INTERNATIONAL JOURNAL OF LEPROSY

Volume 44, Number 3
Printed in the U.S.A.

The Role of Protein Malnutrition in the Pathogenesis of Ulcerative "Lazarine" Leprosy [1,2]

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Two world wars, coupled with a recognition of wars' legacies of famine and pestilence, provided a stimulus for investigation of the mechanisms of reduced resistance to infection under conditions of malnutrition ([4,5]). It was found that protein depletion was reflected in a reduction of the antibody containing serum gamma globulins ([3,6,32,33]), marked depletion of the granulocyte reserves ([1,32]) and delay in the healing of lesions as a result of deficiency in the formation of collagen ([11]). Such deficiencies were noted to be operative and to significantly affect the course of disease even in the case of penicillin treated infections by micro-organisms highly sensitive to this antibiotic ([26]). These factors were all found to play important roles in the incidence and enhanced severity of acute bacterial infections, where antibody formation is an effective element of biological defense.

In the infectious granulomata, in general, serum antibodies and granulocytes have not been demonstrated to play significant roles in combating the respective pathogens ([13-17,25,28]). Yet it is well known that tuberculosis, for example, is rampant in poorly nourished societies, where associated factors of crowded living and poor sanitation may also be contributive. Thus, in 1900 A.D. the tuberculosis mortality rate in Germany was 225 per 100,000 population. This mortality rate fell steadily till in 1913 it was 143 per 100,000. Following the outbreak of World War I the downward trend in the mortality rate ceased and by 1916, when the food supply became inadequate, the mortality rate rose significantly, for the first time in more than a quarter of a century, to 162 per 100,000. In 1917 and 1918 when the blockade caused a desperate food shortage, the tuberculosis mortality rate rose to 230 per 100,000—a rate higher than even that of 1900. By 1921, the war having terminated and the food situation vastly improved, the tuberculosis mortality rate fell to 137 per 100,000, only to rise again briefly during the severe postwar recession of 1921-1923 (Fig. 1). A virtually similar relationship between nutrition and tuberculosis incidence was seen in the other European countries in which severe food shortages and attendant malnutrition were experienced during the war period, though in the case of England, for example, where postwar nutritional recession did not occur, the mortality rate continued a steady decline after the war ([19]) (Fig. 1).

In work with leprosy patients in Hong Kong, a similar relationship between leprous infection and nutritional debilitation was suggested in that, repeatedly, patients encountered in the early 1950's indicated that their disease appeared (which could be mere coincidence) or became notably more severe when they suffered severe food shortage in China during World War II. A 1949 visit to the Presbyterian Mission Leprosarium in Hoihow, Hainan Island also promoted this concept. At that time this institution had only recently received sulfone drugs. Yet the patients were in remarkably good physical condition and there was a complete absence of the odor that was often characteristic of the pre-sulfone era leprosaria. The attendant missionary physicians remarked that on their return to this institution after World War II the patients were in pitiable nutritional status and severe leprous manifestations were the rule. Careful dietary attention and general care, without available specific therapy had resulted in marked improvement in general health together with considerable amelioration, though not cure, of leprous manifestations. A subsequent study of the records of another South China leprosarium, summarized below, covering a period of 43 years further substan-

[1] Received for publication May 1973.

[2] Supported in part by U.S.P.H.S. research grants R22-AI-1034, and AI-03657.

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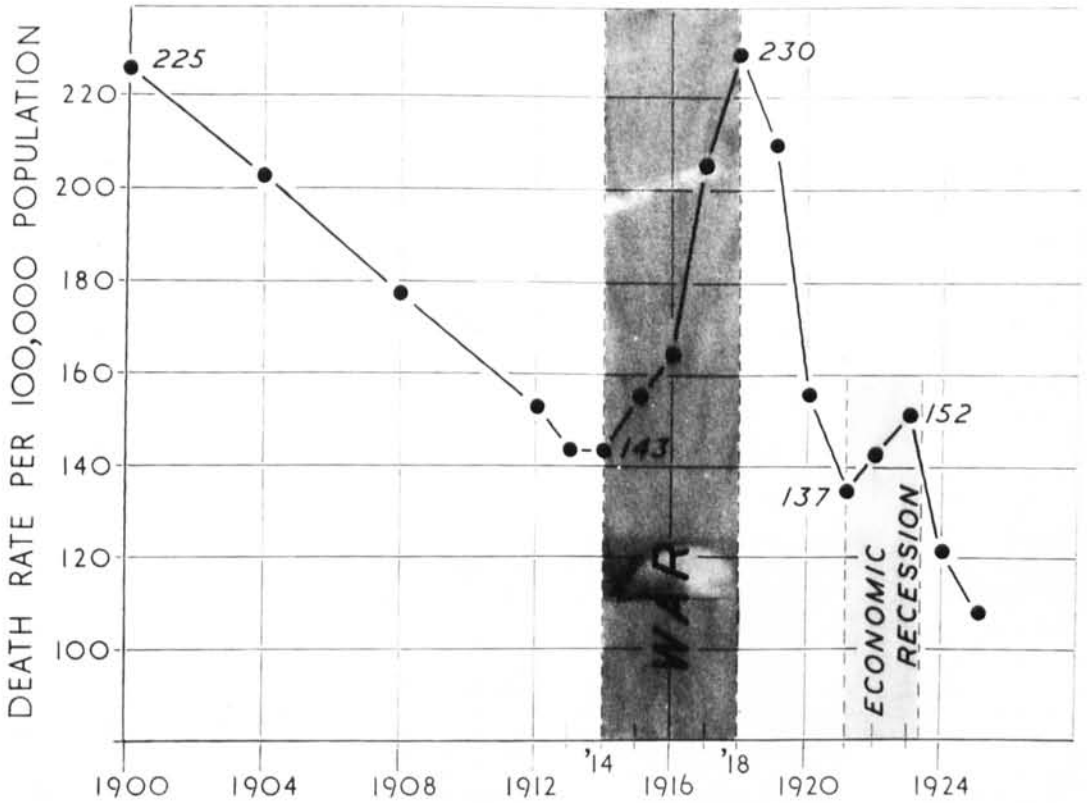

FIG. 1. Influence of wartime malnutrition on tuberculosis mortality ([19]).

tiated these impressions.

Cellular immunity related to macrophage function, rather than antibody generation and granulocytic activity, is the main biological defense in infectious granulomatous disease such as tuberculosis and leprosy. Since protein deprivation denies essential building material for cells and for the production of particular proteins such as antibodies and enzymes, it might be expected that macrophage response and reserves, as well as functional capacity might be limited by such deprivation.

In the absence of an available experimental model for leprosy, resort was had to murine leprosy. Though differing in many respects from human leprosy, this infection has similar characteristics of chronicity, low occurrence of caseation and a pathogen of low virulence and relatively long generation time (about 10 days) in the host.

Clinical and autopsy observations are here briefly noted together with a report of experimental studies utilizing murine leprosy as a model in a preliminary investigation of debilitating mechanisms in cell-mediated mechanisms of biological defense.

CLINICOPATHOLOGIC OBSERVATIONS

A study conducted at the leprosarium in Tungkun, Kwangtung, South China gave suggestive evidence that attention to nutritional status and general care, without specific antileprosy chemotherapy, could influence favorably the course of leprosy and, conversely, that absence of such attention was associated with more rapid progression and earlier death.

The study consisted of a thorough evaluation of the records[4] of the Tungkun Rhenish Mission Leprosarium from its foundation in 1905 through 1949. Fortuitously, the best records were kept during the first five and the last eight years of this period. There was, therefore, opportunity for comparative study of two widely separated periods. Neither sul-

[4] Permission of Dr. Otto Hueck, Medical Superintendent.

fone nor other leprosy-specific therapy was available to the institution for either of the periods of study, though chaulmoogra oil was used to some extent during the latter period. The virtually universal abandonment of chaulmoogra and hydnocarpic oils as therapeutic agents in leprosy after World War II together with prior dissatisfaction with results of this treatment suggests that it was relatively inefficacious and apparently without specific effect. No good therapeutic evaluation is available for settling this issue. It is probable that much of the efficiency earlier reported for these substances was, in fact, the consequence of associated general care and improved nutritional status also available to patients when these therapies were supplied.

Clinical records for the initial period of 1905-1909 are not available, but the available chronological record of patients and their eventual disposition are replete with notes such as:

"Covered with ulcers. Died of exhaustion."

"Ulcerated. Very weak. Bruised one foot. Gangrene set in. Died."

"Covered with ulcers. Used a nail in the wall and a tie (to hang self). Was found dead in the morning. Body not rigid."

Of the 121 patients admitted the first year, 26 died within the year and 23 absconded, commonly for being denied the use of opium. The rest eventually died in the institution. There was no record of discharge because of cure.

In the final period of comparison, 1942-1949, there were only 89 deaths, compared to 191 deaths in the shorter initial period of 1905-1909. Figure 2 compares the total duration of the disease before death in these two groups of patients, and Figure 3 similarly presents the total duration of their leprosarial stay. It is evident that in the period 1942-1949 there was a distinct prolongation of survival after initial appearance of leprosy which was in considerable measure a reflection of increased survival time under institutional care since the average duration of disease prior to leprosarial admittance was, on the average, similar. It was notably characteristic of this period (1942-1949) that the staff paid special attention to maintaining adequate nutrition for the patients in addition to providing careful general supportive care. Since the institution was staffed by German missionaries during the war there was no insurmountable obstacle to the achievement of these goals during the Japanese occupation of South China during that part of the period covered by World War II. During a portion of this period some sulfonamide therapy was used, though antibiotics became available only toward the end of the period, and this undoubtedly helped control secondary infections and played some role in prolonging survival. Nevertheless, the overall indications are that this comparison supports the hypothesis that malnutrition does have a distinct deletorious effect also in chronic infections such as leprosy where the main biological defense is related to cellular immunity.

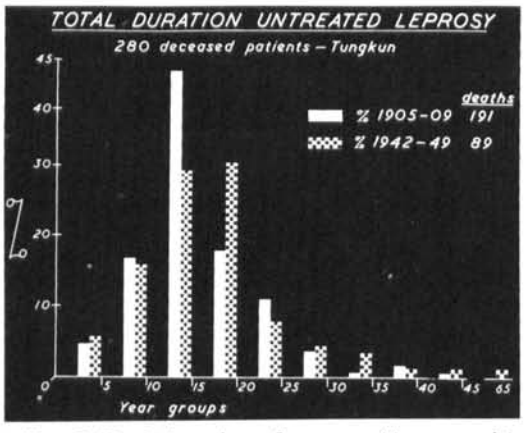

FIG. 2. Total duration of untreated leprosy with the latter period reflecting increased longevity associated with markedly improved nutritional status.

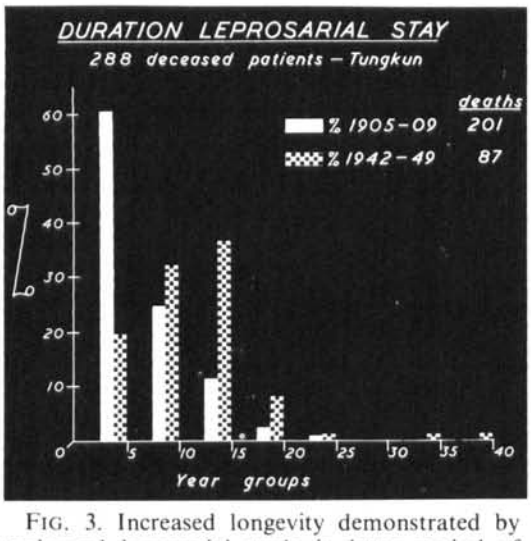

FIG. 3. Increased longevity demonstrated by prolonged leprosarial study in latter period of markedly improved nutrition.

Necropsy indications. In the course of 25 autopsies in Hong Kong on patients having

leprosy, two instances of severe malnutrition were encountered. Both these lepromatous patients presented low serum protein levels of 4.43 and 4.46 gm% respectively and were severely emaciated (Fig. 4). Additionally, they displayed extensive or excessive ulcerative phenomenon (Fig. 5). In one of these patients, during the weeks immediately preceding death, there was edema of the extremities, repeated formations of crops of epidermal blisters, peeling of the epidermis and ulcer formation while the other patient presented with extensive ulceration of extremities.

These two patients, strikingly, presented more widespread and larger visceral lesions (Fig. 6) than were seen in any of the other necropsies in the series ([24]).

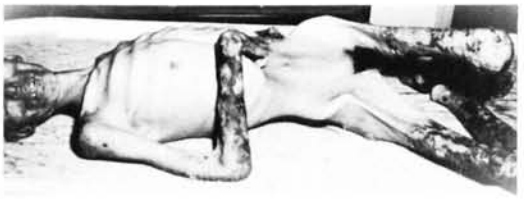

FIG. 4. Severe emaciation (serum proteins 4.43 gms%).

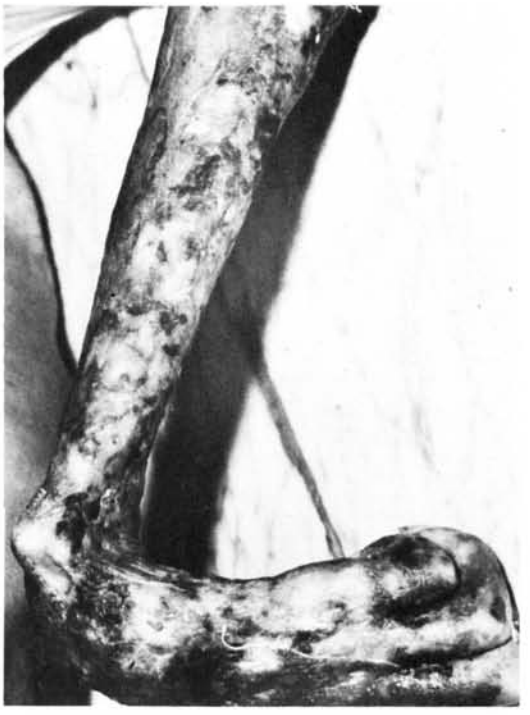

FIG. 5. "Lazarine" leprosy ulcerations. Same patient as Figure 4.

MATERIALS AND METHODS

The Wiersung strain of rats were employed since these animals are known to be relatively susceptible to murine leprosy ([10]) and thus to be more likely to present uniform infection when challenged with experimental inoculum, and to more closely simulate the immunopathologic status seen in lepromatous leprosy. Forty-six adult animals were employed; 24 females weighing 153 to 242 gms, and 22 males weighing 193 to 345 gms before protein deprivation. Two experiments were conducted, one utilizing 25 animals (15 protein deprived and 10 controls) and the other, 21 animals (12 protein deprived and 9 controls). All animals were housed in stainless steel cages with wire-mesh bottoms having no more than five animals to a cage. They were kept in a temperature controlled room at 79° F.

Total serum protein levels were determined for each animal prior to initiating the protein depletion diet and again at the time of challenge inoculation with *M. lepraemurium*. Small blood samples were obtained from the tail vein and the determinations made by the technic described by Barbour and Hamilton ([2]). The Moore and Van Slyke formula was used to calculate the total serum protein:

$$P = 343(G-1.0070)$$

where P = protein in gms% and G represents plasma specific gravity, calculated as specific gravity 20°C/20°C. No protein determinations were made at the times of animal sacrifice for several reasons. There appeared to be no way of correlating any changes that might occur with the progressive course of the experiments; the animals being killed at successive intervals the determinations of varying degree of progressive infection would have to be balanced against progressive debilitation. Further, it is difficult to get adequate plasma samples from severely debilitated small animals. Finally, logic would suggest making total protein determinations of all experimental animals at the time of each scheduled sacrifice for comparative purposes. The process of handling and bleeding these fragile animals is, however, a debilitating process in itself and adds unnecessarily to subject mortality. The purpose of the determinations was therefore limited to determining the state of hypoproteinemia at the onset of infection and subsequently utilizing weight determinations to establish the fact that debilitation was thereafter progressive.

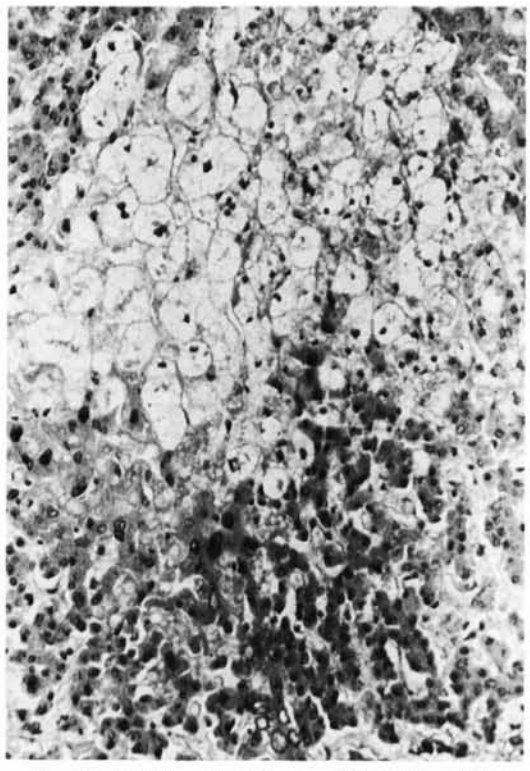

FIG. 6. Proliferative "foam cell" lesion of liver in same patient as Figures 4 and 5.

For these purposes the relatively simple protein determination technics employed were considered to be adequate and to be comparative with the studies cited above as relating debilitation of antibody immune mechanisms to hypoproteinemia.

The protein depletion diet was chemically defined, isocaloric and presented in pellet form (Table 1). Each animal was provided with 20 gm of food per day throughout the experiments and with water *ad libitum*. After about three weeks, when the protein deprived animals had lost significant weight, all animals were inoculated intraperitoneally into the lower left quadrant with 0.25 ml of *M. lepramurium* suspended in Hanks' balanced salt solution.

The bacillary inoculum was prepared from lepromas (liver, spleen, lymph nodes) that had been developed in stock Wiersung rats for five months or longer. Ten ml of Hanks' balanced salt solution were added for each gram of leproma. The tissue was minced and then triturated in a motor driven piston-type Teflon pestle in a glass grinding vessel. The detritus was allowed to settle. Then the supernatant was decanted into sterile culture tubes and this constituted the inoculum. In

TABLE 1. *Composition of diets.*[a]

Diet Constituents	Protein-Depletion Diet %Composition	Protein-Rich Diet % Composition
Casein, VFT, GBI	—	27.00
Primex	—	10.00
Vegetable oil (hydrogenated)	10.00	—
Corn starch	42.50	29.00
Sucrose	42.50	29.00
Salt mix, U.S.P. XIV	4.00	4.00
Cod liver oil	1.00	1.00
	Gm/100 lbs.	Gm/100 lbs.
Alpha-tocopherol	10.2150	10.2150
Calcium pantothenate	2.043	2.043
Choline chloride	272.400	272.400
i-Inositol	13.62	13.62
Menadione	0.1020	0.1020
Niacin	27.24	27.24
Pyridoxine HCl	0.953	0.953
Riboflavin	0.953	0.953
Thiamine HCl	0.953	0.953

[a] Diets formulated and supplied by General Biochemicals, Chagrin Falls, Ohio.

TABLE 2. *Protein depletion findings*

Animal no.	Date sac.	Sex	Initial Findings		Start of Exp.		
			Initial wt.	Initial serum prot.	Wt.	Serum prot.	Wt. at sac.
Control	1 wk	M	203 grams	4.97 Gm/100 cc	246	5.15	258
Depleted	1 wk	M	207	5.04	186	5.14	175
Control	2 wks	M	193	4.87	223	5.04	249
Depleted	2 wks	M	195	4.94	174	4.73	160
Control	3 wks	F	171	5.18	221	5.59	228
Depleted	3 wks	F	210	6.24	173	4.42	161
Control	5 wks	M	221	4.84	255	5.04	309
Depleted	5 wks	M	237	5.04	203	4.25	161
Control	7 wks	F	167	5.08	212	5.32	230
Depleted	7 wks	F	192	5.80	156	4.73	124
Control	9 wks	M	302	4.90	341	5.25	398
Depleted	9 wks	M	258	5.18	215	4.53	144
Control	11 wks-2	F	206	5.17	255	5.59	284
Depleted	11 wks-2	F	153	5.11	124	4.63	80
Control	13 wks-1	F	172	5.18	216	5.59	273
Depleted	13 wks-1	F	181	5.99	149	5.18	94
Depleted	15 wks	M	233	4.90	207	4.29	109
Depleted	15 wks	F	181	5.62	144	4.73	88
Control	18 wks	M	305	4.90	383	5.04	493
Depleted	18 wks	F	191	5.11	166	4.56	105
Control	7 mos.	M	287	5.08	332	5.08	501

each experiment the same inoculum was used for all the animals so that in each experiment each animal received the same challenge dose. Prior to inoculation, smears of the inoculum were made, stained for acid-fast bacilli and evaluated for content of solid-staining organisms which were regarded as presumably viable.

The animals were scheduled to be sacrificed at one week, two weeks, three weeks, and thereafter at two week intervals. However, as they became very debilitated during the course of the experiments, it was occasionally necessary to sacrifice animals a day or two before the intended date. Where this was so it is indicated in Tables 2 and 3.

Visceral organs, brain, salivary glands, sciatic nerve, femur and sternum from each sacrificed animal were fixed in 10% buffered formalin, paraffin sectioned, and stained with Ziehl-Neelsen, hematoxylin-eosin, and TRIFF ([31]) stains. The tissue sections were carefully examined for bacilli and lesions, and scored for bacterial content according to a modification of Ridley's method for determining bacterial indices ([20]). Since Ridley's method is intended for skin smear technic, where the bacilli are fairly evenly dispersed, it had to be modified for use with tissues where lesions containing bacilli are spottily distributed. The modification consisted of regarding individual lesions as separate fields and scoring each according to the scale noted with Table 4. As there noted, each increment represented a tenfold increase in the number of organisms. The method is intended to be comparative only and not to indicate accurate bacillary counts.

RESULTS

Gross evaluation. Three prior pilot experiments had shown that excessive handling of severely debilitated animals significantly increased mortality. Therefore, weight determinations were recorded for only six weeks at weekly intervals and then again at the time of sacrifice. Care had to be exercised in obtaining blood samples, for the protein-deprived animals showed poor tolerance to the ether anesthesia used.

During the initial stages of the protein-depletion diet utilization there was little difference in food consumption between control and deprived animals. As the experiments

TABLE 3. *Protein depletion findings.*

Animal no.	Date sac.	Sex	Initial Findings		Start of Exp.		
			Initial wt.	Initial serum prot.	Wt.	Serum prot.	Wt. at sac.
Control	1 wk	F	229 grams	5.69 Gm/100cc	248	5.76	252
Depleted	1 wk	F	207	5.97	187	4.96	180
Control	2 wks	F	228	5.62	259	5.83	265
Depleted	2 wks	F	173	6.04	154	5.15	149
Control	3 wks	M	278	5.62	323	5.83	355
Depleted	3 wks	M	230	5.62	202	4.73	185
Control	5 wks	M	259	5.83	298	5.72	355
Depleted	5 wks	M	258	5.56	224	4.96	178
Control	7 wks	M	283	5.62	325	5.66	370
Depleted	7 wks	M	312	5.69	268	5.15	207
Control	9 wks	F	197	5.69	224	6.00	272
Depleted	9 wks	F	223	5.69	192	4.73	131

progressed, there was a steady decrease in the consumption of the protein-free diet, while there was little or no change with the animals on the control diet. After six weeks on the diets, the animals on depletion were consuming about half as much diet by weight as were the controls. During the same six week period the control animals recorded an average weight loss of 30-33%.

At the time of challenge with *M. lepraemurium,* after having been on the protein-free diet for three weeks, the deprived animals showed a decrease of 14-17% in their serum protein levels. This was less than that utilized by Cannon *et al* (7) and Skinsnes (26). However, their studies were acute, and prolonged survival of their experimental animals was not necessary. In contrast, the present experiments with murine leprosy required continued observations over a period of several weeks. Hence the study was begun at a point where the animals were less depleted, but conditions of protein deprivation were maintained for the total course of the experiments. Tables 2 and 4 present weight and serum protein level data for the two experiments.

At sacrifice, the visceral organs of the deprived animals were comparatively decreased in size, there was a lack of fat depots, and the bones were softer and more fragile. In the control animals, as the infection progressed, the livers and spleens tended to enlarge and be firm. They were speckled with

TABLE 4. *Relative bacillary distribution in livers, spleens, and bone marrows of control and protein depleted rats infected with* M. lepraemurium.

Interval		Liver		Spleen		Bone Marrow	
		Control	Depleted	Control	Depleted	Control	Depleted
Week	1	+	+	+	+	-	-
	2	+	+	+	+	-	-
	3	+	+	+	+	-	-
	5	+	++	++	++	-	-
	7	+	+++	++	++++	-	++
	9	+++	++++	+++	++++	+	++
	11	++	++++	+++	++++	++	+++
	13	+	++++	++	++++++	++	+++++
	15	+++++	+++++	++++++	++++++	++++++	++++++
	18	++	+++++	+++	++++	++	+++
Month	7	++++++		++++++		++++++	

Each + increment equals a tenfold increase in bacilli.
Intraperitoneal route of inoculation.

discrete yellow-white small nodular lesions. Lesions in the depleted animals had similar gross appearances.

Histopathologic evaluation. Up to the fifth post-inoculation week, bacilli were found in lesions only in the livers and spleens of both groups of animals. By the seventh week, bacilli were noted also in lesions in the bone marrow of the protein-depleted animals, but not till the ninth week in the control rats.

Early host response to *M. lepraemurium* did not appear significantly different on histopathologic section in the two groups of animals up to three weeks. As noted by others ([9, 29]), bacilli were found in Kupfer cells of the liver and in macrophages, particularly around blood vessels. Little other inflammatory change was noted. By the fifth week, however, there were noticeable differences. Well-circumscribed focal accumulations of lymphocytes and epithelioid cells surrounded bacilli-containing macrophages in both groups of animals. The degree of inflammatory change was, however, greater in the control animals while in the depleted rats there were more bacilli per macrophage. As the disease progressed, these differences became more pronounced.

In the spleen, bacilli were first noted in the germinal centers, but later in the course of the infection they were found in abundance in the pulp as well in both group of animals. The most noticeable difference in the two groups of animals were the larger and more widely spread germinal centers in the control animals and the greater number of bacilli per macrophage in the protein-deprived rats (Figs. 7-10).

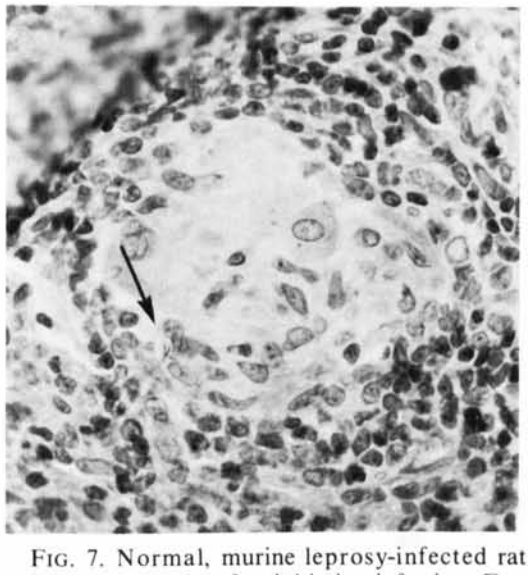

FIG. 7. Normal, murine leprosy-infected rat spleen seven weeks after initiating infection. Few bacilli in large germinal center. TRIFF stain, ×750.

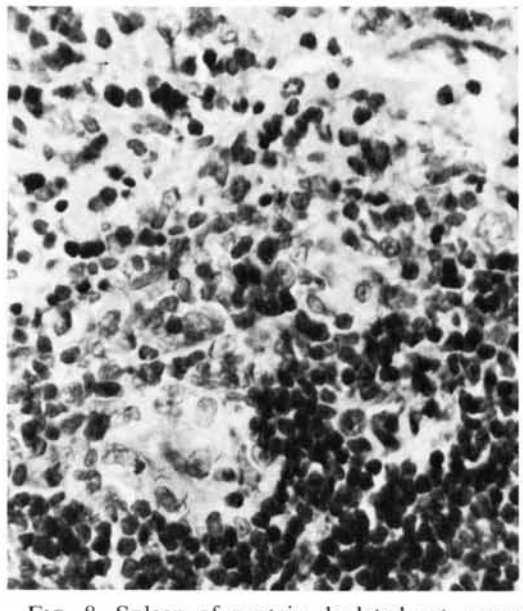

FIG. 8. Spleen of protein depleted rat, seven weeks after initiating infection. Small germinal centers are closely spaced and more bacilli are contained by fewer macrophages than in Figure 7. TRIFF stain, ×750.

Beginning with the seventh week the protein-depleted animals quite consistently showed a greater number of bacilli, both in individual bacilli-containing macrophages and in susceptible organs (Table 4). Since infection with *M. lepraemurium* involves primarily the reticuloendothelial system, it was not surprising that the liver, spleen and bone marrow proved to be the areas of most prominent lesion development. However, of probably equal significance was the considerably more prevalent occurrence of lesions in the protein-deprived rats in other tissues such as adrenals, intestines, stomach, salivary glands, and even in the heart and lungs. This was evident at the 13th and 18th weeks. No protein-deprived animal survived longer than 18 weeks, but the control animal examined at seven months showed a lesion distribution pattern similar to that more strikingly foreshadowed in the debilitated rats at 13 and 18 weeks than in their control counterparts.

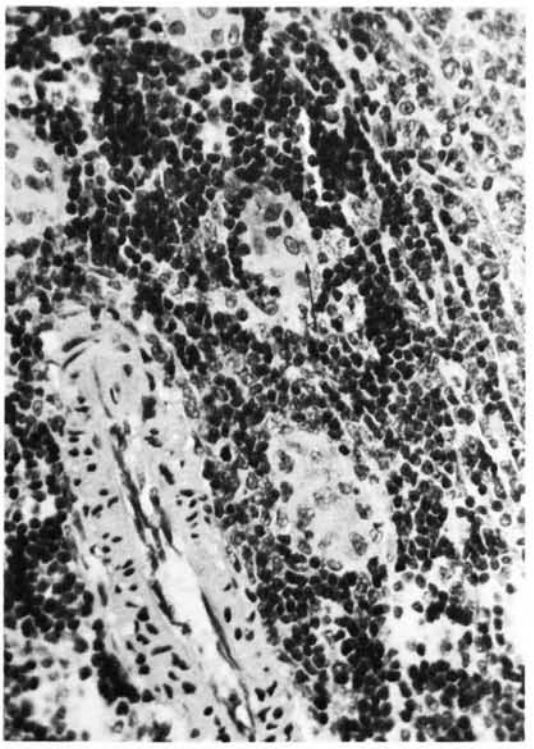

FIG. 9. Spleen of normal, infected rat 13 weeks post-inoculation. ×750.

DISCUSSION

The experimental results indicate that protein deprivation renders the experimental rat more susceptible to dissemination of infection by the murine leprosy bacillus. This appears to be the result of a twofold effect on the macrophages. There are less macrophages available in the debilitated host that can respond to and combat the infection, and the available macrophages permit greater proliferation of the pathogen within their cytoplasm. Thus, as might be expected, protein deprivation affects the mechanisms of cellular immunity as well as humoral antibody-mediated immunity. The results are less dramatic and immediately effective than in the antibody-mediated immunity seen, for example, in acute virulent infections such as that caused by *Diplococcus pneumoniae*. This is in character with the characteristics of cellular immunity, the development or presence of which often modifies rather than abrogates the course of the infection. This is well known from the contrasts between first infection and second infection tuberculosis and tuberculoid versus lepromatous leprosy ([23]).

In the present instance of *M. lepraemurium* infection in Wiersung rat, there is, however, no evidence that acquired cellular immunity is being affected since it is not clear that this host develops enhancement of its cellular immunity mechanisms on challenge by this pathogen. Rather, there seems a strong analogy with lepromatous leprosy where the host appears incapable of such enhancement despite, as is also the case in *M. lepraemurium* infection, the presence of massive quantities of the pathogen. In both instances the defense mechanisms available to the host appear to be pre-eminently those of inherent (native) rather than acquired cellular immunity. The present experiments confirm that such inherent cellular immunity exists since the macrophages of the susceptible Wiersung strain of rats evidently are not totally devoid of ability to destroy *M. lepraemurium* because this capacity can be reduced by protein deprivation. The fact that the macrophages of the depleted animals tended to host more pathogens enhances this impression since there was no evidence of increased phagocytic ability on their part. Likewise, it seems evident that protein depletion is not reflect-

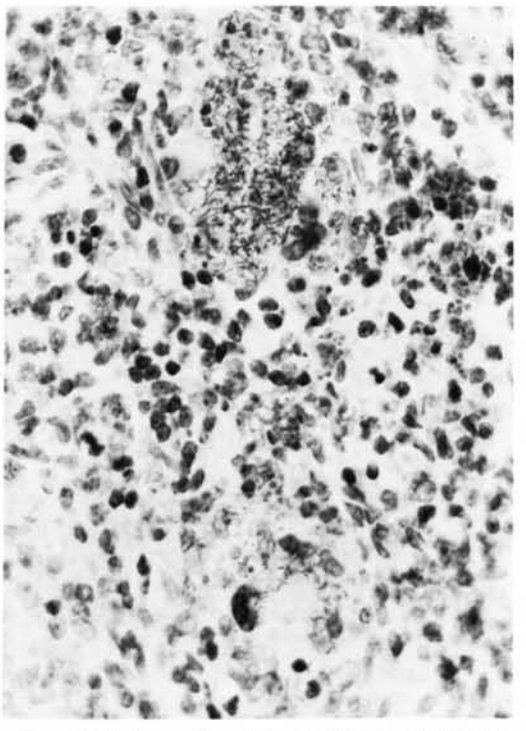

FIG. 10. Spleen of protein depleted rat 13 weeks post-inoculation. Large numbers of bacilli are located in the pulp. Germinal centers small and poorly organized. TRIFF stain, ×750.

ed in any deficiency in the internal milieu of macrophages that would make these cells less suitable for the propagation of the pathogen.

The control animals showed the usual individual variations in resistance to *M. lepraemurium* that can be expected in any study of host susceptibility to a given pathogen. In the deprived animals, however, this variation was significantly leveled out (Table 4) though not completely eliminated. This finding likewise suggests that under this method of debilitation the mechanisms of inherent cellular immunity are severely debilitated. This is borne out by studies ([35, 36]) in which protein depletion had a debilitating effect on macrophage lysosomal enzymes.

The observations are pertinent to the understanding of the pathogenesis of Lazarine leprosy. The name derives from the Biblical account of the beggar Lazarus who, covered with sores, sat at the door of the rich man and vainly begged for the crumbs that fell from his table with only the dogs who licked his sores paying him attention. Medieval tradition declared that this man suffered from leprosy, though the Biblical account carries no such implication. The name, Lazarine leprosy, has been used in the past merely to designate severe, widespread ulcerative phenomena in a patient with leprosy without providing any pathogenic explanation of the phenomenon except when it occurs in Lucio type of leprosy. In 1958, Skinsnes ([24]) suggested that such severe ulcerative phenomenon occurring especially in lepromatous leprosy may be the result of infection in the presence of protein malnutrition with its resultant breakdown in defense mechanisms. Comparison of the enhanced visceral lesions seen in such an instance with the progress of similar *M. lepraemurium* infection in protein deprived rats reinforces this formulation. In the progress of their affliction these patients show the characteristics of tissue edema, repeated blister formation in areas of leprous inflammation and eventual breakdown of such areas of inflammation into multiple ulcers with poor healing capacity. The ulcerations are apparently primarily the result of the breakdown of tissue cellular immunity together with increased proliferation of pathogen and tissue edema. Superimposed is the enhanced susceptibility to secondary pyogenic pathogens such as streptococci and staphylococci resulting from the concomitant debilitation of humoral antibody mechanisms by the same protein deprivation.

The literature related to "Lazarine" leprosy is confused in many instances by failure to discriminate between "Lazarine" leprosy, as here used, and "Lucio" leprosy, the reason being that both conditions relate to ulcerative phenomena in leprosy, usually in lepromatous leprosy. "Lucio" leprosy was first and well described by Rafael Lucio and Ignacio Alvarado in 1851 in Mexico. A translation of this paper is presented by Frenken ([8]) in a monograph reviewing the literature and presenting extended observations.

Lucio ascribed the phenomenon he described to leprous arteritis with resulting hemorrhage, but did not present any supportive histopathologic studies. This was subsequently supplied by Latapi and Chevez ([12]) who describe the Lucio phenomenon as an ischemic necrotic infarction with thrombosis in the vessels (endocapillaritis thrombonecrotica). The phenomenon is further related to *erythema nodosum leprosum* and immediate type hypersensitivity.

In Lucio's original paper he seems to use the term "disease of St. Lazarus" for leprosy, classifying it into two groups as "tuberculosis elephantiasis" (leoninos) and anesthetic (antoninos) and adding as a contribution "the spotted ones" which he also referred to, in parentheses as "lazarinos." He thus used the terminology in two senses, equating the "disease of St. Lazarus" with "Elephantiasis of the Greek" in his title. In the body of his paper he rarely uses the term "leprosy" and throughout speaks of the "spotted form" when referring to the phenomenon that has come to hold his name and of the "disease of St. Lazarus" when discussing leprosy generally. It is on this basis that subsequent writers have coupled the terms "Lazarine leprosy" and the "Lucio phenomenon." In so doing other ulcerative phenomena, probably on a different pathogenetic basis, have been included ([18, 21, 22]). Pardo Castello and Pineyro ([18]) concluded that there was no specific form of leprosy that can be called "lazarine." Latapi and Chevez ([12]) suggested that the term "spotted leprosy" is the best translation of the Spanish word "manchada" and noted that the term "lazarine" had become confused because of its several applications to a variety of ulcerative lesions in leprosy. Wade ([30]) in a review editorial, suggested that the term "lazarine" was no longer necessary,

the term Lucio phenomenon being appropriate to the ulcerative phase described by Lucio and the further term "Lucio leprosy," which Latapi and others have used, being useful for the form as a whole. He further suggested that since the term "lazarine" has so long:

> . . . been employed to signify a bullous-ulcerating condition (or conditions) in neural leprosy, and since some general term for that condition (or conditions) in that type of leprosy is needed, it seems but logical to continue to use it in that way—and to admit the transfer.

In this vein it seems singularly appropriate to use this term to cover ulcerative phenomena in general in leprosy where such phenomena are due to or contributed to by debilitating conditions such as malnutrition for:

> There was once a rich man who used to array himself in a purple and fine linen,and enjoyed a splendid banquet every day, while at his outer door there lay a beggar, Lazarus by name, covered with sores and longing to make a meal off the scraps falling on the floor from the rich man's table (The Bible; Luke 16:19-29).

These conditions with respect to terminology were accepted and recommended for implementation at the Tenth International Congress in 1973 ([27]).

SUMMARY

1. Clinical and necropsy observations in lepromatous leprosy associated with severe emaciation and accompanying hypoproteinemia suggest that protein deprivation may be of pathogenic significance in the ulcerative phenomenon that is designated "Lazarine leprosy."

2. An experimental model utilizing Wiersung rats infected with *Mycobacterium lepraemurium* and maintained on a protein-free diet was developed for the purpose of studying the effect of protein starvation on the course of chronic mycobacterial disease similar to lepromatous leprosy with respect to pathogen and host inflammatory response.

3. It was possible to maintain the experimental animals on a protein-free diet for up to 18 weeks of concomitant *M. lepraemurium* infection. This was long enough for the infection to disseminate to a degree that was evident in control animals only several weeks later.

4. The protein-deprived animals showed decreased inflammatory response to the pathogen, presented more rapid dissemination of the infection and harbored more bacilli per macrophage than did animals similarly infected but maintained on a protein adequate diet. This indicates impairment of native cellular immunity by protein deprivation through decrease in ability of macrophages to inhibit bacillary multiplication.

5. There was no evidence of impairment of macrophage ability to phagocytose the pathogens.

6. Morphologically the increased dissemination of pathogens and decrease in inflammatory response was similar to the increase in number and extent of visceral lesions seen in Lazarine leprosy. Decreased ability to dispose of the infecting bacilli was similar in the two models, human and animal. The animal model does not, as does lepromatous leprosy, involve the skin in the infection. Hence comparable ulcerative phenomena were not replicated in the animals.

7. It is suggested that Lazarine leprosy may result from enhanced lepromatous leprous infection occurring as a result of protein malnutrition. The pathogenic mechanism appears to be impairment of cellular immunity probably enhanced by concomitant impairment of humoral antibody immunity resulting also in decreased resistance to pyogenic and other secondary pathogens. The tissue edema attendant on decreased serum osmotic pressure due to lowering of the serum protein fractions enhances the probability of ulceration.

RESUMEN

1. Las observaciones clínicas y de necropsia en la lepra lepromatosa asociada con emaciación severa e hipoproteinemia concomitante, sugieren que la deprivación proteica puede tener una importancia patogénica en al fenómeno ulcerativo que se denomina "lepra Lazarina."

2. Se desarrolló un modelo experimental utilizando ratas Wiersung infectadas con *Mycobacterium lepraemurium* y mantenidas con una dieta libre de proteínas, con el objeto de estudiar el efecto de un ayuno prolongado de proteínas sobre el desarrollo de una enfermedad micobacteriana crónica, similar a la lepra lepromatosa, con respecto al microorganismo patógeno y a la respuesta inflamatoria del huésped.

3. Fué posible mantener los animales experimentales con una dieta libre de proteínas hasta 18 semanas de infección concomitante con *M. lepraemurium*. Este período fué lo bastante largo como para que la infección se diseminara hasta un grado que fué evidente en los animales controles sólo varias semanas después.

4. Los animales deprivados de proteínas mostraron una respuesta inflamatoria hacia el microorganismo patógeno disminuída, presentaron una diseminación más rápida de la infección y contenían más bacilos por macrófago que los animales infectados en forma similar pero mantenidos con una dieta proteica adecuada. Esto indica una alteración de la inmunidad celular natural por carencia de proteínas, a través de una disminución de la capacidad de los macrófagos para inhibir la multiplicación bacilar.

5. No hubo evidencia de alteración de la habilidad de los macrófagos para fagocitar los microorganismos patógenos.

6. Morfológicamente, el aumento de la diseminación de los microorganismos patógenos y la disminución de la respuesta inflamatoria fueron similares al aumento en número y extensión de las lesiones viscerales que se observan en la Lepra Lazarina. La disminución de la capacidad para deshacerse de los bacilos infectantes fué similar en los dos modelos, humano y animal. El modelo animal no produce compromiso de la piel con la infección, como se observa en la lepra lepromatosa. Por lo tanto, no se observaron fenómenos ulcerativos comparables en los animales.

7. Se sugiere que la Lepra Lazarina puede ser el resultado de una infectión de lepra lepromatosa estimulada a raíz de una malnutrición proteica. El mecanismo patogénico parece ser una alteración de la inmunidad celular, probablemente aumentada por una alteración concomitante de la inmunidad por anticuerpos circulantes, lo que produciría una disminución de la resistencia hacia microorganismos patógenos secundarios y piogénicos. El edema tisular posterior a una presión osmótica sérica disminuída debida a una disminución de las fracciones proteicas del suero aumenta la probabilidad de ulceración.

RÉSUMÉ

1. Des observations cliniques et nécropsiques menées dans la lèpre lépromateuse, dans des cas associés avec un amaigrissement grave et avec de l'hypoprotéinémie, suggèrent que la déficience protéinique peut avoir une signification pathogénique dans le phénomène ulcératif communément désigné sous le terme de Lèpre Lazarine.

2. En vue d'étudier l'effet de la déprivation en protéine sur l'évolution d'une maladie mycobactérienne chronique, semblable à la lèpre lépromateuse en ce qui concerne le comportement de l'agent pathogène et la réponse inflammatoire de l'hôte, on a eu recours à un modèle expérimental consistant en rats de Wiersung infectés par *Mycobacterium lepraemurium* et maintenus à un régime sans protéine.

3. Il a été possible de maintenir des animaux d'expérience à un régime sans protéine pour 18 semaines, tout en étant infectés par *M. lepraemurium*. Cette période était suffisamment longue pour que l'infection se dissémine à un degré semblable à celui observé chez des animaux témoins plusieurs semaines plus tard seulement.

4. Les animaux mis à un régime sans protéine ont présenté une diminution de la réponse inflammatoire au pathogène, de même qu'une dissémination plus rapide de l'infection. Par ailleurs ils hébergeaient un plus grand nombre de bacilles par macrophage que les animaux infectés de façon semblable, et maintenus sous un régime protéinique adéquat. Ceci révèle une atteinte de l'immunité cellulaire originele, à la suite de la carence en protéine, par le truchement d'une dimunition de la capacité des macrophages à inhiber la multiplication bacillaire.

5. On n'a observé aucun signe d'une atteinte de la capacité des macrophages à phagocyter les pathogènes.

6. Au point de vue morphologique, l'augmentation notée dans la dissémination des pathogènes, et al diminution de la réponse inflammatoire, étaient semblables à l'augmentation en nombre et à l'étendue des lésions viscérales contatées dans la Lèpre Lazarine. Dans les deux modèles, le modèle humain et le modèle animal, la diminution de la capacité à se débarrasser des bacilles responsables de l'infection était semblable. Contrairement à ce qui est observé dans la lèpre lépromateuse, l'infection chez l'animal laisse la peau intacte. Dès lors, des phénomènes ulcératifs comparables à la Lèpre Lazarine, n'ont pu être reproduits chez les animaux.

7. On suggère que la Lèpre Lazarine peut être la conséquence d'une stimulation de l'infection lépreuse lépromateuse, par suite d'une malnutrition protéinique. Le mécanisme pathogénique semble consister en une atteinte de l'immunité cellulaire, qui est probablement stimulée par l'atteinte concomittante de l'immunité des anticorps humoraux. Ceci résulte également en une diminution de la résistance aux pathogène pyogéniques et aux autres pathogènes secondaires. L'oedème tissulaire associé à une diminution de la pression osmotique du serum, suite à un abaissement des fractions des protéines sériques, augmente la probabilité de l'ulcération.

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