a) anecdotal reports in the older literature, including citations with insufficient data by current criteria to be included in b), and b) experimental studies, human and animal.

Two problems encountered with reviewing 80 years of literature were: a) changes in nomenclature of leprosy and, b) changes in standards of measurement used at different times. The nomenclature problem was addressed by relating older classifications to that of Ridley and Jopling[2] which was used in this review (Table 2). Current scientific measures are used where possible, along with the laboratory reference range of normal, taken from the standards published in the January 1986 *New England Journal of Medicine,*[3] Davidsohn and Henry,[4] and the National Academy of Sciences.[5]

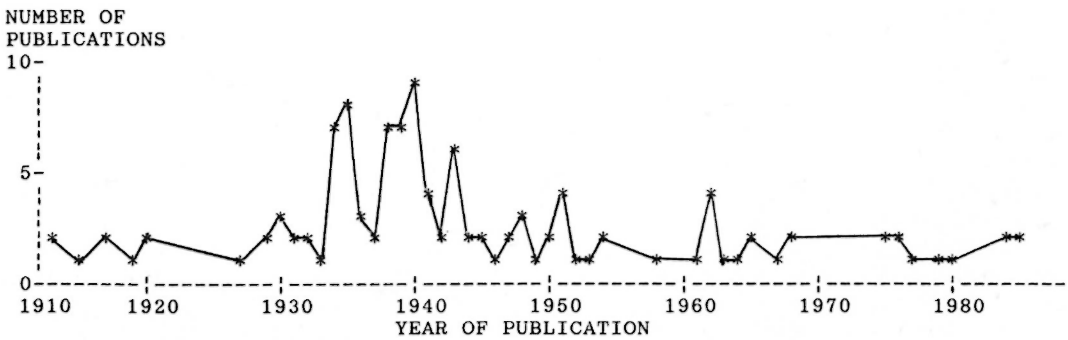
Nomenclature of leprosy

Ridley and Jopling[2] described five types of leprosy ranging from localized disease (TT, polar tuberculoid) through a dimorphous stage (BT, BB or BL designating "borderline tuberculoid," "borderline borderline" or "borderline lepromatous," respectively) to generalized (LL, polar lepromatous) disease at the other end of the spectrum.

LEPROSY AND DIET IN MEDICAL LITERATURE

Anecdotal literature

Sixty-one authors presented anecdotal evidence in 57 articles[1, 6–61] that nutrition is



THE FIGURE. Frequency distribution of articles on diet and nutrition in relation to leprosy.

[2] Ridley, D. S. and Jopling, W. H. A classification of leprosy for research purposes. Lepr. Rev. **33** (1962) 119–128.

[3] Normal reference laboratory values. N. Engl. J. Med. **314** (1986) 39–49.

[4] Davidsohn, I. and Henry, J. B., eds. *Clinical Diagnosis by Laboratory Methods.* 15th ed. Philadelphia: W. B. Saunders Company, 1974, pp. 1–1443.

[5] National Academy of Sciences. Recommended Dietary Allowances. 9th ed. Washington, D.C.: National Academy Press, 1980, pp. 1–185.

TABLE 2. *Ridley and Jopling classification of leprosy as related to older classifications.*

	Ridley and Jopling terminology	Equivalent older terminology[a]
1.	TT	Anesthetic (Dannielssen and Boeck, 1848)
2.	or BT	Maculo-anesthetic (Hansen and Looft, 1895) Neural (Manila, 1931) Tuberculoid (Rio de Janeiro, 1946)
	BT	Mixed (Manila, 1931)
3.	or BB	Uncharacteristic (Rio de Janeiro, 1946)
4.	or BL	
	BL	Nodular (Dannielssen and Boeck, 1848)
5.	or LL	Tuberosa (Hansen and Looft, 1895) Cutaneous (Manila, 1931) Lepromatous (Rio de Janeiro, 1946)

[a] Adapted from Dharmendra[145] and listed in order of progression of leprosy.

[6] Alexander, V. P. Treatment of the neural symptoms in leprosy. Lepr. India. **16** (1944) 10–11.

[7] Annual report. Madras Provincial Council, 1940–41, pp. 1–37.

[8] Atkey, O. F. H. Leprosy in Sudan in relation to climate and diet. Bull. Office Int. Hyg. Publ. **26** (1934) 490–496.

[9] Atkey, O. F. H. The distribution of leprosy in the Sudan with reference to climate and diet. Int. J. Lepr. **2** (1934) 193–200.

[10] Aykroyd, W. R. and Krishnan, B. G. A diet survey of families with leprosy. Indian J. Med. Res. **26** (1939) 897–900.

[11] Badenoch, A. G. and Byron, F. E. The calcium content of the blood serum in some cases of leprosy. Trans. R. Soc. Trop. Med. Hyg. **26** (1932) 253–258.

[12] Badger, L. F. and Patrick, D. W. Effects of intramuscular injection of vitamin B1 on acute leprous neuritis and of oral administration on the general disease; a preliminary report. Public Health Rep. **53** (1938) 969–978.

[13] Balfour, A. The relation of fish to leprosy. Lancet **ii** (1914) 718.

[14] Basu, N. K. Deficiency of vitamin-B2 (G) as an etiologic factor in leprosy. Ztschr. Vitaminf. Berne **3** (1934) 194–195.

[15] Basu, N. K. Diets in relation to diseases with special reference to tuberculosis and leprosy. J. Indian Med. Assoc. **5** (1935) 8–9.

[16] Basu, N. K. Further studies on leprosy and vitamin B2 (G) deficiency. Ztschr. Vitaminf. **7** (1938) 297–298.

[17] Bertellotti, L. Tentativi di inoculazione della lepra umana neiratti in avitaminosi. [Results of inoculation of human leprosy tissue in rats fed on pro-oxidant diets.] Arch. Ital. Sci. Med. Colon e Parassit **17** (1936) 577–609.

[18] Bloss, J. F. E. The control of leprosy among the Azande, Anglo-Egyptian Sudan. Trans. R. Soc. Trop. Med. Hyg. **39** (1946) 423–436.

[19] Bousefield, C. E. The ulcers of leprosy. Int. J. Lepr. **6** (1938) 73–74.

[20] Brown, J. A. K. Some dietetic factors in leprosy with special reference to B avitaminosis. West Afr. Med. J. **8** (1935) 1–7.

[21] Caiger, H., Lytle, W. J. and Nunan, J. The antileprosy campaign and the "keep fit" campaign. Br. Med. J. **25** (1937) 1300–1301.

[22] Chandy, P. J. Leprosy in the Fyzabad district. Lepr. India **13** (1941) 18–22.

[23] Chandy, P. J. Nicotinic acid as an adjuvant in the treatment of leprosy. Lepr. India **40** (1968) 46–51.

[24] Chaudhuri, D. S., Sreenivasamurthy, V., Jayaraj, P., Sreekantiah, K. R. and Johar, D. S. Therapeutic usefulness of garlic in leprosy; a preliminary report. J. Indian Med. Assoc. **39** (1962) 517–520.

[25] Chaussinand, R. A propos de l'action des sapotoxines d'origine alimentaire sur l'infection lepreuse. [The action of sapotoxins of alimentary origin on leprosy infection.] Bull. Soc. Pathol. Exot. **40** (1947) 424–427.

[26] Dalziel, L. M. and Balfour, A. The relation of fish to leprosy in Northern Nigeria. (Correspondence) Lancet 1914 Aug/Sep 525 & 718.

[27] De Raadt, O. L. E. Das ernahrungsproblem in der bekampfung der lepra und tuberkulose. [The problem of nutrition in the combating of leprosy and tuberculosis.] Ztschr. Tuberk. **54** (1929) 492–496.

[28] Denecke, K. Ergebnisse eines statistischen Querschnittes einer westafrikanischen leproserie und untersuchungen der leprosen, deren verwandten und kinder. [Statistics of West African leprosarium.] Arch. Hyg. Bakteriol. **128** (1942) 102–111.

[29] Dutton, A. S. Some deficiency diseases and leprosy. Proc. R. Soc. Med. **13** (1920) 51–57.

[30] Editorial. Colocasia and leprosy. Lepr. India **15** (1943) 3–6.

[31] Ferrier, P. Traitement physiologique de la lepre. [Physiological treatment of leprosy.] Bull. Soc. Pathol. Exot. **24** (1931) 852–860.

[32] Floch, H. and Sureau, P. La vitaminotherapie C dans la lèpre (formes tuberculoides reactionnelles). [Vitamin C therapy in leprosy of the reacting tuberculoid type.] Bull. Soc. Pathol. Exot. **45** (1952) 443–446.

[33] Gavrilov, W., Dubois, A. and Fester, Mme. Influence de l'avitaminose sur l'infection des cobayes par le bacille de Stephansky. [Avitaminosis in rat leprosy infections of guineapigs.] Ann. Soc. Belg. Med. Trop. **19** (1939) 361–366.

important to the prophylaxis, pathogenesis or prognosis of leprosy. Six authors in five articles said diet made no difference.[62–66]

An illustration of excellent data, but insufficient to be reviewed in the experimental section, is that of Atkey[9] who studied the distribution of leprosy in the Sudan with reference to climate and diet. The sentence: "Their staple diet is milk, grain is available in limited quantity, and meat is eaten on festive occasions." illustrates anecdotal data. This data may well be accurate, however, the supporting evidence is not presented.

Another illustration is the detailed dietary study of Aykroyd and Krishnan[10] of 14 families living in Saidapet, a suburb of Madras, India, which showed that the 14 families studied all had deficient diets, and that 13 of the 14 families studied had leprosy patients as members of the family. However, as the authors point out, no conclusions can be drawn from the investigation with regard to the role of malnutrition in leprosy. "All that has been shown is that

[34] Gehr, E. Die Lepra in den Balkanlandern. [Leprosy in the Balkans.] Deut. Trop. Ztschr. **45** (1941) 353–369, 385–403.

[35] Gehr, E. Ist die reinigung des brotgetreides von kornradesamen mitbeteiligt am erloschen der mittelalterlichen lepra? [Purification of cereal foods in relation to the decline of leprosy in the middle ages.] Ztschr. Hyg. Infektionskr. **122** (1939) 238–248.

[36] Gminder, E. Vitamin B1 und lepra. [Vitamin B1 and leprosy.] Deut. Med. Woch. **65** (1939) 1346–1350.

[37] Gramberg, K. P. C. A. The non-specific treatment of leprosy. Doc. Neerland. Indones. Morb. Trop. **3** (1951) 75–82.

[38] Keil, E. C. The importance of nutrition in the prevention and cure of leprosy. Int. J. Lepr. **1** (1933) 393–398.

[39] Keil, E. Ist nervenlepra atiologisch einheitlich? Zur vitamin B1-behandlung der nervenlepra. [Vitamin B1 in nerve leprosy.] Arch. Schiffs. Trop. Hyg. **42** (1938) 1–13.

[40] Lampe, P. H. J. Voordrachten over de endemiologie der lepra. [Endemiology of leprosy.] Geneesk. Tijdschr. Nederl-Indie **74** (1934) 486–496, 522–525.

[41] Lara, C. B. Progress of leprosy treatment at the Culion Leper Colony. Philippine Islands Med. Assoc. **10** (1930) 469–480.

[42] Lengauer, L. Palm oil in leprosy. Lepr. Rev. **16** (1945) 67–69.

[43] McFadzean, J. A. Proteinuria in patients with leprosy in Malaya. Trans. R. Soc. Trop. Med. Hyg. **56** (1962) 404–406.

[44] Montel, R. La methode de Charpy dans le traitement de la lèpre. [The treatment of leprosy by Charpy's method.] Bull. Soc. Pathol. Exot. **38** (1945) 63–64.

[45] Muir, E. Some basic principles in leprosy treatment. Lepr. Rev. **11** (1940) 162–169.

[46] Muir, E. Some factors which influence the incidence of leprosy. Indian J. Med. Res. **15** (1927) 1–14.

[47] Muir, E. and Santra, I. Sample surveys of leprosy in India. Indian J. Med. Res. **20** (1932) 421–434.

[48] Oberdorffer, M. Untersuchungen ueber die pradisponierenden faktoren der lepra in Sud-Nigeria. [Predisposing factors of leprosy in Nigeria.] Arch. Schiffs. Trop. Hyg. **42** (1938) 367–372.

[49] Oberdoerffer, M. and Gehr, E. Die zusammenhange zwischen sapotoxinhaltigen nahrungspflanzen und der lepra. [The association of sapotoxins with leprosy.] Ztschr. Hyg. Inf. **122** (1940) 472–502.

[50] Ota, M. and Sato, S. Reproduction de la lèpre chez les rats blancs par l'inoculation de lepromes in emulsion. [Inoculation of leproma emulsions into white rats.] C. R. Soc. Biol. **109** (1932) 75–77.

[51] Paldrock, A. Untersuchung der Jakutenspeise auf leprabacillen. [Examination of food of Yakoots for lepra-bacilli.] Sitzungsberichte der Naturforscher-Gesellschaft bei der Universitat Jurjew, 1912.

[52] Paldrock, A. Results of specific therapy of leprosy in Estonia during last twenty years. Acta Med. Scand. **108** (1941) 374.

[53] Progress Report. Report of the Silver Jubilee Clinic for the Study of Child Leprosy. Saidapet Health Project (2nd Prog. Report), 1939, pp. 16–23.

[54] Rost, E. R. On the leprosy bacillus and allied bacilli. Trans. 17th Int. Cong. Med., 1913, Sect IV(Pt 2) pp. 111–118.

[55] Ryrie, G. A. Some impressions of Sungei Buloh Leper Hospital under Japanese occupation. Lepr. Rev. **18** (1947) 10–17.

[56] Schwarzmann, B. Beobachtungen ueber die verbreitung der lepra am Kaspischen Meer. [Observations on the spread of leprosy on the Caspian.] Zentralbl. Bakteriol. **112** (1929) 458–460.

[57] Steiniger, F. Die erbliche disposition bei der entstehung der lepra. [Predisposition to leprosy.] Ztschr. Mensch. Vererbungs. Konstitutionslehre **25** (1941) 245–272.

[58] Van Andel, M. A. Quelques figures de lèpreux dans l'art classiques des pays-bas. Janus **24** (1919) 135–145.

[59] Venkatasubramaniam, C. S. Investigations on the biochemistry of leprosy (Part I). Lepr. India **13** (1941) 104–108.

[60] Wayson, N. E. and Rhea, T. Leprosy; observations on its epidemiology in Hawaii. Public Health Bull. No. 212, Washington, D. C., 1934, 32 pp.

[61] Welch, T. B. Some considerations on diagnosis in leprosy and on the treatment of lepers. East Afr. Med. J. **11** (1934) 76–83.

[62] Davey, T. F. Common features in rapidly declining leprosy epidemics. Lepr. Rev. **46** (1975) 5–8.

[63] Innes, J. R. Leprosy in Uganda. East Afr. Med. J. **25** (1948) 379–381.

[64] Lindsay, J. W. The contagiousness of leprosy. Br. Med. J. Sept. 21 1912 682–683.

[65] Mudrow, L. and Schultz, F. Die rattenlepra unter vitaminmangel und bei chronischer sapotoxin-verabreichung. [The influence of vitamin deficiency and prolonged administration of sapotoxin on rat leprosy.] Zent. Bakt. I Abt. Orig. **151** (1943) 50–59.

[66] Wade, H. W. Heredity in susceptibility to leprosy. (Editorial) Int. J. Lepr. **9** (1941) 353–358.

a group with a high incidence of leprosy consumed a very deficient diet." Low numbers of observations and the lack of control observations are the reasons no conclusions can be drawn. Therefore, this valuable study is considered anecdotal.

Some of these papers suggest directions and topics for controlled studies, e.g., in 1939 Gminder[36] noted that polyneuritis occurs in both beriberi and leprosy. In a study to test the idea of the predisposing influence of avitaminosis, he reported improvement in 6 of 8 lepromatous leprosy patients treated with vitamin B1. In two of the patients return of sensation was reported. The prevention and treatment of loss of sensation in leprosy is a most important aspect of the disease that needs more attention.

Experimental data

Wade,[66] in an editorial in 1941, observed that only experimental investigation on animals susceptible to leprosy could give definite evidence as to the role of nutrition in leprosy. However, to us, human dietary studies in leprosy are of even greater interest.

Epidemiology. In 1906, Hutchinson[67] reported a higher incidence of leprosy in many countries where fish was eaten in a state of partial decomposition, and concluded that something in decomposed fish was etiologically related to leprosy. Bergel[68] believes that it is the unsaturated fatty acids in the putrid fish that produce free oxygen radicals that favor the growth of *M. leprae* by damaging leukocyte lysosome membranes.[69]

Mayer,[70] in 1930, observed in Nigeria that the highest leprosy rates occurred in the southern wet zone. Famines, deficient diet, frequent religious fasts, uncleanliness, sexual promiscuity, and the prevalence of yaws, syphilis, and helminthic and malarial infections were more prevalent in the southern than in the central elevated areas of the country, which had the lowest leprosy rates.

In 1934, Rodriquez and Plantilla[71] studied 1313 persons living in houses with a leprosy patient and 1817 controls in Cebu, The Philippines. They found that the diets of leprosy patients and their families included more rice and raw shellfish but less vegetables and fresh fish than those of households not having a known leprosy patient.

In 1965, Williams, *et al.*,[72] at the National Hansen's Disease Center in Carville, Louisiana, U.S.A., found that concomitant amyloidosis was present in 40–50% of 101 leprosy patients. In contrast, in 119 patients studied at Guadalajara, Mexico, amyloidosis was diagnosed in only 6%. Dietary factors were considered as a possible explanation for this marked difference. Both diets had similar calories (Carville = 2000; Mexico = 2500). In the Carville diets, the average percentage of calories contributed by protein was 16% and by fat, 40%; 80–90% of fat calories were derived from saturated animal fat. In the Mexican diets, the average percentage of calories contributed by protein was estimated at 13% and by fat, 22%; one third of the fat calories were made up of animal fat, two thirds were derived from plant sources.

In contrast to the Carville experience, in 1980 Gupta and Panda[73] reported studying 1445 biopsies from 1222 Indian vegetarian leprosy patients over a 10-year period. Unlike the Carville-Guadalajara study using primarily gingival biopsies, this study examined other tissues including liver, skeletal muscle, kidney, lymph node, larynx, and skin. They did not find amyloid in any of these biopsies from patients having had leprosy from 1 to 20 years. Because of the lack of sufficient details of their technique, we cannot draw any conclusions.

The prevalence of leprosy in 35 villages and field areas studied in South India correlated with malnutrition in children aged

[67] Hutchinson, J. On leprosy and fish-eating. A statement of facts and explanations. London: Archibald Constable & Co., 1906, pp. 1–409.

[68] Bergel, M. The Hutchinson dietetic hypothesis of fish-eating as a cause of leprosy; a reappraisal in the light of the influence of pro-oxidant nutritional conditions. Lepr. Rev. **31** (1960) 302–304.

[69] Bergel, M. Lysozomes—their relationship with vitamin E and leprosy. Lepr. Rev. **38** (1967) 189–192.

[70] Mayer, T. F. G. The distribution of leprosy in Nigeria with special reference to the aetological factors on which it depends. West Afr. Med. J. **4** (1930) 11–15.

[71] Rodriguez, J. and Plantilla, F. C. Leprosy in Cebu. Philippine J. Sci. **53** (1934) 1–46.

[72] Williams, R. C., Cathcart, E. S., Calkins, E., Fite, G. L., Barba Rubio, J. and Cohen, A. S. Secondary amyloidosis in lepromatous leprosy; possible relationships of diet and environment. Ann. Intern. Med. **62** (1965) 1000–1007.

[73] Gupta, J. C. and Panda, P. K. Amyloidosis in leprosy. Lepr. India **52** (1980) 260–266.

1–4 ($p = 0.012$), but not with adults. Sommerfelt, *et al.*[74] estimated malnutrition by measuring the mid-upper-arm circumference.

We feel that the conclusions of an unnamed editor in 1943,[75] made after a thorough review of the literature, are still most appropriate today: ". . . there appears to be a definite indication on the point that in countries where leprosy is common and in persons suffering from leprosy there generally prevails a state of malnutrition and undernourishment. On general grounds one would expect this state of malnutrition to play an important role in predisposing to leprosy. However, there is no satisfactory evidence on this point since it has not been shown that the diet of persons suffering from leprosy is more deficient than that of persons living under similar conditions but not suffering from leprosy." The editorial ends with the plea, still timely: "Further work on the relationship between malnutrition and susceptibility to leprosy is urgently needed."

Fat-soluble vitamins. Because of the lipopolysaccharide nature of the formidable cell wall of the Hansen's bacillus, fat-soluble substances have long been of interest as possibly being able to penetrate this barrier.

Vitamin A. In 1981, Sher, *et al.*[76] measured vitamin A levels in 53 lepromatous leprosy and 30 tuberculoid leprosy patients and in an unstated number of apparently healthy controls:

	Mean serum vitamin A (IU/ml ± S.E.)
Controls	50–200
TT + BT	111.2 ± 8.5
BL	78.5 ± 5.8
BL + LL	67.1 ± 4.7
LL	49.9 ± 6.5

Reference range 0.15–0.60 μg/ml based on 0.3 μg/IU = 50–200 IU/100 ml

Serum vitamin A levels in the lepromatous group of patients were significantly lower than those in the tuberculoid group ($p < 0.001$). Furthermore, there was a significant difference between the borderline lepromatous cases and the true lepromatous cases ($p < 0.005$). Thus, a lower serum vitamin A level was seen in the more severe leprosy types. Sher, *et al.*[76] note that vitamin A is required for normal epithelial structure and function as well as for stimulating the immune response. They recommend dietary supplementation with vitamin A in patients with ulceration due to sensory loss.

Gomes,[77] in 1940, observed the growth of *M. lepraemurium* inoculated into the right flank of three groups of rats: Group 1, injected weekly for 5 weeks with 0.5 ml 2% carotene emulsion (vitamin A precursor), had the least growth. Group 2, given one injection of 0.5 ml carotene at the time of inoculation, had intermediate growth. Group 3, given no carotene, had the greatest growth.

Ribeiro,[78] in 1940, characterized a refined vegetable carotinoid fraction that protected against the growth of *M. lepraemurium* in mice. This fraction was a yellow, resinous substance, soluble in fatty solvents and in alkaline solutions. The leprosy-protective effect could be demonstrated to protect the liver from the growth of *M. lepraemurium* injected into mice.

Colizzi and Malkovsky,[79] in 1985, found that mice inoculated intravenously with 3×10^7 viable *M. bovis* BCG cells react to purified protein derivative (PPD) of mycobacteria by foot pad swelling ($p < 0.001$) and an inflammatory reaction seen on histology, but only if vitamin A acetate (VAA) (0.5 g/kg conventional diet) was added to the diet. In addition, spleen cells taken from the VAA-supplemented group produced more interleukin-2 (IL-2) *in vitro*. The authors concluded that the mechanism of action of dietary VAA in stimulating the immune system may be related to an increase in IL-2 production by spleen cells.

[74] Sommerfelt, H., Irgens, L. M. and Christian, M. Geographical variations in the occurrence of leprosy: possible roles played by nutrition and some other environmental factors. Int. J. Lepr. **53** (1985) 524–532.

[75] Editorial. Diet and susceptibility to leprosy. Lepr. India **15** (1943) 67–75.

[76] Sher, R., Shulman, G., Baily, P. and Politzer, W. M. Serum trace elements and vitamin A in leprosy subtypes. Amer. J. Clin. Nutr. **34** (1981) 1918–1924.

[77] Gomes, J. M. Lepra murina. Pesquizas com os pigmentos carotenoides. [Murine leprosy. Research with carotene.] Brasil-Medico **54** (1940) 140–143.

[78] Ribeiro, F. Murine leprosy and carotinoids. Int. J. Lepr. **8** (1940) 179–192.

[79] Colizzi, V. and Malkovsky, M. Augmentation of interleukin-2 production and delayed hypersensitivity in mice infected with *Mycobacterium bovis* and fed a diet supplemented with vitamin A acetate. Infect. Immun. **48** (1985) 581–583.

Vitamin D. In 1948, Capurro and Guillot[80] treated five tuberculoid leprosy patients in reaction with intramuscular injections of vitamin D. The doses were 600,000 units three times a week for 1 week, then two times a week for 3 weeks, and then weekly for 4 months. Similarly, a second group of 10 patients were treated with the same dose of vitamin D, three times a week for 3 weeks. These dosages represent an estimated 1500 times the recommended daily allowance of vitamin D.[5] They noted improvement in the reactional state within 7–21 days, evidenced by reduction of nasal obstruction, fading of macules, and desquamation in both groups. No control group was reported.

Vitamin E (Tocopherol). In 1959, Bergel[81] reported the effect of pro-oxidant diets on the growth of *M. leprae* in male rats. A pro-oxidant diet, characterized by deficiency of vitamin E and an excess content of highly unsaturated rancid oils, began on the 21st day of life. On the 57th day, the rats were inoculated into both testes with 0.1 ml of a suspension of *M. leprae*. The control diet was a balanced diet of fresh vegetables, bread, and milk. At 7 months, the controls showed only a few granular bacilli, while the four vitamin-E-deficient groups had "massive" infection of the testes and other organs. Groups receiving cod liver oil and rancid linseed oil showed increased numbers of bacilli at the 5th month. Bergel concludes from this study and many other studies over two decades[68, 82–85] that there is a "connection between the autoxidation of lipids and the pathogenesis and therapy of leprosy." There is a growing body of biomedical literature showing that the nutritional antioxidants, selenium and vitamins E and C, have significant immunostimulant, anti-inflammatory, and anti-carcinogenic effects.[86] These data agree with the pioneer work of Hutchinson[67] who, 60 years earlier, noted a positive relationship between the consumption of rancid fish and leprosy.

Mason,[87] in 1962, injected *M. leprae* into the testes of rats fed a vitamin-E-deficient diet containing 15% cod liver oil. He found significant multiplication of *M. leprae* in these rats. However, Wilkinson[88] found no evidence of multiplication in his 138 vitamin-E-deficient rats or in the control groups examined 4–21 months after inoculation. Could the addition of cod liver oil to the diet account for the difference? Our initial experience suggests that higher levels of dietary fat favor the growth of *M. leprae* in the mouse foot pad model (unpublished data).

Bergel,[69] in 1967, reviewed the experimental data that connect lysosomes with leprosy and vitamin E. He concluded that leprosy develops in auto-oxidant conditions which make the lipoprotein membranes of lysosomes unstable. The role of vitamin E as an antioxidant and as a stabilizer of cell membranes (Beisel[89]) may be related to the reduced growth of *M. leprae*.

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[80] Capurro, E. T. and Guillot, C. F. Vitaminoterapia D2 a altas dosis en el tratamiento de la reaccion leprosa tuberculoides. [Treatment of the leprous reaction in tuberculoid leprosy with vitamin D2 in large doses.] Rev. Argent. Dermatosifil. **32** (1948) 287–293.

[81] Bergel, M. Influence of various pro-oxidant nutritional conditions on the growth *in vivo* of *M. leprae*. Lepr. Rev. **30** (1959) 153–158.

[82] Bergel, M. Activisma y acelerada reproduccion del bacilo de Hansen inoculado a ratas en severas condiciones de prooxidacion. [Activation and accelerated reproduction of Hansen's bacillus inoculated in rats under severe conditions of pro-oxidation.] Semana Med. **113** (1958) 1119–1124.

[83] Bergel, M. Valoracion de actividad quimioterapica sobre el *Mycobacterium leprae* en animales con dietas prooxidantes. [Assay of chemotherapeutic activity on *Mycobacterium leprae* in animals on pro-oxidant diets.] Rev. Asoc. Med. Argent. **77** (1963) 99–112.

[84] Bergel, M. Lepra lepromatosa producida por la inoculacion del *M. leprae* in la almohadilla plantar de ratas con dietas prooxidantes. [Lepromatous leprosy produced by inoculation of *Mycobacterium leprae* in the footpads of rats on pro-oxidant diets.] Dermatol. Trop. **3** (1964) 115–121.

[85] Bergel, M. Reproduccion del *Mycobacterium leprae* inoculado a ratas alimentadas con carne vacuna en estado de putrefaccion. [Multiplication of *Mycobacterium leprae* in rats fed on meat in a state of putrefaction.] Rev. Latinoam. Microbiol. **17** (1975) 5–8.

[86] Crary, E. J. and McCarty, M. F. Potential clinical applications for high-dose nutritional antioxidants. Med. Hypotheses **13** (1984) 77–98.

[87] Mason, K. E. Inoculacion del *Mycobacterium leprae* en animales en condiciones dieteticas especiales. [Inoculation of *Mycobacterium leprae* in special dietary conditions.] An. Inst. Nac. Microbiol. (Buenos Aires) **1** (1962) 1–6.

[88] Wilkinson, F. F. Inoculation of *Mycobacterium leprae* to rats fed a pro-oxidant diet. Int. J. Lepr. **30** (1962) 457–464.

[89] Beisel, W. R. Single nutrients and immunity. Am. J. Clin. Nutr. **35** Feb. Suppl. (1982) 417–468.

In 1968, Bergel[90] surgically grafted tissue from lepromatous patients onto control rats on normal diets and onto rats on vitamin-E-deficient diets containing 15% cod liver oil (containing nil or only traces of vitamin E). Tissue sections of the grafts 1 year later showed essentially complete disappearance of the bacilli in the controls and enlargement of lepromatous nodules with enormous globi (clumps of bacilli) and abundant scattered bacilli in the rats on the oxidizing diet.

Water-soluble vitamins. *Ascorbic acid.* Concepcion and Camara,[91] in 1939, found plasma ascorbic acid levels in 96 leprosy patients lowered in proportion to the severity of their disease. Intramuscular (i.m.) injections of 50 mg of ascorbic acid restored the plasma levels to normal.

In 1950, Ferreira[92] gave 0.5 g of ascorbic acid intravenously to 25 leprosy patients daily for 10–30 days. He found no change in the number or granularity of the patients' bacteria as monitored by skin smears during the subsequent 6 months.

Dharmendra and Sen[93] found little improvement from i.m. injections of 0.5 g ascorbate daily 6 days a week for 8–10 weeks to Indian tuberculoid leprosy patients in reaction.

Boenjamin,[94] in 1951, found normal blood ascorbate levels in 60 tuberculoid leprosy patients (characterized by depigmented macules) and 95 apparently healthy housemates of these patients:

	Blood ascorbate (mg/100 ml ± S.E.)
95 Normals	1.00 ± 0.05
60 TT-BB	1.03 ± 0.05
38 BB-LL	0.72 ± 0.05
Reference range	0.4–1.5

However, the 38 lepromatous patients, without depigmented skin macules, had lower blood levels of ascorbic acid than did the tuberculoid patients. The author concluded that the depigmentation seen in tuberculoid leprosy was not related to low ascorbic acid levels.

In contrast with Boenjamin,[94] who found the lowest ascorbate levels in lepromatous patients, in 1984 Sinha, *et al.*[95] found the lowest levels in tuberculoid patients:

	Blood ascorbate (mg/100 ml ± S.D.)
25 Normals	0.63 ± 0.20
27 Tuberculoid	0.20 ± 0.08
51 Lepromatous	0.36 ± 0.12
Reference range	0.4–1.5

The average level of blood ascorbic acid in 27 cases of lepromatous leprosy, untreated and treated (both without reaction), was lower (p = <0.001) than 25 controls. Sinha, *et al.* then supplemented the diet with 0.5 g of ascorbic acid daily for 60 days which brought the blood level of ascorbic acid to near normal. In lepromatous patients with trophic ulceration, marked ulcer healing was observed. The effect of the supplementation on the tuberculoid patients is not reported.

In 1943, Prudhomme[96, 97] measured the ascorbic acid content of various organs of rats infected with *M. lepraemurium.* The tissues infiltrated with bacteria were high in ascorbic acid, which was present in the supernatant fluid after centrifuging an emulsion of the tissue. Cells nearly destroyed by a mass of bacilli contained more of the vitamin than normal cells. This may be evidence that ascorbate is specifically involved in the leprosy granuloma or may simply be an example of the known concentration of ascorbate in white cells. In any case it would appear that it is important to maintain adequate vitamin C levels in the prevention and treatment of leprosy.

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[90] Bergel, M. Estudio histobacteriologico del injerto de tejido lepromatoso en ratas alimentadas con dietas pro-oxidantes. [Histobacteriological study of graft in lepromatous tissue in rats fed on pro-oxidant diets.] Dermatol. Int. **7** (1968) 23–32.

[91] Concepcion, I. and Camara, S. F. Studies on vitamin C: VI. The blood ascorbic acid in leprosy. J. Philippine Med. Assoc. **19** (1939) 733–740.

[92] Ferreira, D. L. A vitamina C na leprose. [Vitamin C in leprosy.] Publicacoes Medicas **20** (1950) 25–28.

[93] Dharmendra and Sen, N. R. Vitamin C in the treatment of reactions in tuberculoid leprosy. Bull. Calcutta Sch. Trop. Med. **2** (1954) 16–17.

[94] Boenjamin, R. Vitamin C in the blood of lepers and their healthy housemates. Doc. Neerland. Indon. Morb. Trop. **3** (1951) 245–249.

[95] Sinha, S. N., Gupta, S. C., Bajaj, A. K., Singh, P. A. and Kumar, P. A study of blood ascorbic acid in leprosy. Int. J. Lepr. **52** (1984) 159–162.

[96] Prudhomme, R. O. Acide ascorbique et lèpre murine. [Ascorbic acid and rat leprosy.] Ann. Inst. Pasteur **69** (1943) 215–218.

[97] Prudhomme, R. O. L'acide ascorbique dans la lèpre murine. [Ascorbic acid in rat leprosy.] C. R. Soc. Biol. **126** (1937) 1004–1005.

Hastings, *et al.*[98] in 1976 showed that the level of dietary ascorbate influences *M. leprae* growth in the mouse foot pad. They fed ascorbic acid at three concentrations, 0.05%, 0.15% and 0.45% (weight of ascorbate/weight of food), respectively, to three groups of mice, and found that the animals that received 0.15% and 0.45% ascorbic acid had significantly fewer acid-fast bacilli (AFB) harvested than did the control mice.

The deficiency of ascorbic acid seen in leprosy patients may be a result of the disease or, conversely, a pre-existing deficiency of vitamin C may lower the immune response[89] and predispose to the disease, or both. Further work is needed to explain this association.

Vitamin B complex. In 1928, Muir and Henderson[99] studied vitamin-deficient rats experimentally infected with *M. lepraemurium,* using subcutaneous and transcutaneous (scarification) or intraperitoneal inoculation routes. They found a 92.5% positive growth rate in 40 rats. Vitamin-B-free diets did not increase the severity of the infection or decrease the incubation time as compared with diets containing adequate vitamin B complex.

Lamb,[100] in 1935, also found that vitamin B deficiency or adequacy made little difference using subcutaneous routes of inoculation as did Muir and Henderson.[99] However, with the intracardiac route, a combination of deficiencies of both protein and vitamins of the B complex was associated with an extensive increase in hepatic lepromatous lesions. To a lesser extent, the spleen, lungs, and lymph nodes were also more infiltrated in deficient animals that in controls. The effect of vitamin B complex and protein deficiency in the first generation continued to increase the growth of *M. lepraemurium* to the fourth generation.

The same year (1935) Lampe, *et al.*[101] sought to ascertain if rat leprosy could be transmitted by contact with infected soil. They weekly shaved the bellies of 95 rats to the point of bleeding and kept them in contact with mud from native houses infested with *M. lepraemurium*-infected rats. In some of the rats, the mud was rubbed into the abdominal skin a total of eight times. The shaved group of 95 rats was divided into two dietary groups, normal and vitamin B deficient. The deficient group of shaved rats had a high intercurrent infection mortality. Three hundred control rats were unshaved. Leprosy developed in only 11 rats, all of them shaved, and in the vitamin-B-deficient group. Evidence of *M. lepraemurium* infection did not appear until after 12 months of exposure. The evidence of infection included peri-glandular, subcutaneous and skin lepromata, and miliary development of leprosy in enlarged internal organs. This study appears to indicate that exposure alone is not sufficient to produce leprosy in these rats. A vitamin B deficiency was necessary for *M. lepraemurium* infection in these circumstances. This is in harmony with the observed human epidemiological data where it is assumed that everybody in a given population is exposed but, by some selection process, only certain ones develop clinical leprosy. This study would suggest that vitamin B complex deficiency may be part of that selection-for-disease process.

These findings of Lamb[100] and Lampe, *et al.*[101] appear to agree with the hypothesis proposed by Stoner[102] in 1981. Stoner suggests that when bacilli enter the body via the blood stream, splenic central lymphocyte stimulation causes the development of suppressor cells which would allow the survival of *M. leprae* within the cells of the reticuloendothelial system. If the bacteria enter through the skin, peripheral lymphocyte stimulation results in the development of activated T cells which result in the destruction of the intracellular bacteria. It

[98] Hastings, R. C., Richard, V., Jr., Christy, S. A. and Morales, M. J. Activity of ascorbic acid in inhibiting the multiplication of *Mycobacterium leprae* in the mouse foot pad. Int. J. Lepr. **44** (1976) 427–430.

[99] Muir, E. and Henderson, J. Rat leprosy; a record of experimental work carried on at the School of Tropical Medicine and Hygiene, Calcutta, between October 1925 and August 1927. Indian J. Med. Res. **15** (1928) 807–817.

[100] Lamb, A. R. The effect of malnutrition on the pathogenesis of rat leprosy. Am. J. Hyg. **21** (1935) 438–455.

[101] Lampe, P. H. J., De Moor, C. E. and Van Veen, A. G. Ratten-lepra. [Rat leprosy.] Geneesk Tijdschr. Nederl-Indie **76** (1936) 2204–2227.

[102] Stoner, G. L. Hypothesis: do phases of immunosuppression during a *M. leprae* infection determine the leprosy spectrum? Lepr. Rev. **52** (1981) 1–10.

would be interesting to know the effects of different infection routes and dietary deficiencies on T4:T8 ratios.

In 1935, Badger and Sebrell[103] found that thiamine-deficient diets resulted in shorter leprosy incubation periods. In three controlled experiments, 236 rats were inoculated subcutaneously with *M. lepraemurium*. At 2 weeks post-inoculation, none of the controls and 4 of 45 (8%) deficient rats showed palpable lesions at the site of inoculation. At 8 weeks, when the experiments were terminated, 86 of 112 (77%) of deficient rats and 27 of 85 (32%) control rats had palpable lesions.

Five years later (1940) with the same model, Badger, *et al.*[104] showed, using 504 rats in 22 experiments, that not only is the incubation period shortened by thiamine-deficient diets, but there is also an increase in generalized infection not seen in the controls.

Hou,[105] in 1938, found that all 31 randomly selected Shanghai leprosy patients had vitamin B1 deficiency determined by nil or below normal B1 urinary excretion. Following supplementation of 5 mg orally or by i.m. injections, the body became saturated, as determined by urinary B1 excretion. Leprosy type, duration, or lesion type, concurrent fever, iodides or chaulmoogra preparations administered concurrently had no effect on uptake or excretion of vitamin B1. Following a food intake survey, Hou concluded that the deficiency was dietary. No clinical results of supplementation are reported.

Minerals. *Calcium and magnesium.* In 1920, Underhill, *et al.*[106] measured calcium intake and output in two leprosy patients and two apparently normal subjects. They found that the leprosy patients retained supplemental calcium while the normal patients excreted it. Supplemental magnesium was eliminated by both patients and normal individuals. They concluded that leprosy patients appeared deficient in calcium but not magnesium.

In 1932, Badenoch and Byron[11] found low serum calcium in 81 leprosy patients (particularly with leprosy reactions). Their findings can be summarized:

	Serum calcium (mg/100 ml)
54 Leprosy patients in reaction or with intercurrent infections	9.2
27 Apparently healthy leprosy patients	10.2
Reference range	8.5–10.5

A rise in serum calcium was observed to accompany clinical improvement. The higher calcium in the hospital diet, compared with the patient's home diet, was felt to contribute to the improvement seen with hospital treatment.

In 1940, Badger, *et al.*[104] found that 34 rats on calcium-deficient diets had greater rates of growth of inoculated *M. lepraemurium* than did control rats. The effects of calcium deficiency were reversed by thiamine supplementation. The rats on calcium-deficient diets, but adequate dietary thiamine, developed thiamine deficiency. The authors postulated a calcium dependency for thiamine absorption.

Nigan, *et al.*,[107] in 1981, measured serum calcium and magnesium in 70 leprosy patients and 25 apparently normal subjects and found:

	Serum calcium (mg/100 ml) ±S.D.	Serum magnesium (mEq/L ± S.D.)
Controls	9.8 ± 0.75	1.8 ± 0.26
T leprosy	9.1 ± 1.0	1.1 ± 0.4
BL leprosy	8.1 ± 1.0	1.2 ± 0.3
L leprosy	8.4 ± 0.7	1.0 ± 0.2
Reference range	8.5–10.5	1.5–2.0

Serum calcium is lower than normal in the borderline (BL) ($p < 0.05$) and in lepromatous (L) ($p < 0.001$) patients and serum

[103] Badger, L. F. and Sebrell, W. H. Leprosy; the effect of a vitamin B1 deficient diet on the incubation period of rat leprosy. Public Health Rep. **50** (1935) 855–863.

[104] Badger, L. F., Masunaga, E. and Wolf, D. Leprosy: vitamin B1 deficiency and rat leprosy. Public Health Rep. **55** (1940) 1027–1041.

[105] Hou, H. C. Vitamin B1 in treatment of leprosy. Int. J. Lepr. **7** (1939) 455–462.

[106] Underhill, F. P., Honeij, J. A. and Bogert, L. J. Studies on calcium and magnesium metabolism in disease. I. Calcium and magnesium metabolism in leprosy. J. Exp. Med. **32** (1920) 41–63.

[107] Nigan, P., Dayal, S. G., Sriwastava, P. and Joshi, L. D. Serum calcium and magnesium in leprosy. Asian J. Infect. Dis. **3** (1979) 81–83.

magnesium is decreased ($p < 0.001$) in all patients.

Rao and Saha,[108] in 1986, compared levels of serum calcium and magnesium in two economic groups of apparently healthy controls and leprosy patients. They found:

Economic strata	Serum calcium (mg/100 ml)	Serum magnesium (mEq/L)
High		
65 Controls	11.0	2.00
42 Patients	7.2	1.53
Low		
28 Controls	9.8	2.10
46 Patients	6.9	1.44
Reference range	8.5–10.5	1.8–3.0

This study confirms Nigan's[107] finding of lower than normal serum calcium and magnesium in leprosy patients. This study shows that in these Indian subjects, Hansen's disease rather than economics is positively related to low serum values.

Iron. In 1943, DeCaires[109] measured hemoglobulin levels of patients in the Mahaica leprosy hospital in British Guiana. An inverse relationship between hemoglobin level and severity of disease was noted:

	% Normal
Healthy attendants	85.24
Able-bodied patients	62.85
Advanced lepromatous disease	50.75

He claimed that patients benefited from 30 grains (2 grams) t.i.d. iron citrate dietary supplementation.

In 1981, Sher, *et al.*[76] reported differences in average serum iron levels of 28 tuberculoid and 32 lepromatous patients ($p < 0.001$):

	Serum iron (μg/100 ml)
Tuberculoid patients	99.3
Lepromatous patients	50.1
Reference range	50–150

The hemoglobin levels were also correspondingly lower in the lepromatous as compared to the tuberculoid leprosy patients. However, no significant difference in transferrin levels between the two groups of patients was found.

Zinc and copper. In 1981, Sher, *et al.*[76] also found lower serum levels of zinc ($p < 0.001$) in 61 lepromatous leprosy compared to 27 tuberculoid leprosy patients:

	Serum zinc (μg/100 ml ± S.D.)	Serum copper (μg/100 ml ± S.D.)
Normals	51–122	70–140
Tuberculoid patients	83.9 ± 3.2	114.9 ± 3.6
Lepromatous patients	70.5 ± 1.5	137.1 ± 3.9
Reference range	50–150	100–200

However, values for both groups are within the normal serum zinc levels. They also found elevated serum copper levels in lepromatous compared to tuberculoid leprosy patients ($p < 0.001$). Copper levels were also within the normal range. These authors suggest a therapeutic trial of dietary zinc supplementation for leprosy patients with plantar ulcers.

Rao and Saha[108] also found lower serum zinc and elevated copper levels in leprosy patients as compared with apparent normals:

	Serum zinc (μg/100 ml)	Serum copper (μg/100 ml)
Normals	109.9	103
Leprosy patients	69.5	207
Reference range	50–150	100–200

In 1984, Mathur, *et al.*[110] reported regrowth of eyebrows in eight lepromatous leprosy patients receiving zinc supplementation. They divided 25 previously untreated lepromatous patients into two groups to study the effect of 220 mg of dietary supplemental zinc sulfate. Both groups were of similar socioeconomic status and age (20–50 years). The authors did not state whether the groups were age matched. Both groups also received 100 mg dapsone daily. The study continued for 18 months. The first group of 15 patients (of which eight had no eyebrows) received zinc. Regrowth of eyebrows began in all eight cases after about 6 months, and full growth occurred within 18 months. The second group (10 patients, of

[108] Rao, K. N. and Saha, K. Further studies on undernutrition in lepromatous Hansen's Disease. The Star, Apr. 1986 6–7.

[109] DeCaires, P. F. Iron therapy in severe cutaneous leprosy. Br. Guiana Med. Ann. **27** (1943) 132–136.

[110] Mathur, N. K., Bumb, R. A., Mangal, H. N. and Sharma, M. L. Oral zinc as an adjunct to dapsone in lepromatous leprosy. Int. J. Lepr. **52** (1984) 331–338.

which six lacked eyebrows) did not receive supplemental zinc. No patients showed eyebrow regrowth during the 18 months of observation. The first group of 15 patients receiving zinc and dapsone showed faster clinical improvement, suggested by a more rapid decrease in erythema, edema, and infiltration of skin lesions, compared with the 10 patients receiving dapsone alone. The authors proposed an immunostimulant role for zinc. Beisel[89] presents evidence that zinc is required for lymphocyte and phagocyte function and thymus integrity and function. However, the mechanism of action of zinc in hair growth is not clear.

Mathur, *et al.*,[111] found serum zinc levels in 146 previously untreated leprosy patients of all types and in 40 healthy controls from the same socioeconomic group and of similar dietary habits as follows:

	Mean serum zinc (μg/100 ml ± S.D.)	p value
Normals	110.2 ± 12.4	
TT	110.0 ± 11.2	NS*
BT	99.5 ± 7.4	NS
BL	83.5 ± 15.4	<0.01
LL	68.7 ± 13.9	<0.01
Reference range	50–150	

* NS = not significant.

A gradual lowering of serum zinc levels was observed as leprosy advanced from the tuberculoid (least severe) to the lepromatous (most severe) end of the leprosy spectrum. However, after 18 months of dapsone treatment alone, zinc levels were not significantly improved. The authors suggest that *M. leprae* may metabolize zinc, contributing to the hypozincemia in lepromatous leprosy. They also suggest the possibility of zinc-deficient diet predisposing to lepromatous leprosy. However, they stated that their controls and patients had similar dietary habits. Data regarding dietary intake would assist in deciding whether deficient diets favor the progression of leprosy or whether leprosy induces the deficiency. These zinc studies underline the need for precise dietary data relating nutritional intake in leprosy studies.

[111] Mathur, N. K., Sharma, M., Mangal, H. N. and Raj, S. M. L. Serum zinc levels in subtypes of leprosy. Int. J. Lepr. **52** (1984) 327–330.

Oon, *et al.*,[112] in 1974, studied serum zinc levels in leprosy, tuberculosis, dermatitis herpetiformis and normal individuals, finding:

Clinical group	No.	Serum zinc (μg/100 ml ± S.E.)	p value
Leprosy with ulceration	21	89.9 ± 4.0	<0.02
Leprosy without ulceration	18	89.8 ± 4.6	<0.02
Pulmonary tuberculosis	16	85.0 ± 3.9	<0.0005
Dermatitis herpetiformis	5	86.9 ± 3.1	<0.0005
Controls	33	102.4 ± 3.0	
Reference range		50–150	

They conclude that this finding is a nonspecific metabolic consequence of chronic disease, since low serum zinc levels are found in chronic diseases other than leprosy.

Nutrients and foods in combination. In 1936, Tolentino[113] reported that obesity had an unfavorable effect on leprosy treatment. Patient parole data over a 5-year period were used to determine treatment success. He classified patients by observation as being thin, normal or obese:

Nutritional status	Cases treated	Paroled	Percent
Thin	71	33	46.48
Normal	348	129	37.07
Obese	28	6	21.43

This observation is in harmony with a growing body of data which indicate that overnutrition is more detrimental than undernutrition after childhood or infancy.

Because wheat is known to contain more protein than does rice, Cochrane, *et al.*,[114] in 1940, replaced rice with wheat in the diets of Indian leprosy patients and observed that Hansen's neuritis and arthritis were improved without otherwise altering the overall course of the disease. We assume the patients were their own controls, their prior

[112] Oon, B. B., Khong, K. Y., Greaves, M. W. and Plummer, V. M. Trophic skin ulceration of leprosy: skin and serum zinc concentrations. Br. Med. J. **2** (1974) 531–533.

[113] Tolentino, J. G. Certain factors supposed to influence the results of the treatment of leprosy. Philippine J. Sci. **59** (1936) 163–175.

[114] Cochrane, R. G., Paulraj, M. and Salmond, M. D. The effect of wheat diet in the relief of certain painful complications and sequelae in leprosy. Indian J. Med. Res. **27** (1940) 963–969.

course being known. The meaning of this is uncertain without having specific details of the rice and wheat or other dietary changes.

Davey and Ross,[115] in 1944, studied the influence of dietary coco-yam on leprosy in 56 Nigerian children divided into control and test groups that were age-, sex-, and leprosy-type-matched. For 4 months, two pounds of coco-yam, traditionally prepared (boiled, then pounded), was added to the diet of each of 28 children in the test group. The control group of children had the same diet but without coco-yam. No differences between leprosy status or well being of the groups were noted during 1 year of observation. They concluded that the slight toxicity of sapotoxins in yams, a glucoside toxic to the kidney, adrenals and liver, did not predispose to leprosy in Nigerian children.

Collier,[116, 117] in 1940, reported preliminary results which appear contradictory to the studies of Davey and Ross.[115] He inoculated tissue from advanced lepromatous humans into the subcutis of 19 rhesus monkeys. These monkeys were divided into two dietary groups. Within 3–12 months, the group that was fed boiled coco-yam tubers developed positive nasal smears and ear clips and cutaneous facial lesions similar to human leprosy. One monkey developed an enlarged ulnar nerve. None of the control animals not fed coco-yams developed evidence of leprosy within the year. An editorial[30] in 1943 reviewed the published evidence for and against the theory that eating coco-yams has a causal relationship with leprosy. The editor made the following observation concerning Collier's[116, 117] work: "The tissues of the monkeys which were supposed to be infected with leprosy were later examined histologically and bacteriologically in London and the report was that the tissues showed no acid-fast bacilli and no evidence of leprous change." The editor concluded that no evidence could be substantiated to show any relationship between coco-yam consumption and leprosy.

In 1977, Sehgal, *et al.*[118] studied the causes of reactions in 1053 patients. Of the 103 patients (9.7%) who had reactions between 1970–1975, three factors common to these patients were reported in order of frequency: a) dapsone, b) intercurrent infection, and c) malnutrition. Erythema nodosum leprosum (ENL), reversal reactions, and acute neuritis reactions are expressions of immune responses to *M. leprae* antigens. In contrast, Skinsnes and Higa[119] and Ryrie[55] found that under conditions of severe malnutrition, associated with war shortages, reactions ceased entirely or were greatly reduced in number. Reactions may be viewed as misdirected immune responses which lesser degrees of malnutrition appear to increase, while starvation results in immune system failure with severe intercurrent infections and no reactions.

Cruz,[120] in 1935, observed low serum lipids following lepra reactions. He tried supplementing the patients' diets with cod-liver oil, butter, and eggs to see if a high-fat diet would be therapeutic. It was not found to be.

In 1976, Skinsnes and Higa[119] studied severe protein deprivation in rat leprosy induced by intraperitoneal inoculation with *M. lepraemurium*. Rats that survived a protein-free diet up to 18 weeks were studied microscopically. Rats on a balanced diet containing adequate protein were used for controls. Leprosy in the protein-starved rats spread more rapidly and showed less inflammatory response than the controls. Beginning with the 7th week of protein starvation, a greater number of bacilli were consistently seen, both in macrophages and in susceptible organs.

McMurray and Yetley,[121] in 1983, subjected guinea pigs to the four possible combinations of high and low dietary protein

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[115] Davey, T. F. and Ross, C. An investigation of the effects of cocoyam on leprosy. Lepr. Rev. **15** (1944) 3–12.

[116] Collier, D. R. Inoculation of monkeys with leprosy, following a diet of puak (Colocasia); a preliminary report. Lepr. Rev. **11** (1940) 135–140.

[117] Collier, D. R. Inoculation of monkeys with leprosy, following a diet of puak. Thailand Sci. Bull. **2** (1940) 101–108.

[118] Sehgal, V. N., Rege, V. L. and Mascarenhas, M. F. Pattern of reactions in leprosy: a clinical appraisal Lepr. India **49** (1977) 221–228.

[119] Skinsnes, L. K. and Higa, L. H. The role of protein malnutrition in the pathogenesis of ulcerative Lazarine leprosy. Int. J. Lepr. **44** (1976) 346–358.

[120] Cruz, M. C. Trial of high fat diet and fixation-abscess in lepra reaction. J. Philippine Med. Assoc. **15** (1935) 214–220.

[121] McMurray, D. N. and Yetley, E. A. Response to *Mycobacterium bovis* BCG vaccination in protein- and zinc-deficient guinea pigs. Infect. Immun. **39** (1983) 755–761.

and zinc: a) 30% protein and 50 ppm zinc; b) 30% protein and 0 ppm zinc; c) 10% protein and 50 ppm zinc; and d) 10% protein and 0 ppm zinc. They then inoculated them with viable *M. bovis* BCG and skin tested them 7 weeks later with PPD. The animals deficient in both protein and zinc showed marked increases in tissue levels of viable *M. bovis* BCG in inguinal lymph nodes and the subcutaneous inoculation sites as compared with those deficient in protein or zinc alone. Peripheral lymphocytes were also tested *in vitro* for T-cell blastogenesis. The combination of both low protein and zinc significantly decreased T-cell blastogenesis at all levels of mitogen stimulation. Animals maintained on the 10% protein diets, irrespective of zinc level, were significantly impaired in their PPD responses (average diameter of induration less than half that of the 30% protein dietary groups). These findings suggest that dietary protein and zinc deficiencies, alone or in combination, interfere with immunological responses of the host vaccinated with *M. bovis* BCG.

Mester de Parajd and Garnier[122] reported in 1985 that 0.5 g/day of a dietary supplement containing tryptophane, unsaturated fatty acids, and glucose (Nutrition Anti-Leprosy, "NAL," by Nestlé S. A., Vevy, Switzerland) was as effective as 20 mg/kg of body weight dapsone per day in suppressing growth of *M. leprae* injected into mouse foot pads. NAL has been shown to increase the production of deoxyfructo-serotonin (DSF), a naturally occurring metabolite of tryptophane. DSF has been shown to inhibit the incorporation and utilization of L-DOPA by *M. leprae* and to be highly effective in suppressing the multiplication of Hansen's bacilli. Such a naturally occurring, possibly therapeutic substance as DSF, which might play a role in both treatment and prevention of leprosy, warrants further study.

In 1975, Bergel[85] fed rats with beef which was bought daily at a local market in Argentina, and was kept for 48 hr at room temperature. The control animals were fed a standard lab rat diet made of dried green vegetables. He then inoculated *M. leprae* into the foot pads of both groups of rats. The rats fed putrefied beef showed >100 times the increase in bacterial growth than the controls showed. Bergel concludes that putrefied meat in the diet favors the growth of *M. leprae*. Putrescine, an amine formed from the amino acid, arginine, during putrefaction, has been reported to be found in the blood of lepromatous leprosy patients who harbor viable *M. leprae* in their skin[123] but is not found in patients in whose skin no *M. leprae* are found. Bergel suggests that putrescine may be one of the metabolites required by Hansen's bacilli, and may be required in the culture medium still to be developed for this bacillus.

The apparent positive association of malnutrition early in life with the development of leprosy later in life is an important area for further research due to the widespread prevalence of malnutrition. The possible role of specific foods or nutrients that may increase the level of DSF, which may be as effective as dapsone in the control and treatment of leprosy, should be further investigated.

REVIEWS AND EDITORIALS

A characteristic of previous reviews and editorials is the stated paucity of hard data linking diet and leprosy. Dharmendra,[124] in 1949, after reviewing the available evidence for the predisposing influence of an inadequate diet on infections in general and leprosy in particular, in both laboratory animals and man, concludes: "Though there is no definite experimental proof to the effect that malnutrition predisposes to leprosy, there is considerable evidence to that effect." The evidence cited included data reported by the Leprosy Investigation Center, Bankura (West Bengal), which showed a fairly stable total number of registered cases (424–429) for the years 1937 until 1943 when a famine occurred. The total number of patients in 1944 declined to 392 due to a large number of deaths, especially among the lepromatous patients. In subsequent years, there was a steady increase in the total number of patients registered each year (490–507), with the number of lepromatous

[122] Mester de Parajd, L. and Garnier, J. P. Nutritional aspects of leprosy. Acta Leprol. (Genève) **95** (1984) 293–303.

[123] Ishikawa, M. Putrescine in the blood of lepromatous leprosy patients. Lepro **36** (1967) 238–239.

[124] Dharmendra. Diet and susceptibility to leprosy. Lepr. India **21** (1949) 180–192.

patients remaining lower (70–75 compared to 91–96 in the pre-famine years).

Duncan,[125] in a 1985 editorial, suggests that nutritional improvement, possibly with a zinc supplement, along with triple drug therapy may prove beneficial in decreasing the relapse rate of leprosy in pregnant women and the risk of infecting the unborn baby with leprosy.

Edelman[126] reviewed the literature on malnutrition and leprosy in 1979, as did Rees[127] in 1981. Both came to the conclusion that the evidence was insufficient to prove a relationship between diet, nutrition, or malnutrition, and the etiology or prognosis of leprosy.

SUMMARY AND CONCLUSIONS

The literature relating diet to leprosy is abundant between 1900 and 1960, peaking around 1940. Dietary factors that appear to influence the etiopathogenesis of Hansen's disease include:

vitamin A[76–79]
vitamin B group[100, 101, 103–105]
vitamin C[91, 95–98]
vitamin D[80]
vitamin E[69, 81, 82, 84, 87, 90]
calcium[11, 104, 106–108]
zinc[76, 108, 110–112, 121]

We noted a frequent lack of detailed dietary data in much of the literature cited. This is particularly true when the thrust of the investigation is not dietary.

The literature strongly suggests the beneficial influence of adequate diet on the outcome of Hansen's disease and the deleterious effect of a deficient diet. In contrast with the paucity of reported hard data in the previous reviews concerned with the effect of nutrition and diet on leprosy, is the increasing volume of literature reviews and experimental studies showing the profound impact of nutrition and diet on the immune system of man and laboratory animals.[89, 128–142] That diet has a global, if poorly understood, effect on the immune system

[125] Duncan, M. E. Leprosy in young children—past, present and future. Int. J. Lepr. **53** (1985) 468–473.

[126] Edelman, R. Malnutrition and leprosy—an analytical review. Lepr. India **51** (1979) 376–388.

[127] Rees, R. J. W. Non-specific factors that influence susceptibility to leprosy. Lepr. Rev. **52** Suppl. 1 (1981) 137–146.

[128] Agius, L., Rolls, B. J., Rowe, E. A. and Williamson, D. H. High-energy diets produce different effects on fatty acid synthesis in brown adipose tissue, white adipose tissue and liver in the rat. Biochim. Biophys. Acta **750** (1983) 383–387.

[129] Barash, H., Poston, H. A. and Rumsey, G. L. Differentiation of soluble proteins in cataracts caused by deficiencies of methionine, riboflavin or zinc in diets fed to Atlantic salmon, Salmo salar, rainbow trout, Salmo gairdneri, and lake trout, Salvelinus namaycush. Cornell Vet. **72** (1982) 361–371.

[130] Beach, R. S., Gershwin, M. E. and Hurley, L. S. Zinc, copper, and manganese in immune function and experimental oncogenesis. Nutr. Cancer **3** (1982) 172–191.

[131] Beisel, W. R. Magnitude of the host nutritional responses to infection. Am. J. Clin. Nutr. **30** (1977) 1236–1247.

[132] Bell, R. G. and Hazell, L. A. Influence of dietary protein restriction on immune competence. I. Effect on the capacity of cells from various lymphoid organs to induce graft-vs.-host reactions. J. Exp. Med. **141** (1975) 127–137.

[133] Briscoe, J. The quantitative effect of infection on the use of food by young children in poor countries. Am. J. Clin. Nutr. **32** (1979) 648–676.

[134] Corman, L. C. Effects of specific nutrients on the immune response. Med. Clin. North Am. **69** (1985) 759–790.

[135] Cunningham-Rundles, S. Effects of nutritional status on immunological function. Am. J. Clin. Nutr. **35** (1982) 1202–1210.

[136] Dreizen, S. Nutrition and the immune response—a review. Int. J. Vitam. Nutr. Res. **49** (1979) 220–228.

[137] Edelman, R. Obesity: does it modulate infectious disease and immunity? Prog. Clin. Biol. Res. **67** (1981) 327–337.

[138] Gross, R. L. and Newberne, P. M. Role of nutrition in immunologic function. Physiol. Rev. **60** (1980) 188–249.

[139] Hansen, M. A., Fernandes, G. and Good, R. A. Nutrition and immunity: the influence of diet on autoimmunity and the role of zinc in the immune response. Annu. Rev. Nutr. **2** (1982) 151–177.

[140] Horrobin, M. S., Manku, M. S., Oka, R. O., Morgan, R. O., Cunnane, S. C., Ally, A. I., Ghayur, T., Schweitzer, M. and Karmali, R. A. The nutritional regulation of T lymphocyte function. Med. Hypotheses **5** (1979) 969–985.

[141] Johnston, D. V. and Marshall, L. A. Dietary fat, prostaglandins and the immune response. Prog. Food. Nutr. Sci. **8** (1984) 3–25.

[142] Vitale, J. J. and Broitman, S. A. Lipids and immune function. Cancer Res. **41** (9 Pt 2) (1981) 3706–3710.

[143] Sansarricq, H. Recent changes in leprosy control. Lepr. Rev. Special Issue (1983) 7S–16S.

[144] Noordeen, S. K. and Bravo, L. L. The world leprosy situation. World Health Stat. Q. **39** (1986) 122–128.

[145] Dharmendra. *Leprosy, Volume 1*. Bombay: Kothari Medical Publishing House, 1978, pp. 1–732.

is being increasingly recognized. The difficult question that remains is how to use this information in the control and prevention of disease. Therefore, we believe that more emphasis should be given to diet in the study of this important worldwide disease in light of the current understanding of biochemistry and immunology.

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