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Immuno-Pathology of Leprosy: The Century in Review

Pathology, Pathogenesis, and the Development of Classification

Olaf K. Skinsnes[1]

Chung-kuei, demon killer.

Early rationale. The main progress in the understanding and treatment of leprosy has occurred chiefly within the century just passed. Since, however, leprosy involves predominantly the skin and peripheral nerves, its manifestations were in considerable measure readily evident and empirically documented long before pathologic understanding of disease processes began to develop. Thus, in China, the *Nei Ching Su Wen* (225), the authorship of which is traditionally attributed to the Emperor Huang Ti (trad. B.C. 2698-2598) but now regarded as having been compiled in about B.C. 500, in its description of leprosy using the term *li-feng* ("severe paralysis") notes loss of eye-brows, nodules, ulcerations, "and because of the stagnant movement of the *wei-chi* ('defensive forces') numbness results. . . . The vital spirits degenerate and turn cloudy causing the bridge of the nose to change color and rot, and the skin to ulcerate:" In India the *Sushruta samhita* (56), compiled in about B.C. 600, under the terms *vat-rakta* and *vatsonita* described hyperesthesia, anesthesia, formication and deformities. Under the designation *kustha* it recognized two kinds of skin manifestations. In one, the prominent symptoms and signs were local anesthesia and deformities. In the other, the features were ulceration, falling off of fingers and sinking of the nose. In about 150 A.D., Aretaeus (2), prominent Greek physician presented the first comprehensive medical description of leprosy from Europe. He described changes similar to those just noted and spoke of *leonine facies.* Remarkably, he did not record anesthesia or numbness or give other evidence of specific awareness of neural involvement. In China his contemporary, Hua T'o (102), wrote, "The symptoms of leprosy may first appear on the skin, but the poison is actually stored in internal organs. The skin is first numb without sensation, gradually red spots appear on it, then it is swollen and ulcerated without any pus. And later the disease develops to such an extent that the eyebrows fall, the eyes may become blind, the lips deformed and the voice hoarse. The patient may also experience ringing in his ears and the soles of his feet develop rotted holes; his finger joints may become dislocated and the bridge of his nose flattened." Soon thereafter, again in China, Ko Hung (125) wrote, "The first symptoms of *lai-ping* ("leprosy") is numbness of the skin, or a sensation of worms creeping."

These Oriental writings with respect to leprosy were not known or recognized in western medicine. Andersen (3) reviewed the Greek and Latin writings regarding leprosy *in extensio*, but does not record from them any significant description of numbness, paralysis or anesthesia as related to leprosy. His brief summary of the Arabic literature is equally sterile with respect to neural symptoms, though mutilation of the extremities was clearly recognized. It was first in the writing of Gilbertus Anglicus (c. 1290 A.D.) that he encountered mention of anesthesia, ". . . anaesthesia of the little finger side of the hand and forearm is for the first time mentioned as a diagnostic sign; . . ." and in the work of Johannes de Gaddesden (c. 1305 A.D.) he found reference

[1] O. K. Skinsnes, M.D., Ph. D., Professor of Pathology. ALM Leprosy Atelier, Department of Pathology, University of Hawaii School of Medicine.

"Tubercular" leprosy[2]

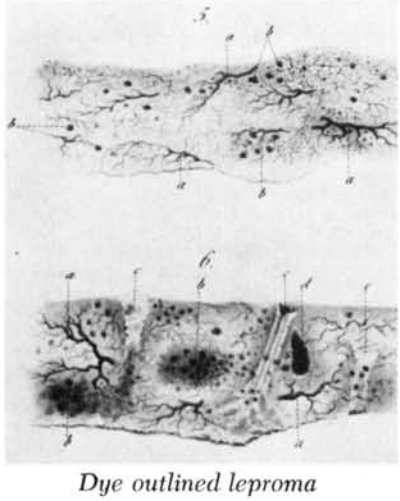
"Neural" leprosy

to loss of sensation in the individual skin lesions. Paracelsus (1493-1541 A.D.), Andersen noted, mentioned loss of sensation and paralysis of the face, and Conradus Gesner (1516-1565 A.D.) noted deprivation of sensation as being extensive at times and described failure to feel the "prick of a needle."

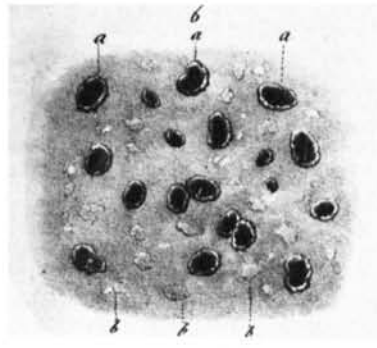
This sparse reference to anesthesia, numbness and related symptoms in the writings of western medicine is remarkably reflected by a similar sparsity of reference in literary works dealing with leprosy ([184]). Though mutilation and all the other characteristics that could be cited in support of the pervasive opprobrium relating to leprosy are widely used, there is striking mutescence regarding anesthesia and its analogs.

Thus stood the understanding of the pathology of leprosy at the dawn of the "century" of its flowering—a "century," however, which began more than 25 years before this commemorative century of Hansen's discovery of *Mycobacterium leprae.* Real advance in pathologic understanding began with the publication of the *Atlas Coloríe de Spedalskhed* and *Om Spedalskhed* by Hansen's father-in-law, Danielssen, and the latter's collaborator, Boeck, in 1847 ([25, 47]). Virchow termed this the beginning of the biologic knowledge of leprosy, and so it was. Their work was based on both clinical and necropsy studies and illustrated lesions both external and internal. Understandably, in the absence of knowledge concerning etiologic agents of disease, many of the gross internal lesions they illustrated were evidently due to concommitant tuberculosis. They illustrated a variety of skin manífestations common to leprosy and showed also bizarre, piled up epidermal lesions evidently caused by scabies, the mite of which they also depicted. They showed mutilations and deformities of hands and feet, including muscle atrophy, and made note of neural involvement. Histopathologic tissue staining technics were not yet available, but they presented unstained skin sections and outlined lepromas on gross section by intravascular dye permeation. Nasal, laryngeal and tracheal lesions were noted and illustrated. Their classification of the disease types was anatomical: "tubercular" (skin nodules) and "neural." This was the classification that was to remain in effect through long debate until the Havana Congress in 1948 officially accepted the concept of the two immunopathologic polar types, "lepromatous" and "tuberculoid" with an intermediate spectrum later appropriately designated "intermediate" and early, indefinable lesions termed "indeterminate." Before that concept could emerge, extended histopathologic studies related to clinical findings were needed, together with some understanding of the immunology of the disease.

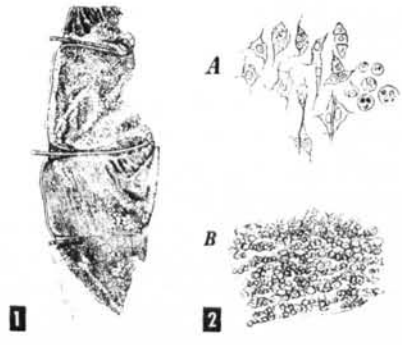
[2] All illustrations accompanying this review, save the first and last and that attributed to Virchow, are from the atlas by Danielssen and Boeck.



Dye outlined leproma



"Brown bodies"



Virchow'e sketches of lepra cells[3]

Development of understanding through clinically related histopathology. Danielssen found some odd-looking granular masses resembling frog sperm in biopsy material. He showed these to Rudolph Virchow when that renowned pathologist visited him in 1859 and Virchow expressed the opinion that these were degenerate cells showing hydropic degeneration ([208]). These observers were working without the advantage of stained tissue preparations for it was not until 1862 that Bencke initiated a revolution in the practice of histopathology by introducing the use of aniline dyes as tissue stains. It was not long before these granular masses were found to be made up of large, vacuolated cells which came to be variously known as "Virchow cells," "foam cells," or "lepra cells" and to be recognized as being macrophages. Unna suggested that the vacuoles contained fat, and Neisser's application of the new staining methods to leprous tissue sections showed that they were filled with bacilli. Neisser also regarded the cell vacuoles as containing fat as early as 1879, but regarded its presence as indicative of fatty degeneration of the cells themselves. By 1918 the lipid nature of these vacuoles had been well demonstrated by Cedercreutz ([39]) and by Mitsuda ([146]) as well as by others. Investigators have held varying opinions as to the origin of the stored fat, some holding that it is derived from fatty phanerosis of the phagocytosing macrophages, others that it comes from pinocytosis of fat derived from degenerating tissue fat, while others contend that it consists of lipid residues from dead, engulfed bacilli. It now seems reasonable to hold that in large measure, if not *in toto*, the stored lipid is bacillar and reflects the difficulty that the lepromatous host macrophages have in disposing of this pathogen ([174, 175]). The sequential development of lipid storage in the lepra cell was studied by Harada ([91, 92]). In its early stages the lepra cell, in addition to bacilli, was found to contain fatty acids, phospholipids and unsaturated lipid while neutral fat was slight or absent. The well-developed foam cell, on the other hand, in addition to acid-fast granules and debris with only occasional bacilli, contained primarily neutral fat and acidic lipid.

Many morphologic studies and reports ([179]) over the years have led to the understanding that the tissue response in lepromatous leprosy consists essentially of an

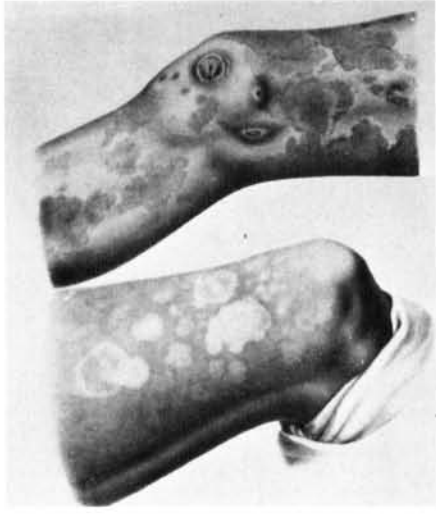
[3] Reproduced from this JOURNAL **22** (1954) 208.

outpouring of histiocytes or macrophages which apparently have effective phagocytic ability and readily engulf large numbers of bacilli. Whether or not bacilli proliferate within the macrophages has not been firmly established, though apparently they do, and few bacilli are seen outside the cells. Hanks (86) found an average of 2.5 x 10^9 bacilli per cubic centimeter of tissue in six lepromas. This profusion of intracellular bacilli led Suter (200) to discuss the problem in terms of "intracellular parasitism," and it is not uncommon to find expression of the view that *M. leprae* is an obligate intracellular parasite, though this has not been proven. The same concept has long been held regarding *M. lepraemurium* but it has recently been shown (57, 168) that this mycobacterium can achieve multiplication in the absence of cells within millipore chambers implanted in the peritoneums of mice. It is not inconceivable that *M. leprae* may be shown to have the same capability, in which case their intracellular status in lepromatous leprosy may stand as witness to remarkably effective phagocytic ability on the part of responding macrophages. Recently, extracellular bacillary globi have been found in tissues of an armadillo infected with *M. leprae* (121). This is suggestive though it does not prove extracellular bacillary proliferation.

It was early recognized that some cases of leprosy presented a variant histopathologic expression in which tubercle-like structures without caseation were characteristic and in which bacilli were extremely scarce and often not demonstrable in histopathologic sections. Jadassohn (106) seems to have been the first to describe this tissue expression as "tuberculoid." The concept was elaborated by Klingmuller (122) and others. Subsequently Wade (210), in an extended series of studies delineated the tuberculoid pole of the leprosy spectrum on a histopathologic basis. Its fundamental characteristic, histopathologically, came to be recognized as the development of distinct, tubercle-like structures without caseation in which macrophages transformed to epithelioid morphology are the characteristic cell while foamy macrophages are not in evidence. The epitheliod cells exhibit virtually no lipid in their cytoplasm (8, 50). This response is morphologically a granuloma rather than the agglomeration of masses of foamy macrophages which characterizes the response in lepromatous leprosy and which is better designated as a leproma (183).

With the established recognition of these polar types of histopathologic response in leprosy and the fact that the tuberculoid patient also gives a postive lepromin test while the lepromatous does not, *vide infra*, it was also recognized that many patients did not fit into either distinct category and that there were variations on the polar types. Thus there were atypical tuberculoid and atypical lepromatous variants lying close to the polar types both clinically and histopathologically, as well as a broad spectrum of others which came to be recognized as "intermediate" in type. In part, this recognition revolved around the controversy over whether or not either of the two polar types can transform into its opposite. This discussion was warmest with respect to the question of whether or not the tuberculoid type could downgrade toward the lepromatous pole. In addressing themselves to this problem, Wade and Rodriguez (211) employed the term "borderline tuberculoid" in the presentation of a series of cases which would probably be included in the present classification as "borderline," "intermediate" or "dimorphous." In recent years, type movement within the intermediate portion of the leprosy spectrum has been generally accepted as occurring in some instances and movement toward the tuberculoid expression is spoken of as an "upgrading reaction" while the converse is referred to as "downgrading."

An inordinate amount of discussion and publication was devoted to the problem of classification during the first half of the century following Hansen's discovery of the leprosy bacillus. There developed a Panamerican classification, a South American classification and an Indian classification, among others, and vestiges of these strongly held concepts still intrude into, or are used to expand on the presently established classification in occasional publications. At the time of the IVth International Congress in



Dimorphons leprosy

Cairo in 1938, the official classification still was based on the earlier anatomical basis of lepromatous, L, and neural, N, with also a mixed or LN group. Varying degrees of severity of skin or nerve involvement were indicated by numbers affixed to the designating letter. By the Vth International Leprosy Congress in Havana in 1948, immunopathologic understanding and agreement had advanced to the stage where a viable and reasonable classification could be adopted. This was simply the recognition of the tuberculoid and lepromatous poles, representing relatively high and low tissue resistance to *M. leprae*, with an interlying spectrum of manifestations grouped as "indeterminate." This classification included an understanding of the response to lepromin in the various classification categories. At the next congress, held in Madrid in 1953, Khanolkar and Cochrane ([118]) used the designation "dimorphous" and this congress officially adopted the term "borderline," with "dimorphous" as an alternate, for the Havana Congress adopted "indeterminate," thus leaving three designations in use for the same concept. Of these, "intermediate" suffers from being frequently confused in usage with the term "indeterminate," and "borderline" seems a relatively poor designation in the light of present understanding since the broad immunopathologic spectrum it covers is neither a border nor a line but a fluctuant spectrum. The term "dimorphous" is descriptive in its connotation that the various manifestations of this intermediate group of cases present varying combinations in intensity and proportions of the morphologic and immunologic manifestations that are characteristic of the polar types.

In 1961 Cochrane ([45]), on the basis of long effort, tabulated and correlated the histopathologic morphologies of the various classification types of leprosy with their clinical characteristics and in 1962 Ridley and Jopling ([166]) presented a similar, codified summary and standardization of terminology that has been widely accepted. The latter utilizes the notations, TT = tuberculoid, BT = borderline tuberculoid, BB = borderline, BL = borderline lepromatous, and LL = lepromatous, retaining the term "indeterminate" for those instances not readily classifiable on the TT to LL scale. Essentially, the BL designation corresponded to the older "atypical lepromatous" and the BT designation to the "atypical tuberculoid" groups. The system was further upgraded in 1966 ([167]).

Variant morphologies in leprosy. There are several variants in the manifestations of leprosy that are not clearly consonant with the classical morphologies of the major classification groupings. The pathogenic bases for these variants are not clear. The following three are illustrative and most striking.

Lucio leprosy is also variously known as "diffuse leprosy of Lucio and Latapi," "la lepra bonita," "diffuse lepromatous leprosy," and "spotted leprosy" and has at times had, confusingly, the term "Lazarine leprosy" as a designation. First described by Rafael Lucio in 1851, it was rediscovered and extensively studied by Latapi and his colleagues ([70, 128, 205]) in the 1940s and subsequently. Reported primarily from Mexico, where it is not uncommon, this variety has been seen in only a few instances in other parts of the world. It is now recognized as being essentially a diffuse lepromatous leprosy characterized by its relatively slight inflammatory response and by

a vasculitis which results in thrombosis of cutaneous vessels with resulting ulcerative infarcts in the skin. This ulcerative phenomenon is referred to as the "Lucio phenomenon" and is analogous to *erythema nodosum leprosum*. Since vasculitis is commonly seen in other forms of leprosy ([68]) and is a prominent feature of *erythema nodosum leprosum*, but is generally not accompanied by thrombosis. The characteristic thrombosis in the Lucio phenomenon presents an intriguing puzzle for which no satisfactory explanation has been presented.

Lazarine ulceration

Lazarine leprosy. The designation refers to manifestations of marked ulceration seen at times in association with leprosy. It derives from the Biblical account (Luke 16: 19-31) of the beggar Lazarus who, covered with sores, sat at the door of the rich man, Dives, vainly begging for the crumbs that fell from the latter's table. Medieval tradition held that Lazarus suffered from leprosy though the Biblical account carries no such implication. Lucio associated the term "lazarine" with Lucio leprosy and this practice was continued by Latapi and other students of the Lucio phenomenon. Other literature, as exemplified by Klingmüller ([123]) and Wade ([213]), presents many discussions of ulcerative phenomena in association with both tuberculoid ("neural") and lepromatous leprosy and often describes small vesicles or bullae as preceding ulceration. Skinsnes and Higa ([178, 180]) have noted similar vesiculation followed by severe and extensive ulceration in association with marked protein malnutrition in leprosy and suggest that such ulceration may result when, as a result of malnutrition, the host defense mechanisms break down. There is presently no consensus of opinion, but it might be reasonable to recognize the unique ulceration in Lucio leprosy under the designation "Lucio phenomenon" as is often done and, despite the historical association of the term "lazarine" with Lucio leprosy, reserve this term for severe ulceration associated with other pathogenic mechanisms, particularly with severe debilitation since this also has historical validity and since the term "lazarine" has its origin in the account of a presumably malnourished individual.

?Histoid leprosy

Histoid leprosy. This histopathologic inflammatory pattern in leprosy was first described by Wade ([215]) in 1963, well into the era of sulfone therapy. Essentially these cases are distinguished by an inflammatory response consisting of spindle-shaped histiocytes associated with fibrosis as the lesions age. They contain abundant bacilli which are reportedly distinctly longer than in lepromatous leprosy and which do not form globi though they may be arranged in packets. Wade noted that these patients did not have episodes of ENL, but subsequent reports have not confirmed this as a salient characteristic. Rodriguez ([171]) found histoid tissue response also in borderline lepromatous (BL) patients and noted that most frequently the histoid response was to be found in treated but relapsed cases. He suggested that the response might be due to mutant, drug-resistant *M. leprae*, presumably due to some metabolic change in these organisms. Desikan and Iyer ([54]), in contrast, point to the possibility that the cell population of histoid lepromas may be derived from biologically

distinct histiocytes which do not exhibit the classical behavior of macrophages when confronted with large loads of *M. leprae.* Fite ([69]) noted that in early leprosy lesions many of the cells are simply large phagocytic cells of unidentified origins while others are elongated or spindle-shaped and not distinguishable from fibroblasts except that they lack fibrils. Any possible correlation between the histoid response and possible tendency on the part of these subjects to keloid formation has not been reported and seems not to have been considered. Thus, it has not been reported whether or not there is an increase in mucopolysaccharide ground substance in these lesions as is characteristic for keloids ([21]). Ciaccio ([100]) did review the subject of keloids in leprosy in a paper not available at this writing. Some indication of the possible frequency of this response is given by Sanchez ([176]) who in a review of more than 5,000 tissue slides from cases of leprosy in Mexico, found seven that fulfilled the criteria for this reaction. One wonders if Malassez ([140]) encountered this reaction since he regarded leprosy as a sarcomatous process.

Visceral involvement in leprosy. Several necropsy series ([16,20,53,90,114,124,147,164,198]) have been reported, the earliest of which was the report by Hansen and Looft in 1894. These are additional to the atlas presentation of Danielssen and Boeck already alluded to. Mitsuda is reported to have performed over 1,000 autopsies on persons with leprosy and many of his findings are contained in a five volume collection of his papers in Japanese. His *Atlas of Leprosy* ([148]) in English, volume VI in the series, presents color plates which illustrate some of his findings.

Modern understanding of disease has its roots in pathologic anatomy, gross and microscopic. It follows that morphology is evidence. Like all evidence, it requires judicious, comparative evaluation and its interpretation is, of course, advanced and enhanced by any other technics that are developed and bear on the problems revealed by morphologic studies. It is on the basis of such evidence, often questioned, that despite its evident involvement of skin and nerves, leprosy has slowly been accepted as

Laryngeal stenosis

being a systemic infection with the heaviest concentration of lesions (apart from those in skin and nerves) being in the organs representing the reticulo-endothelial system, but also with widespread deposition of bacilli, and sometimes of lesions of generally lesser intensity, in most tissues. Not all workers will agree with this assessment, for some hold that the presence of bacilli in organs such as lymph nodes, spleen and liver merely represents clearance of bacilli from the blood circulation and, believing that *M. leprae* can survive and proliferate only at temperatures lower than 37°C, further hold that the bacilli in these locations will not long survive and do not there proliferate. The question remains unresolved since the demonstration of viable bacilli in these organs is subject to either interpretation. Similar morphology for virtually any other bacterial or mycotic infection would, however, probably be accepted as evidence of active infection.

On the basis of morphology it was recognized at the time of the IInd International Leprosy Congress (1909) that there probably was hematogenous spread in leprosy and bacillemia was demonstrated by Rivas ([169]) in 1912, well established by Rhodes-Jones ([165]) in 1963 and found to be virtually continuous in untreated lepromatous patients by Drutz and associates ([59]) in 1972. Manja and collaborators ([141]) demonstrated that bacilli in the blood are viable. Bacillemia having been well demon-

strated for lepromatous leprosy, confirming prior interpretation of morbid anatomical findings, the similar lesion distribution in other forms of leprosy then indicate that bacilli in all forms of leprosy, though not necessarily in all instances, gain access to the blood circulatory system, and tend to be removed by the reticulo-endothelial system though presumably they may be deposited also in any locale reached by the circulation. Whether or not they produce significant lesions in such areas depends on many factors, dominant among which presumably are the size of the inoculum introduced into the area and/or the suitability of the area for *M. leprae* proliferation.

Lepromatous lesions of the viscera are the most pronounced and extensive. The liver often shows numerous scattered miliary lepromas composed of lipid-laden foam cells containing many acid-fast bacilli. The lepromas are prominent in the paraportal areas but are also present as smaller focal lesions in the lobules, both as small lepromas and as bacillary presence in prominent Kupffer cells and sinusoid lining endothelial cells ([53, 207]). The spleen and lymph nodes, likewise, may show similar miliary lepromas but, presumably because of the lack of intervening parenchymal tissue, often show diffuse involvement with broadly spread foam cells. Mesenteric and thoracic lymph nodes usually are not involved, apparently because they drain organs (intestines and thoracic viscera) which do not harbor leprous lesions ([53, 71, 177]). Testes and epididymides, as noted long ago by Hansen and repeatedly since, are involved in most instances of lepromatous leprosy, almost all testes showing lepromatous infiltration and atrophy at necropsy. Acid-fast bacilli have been reported in semen. The adrenal glands also frequently contain lepromas and Mitsuda stated that they were always involved if both the liver and spleen showed lesions. Other endocrine glands do not commonly show leprous inflammation. The larynx may be involved and in the pre-sulfone era indwelling tracheostomy tubes were not uncommon in many leprosaria. Lie ([132]), among others, reported tracheal and bronchial leprous infection with local nerve involvement.

Tuberculoid and dimorphous visceral lesions are less well known, in part because these forms of leprosy are often self-healing. The general absence of caseation in leprous lesions, in contrast to those of tuberculosis, permits healing without distinctive scarring. Biopsy studies ([37, 38, 113, 135, 157, 189]) indicate that lesions having granulomatous morphology and epithelioid cells are sufficiently frequent in visceral distribution to be encountered by the biopsy needle and in sternal puncture. Their morphologies correspond with the skin manifestations in the same patients. Bacilli are scarce or not demonstrable by the relatively insensitive histopathologic technics. At a concentration of 10^4 bacilli per gram of tissue, bacilli are not likely to be found in acid-fast stained paraffin section.

Reports on leprosy in lymph nodes are more limited. In a series of nodes examined by Turk and Waters ([204]) no specific leprous lesions were demonstrated in tuberculoid nodes but lesions were found in dimorphous lymph nodes whose morphologies ranged from epithelioid granulomas near the tuberculoid end of the spectrum to lesions with more foamy macrophages toward the lepromatous end. A similar picture seems to obtain in the bone marrow with perhaps relatively fewer lesions being present. Significant lesions of testis and adrenal gland seem not to have been reported in tuberculoid leprosy, though Job and Macadan ([109]) found epithelioid granulomas in dimorphous cases in reaction. Arning ([6]) claimed to have demonstrated visceral tuberculoid lesions from 11 of 17 post-mortem examinations as early as 1898, but it seems that this was not generally accepted, perhaps because there was some caseation necrosis in lesions demonstrated.

Significance of visceral lesions. In reviewing the findings up to 1955 with respect to liver function test results in leprosy, Ross ([172]) concluded that they showed little or only marginal abnormalities. Bechelli and Supuppo ([13]) concluded that though liver lesions are to be found at autopsy in nearly all lepromatous cases, hepatic function is little affected, probably because leprous lesions are predominantly paraportal and lesions in the parenchyma are usually too small to adversely affect function. The fact that caseation necrosis is not a character-

istic of leprous lesions and that *M. leprae* apparently does not exert any direct toxic effects are perhaps also factors. More recently Verghese and Job ([207]), in a correlative study of liver lesion morphology and liver function, noted diminished liver function as estimated by the bromsulfalein test in 6 of 19 cases but found that this was not related to the Bacteriologic Index, the duration of the disease or the presence of lepromas. No study of liver function in instances of *erythema nodosum leprosum* are available. Such study might be rewarding.

Gynecomastia is reported to occur in from 6% to 19% of lepromatous, but not in tuberculoid, patients. Kinnear and Davison ([120]) studied estrogen, gonadotropin and 17-ketosteroid excretion levels as well as liver function in 18 lepromatous patients with gynecomastia, 20 lepromatous cases without gynecomastia, 20 tuberculoid cases and 20 normal control subjects. They noted marked liver dysfunction in lepromatous cases whether or not they had gynecomastia, but could find no correlation between gynecomastia and liver dysfunction or estrogen excretion, or between liver dysfunction and estrogen excretion.

Renal change, usually designated as nonspecific pyelonephritis, is frequently reported in association with leprosy ([218]) and renal failure is reported as a leading cause of death in leprosy. In Oriental populations it is exceeded by tuberculosis as the cause of death, but in Occidental leprosy groups it ranks first, being of higher incidence because of the marked tendency to amyloid involvement in the latter group ([17, 164]). Amyloidosis, being a secondary effect and not a part of direct leprosy change, will not be considered further in this review. Studies on possible pathogenetic mechanisms for renal change are noted below in the discussion on the nature of *erythema nodosum leprosum*.

Severe laryngeal stenosis in leprosy has been referred to above. Blockage of such stenotic orifices has been reported as a cause of death.

As was pointed out at the VIIth International Leprosy Congress ([180]), leprosy patients, especially when the disease is severe or in reaction, present many clinical evidences of being markedly indisposed, including fever, malais and loss of appetite. These signs are nonspecific with respect to any measurable organ function but are summational in response, not only to skin and nerve lesions, but also to visceral insults. The biological entity that is the patient is expressing an awareness of illness, and this expression through loss of appetite and fever, for example, may be reflected in increasing malnutrition which may itself lower the resistance of the patient to his infection.

Pathology and pathogenesis of neural involvement. During the century just passed, neural involvement in leprosy has been a cardinal recognition, so much so that it is not uncommon to read statements to the effect that "leprosy is a neural disease." Bacilli have been demonstrated in virtually all parts of the nerve fiber. Vater-Pacini and Meissner sensory corpuscles have been shown to be invaded and, in time, to become atrophic or to be obliterated ([199, 201]). It has been recognized that sensations of heat and cold are lost before those of touch and pain, but the anatomical basis—if such there be—for this differential remains unclear.

Claw hand

The histopathologic morphology of cutaneous nerves in the various types of leprosy has been described repeatedly ([48, 51, 73]). In tuberculoid leprosy the typical active cutaneous nerve lesion can best be described as a granulomatous replacement of the nerve. Occasional remnants of nerve fibers can be seen, but predominantly there is nodular accumulation of epithelioid cells surrounded by varying intensities of lymphocyte infiltration. Acid-fast bacilli are rarely demonstrable. In lepromatous lep-

rosy the inflammatory process develops more slowly with initial infiltration by acid-fast bacilli and by phagocytic cells. These phagocytes soon become typically foamy, and together with bacilli are found not only in perineurium and endoneurium but also between nerve fibers. Concomitantly there develops a slow fibrous thickening of perineurium and endoneurium, eventually proceeding to complete replacement fibrosis with disappearance of nerve fibers. Often this fibrosis assumes an "onion-skin" pattern.

As might be expected, dimorphous nerve lesions present varied morphologies reflecting the morphology of their associated skin lesions. In early, indeterminate cases, on careful search, occasional acid-fast bacilli may be found, particularly in Schwann cells.

These cutaneous nerve changes are of notable importance in establishing biopsy diagnosis of leprosy and no biopsy report on a skin specimen relating to the problem of leprosy should be regarded as complete if it does not contain reference to the status of the nerves. The tuberculoid pattern of nerve change is of particular importance in the identification of leprosy among the epithelioid cell granulomas of the skin as has recently been lucidly detailed by Wiersema and Binford ([223]).

Brand ([27]), on the basis of a clinical study of over 1,000 cases of paralysis involving the upper extremity, compiled the following pattern of muscle paralysis in these extremities as being characteristic and quite specific.

COMMONLY PARALYZED
- All the intrinsic muscles of the hand: lumbricales, interossei and of the thenar and hypothenar eminences.
- Flexor carpi ulnaris.
- Flexor profundus to 5th finger (less commonly).
- Flexor profundus to 4th finger (rarely).

SOMETIMES PARALYZED (less than 1%)
- All the extensors of the wrist.
- The long extensors of the fingers and thumb.
- Abductor pollicus longus.

VERY RARELY PARALYZED
- Flexor digitorum sublimis, all fingers.
- Flexor profundus, index and long fingers.
- Flexor pollicis longus.
- Flexor carpi radialis.
- Palmaris longus.
- All upper arm and shoulder muscles.

This translates into a recognition that the involvement is primarily and most severely of the ulnar and median nerves, particularly in their branches in the hand, and that the extensors (innervated by the radial nerve) are more commonly involved than the flexors (from the median and ulnar nerves).

No similar evaluation of muscle paralysis in the lower extremity has come to attention. Even without such, the pattern can readily be seen to be similar, with most extensive involvement of the muscles in the feet and of flexor and extensor muscles innervated by the posterior tibial and common peroneal nerves.

A singular peculiarity of lesion distribution in the peripheral nerves has been noted by many observers ([28, 29, 63, 111]). In the words of Job and Desikan ([111]):

> It is well known that certain specific sites in the peripheral nerve trunks are vulnerable to leprosy lesions. The general pattern of paralysis manifested in leprosy suggests that the lesions are largely confined to these sites of predilection, which are as follows: ulnar nerve at the region of the medial epicondyle, and at the wrist; median nerve just above the carpal tunnel; radial nerve at the wrist and slightly above the elbow; posterior tibial nerve at the flexor retinaculum; common peroneal nerve as it turns around the neck of the fibula; facial nerve as it crosses the zygomatic process of the maxilla; and great auricular nerve as it crosses over the sternomastoid muscle.

The question early arose as to whether involvement of these peripheral nerves was due to centrifugal or centripetal spread of the infection. Hoggan and Hoggan ([99]), noting the marked involvement of the ulnar nerve at the elbow, held that the primary affection was in the nerve trunk and the above quotation seems, in part, to reflect this view. The weight of observation and opinion, however, was contrary and Neisser ([154]) as well as Lie ([131]) found for primary involvement of nerves of the skin with slow extension up the major trunks with areas of particular localization as noted.

From this question there followed the presently still unresolved question as to the manner of extension of leprous inflammation in nerves. This process, according to Lie ([131]) is concentrated in the nerve sheaths. On the basis of Gerlach's study of peripheral nerves in a maculo-anesthetic case ([74]), Dehio, his mentor, made the following summary statement at the First International Leprosy Congress in Berlin (1897):

> At first a small area of the skin becomes diseased, and a leprous macule is formed. This area loses its sensitivity, not on account of affection of the corresponding nerve trunk but because the terminal sensory branches in the skin are destroyed. Next there is an ascending degeneration above the macules. Ascending still further this degenerative process involves the mixed nerve trunks. The process develops slowly, and in its course there appear round- and epithelioid-cell infiltration. The muscular branches soon become involved, and finally the process reaches the terminal areas, as for example the bend of the elbow in the ulnar nerve. This leads to degeneration and atrophy of all the nerve branches situated below, though they themselves may be free from the leprous process, and as a result there develop atrophies and mutilations, and anesthesia of cutaneous areas which formerly had not been affected. ([52]).

Ermakova ([63]) recognized the difference between nerve lesions in lepromatous and tuberculoid (maculo-anesthetic) leprosy as early as 1936, noting that the numbers of bacilli in nerves correspond roughly to the numbers in the cutaneous lesions of the same patients, that the infiltrate in lepromatous leprosy is of foam cells while that of tuberculoid leprosy is of epithelioid cells, and that the greater rapidity and intensity of inflammation in the latter leads to early and quicker evidence of impairment while in the lepromatous type the slow organization of the fibrosis results in slower increase in clinical expression.

Leprous nerve abscesses have been found to be relatively uncommon but have been reported as occurring most frequently in the following nerves: ulnar, median cutaneous of forearm, great auricular and sural. They consist of elongated caseous masses within the perineurium, through which they may occasionally rupture. Histopathologically they present a great amount of caseous matter surrounded by typical tuberculoid granulomatous tissue (since they occur in tuberculoid or near-tuberculoid leprosy) with large epithelioid and giant cells. Bacilli are usually not detected.

Discussion continued as to the manner of extension of the infection to nerves, or centripetally in nerves. In the presence of demonstrated bacillemia, the possibility of hematogenous, metastatic foci of infection has not been overlooked. The locales of heaviest involvement in the nerves, as noted above, are areas where the nerves lie closest to the skin and are potentially most exposed to varying degrees of insult or injury. These have been regarded by some as areas of *locus minoris resistentia* ([36, 100]) where hematogenously transported bacilli may be more readily localized. Though such mechanisms are probably operative, they are not adequate for explanation of the slow. progressive extension of infection up nerve trunks. Nor does, for example, the establishment of nerve infection at the elbow level by such a mechanism account for the initial peripheral sensory and motor manifestations with following broadening of involvement. Fite ([69]) was of the opinion that macrophages containing bacilli, for the most part infiltrate the nerves along vascular pathways and along clefts between nerve fibers. Ermakova's description ([63]) is suggestive:

> The number of bacilli found in these nodular cases (referring to lepromatous nerves) is very great. They fill the cytoplasm of the foamy cells and litterally clog the lymphatic spaces, forming dense clumps that appear as globi. In preparations along the length of the nerve it is clearly seen how the bacilli disseminate towards the center from the place of the lesion, especially in the case of lesions in which the presence of bacilli has not yet caused any reaction.

Job and Desikan ([111]) presented a detailed histopathologic evaluation of upper extremity nerves from four lepromatous necropsies. They were impressed with the preponderant nerve involvement at the above noted sites of most intense involvement and it seemed to them that the lesions in nerves are produced by a blood borne infection with localizaton in these areas because, they postulated, following Binford's hypothesis ([19]), *M. leprae* is probably a temperature dependent organism with an optimum temperature for proliferation lying

slightly lower than the normal body temperature. Brand ([28]) had earlier followed a similar path of thought. Whether selective localizaton be due to factors in *locus minoris resistentia*, optimum bacillary growth temperature, or both, the assumption of primary pre-eminent development of lesions in the locales noted does not readily explain the usual pattern of extension of sensory and motor manifestations centripetally from the periphery. In our own study ([185]) of 24 ulnar nerves from 14 necropsies, we found considerably more involvement of nerves in deeper lying areas of the forearm than is usually regarded as being present, and noted extensive spread of infection in both perineurium and endoneurium as well as between nerve fibers. Ermakova ([65]) noted similar involvement of nerves, albeit in other areas. Fite ([69]) dismissed the probability of a lymphatic role in dissemination of infection in peripheral nerves on two counts. His first objection was a quotation from Maximow to the effect that nerve trunks do not have lymphatics. However, though nerve trunks have not been shown to have lymphatics, such vessels seem to be present in perineurium and possibly in endoneurium. Fluid in spaces between nerve fibers may drain into such lymphatics. In any case, bacilli and bacilli-laden cells may well be disseminated by lymphatics and thus localized in perineurium and endoneurium, from whence bacilli may spread directly into tissue spaces or areas or lesser mechanical barrier. The kneading action of muscle movement might help such spread. Fite's second objection was that the perineural spaces are obliterated by fibrosis in leprosy and hence not available for bacillary dissemination. Fibrous obliteration, however, follows on inflammation and inflammation derives from the presence of bacilli. In other words, dissemination occurs before the fibrosis, and the objection seems inapplicable.

Weddell ([220]) reported that even in healthy skin there is a constant process of nerve degeneration and regeneration. He found that such changes are most marked in the growing child and in areas of skin which are subject to friction or mild trauma, such as the skin of the buttocks, back face, knees and elbows. Khanolkar ([116]) cited these observations in postulating, on the basis of his own studies, that *M. leprae* have a predilection for migrating toward degenerating and regenerating nerve fibers. There follow, he stated, accumulations of histiocytes around these foci of bacillary aggregation with invasion and fragmentation of nerve fibers, and from this follows the pigmentary, sensory and related local skin changes. In other publications Khanolkar ([115, 117, 119]) extended his observations and interpretations into the concept that *M. leprae* are taken into the axoplasm of sensory nerve fibers through the growing tip (growth cone) of a regenerating axon. The bacilli are then transported along the nerve axons, almost as if in a stream, and in this fashion reach the dorsal root spinal ganglia. They may break through the axon and be taken up by adjacent Schwann cells and also by histiocytes which invade in response to their presence. Type-typical skin and nerve lesions then develop depending on the host's immunologic capacity.

Weddell ([219]) and Lumsden ([138]) have also conducted extensive studies on nerve involvement in leprosy, and entertain similar concepts regarding the prime importance of Schwann cells in this neural engagement. Lumsden argued that, aside from the skin, the bacilli are enormously preponderant in peripheral nerves as compared to tissues (questionable in the ligh of the above review of visceral involvement) and that this predilection for peripheral nerves reflects centripetal neural spread, as opposed to hemic dissemination. He further held that the bulk of bacillary spread and multiplication occurs along the columns of Schwann cells enveloping the individual nerve fibers, and not intra-axonally as suggested by Khanolkar. He indicated that lepra cells in nerve trunks are altered Schwann cells, as has been held also by others though many will probably not agree that they are only of Schwann cell derivation, and that Schwann cells investing the non-myelinated filaments of the sensory cutaneous plexus provide the main reservoir of macrophages forming the dermal lepra cells. He carried the hypothesis

to the point of speculating that possibly during the incubation period of leprosy there are "sporadic caravans of Schwann cells migrating through the epidermis to the nerve plexuses, transporting their modest burdens of innocuous bacilli destined eventually to devastate the peripheral nervous system by growing within Schwann cells and being handed on from Schwann cell to Schwann cell." Weddell and Palmer ([221]) also concentrated attention on the role of Schwann cells but hypothesized that:

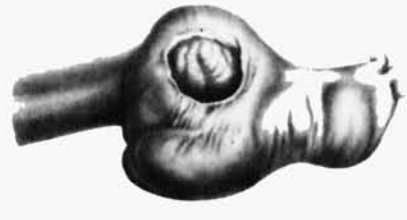
> *M. leprae* invade the body by the blood stream, by inoculation through the skin and, although we have no evidence for this, through the lungs and the intestinal walls. . . . Once in the blood stream the organisms are carried to their target organ, the Schwann cell of the sensory nerves, in which they lie protected by the basement membrane . . . and multiply. . . . Those Schwann cells which lose their protective basement membrane and assume the role of phagocytes proceed to remove both the neural debris and microorganisms from the Schwann cells related to the degenerating nerves. If the number of organisms they contain is few then we can assume that the phagocytes will be able to digest them and dispose of them and thereby acquire further antibody, if natural immunity is present. This will presumably result in the subject becoming lepromin positive and they will exhibit no lesions. . . .

These views of the role of the Schwann cells are perhaps a little too exuberant for general acceptance, but there is no denying the increasing recognition of the fact that Schwann cells play a significant role in nerve involvement by *M. leprae* as is being brought forth by electron microscopic studies, too many and detailed for review in this presentation.

Neural involvement occurs in experimental mouse foot pad infection with *M. leprae* and also in the armadillo infection. The involvement, however, is relatively late in the course of the infection and relatively mild as compared to the general involvement, particularly in the armadillo. It would seem that in these animals, though Schwann cells are involved, their role is not as dominant as claimed in the above hypotheses. Likewise, the heavy involvement of lymph nodes, liver and spleen in lepromatous leprosy speaks to histiocytic macrophage involvement rather than a dominant Schwann cell milieu.

Involvement of the nervous system other than that of the peripheral nerves has occasionally been reported. At the beginning of the century under review there was considerable discussion concerning the possible relation between syringomyelia and leprosy but this concept was discarded. Another discussion concerned the reported findings of degeneration in the posterior columns of the spinal cord, but this was in due course recognized as probably being due to concomitant syphilis. The occurrence of bacilli in the spinal, Gasserian and other ganglia in cases of heavy infection has been established. The central nervous system, however, is not significantly involved though occasonal findings have been reported. Thus, de Beurmann and associates ([18]) reported an instance of leprous meningitis and pleuritis, and Hirai and co-workers ([97]) recently reported an instance of fatal leprous bulbar palsy.

Pathology and pathogenesis of deformity. The crippling and mutilating effects of leprosy in general, regardless of classification type, have long been recognized and several are illustrated in the atlas by Danielssen and Boeck.



Deformity of foot

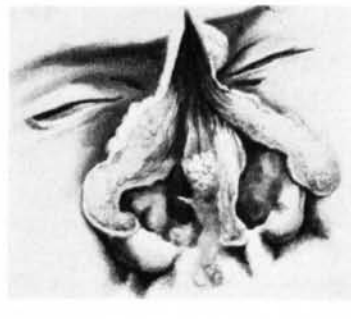
The pathogenesis of scar formation and its effects is not difficult to understand, nor is the passage of the pathogen to tissues where such effects may be important when the mode of passage is hematogenous or lymphatic. The same is generally true for scarring and damage secondary to loss of function such as nerve damage paralysis of eyelids and the effects of entropion and lagophthalmos, as well as the effects of foot drop, claw hand and other sequelae of motor paralysis.

Less easily explained is the presence of leprosy bacilli in nonvascular tissue such as portions of the eye. Here characteristics of *M. leprae* provide a clue, though experimental verification is lacking. An organism of generally agreed low virulence, it is also an organism which, except when developing or developed hypersensitivity and immunity is a factor, also incites only low grade inflammation and thus low grade obstruction to its passage. This is in marked contrast to the response, for example, to pyogenic staphylococci where mechanisms such as the development of a "pyogenic membrane" and local vascular thrombosis as well as tissue destruction and extensive death of inflammatory cells are striking features. In all probability factors such as the massaging effect of muscle and other tissue movement on intercellular fluid, as well as otherwise induced tissue and organ fluid movement, may facilitate spread of the bacillus. Additionally, this pathogen sheds, with or without enclosing cells, from surfaces such as the palpebral conjunctiva, the endothelium of Descemet's membrane of the eye, the retina (148, plates 17 and 18) and possibly the epidermis. Bacilli may well be moved about, for example, by motion in the vitreous body.

In the face, eyes and extremities deformities have in general been found to be due to direct leprosy infection, secondary infection, and to the sequelae of loss of nerve function, both sensory and motor. Implicit in direct leprous infections are the consequences also of inflammation enhanced by either immediate hypersensitivity, delayed type hypersensitivity, or both. Generally speaking, the consequences of immediate type hypersensitivity are most pronounced in lepromatous infection, and of delayed type hypersensitivity in tuberculoid leprosy, while both types of hypersensitivity seem to be operative in dimorphous leprosy in varying proportionalities (*vide infra*).

Detailed understanding of these processes in the various affected parts of the body is now too extensive to be here reviewed, apart from a brief assessment. The effects of motor paralysis are illustrated by lagophthalmos and its sequelae as well as by paralysis of lower extremity muscles with resulting foot drop and *pes abductus* or *adductus* with their instabilities and deformties. Complications of anesthesia are evident in injuries to feet by nails or stones and to hands by cigarette burns or work abrasions, from all of which ulcers with localized or spreading secondary infection may develop. Less apparent, but of considerable significance, are pressure atrophies and ulcerations that may occur from too long standing in one position on insensitive feet, or from the intense pressure that insensitive hands may exert in the holding and handling of tools.

Many of the pathogenic mechanisms of deformity are well illustrated by bone changes in leprosy. Möller-Christensen (151) discovered and worked on what is probably the oldest leprous material available when he found and studied skeletons in a leprosy graveyard at Naestved, Denmark, dating to the 13th and 14th centuries. Making a diagnosis on the basis of the well-known and characteristic osseous changes in hands and feet, Möller-Christensen (150) called attention to skeletal changes which he designated as *facies leprosa*. These changes are characterized by atrophy of the anterior nasal spine, either alone or combined with central atrophy of the central maxillary process, and always in addition, inflammatory changes in the superior surface of the hard palate (209). Hjörting-Hansen and associates (98) reported the presence of intraosseous leproma in such a case, suggesting that specific leprous osteomyelitis may be a pathogenic mechanism in addition to the previously postulated pressure effect of adjacent tissue inflammation (209). Additionally, in lepromatous leprosy there may de-



Leprosy of nose with septal perforation

velep a "saddle nose." Antia ([4]) noted that lepromatous infiltration of the nasal mucous membrane ulcerates, leading to exposure and loss of blood supply to the underlying cartilage and bony framework of the air passages. This is aggravated by secondary infection, the combined processes leading to "exposure necrosis" of cartilage and bone with perforation and complete collapse in more advanced cases. What contributing effect neural involvement may have is not known.

"Saddle nose"

The pathogenesis of skeletal deformity of hands and feet in leprosy was studied as early as 1886 by Heiberg ([96]) who assumed that the changes were due to neurotropic disturbances, as indeed they are in major measure. The term "neurotropic" has been widely used in leprosy studies but has never had any specific pathogenic explanation, and the road to reasonably approximate understanding was to be a long one. Concentric atrophy of bones, mainly of phalanges, was described by Harbitz ([93]) in 1910. He attributed the change to nerve implication. It was thought by many that there was no actual leprous infection of bones but in 1948 Erickson and Johansen ([62]) reported leprous bone infection with cyst formation and leprous periosteitis and in 1963 Job ([108]) demonstrated that the roentgenologic bone "cysts" were due to destruction of bone trabeculae by lepromas. Paterson ([161]) and Lechat ([130]) each published reports of comprehensive roentgenologic studies from which classifications were derived of the multifaceted factors which play a role in the observed changes. By angiographic studies Paterson ([160, 161]) additionally demonstrated marked vascular dilatation and other changes associated with bone resorption. Johnson ([112]) in 1964 suggested that such vascular changes are probably basic to the neurotropic effect on bone changes and Skinsnes and associates ([187]) have supported this conclusion on the basis of morphologic study of whole specimen large histopathologic cross-sections of a number of amputated extremities. The dictionary definition of neurotropism as relating to "the nutrition and maintenance of tissues as regulated by nervous influences," thus takes on meaning as relating to vascular changes secondary to change in the vascular neural reflex arc. Passive hyperemia with its high tissue fluid protein and low oxygen tension associated with slow flow rate induces osteoblastic activity whereas active hyperemia with its high oxygen tension and elevated metabolic activity supports and induces osteoclastic activity and bone resorption. In normal bone metabolism both processes are in balance, this balance being maintained by neurovascular control. With the loss of such control and the resulting dilation of supplying arterioles in leprosy, the balance is thrown to the side of osteoclastic resorption. Of course, this balance is also influenced by the other factors of local inflammation, secondary inflammation, abnormal pressures and strains as alluded to above.

IMMUNO-PATHOLOGY

In large measure, the understanding of immunologic mechanisms in leprosy has its basis in the development in understanding of morbid anatomy just reviewed. This has come chiefly from comparisons between the manifestations of the contrasting polar tuberculoid and lepromatous types.

Lepromin and the search for immunity. Yoshinubu Hayashi, then first assistant to Kensuke Mitsuda at the Zensei-en prefectural leprosarium near Tokyo, in attempting to grow leprosy bacilli by incubating

thin slices of lepromas in Ringer's solution produced a suspension of bacilli so obtained. He sought a test analogous to the tuberculin reaction and expected to obtain a strong reaction in lepromatous patients and weakly positive reaction in neural-type cases. The results were completely opposite, the lepromatous patients giving few positive and many negative responses. He published these results in 1918 ([95]). Mitsuda took up the matter, developing the prototype of lepromin as it is usually made, and observed the reactions during the first few days and in subsequent weeks. Thus he discovered the delayed reaction which appears at three to four weeks in what are now known as tuberculoid cases—the reaction which bears his name and which he reported in 1919 ([149]) and not in 1916 as later erroneously stated, and subsequently widely quoted, by a then junior assistant Fumio Hayashi ([94]). This work was unknown outside of Japan until Mitsuda reported it at the Strasbourg Conference in 1923. In the following three years there appeared four reports of similar work by Mariani ([142, 143]) and Bargehr ([11, 12]). They did not mention Mitsuda's report and it is not known if they were influenced by it.

Mitsuda considered the possible use of lepromin in the diagnosis of *L. nervosa* (high resistance leprosy) as it was then designated, but found against it because he found also that some persons not having leprosy gave a positive reaction. He also considered its possible value as an immunizing agent, bnt there is no evidence that he pursued the matter. Bargehr ([11]) in Indonesia, with whom the term "lepromin" originated, undertook to immunize nonreactive persons by repeated inoculations. He induced lepromin reactivity in most of his subjects, with more success among adults than children. Subsequent studies were sporadic with equivocal results and handicapped by the difficulty of obtaining an adequate amount of lepromin for a mass trial. The long incubation period of leprosy also presented a serious handicap to evaluative study. Attention shifted to studies in children, centered about the possibility of achieving lepromin conversion to positivity by repetitive lepromin inoculation. A number of studies were carried out ([103, 127, 190, 191]) but the results were inconclusive there being some who became lepromin positive but many who remained negative. Theoretical considerations also militated against the use of lepromin for immunization since it is difficult to see how patients prone to develop lepromatous leprosy and who then are incapable of developing lepromin-type reaction in the presence of large quantities of bacilli and bacillary products in their tissues can be expected to develop hypersensitivity or resistance to the relatively minute quantities of materials, heat altered as well, present even in repeated injections of lepromin. Lepromin thus failed to reveal itself as a useful and practical immunogenic agent.

In the meanwhile another concept came to the fore when Fernandez ([67]) in 1939 reported vaccinating with BCG a group of orphanage children, who were negative to both tuberculin and lepromin and who had had no contact with leprosy. Of the 123 children only ten (8%) remained lepromin negative one month later while 113 (92%) were positive to some extent, 87 (71%) being definitely so. Many investigators, prominent among whom were Ginez and Poletti, Souza Campos, Chaussinand, Floch and Camain, and Azulay, took up the study. These earlier studies were well, though briefly reviewed by Wade ([214]) and by 1953 Souza Campos ([192]) who cited 81 pertinent references in his review. Doubts remained as to the effectiveness of BCG vaccination, some workers being unable to see any strong correlative relationship while a strong school of supporters, particularly in South America, found hope in the possibilities of BCG and strongly urged its use. Low and McNulty ([136]) posed the question, "Can BCG be recommended in the prophylaxis of leprosy? The evidence is incomplete and some of it appears contradictory. There still remains doubt in the minds of some workers whether a positive lepromin test (particularly if induced by BCG) really indicates immunity." A major problem lay in the lack of adequate controls in most of the studies and another problem related to the absence of a suitable animal model in which controlled studies could be carried

out. Hanks and Fernandez ([88]) improvised such a model by using murine leprosy. This model also posed the dilemma, as Hanks ([89]) later summarized it, "The most significant point in regard to immunization against murine leprosy is the fact that, even after using an efficient method for elevating immune response, the most susceptible animals remain so incompetent. Once disease was detected, these animals developed fulminating infections. Despite some delay in onset of the disease, they did not perform as well as the more capable individuals which had received no prior immunzation." In this respect the animal model reflected significantly the problem of attempting to immunize a potentially lepromatous individual.

In 1955 Chaussinand ([41]), while one of the originators of the theory that tuberculosis gives some immunity to leprosy ([40]), called for controlled studies that would solve the problem. Three field studies, designed with controls, were initiated: one was begun in Uganda in 1960, the second in Eastern New Guinea in 1962 and a third in Burma in 1964. These studies have not yet run their course, but the preliminary results do not suggest that BCG will have substantial immunizing effects and the WHO Expert Committee on Leprosy ([222]) judged in its report of 1970 that it was premature to recommend general use of BCG vaccination and recommended that the studies be continued for at least ten years.

Understanding of the lepromin reaction was proceeding apace. Fernandez ([66]) studied and described the early 24-hour reaction to lepromin which bears his name and which is analogous to the tuberculin reaction. Dharmendra ([55]) prepared a purified lepromin, or leprolin, by chemical fractionation of *M. leprae* and isolated a protein antigen which gave the early (Fernandez) delayed type of reaction. It soon became evident that the Fernandez reaction was an expression of already existing delayed type sensitivity while the Mistuda reaction, occurring either in non-hypersensitive persons or in persons already hypersensitive, provided a measure of the potential ability to develop hypersensitivity ([212]), and presumably associated immunity. This distinction is not always recognized or utilized in research work and publications often fail to mention which type of lepromin and reaction is being utilized. The classical Mitsuda type antigen and the Mitsuda reaction is that most commonly utilized and has been shown to have prognostic significance ([193]).

There was a great deal of debate about the lepromin reaction and lepromin, many decrying lepromin as being an unreliable suspension of bacillary products and tissue debris. Dharmendra's work and long practical use and study by many has demonstrated that the lepromin test has biologic significance. Though there was disappointment that it was not a diagnostic test, because it was negative in lepromatous leprosy the most malign form of the infection, it has come to be recognized that the reason the test can not be diagnostic is that a segment of the leprosy immunologic spectrum is virtually pathognomonically characterized by an inability to develop cell-mediated immunity and delayed type hypersensitivity ([181]). Through this identification, when accepted and understood, the lepromin test lays the foundation for an understanding of the immunologic dichotomy in leprosy.

The immunologic dichotomy in leprosy. When contemplating the immunologic diversity of manifestation in leprosy one might be surprised by the perceptiveness of Leloir who in 1885 stated, "There is only one leprosy, variable in evolution," were it not for the fact that even in primitive societies there seems to have been no difficulty in recognizing leprosy as leprosy regardless of its variance. This is probably so because of the unifying involvement of peripheral nerves and attendant deformities, which is characteristic of all leprosy, whether or not skin lesions are present, absent or variable in appearance.

The morphologic expression of this dichotomy has been traced, in part, in the above description of the evolution of the classification of leprosy and the recognition of the morphologic distinctions of its polar types. Recognition of the immunologic basis for this morphologic dichotomy was slow in evolving, in large measure because

TABLE 1. *Characteristics of immunologic dichotomy.*

Tuberculoid	*Lepromatous*
Localized, well-defined, circumscribed lesions	Extensive, diffuse, poorly-delimited lesions
Few bacilli demonstrable	Myriads of bacilli
Intense macrophage (epithelioid) cell response with effective phagocytosis and disposal of bacilli	Abundant macrophage (foam cell) response, with efficient phagocytosis but ineffectual disposal of bacilli
Lepromin reaction (cellular hypersensitivity) positive	Lepromin reaction negative
Granulomatous inflammation	True granuloma generally absent
Circulating (humoral) antibodies insignificant or poorly demonstrable	Humoral antibodies (to polysaccharides) readily demonstrable
Immunologic "reactional" exacerbations characterized primarily by reactions of cellular hypersensitivity	Immunologic "reactional" exacerbations (e.g., *erythema nodosum leprosum*) characterized primarily by the reactions of immediate type (anaphylactoid) hypersensitivity.
Effective accelerated therapeutic response to specific therapy	Sluggish therapeutic response

immunologists on the whole, until the 1950's and 1960's, in major measure thought of biologic immunity largely in terms of humoral antibodies. The manifestations now regarded as cell-mediated immunity were generally thought of in concepts of antibodies adherent to cells or possibly held within cells.

Lowe (137) in 1955 first delineated the dichotomy in pointing out the then remarkable observation that in lepromatous leprosy, though antibodies were abundantly demonstrable, the body is unable to dispose of the leprosy bacilli, whereas in tuberculoid leprosy bacilli are readily overcome in the absence of demonstrable humoral antibodies. The tuberculoid manifestation thus is similar to the situation which was well-known in tuberculosis but in tuberculosis there is no counterpart to the situation in lepromatous leprosy (181). Wilson (224), at about the same time, pointed to a similar immunologic dichotomy in coccidioidomycosis and other systemic fungal disease. Hanks (89), in discussing this dichotomy in leprosy, noted, "The fact that both types of immune response are exaggerated by lipo-polysaccharides, and tend to be sequential, is small reason for a persistent faith that cellular allergy must be explained in terms of 'anti-body precursor' or 'intracellular antibody'. Such conviction implies that the varied systems in tissue cells exist solely in order to embroider the hems of globulin molecules."

The main manifestations of the immunologic dichotomy may be succinctly summarized as in Table 1 (186).

Namba and Fujiwara (152), Hoxter *et al* (101), and Ishihara (105) reported on electrophoretic studies of serum proteins and, in general, agreed that there was an increase in gamma globulins in lepromatous leprosy but a normal pattern in nonlepromatous cases, and that in the former the albumin/globulin ratio was below 1.0. Several quantitative studies of immunoglobulin fractions have been reported (32, 107, 133). The findings varied and are difficult to compare because of differences in experimental design, including duration of treatment of the subjects. In general, Lim and Fusaro (133) found elevation of IgG and IgM in lepromatous patients while in tuberculoid cases there was elevation of IgG and IgA. They concluded that the patterns were "distinctively different" in the various forms of leprosy. Jha and associates (107) noted elevation of IgG and IgA but not of IgM in lepromatous cases whereas in tuberculoid only IgG was elevated. Bullock *et al* (32) reported elevation of all three fractions in lepromatous patients with a tendency for IgM to decline significantly under prolonged therapy, but found no elevation in any fraction in tuberculoid leprosy.

Evidence for the major role of cell-medi-

ated immunity in tuberculoid leprosy was slow in recognition. Initially the understanding was based largely on histopathologic morphology compared with that of granulomata such as tuberculosis, and by contrast with the histopathology of lepromatous leprosy. The contrast in the lack of demonstrable humoral antibodies in tuberculoid as compared to lepromatous leprosy played a role. The first experimental demonstration reported, though too early to be placed in the context of cell-mediated immunity, was the tissue culture demonstration of variant tuberculoid and lepromatous fibroblast response to leprosy bacilli by Hanks [87] in 1947. Davey [49] in his 1946 review spoke of the significance of allergy in tuberculoid leprosy but thought of allergy in terms of antibodies and stated, "Clinical tuberculoid leprosy arises when the original concentration of antibody in the skin has fallen to an ineffective level." Lowe [137] in presenting the concept of the dichotomy in leprosy at a joint tuberculosis and leprosy symposium in 1955, while rejecting the role of circulating antibodies to polysaccharides as significant in the defense against leprosy, spoke of sensitization of cells by whole bacilli as constituting the main factor in the resistance to *M. leprae*. Hanks [89] in 1961 disavowed the role of antibodies and defined cellular allergy as an antigen-specific, physiologic alteration of mesenchymal cells which improves their capacity to hydrolyze bacterial cell walls and is associated with the synthesis of factors which create and transfer tuberculin type hypersensitivity. He further postulated that, "The apparent dichotomy between skin reactivity and serological reactivity in leprosy disappears the moment it is recognized that skin reactions titrate response to protein moieties [It will be recalled that Dharmendra [55] found a protein to be responsible for the lepromin reaction—author] of the microbe, whereas the serological reactions studied to date seem to be the titrations of antibodies against polysaccharides." Navalkar [153] recently demonstrated two polysaccharide antigens, designated *beta* and *delta*, and the probability of a protein antigen derived from *M. leprae* or BCG and which elicted Fernandez reactions in leprosy patients. This protein gave evidence of leprosy bacillus derivation.

By 1964 a review of the immunologic spectrum of leprosy [179] was able to delineate and present postulates regarding the dichotomy found in leprosy in terms of "cellular immunity" and "humoral antibody immunity."

The dichotomy in polar type lepra reactions. Exacerbations and reactions in leprosy were repeatedly referred to in the older literature as being the result of allergy or immune reactions, but the nature of these were obscure. The advancement in understanding of the morphologic manifestations of hypersensitivity reactions due to antigen-antibody reactions, received much impetus from the study of hypersensitivity reactions to sulfa drugs and of "serum sickness" and related processes, and was complemented by developing understanding of the morphologic characteristics of delayed type hypersensitivity. In general these characteristics are as outlined in Table 2.

On the basis of comparative histopathologic morphology [64, 110, 139], clinical characteristics and analogy with the histopathologic morphology of the Mitsuda reaction, it was possible by 1964 [179] to venture the opinion that *erythema nodosum leprosum* and other evidences of immunologic reactions in lepromatous leprosy are an expression of antigen/humoral antibody reaction or, in present day parlance, an "immune-complex" reaction, while the reaction in tuberculoid leprosy is an expression of delayed type hypersensitivity. It was further postulated that reactional states in dimorphous leprosy are difficult to analyze histopathologically because they probably represent various admixtures of immediate and delayed type hypersensitivities. Recently Bonomo and associates [26] demonstrated the presence of the mixed IgM-IgG globulin type in lepromatous serum, and owing to the antigammaglobulin activity consistently detected in the IgM fraction, such cryoglobulins were considered to be immune complexes of the IgG/anti-IgG type. Waters *et al* [217] by immunofluorescent studies of *erythema nosodum leprosum* found, in skin biopsies from 20

TABLE 2. *Histopathologic characterization of immediate and delayed type hypersensitivities.*

Immediate type hypersensitivity	*Delayed type hypersensitivity*
Vascular endothelial damage	Accumulation of lymphocytes and macrophages around vessels in close relation to antigen containing tissues
Necrotizing inflammatory vasculitis	Further increase of these cells by proliferation or accumulation
Focal necrosis from arteriolar and capillary thrombosis	Tendency for macrophages to become epithelioid
Focal degeneration of collagen	Direct destruction of antigen containing elements by macrophages
Purpura	Development of granulomatous type of inflammatory response and death of sensitive cells with resultant tissue necrosis, which may be caseous in some instances
Tissue eosinophilia	Sparsity of plasma cells
Polymorphonuclear response	Often an accumulation of lymphocytes
Often the presence of plasma cells	

of 38 ENL patients, that the lesions contained both immunoglobulin and complement (BIC/BIA globulin), whereas control biopsies from 13 lepromatous patients not suffering from ENL were uniformly negative. Previously Azevado *et al* ([7]) had demonstrated significant reduction in serum complement during ENL reactions. Waters *et al* ([217]) in studies of lymph nodes obtained from 15 dimorphous patients undergoing reaction found paracortical area changes which they considered compatible with changes in cell-mediated immunity. Findings such as these have recently raised speculation as to the possibility of "immuno-complex" reactions playing a role in the pathogenesis of renal disease in leprosy, but no published evidence of this is presently available.

Genetic relationship in immunity. The studies on possible familial and racial susceptibility or resistance to leprosy are too numerous to review here, save for a brief mention of some seemingly accepted relationships. Danielssen and Boeck in 1848 noted that of 68 patients with anesthetic type leprosy, 58 were related to others having the same type; of 145 who had what is now termed lepromatous leprosy, 127 had relatives having the same type. One hundred and twenty-five years later Balina and associates ([9]) reported statistically significant correlation between lymphoblast transformation response to PHA (phytohemagglutinin) and lepromin in lepromatous patients and their healthy consanguinous offspring (sons and grandsons). The authors recognized that their suggestion that this finding supports the concept of a genetic basis for susceptibility is tentative. Cochrane ([43]) in 1935 noted that Africans living in the West Indies developed forms of leprosy characteristic of Africans living in their native land and similarly Indians and Chinese showed forms of leprosy found in the native populations of India and China. In 1947 he stated ([44]) that Europeans and Mongoloids are more likely to contract the lepromatous form of the disease than are Indians or Africans. These subjects seem not to have received as much study in recent years as previously, but there seems to be a general recognition that there is probably a genetic basis for susceptibility to leprosy. Thus far no significant relationship has been shown with genetic markers such as the various blood groups. The reader is referred to the reviews by Spickett ([194, 195, 196]). He concluded ([197]) that, "it is now apparent that resistance and susceptibility to leprosy are, in part, attributable to genetic variability in the human host. It has been shown that a single irregularly dominant gene controls susceptibility to leprosy and that penetrance of this gene varies between population. Although the main effect is due to a single gene, irregular dominance and variation in penetrance

between populations implies a strong possibility of there being other genes influencing susceptibility."

The immunologic defect in leprosy. In 1965 Wade ([216]), in his last but two editorials, demonstrated his continuing perspicacity by reviewing the concept of lysosomes, relating these to possible significance in leprosy, and introducing this concept to the pages of this JOURNAL for the first time. In the meantime Brieger and Allen ([30]) in electron microscopic studies of lepra cells had noted in these cells well-defined osmiophilic cytoplasmic inclusions closely resembling the lysosomal bodies described previously by Novikoff and Essner in Kupfer cells in the liver, and Nishiura ([155]) and Imaeda and Convit ([104]) had described similar structures under the designation of opaque bodies. The study by Brieger and Allen ([30]), though conducted in part on the electron microscopic, in-so-far as it related to localization of acid phosphatase in the lepra cell was less precise in that it was carried out at the light microscope level. Subsequently Aquino and Skinsnes ([5]) utilized a cytochemical method to determine the ultrastructural localization of acid phosphatase and concluded that the degeneration of bacilli in globi and in foam cell lepromatous inclusions is not due in major part to enzymatic digestion. Some slight lysosomal activity noted was compatible with the concept of probable cellular activity compatible with inherent immunity but not what might be expected if enhanced cellular immunity includes an increase in lysosomal activity. Similar tuberculoid epithelioid cell studies have not been completed. Yang and Skinsnes ([227]), however, utilizing murine leprosy in mice as a model, found that peritoneal macrophages of immunized mice responded to infection with greater intracellular acid phosphatase, lipase and esterase activity than did non-immunized and protein-starved animals. The macrophages of the immunized animals, as studied by electron microscopic, radioautographic technics, incorporated isotope labeled amino-acid into protein which had the lysosomal enzyme distribution pattern and which followed the same path as lysosome transportation leading to phagocytic vacuoles. Hadler ([80]) utilized guinea pig and rabbit response to *M. leprae* and *M. lepraemurium* to simulate tuberculoid leprosy, and a similar rat model to simulate lepromatous leprosy. The former responded with epithelioid cells which were able to lyse the phagocytosed mycobacteria and displayed a high degree of alkaline and acid phosphatase activity. These cells quickly split off lipids, reflecting a high degree of lipase activity. In the rate the macrophages were unable to lyse the phagocytosed mycobacteria, showed feeble alkaline and acid phosphatase activity, and the cells transformed into lepra-like cells containing a great amount of bacilli and lipid droplets within the cytoplasm.

Barbierri and Correa ([10]), utilizing tissue cultures of human white blood cells, 35 of which were from tuberculoid leprosy, 40 from lepromatous patients and 50 from healthy persons, found that macrophages from tuberculoid and from lepromin positive healthy persons showed lytic activity against autoclaved *M. leprae* whereas those from lepromatous and Mitsuda negative healthy persons did not. Beiguelman ([14, 15]) showed similar results with macrophages from tuberculoid and lepromatous patients. Godal and Rees ([75]) in a study of five tuberculoid and five lepromatous patients were unable to confirm these findings. Nevertheless, Pisani and associates ([163]), from similar continuing studies involving 10 lepromatous, 10 tuberculoid, 10 dimorphous, 17 indeterminate and 7 cases of uncertain classification and utilizing a refined technic, report that tuberculoid macrophages showed lytic activity while lepromatous macrophages did not, and that dimorphous macrophages were predominantly weakly lytic while indeterminate type macrophages were represented by all three types of reaction.

General interest in the concept of cell-mediated immunity and delayed hypersensitivity received considerable stimulation from the promulgation of the clonal selection theory of acquired immunity by Burnet ([35]). This was followed rapidly by recognition of some disorders of the immune system and the discovery of the essential role of the thymus in developmental im-

munobiology ([79]). The earlier discovery by Landsteiner and Chase ([126]) that delayed hypersensitivity can be transferred by cells from sensitive to non-sensitive animals, and the demonstration of the transfer factor by Lawrence ([129]) were highly provocative. This burgeoning interest in, and understanding of, cell-mediated immunity and related phenomena has swept into the field of leprosy research and many have come to realize that in leprosy there is a unique immunologic spectrum covering both humoral antibody immunity and cell-mediated immunity, all in a single host species as a response to a single pathogen. Already the literature is too vast for comprehensive review in this presentation. Thus, concepts and technics relating to autoimmunity, immunologic unresponsiveness (tolerance), transfer factor, transplantation immunity, immunologic injury, immuno-suppression, immunologic reconstitution, lymphocyte factors, are all being examined and increasingly utilized in the investigation of the immunologic defect in leprosy. Only a few indicative lines of approach can be here touched on for the answers are not yet in, and despite hypotheses postulated, the nature of the defect is not yet evident.

A considerable number of recent reports provide evidence that in lepromatous leprosy as compared to tuberculoid there is a significant failure to develop contact hypersensitivity ([31]), a defective lymphoblast transformation ([58,85,159,226]), prolonged survival of skin allografts ([82]), defective capacity to induce the lymphocyte transfer reaction ([83]), limited capacity to produce lymphotoxin in response to both the specific antigen leprolin and the nonspecific agent PHA-M ([84]), as well as depressed production of the macrophage migration inhibitory factor ([81]). The persistence of hepatitis-associated antigen, Australia antigenx ([23, 24]), in lepromatous leprosy has also been associated with a depression of cell-mediated immunity.

The possibility of increased risk of cancer morbidity in leprosy as a possible expression of impaired cell-mediated immunity has been examined. An early study of the relationship of cancer to leprosy by Soegaard ([188]) in 1910, found only 19 cases of cancer in 2,269 leprosy patients in Norway. He concluded that leprosy patients were relatively immune to cancer, and the findings of Toyama ([202]) in Japan in 1913 seemed to confirm this concept. The concept that leprosy confers some degree of immunity to cancer was generally held, despite contrary reports to the effect that cancer in leprosy did not occur to a lesser extent than in the normal population, until 1937 when Martins de Castro and Martins de Castro, Jr. ([144]) published the highest series of leprosy associated cancers thus far recorded. In a review of the relationship of malignant tumors of the skin and leprosy Michalany ([145]) in 1966, reported 539 skin malignancies among 60,000 histopathologic examinations, the greater part of which were for leprosy diagnosis and follow-up. He did not record the total number of patients represented by the examined material, but did note that 37.5% occurred in lepromatous leprosy. Rodriquez *et al* ([170]) reported six cases of leprosy developing malignant lymphomas 10 to 20 years after the apparent onset of leprosy and suggested that this association may be frequent. That, however, is not borne out in the necropsy studies noted above. Oleinick ([158]) did not find such an association in his review of cancer morbidity in patients at Carville and concluded that there was no significant excess of cancer mortality among leprosy patients.

Correlative concepts relating to the immunologic defect in leprosy. Godal and associates ([77]), accepting the lymphocyte transformation test as a measure of immune response to *M. leprae*, found similar test responses in healthy leprosy contacts and tuberculoid cases and wondered at why, since the test results were similar, some persons developed the disease while others did not. Hypothesizing from this and related information they postulated that the eventual result of contact with a challenge dose of *M. leprae* is a function of the time required by the host to initiate the immune response. If the response is early, bacilli are eliminated and no lesion occurs. If the host responds late (say 2-3 years) the bacilli will have time to multiply to such an extent that when the immune response is

triggered, a lesion will appear. The longer the time taken before the immune response is established, the closer the leprosy type will be to the lepromatous pole (say 5-20 years). In another publication ([78]) it is held that lepromatous leprosy, when developed, represents a state of immune tolerance ('Central failure'). Possibly pertinent literature on leprosy in children and infants is difficult and not extensive. Nolasco and Lara ([156]), however, reported an autopsy on a 17 month old infant in whom lepromatous lesions were found in skin and one lymph node. They reference other cases which may have a bearing on the hypothesis. In any case, further information from leprosy in young children as well as other early cases of leprosy would seem desirable. Interestingly, Ryrie ([173]), 24 years earlier considered a similar time relationship, expressed in different terminology and utilizing the first lesion as a starting point, came to a virtually opposite conclusion on the basis of considerable long clinical experience.

Turk and Waters ([204]) presented a widely quoted report on 77 lymph nodes garnered from 62 leprosy patients representing the whole spectrum of leprosy immunity. They found that in lepromatous patients the paracortical areas were infiltrated by macrophage-like cells which failed to eliminate bacilli. Increasingly, toward the tuberculoid pole, histiocytes were more differentiated, eventually appearing epithelioid and this was paralleled by increasing numbers of small lymphocytes, while in tuberculoid lymph nodes the paracortical areas were well developed and populated with lymphocytes and immunoblasts. The lymph nodes thus reflected the well known histopathologic morphology found in the skin across the leprosy spectrum. This is, of course, not unique to the lymph nodes. In-so-far as autopsy and biopsy evidence is available, the immunologic spectrum is reflected morphologically in the leprous lesions in the viscera generally. The significance of the lymph node involvement ([203]), the authors postulated, lies in the role of lymph node cortical lymphocytes in cell-mediated immunity. They suggested that when leprosy develops in patients having a genetically determined intrinsic constitutional defect the pathogen is allowed to proliferate to such an extent that a state of specific immunologic tolerance develops. This state affects the cell-mediated immune process only leaving humoral antibody producing mechanisms intact. Nonspecific impairment of cell-mediated immunity (e.g. hypersensitivity to DNCB; 2-4 dinitrochlorobenzene) would then be a secondary rather than a primary event, and would be the result of the replacement of those parts of the lymphoid tissue where lymphocytes proliferate during the development of a cell-mediated immune response, by macrophages containing mycobacteria. This would explain the continuing antibody formation in lepromatous leprosy and therefore the occurrence of *erythema nodosum leprosum*. A problem arises in this interpretation in its apparent assumption that the findings in biopsied lymph nodes from areas usually draining leprous lesions is representative of the lymphoid tissue generally. As noted above, the available autopsy studies on leprosy patients indicates that, even in advanced lepromatous leprosy, the thoracic and mesenteric lymph nodes are usually not involved. This being the case, certainly the less heavily infected and probably even advanced cases, may well have sufficient uninvolved lymphoid tissue to vitiate the hypothesis. Additionally, though the morphology of lymph node lesions reflects that of the skin lesion type, it does not follow that the quantitative extent of lymph node involvement is similarly titrated or graded across the immunologic spectrum nor even reflected in a given case. Examination of a single lymph node, or even two, per case does not yield quantitative information that permits confidence in the additional hypothesis required, namely that there is indeed a total lymph node lymphocyte depletion.

The possible presence of a defect in thymus type lymphocytes (T cells) and in lymphocyte/macrophage interaction is, at the present, the most actively pursued area of investigation relating to the immunologic spectrum of leprosy. Experimental evidence for this has already been referred to. Supportive evidence is accruing. Thus, Godal

and co-workers ([76]) reported *in vitro* studies in which blood derived macrophages from tuberculoid patients were stimulated to proliferate in the presence of killed *M. leprae* if their lymphocytes were present, but not in the absence of the lymphocytes. The same change did not occur in lymphocyte rich cultures of macrophages from lepromatous patients. Bullock and associates ([34]) noted that delayed hypersensitivity reactions, of a transient nature, to *M. leprae* could be achieved in lepromatous patients with lymphocytes or transfer-factor derivative obtained from normal donors who had delayed skin reactivity to antigen of *M. leprae*. Additionally, Lim *et al* ([134]) have claimed remission of clinical, histologic and bacteriologic findings in four leprosy patients treated over a period of three to four months with intravenous infusions of leukocytes from normal blood donors. They did not, however, support their findings with Bacteriologic Index or Morphologic Index determinations. It is recalled that in 1940 considerable newspaper publicity was given to reports from Pretoria, South Africa relating to the beneficial results in seven leprosy patients subjected to a course of six blood transfusions over a period of several months. It was thought that the method, if it should not have a curative effect, would at least provide considerable relief for the patients ([22]). Curiously, a report ([46]) of a subsequent two day conference on leprosy, also held in Pretoria, four years later made no further mention of blood transfusions. But then, that early work was not supported by the sophisticated theoretical formulation accompanying the present attempt. Finally, just as this review goes to press, two reports ([60, 72]), published simultaneously in the same journal, report a significant increase in bone-marrow-derived (B) lymphocytes ([60, 72]) and a significant decrease in the absolute numbers of thymus-derived (T) lymphocytes ([60]) in the peripheral blood of lepromatous patients.

Inherent in all studies of immunity in leprosy is the necessity of recognizing the presence of an apparently inherent defect in the cell-mediated immune system which relates primarily to the inability of the lepromatous macrophage, and to some degree dimorphous macrophages, to effectively dispose of the leprosy bacillus. This defect is further defined to include a marked sluggishness in metabolizing the leprosy bacillary debris. Whatever abnormality may be involved in the lymphocyte-macrophage relationship, be it of primary or secondary import, there remains the possibility of an inherent macrophage dysfunction or defect to be accounted for. Thus, whatever the final analysis be it seems that it will be one involving immuno-ezymology.

Cosmic balance of contrasts

The past century has seen leprosy emerge from the mists of misunderstanding, pass through pathologic anatomic and histopathologic analysis to an understanding of its nature and immunologic spectrum, and finally to stand out as a unique immunopathologic model which tests the ingenuity of the dynamically developing technics of immuno-pathology and immuno-enzymology for its solution. Leprosy remains the single known disease model with a single host and a single pathogen which titrates and merges the spectrum of immunologic understanding from cell-mediated to humoral antibody mediated immunity; an immunologic microcosm. It presents a shading of apparent opposites and contradictions into a modulated whole which is not just a sum of contrasts but which is, by force of biologic and social response a unique individual in history—the leprosy patient.

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