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Resistance and Susceptibility of Mice to Bacterial Infection: Histopathology of Listeriosis in Resistant and Susceptible Strains

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C57BL/10 mice have previously been shown to be 100 times more resistant to intravenously injected *Listeria monocytogenes* than are BALB/c mice due to the action of a single gene, *Lr*. Differences in the histopathology of listeriosis in the two strains were sought. Of the tissues examined, only liver, spleen, blood, and thymus showed changes. In the liver, *Listeria* localized in Kupffer cells within 3 h of infection. By 24 h these cells became surrounded by neutrophilic polymorphonuclear leukocytes. After high doses of *Listeria*, the susceptible BALB/c mice showed many foci surrounded by few polymorphs, whereas in the resistant C57BL/10 mice there were relatively few foci surrounded by many polymorphs. By 4 days in sublethally infected mice the polymorphs in the liver of both strains were being replaced by monocytes and macrophages. Liver morphology returned to normal by 8 days postinfection. In the blood of both strains there was a rise in total lymphocyte numbers at 24 h, followed by a fall in T-lymphocytes and recovery at 5 days. C57BL/10 mice showed an early monocytic response in the blood, whereas BALB/c mice showed a polymorph leukocytosis. In the spleens of both C57BL/10 and BALB/c mice there was an early neutrophil response and red pulp hyperemia. This was followed by a dramatic lymphocyte depletion in the T-dependent periarteriolar regions in both strains beginning 2 days after infection. Absolute numbers of Thy-1$^+$ cells in spleen cell suspensions also fell to 10% of normal, recovering 6 to 8 days postinfection. Surface immunoglobulin-positive B-lymphocytes and Thy-1$^-$, immunoglobulin-negative "null" cells rose in both strains at days 4 to 5, returning to normal levels on days 10 to 12. Whether the null cells represent lymphocytes or other cell types remains unresolved. Thymus atrophy was seen in the BALB/c mice but not in C57BL/10 mice.

The study of the genetic basis of resistance or susceptibility to infection is potentially important in both human and veterinary practice. Previous studies have indicated that *Listeria monocytogenes* infection of mice is an ideal model in which to study the genetics of a purely cell-mediated immune response (3, 4, 21).

Intravenous infection of mice with *L. monocytogenes* results in an acute, potentially lethal infection in which the bacteria survive and multiply within macrophages, principally in the liver and spleen (10). Acquisition of immunity depends on activation of T-lymphocytes by listeria antigens and release of lymphokines which both stimulate the bactericidal activity of the macrophages and attract more bone marrow-derived monocytes to the site of infection (7, 16, 18). Antibodies apparently play no part in immunity to listeriosis, since they are not formed during primary infection (20) and are not protective in passive transfer (12).

It has previously been shown that inbred mouse strains fall broadly into two groups with an approximately 100-fold difference in their 50% lethal dose (3). C57BL/10, C57BL/6, SJL, and NZB strains were resistant (50% lethal dose, about 2×10^5 bacteria), whereas BALB/c, CBA, DBA/1, C3H, A/WySn, WB/Re, LP.RIII, and 129/J strains were susceptible (50% lethal dose, about 2×10^3 bacteria). When C57BL and BALB/c mice were compared, it was shown that the large difference in resistance was due to a single autosomal gene, *Lr*, not linked to the major histocompatibility complex, immunoglobulin allotype, or *H-1*, *H-3*, *H-4*, *H-8*, *Thy-1*, *Hc*, or coat color genes. Resistance was reflected in the restricted growth of *L. monocytogenes*, especially in the liver, of resistant C57BL mice and in the earlier onset of specific acquired immunity (4).

There is surprisingly little information on the histopathology of murine listeriosis despite the extensive studies on cell traffic and proliferation in mice with this disease (17-19). We therefore

examined various organs of resistant (C57BL/10) and susceptible (BALB/c) strains to seek differences in their histopathology. The tissues were examined by light, and in some cases electron, microscopy, and splenic and peripheral blood leukocytes were enumerated for B- and T-lymphocytes by direct and indirect immunofluorescence, respectively. Differences detected were an early, mainly monocytic response in the blood of resistant C57BL/10 mice and a predominantly polymorphonuclear neutrophil response in the blood of susceptible BALB/c mice. This contrasted with the greater polymorph response in the livers of lethally infected C57BL/10 mice. Fewer foci of infection were detected at 24 h in the C57BL/10 livers than in the BALB/c livers, although localization at 3 h was similar in the two. The most dramatic finding was common to both strains: a marked depletion of the T-dependent areas of the spleen, which corresponded with a fall in numbers of Thy-1^+ cells in spleen cell suspensions.

MATERIALS AND METHODS

Mice. Inbred female BALB/c and C57BL/10 mice were maintained under conventional conditions in the Microbiology Department Animal Breeding Unit and were infected at 6 to 8 weeks of age.

Bacteria. *L. monocytogenes* was obtained from R. V. Blanden (Australian National University) and maintained by weekly subculture on horse blood agar. It was renewed from freeze-dried stock after fewer than 50 passages. The 50% lethal dose for BALB/c mice was 2×10^3 and that for C57BL/10 was 2×10^5.

Infection and examination of mice. Twenty-four-hour actively growing cultures of *Listeria* were washed from nutrient agar plates with 1% horse serum in distilled water. The inoculum was standardized turbidometrically, using an EEL colorimeter, and injected intravenously in 0.2 ml. The dose was checked retrospectively by viable counts (13). At intervals after infection, mice were anesthetized with ether and bled from the heart. Blood was mixed with 1 drop of preservative-free heparin (Commonwealth Serum Laboratories, Melbourne, Australia) for preparation of smears or quantitation of T- and B-lymphocytes. The following organs were removed and a piece of each was placed in Bouin fixative: spleen, liver, thymus, inguinal and mesenteric lymph nodes, Peyer's patches, heart, lungs, brain, and uterus. For electron microscopy, small pieces of liver were placed in diluted (ca. half-strength) Karnovsky fixative (8). In some experiments spleen, liver, and thymus were weighed before fixing. A weighed fragment of spleen or liver was homogenized for viable bacterial counts while another weighed fragment of spleen was teased carefully into Eisen balanced salts solution containing 10% fetal calf serum and was used to count total nucleated cells and the proportions of T- and B-lymphocytes and "null" cells.

Immunofluorescence. Spleen and peripheral blood cells were examined for T-, B-, and null cells by immunofluorescence, using a Leitz Othromat microscope equipped with Ploem optics and a 200-W mercury burner. After incubation with appropriate antisera (see below) and washing, the cells were examined with a ×10 eyepiece and a ×50 water immersion objective, giving a final magnification of ×650. B-lymphocytes were assayed by direct immunofluorescence, using fluoresceinated polyvalent sheep anti-mouse immunoglobulin. This antiserum was previously titrated and shown to be specific for B-cells (less than 1% of normal T-cells were stained). T-cells were assessed by counting all cells stained with an anti-Thy-1.2 antiserum (14), kindly supplied by J.F.A.P. Miller, followed by the fluoresceinated sheep anti-mouse immunoglobulin serum. Thus, both T- and B-cells were stained, and the percentage of T-cells was obtained by subtracting the counts of directly stained cells from the total stained cells seen with indirect immunofluorescence. In each sample a percentage of small mononuclear cells remained unstained, and these immunoglobulin-negative Thy-1^- cells were referred to as null cells. In each sample 100 to 200 cells were counted.

RESULTS

Tissues were taken from inoculated mice at daily intervals for the first 5 days after infection and then at 2- to 3-day intervals until day 14. Doses of *Listeria* ranging from 2×10^3 to 2×10^5 were used. With the higher dose, susceptible BALB/c mice generally died within the first few days and some resistant C57BL/10 mice also died. However, mice still alive at 5 days survived and remained healthy. Figure 1 shows the listerial numbers in spleen and liver of sublethally infected mice, showing the characteristic restriction of early growth in the liver of resistant mice and the earlier onset of bactericidal activity in these mice (4).

No pathological changes were seen in the brain, kidney, lymph nodes, and heart at any infecting dose examined. The thymus of the BALB/c mice showed rapid loss of cortical tissue within the first 1 to 2 days and this persisted until week 2, when a gradual return to normal occurred. The histological change paralleled the decrease in thymic weight (Fig. 2). No specific focal changes were seen in the thymus, and the tissue in the resistant C57BL/10 mice remained essentially normal.

In the liver, electron microscopy revealed *Listeria* organisms within Kupffer cells 3 h after infection with 10^8 bacteria (Fig. 3). This massive lethal dose was necessary to find bacteria readily in the ultrathin sections and led to multiple infection of the cells. At this time, equal numbers of viable bacteria accumulated in both strains (Table 1), and equivalent numbers of infected cells were seen by light microscopy. By 24 h postinfection, there were more viable bacteria in the susceptible mice (Table 1) and more foci of infection (Fig. 4a and b).

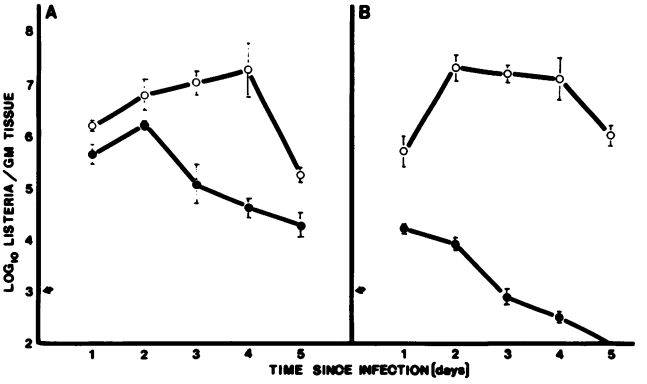

FIG. 1. *Numbers of Listeria in spleen (A) and liver (B) of C57BL/10 (●) or BALB/c (○) mice infected intravenously with 10^3 organisms (arrow).*

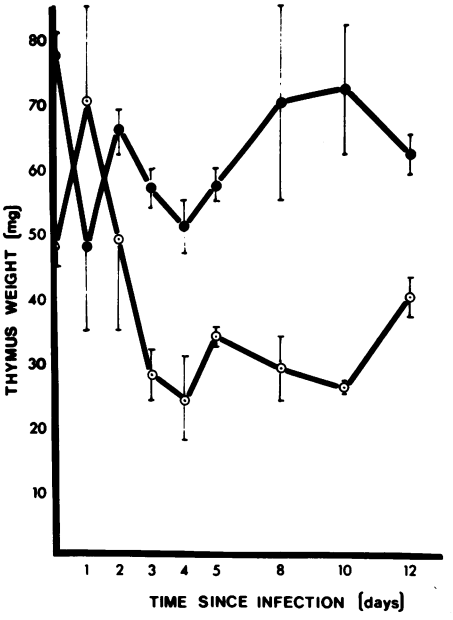

FIG. 2. *Thymic weight of C57BL/10 (●) or BALB/c (○) mice infected intravenously with a sublethal dose (10^3) of L. monocytogenes.*

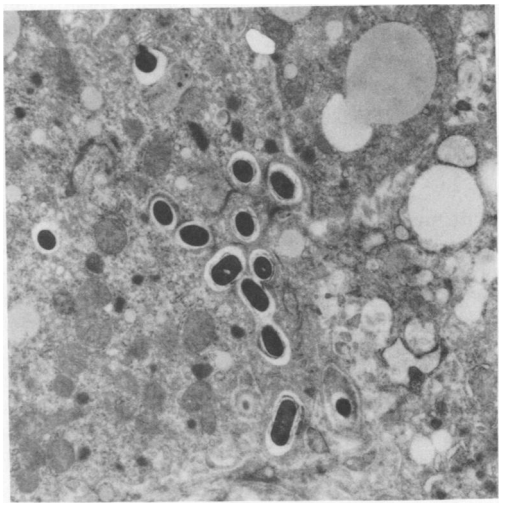

FIG. 3. *Electron micrograph of a portion of the cytoplasm of a Kupffer cell showing numerous ingested Listeria. The sample is from a BALB/c mouse infected 24 h previously. ×10,000.*

Histological changes in the livers of infected mice of both strains consisted of focal areas of granulocytic infiltration with microabscess formation. In the resistant C57BL/10 strain, these focal lesions appeared during the first 48 h and were generally large but rather sparse. A notable feature was the massive infiltration of granulocytes and some mononuclear cells into well-defined foci (Fig. 5). The infiltration was associated with hepatocyte necrosis both within and surrounding the infiltrate. No bacteria were seen within polymorphs by light or electron microscopy. By days 3 and 4, most granulocytes were disintegrating and a few peripheral mononuclear cells were present at the edge of the lesion. Over the next few days the disintegrating polymorphs were removed and the lesion was gradually infiltrated with large mononuclear cells (Fig. 6). By 2 weeks complete resolution of the lesions had occurred without obvious scarring. In some mice which had received larger inocula, large areas of hepatic necrosis were present, and these were frequently not associated with granulocytic infiltration. Similar lesions were seen in the susceptible BALB/c mice at lower infective doses of *Listeria* (Fig. 7).

In contrast to the resistant strain, the susceptible BALB/c mice developed numerous but small hepatic lesions in the first few days after infection (Fig. 8). These were widely distributed and differed from the lesions seen in the C57BL/

TABLE 1. *L. monocytogenes in livers of intravenously infected susceptible or resistant mice*

Dose of *Listeria*	Log_{10} *Listeria*/g of liver ± standard error			
	3 h		24 h	
	C57BL/10	BALB/c	C57BL/10	BALB/c
10^3	<2.00	<2.00	4.00 ± 0.28	5.28 ± 0.10
10^5	3.80 ± 0.10	3.91 ± 0.12	5.79 ± 0.09	6.84 ± 0.03
10^7	5.81 ± 0.11	5.70 ± 0.18	8.00 ± 0.13	9.68 ± 0.10
10^9	7.93 ± 0.09	7.61 ± 0.14	Dead	Dead

10 mice in being much smaller and containing few granulocytes. These early hepatic lesions also showed a more rapid disintegration of the polymorphs. In sublethally infected susceptible mice, the appearance of large mononuclear cells in the liver lesions did not appear until 3 to 4 days. The BALB/c mice, even when inoculated with small doses of *Listeria*, showed much more hepatic necrosis and more extensive and longer-lasting lesions which often developed into microabscesses (Fig. 9). Frequently, large areas of necrotic and noninfiltrated tissue were also present, suggesting the possibility of infarction (Fig. 7).

The major microscopic change in the spleen of both strains was a striking loss of lymphocytes in the T-dependent periarteriolar regions. The changes were of similar magnitude in both strains and occurred even in sublethally infected mice. Loss of lymphocytes was present by 2 days, and on days 3 and 4 the periarteriolar lymphoid tissue was virtually totally ablated and was frequently replaced by numerous granulocytes (Fig. 10). The polymorphs were initially intact but rapidly degenerated to form microabscesses (Fig. 11). After day 5 the T-dependent area was gradually repopulated with lymphocytes. A notable feature was the almost complete sparing of the B-dependent areas of the splenic white pulp. The red pulp was hyperemic and occasionally edematous, and, in a few instances, it developed foci of granulocytic infiltration and microabscesses. However, it is possible that such foci represent a spread of the microabscesses from the adjacent T-dependent area. The red pulp also reverted to normal during week 2. There were no obvious histological changes in the hemopoietic elements present in the red pulp. Gram stains showed *Listeria* organisms scattered throughout the spleen tissue with no preference for red or white pulp or T- or B-dependent areas.

In the spleen the quantitative response of T- and B-cells in the two strains paralleled the histology. Figure 12 shows the absolute number of cells in the spleen during infection of C57BL/10 and BALB/c mice with a sublethal dose of *Listeria*. Both strains showed a striking loss of fluorescein-stained Thy-1^+ T-cells which reached minimum levels (about 10% of normal) on days 3 to 4 (Fig. 12). Thus, at this time, T-cells represented only 0 to 5% of the splenic mononuclear cells, in contrast to the normal 35 to 40%. Both strains also showed similar patterns of recovery, starting on day 5 and reaching preinjection levels by days 8 to 10. B-cells, in contrast, showed a rapid rise to well above preinjection values beginning on days 4 to 5 (Fig. 12). High numbers of B-cells were sustained until day 10. The rise in immunoglobulin-negative Thy-1^- null cells also occurred after day 3 and reached levels two to four times greater than normal (Fig. 12). Spleen weights did not correspond with the rise in total cell numbers, being greater in the BALB/c than in the C57BL/10 mice (Fig. 13). This may reflect the degree of hyperemia and edema seen particularly in the BALB/c mice.

Quantitative estimates of cells in the peripheral blood and spleen of the two strains were generally similar with the notable exception that, in their peripheral blood, the resistant C57BL/10 strain developed an early monocytosis which was not apparent in the BALB/c mice (Fig. 14). In contrast, the BALB/c mice developed a slight but transient neutrophil granulocytosis. In both strains lymphopenia developed over the first few days and was followed by a lymphocytosis by the latter part of week 1. The lymphopenia was due to a marked loss of Thy-1^+ cells (Table 2).

DISCUSSION

It has previously been shown that a single gene, *Lr*, controls *Listeria* resistance in mice and appears to act on very early events following intravenous infection (3, 4). Thus, although the bacteria show the same pattern of initial localization in the spleen and liver of resistant and susceptible mice, by 24 and 48 h there are more bacteria, particularly in the livers of susceptible mice. The onset of immunity is later in the susceptible mice and, at higher doses of bacteria, may not be achieved before the mice die. The

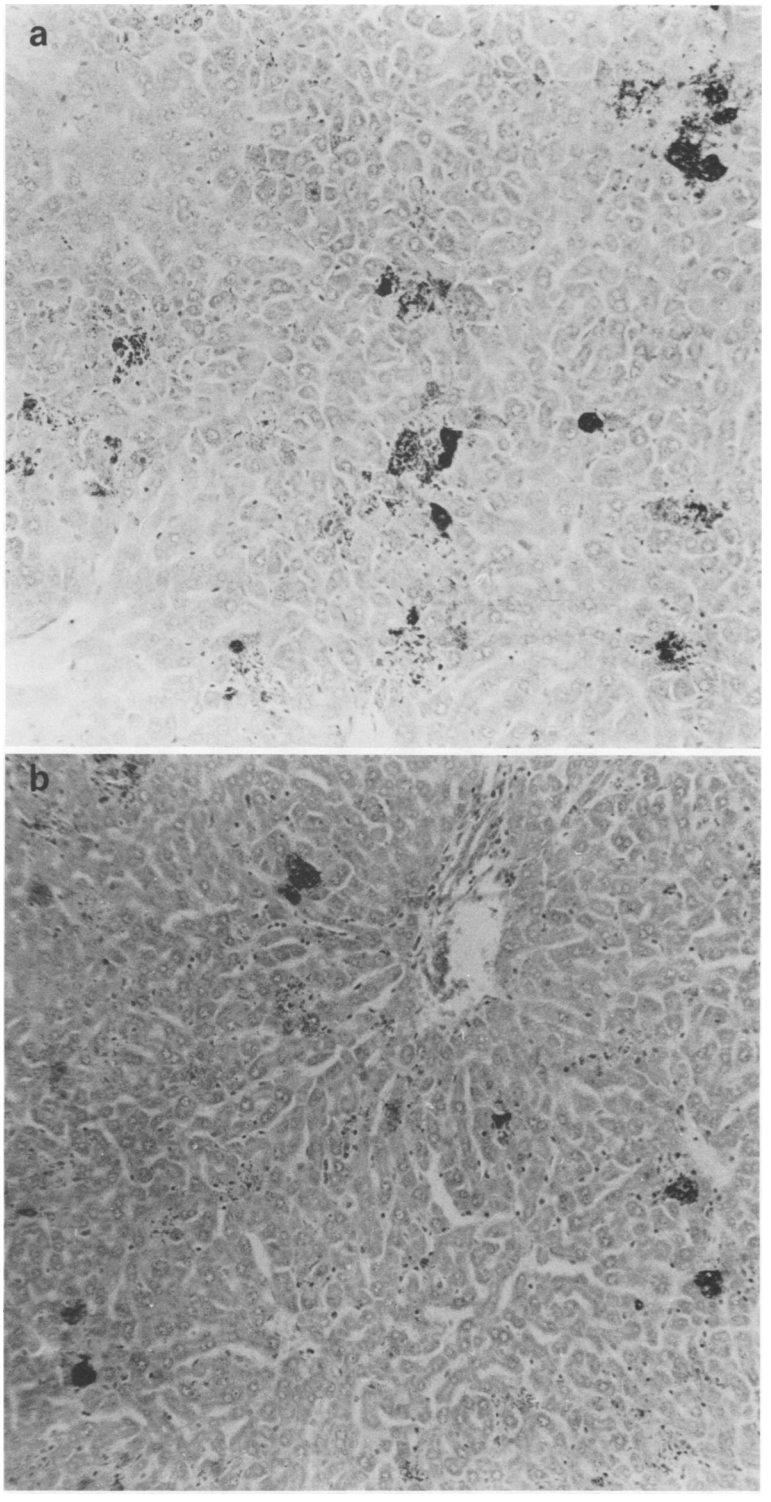

FIG. 4. *(a) Gram-stained section of liver of a BALB/c mouse 24 h after infection with Listeria, showing numerous foci of bacteria. ×270. (b) Similar preparation from a C57BL/10 mouse given an identical dose of Listeria, showing few foci. ×270.*

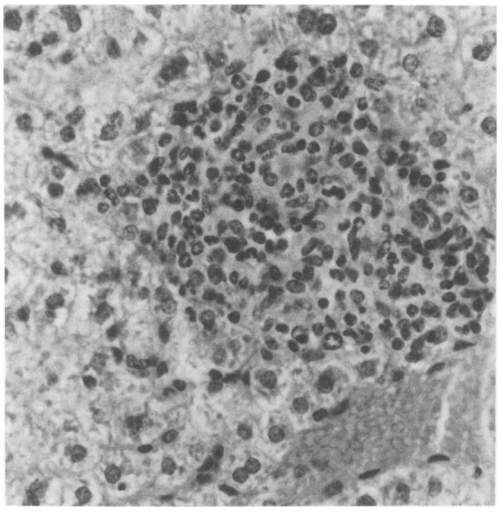

FIG. 5. *Early liver lesion in a C57BL/10 mouse 2 days after infection with a sublethal dose of Listeria. The lesion consists of a focus of infiltrating cells, the majority of which are apparently intact granulocytes. There is also a scattering of mononuclear cells which may represent Kupffer cells. ×300.*

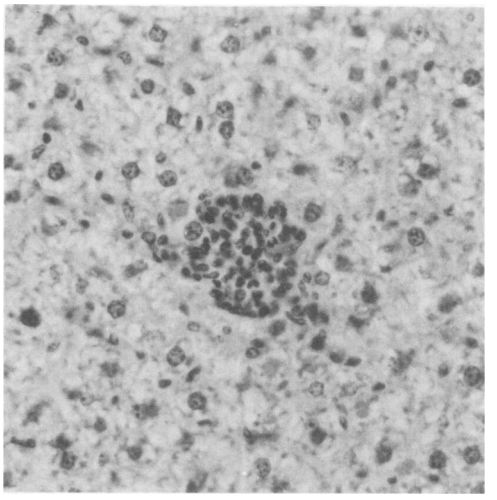

FIG. 6. *Resolving infiltrating focus in the liver of a C57BL/10 mouse 5 days after infection. Very few polymorphs are present and the lesion consists of a focus of mainly small and medium sized mononuclear cells. The surrounding hepatocytes are undamaged. ×300.*

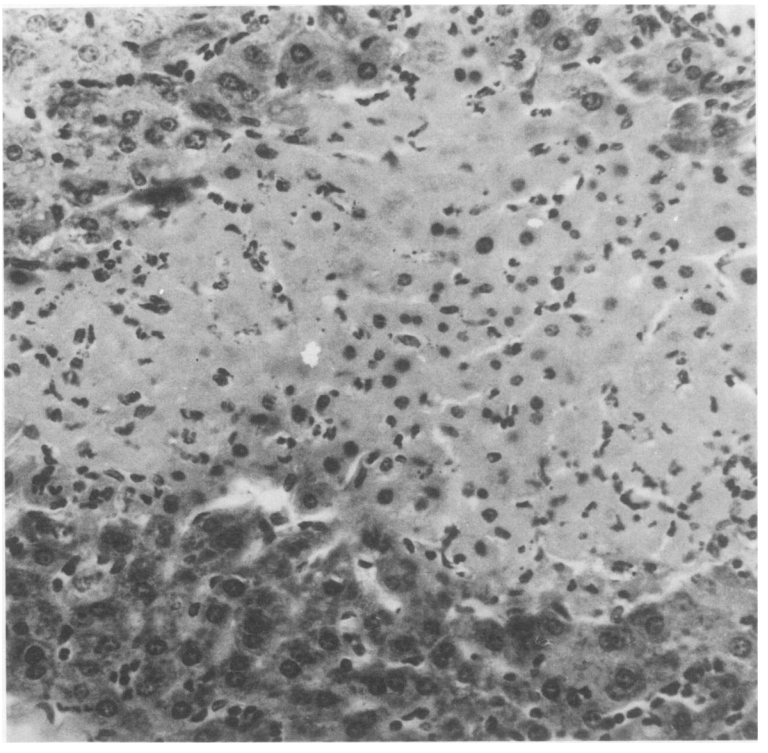

FIG. 7. *Lesion in BALB/c liver 4 days after infection. A large area of necrosis is present, and there are relatively few inflammatory cells visible. ×450.*

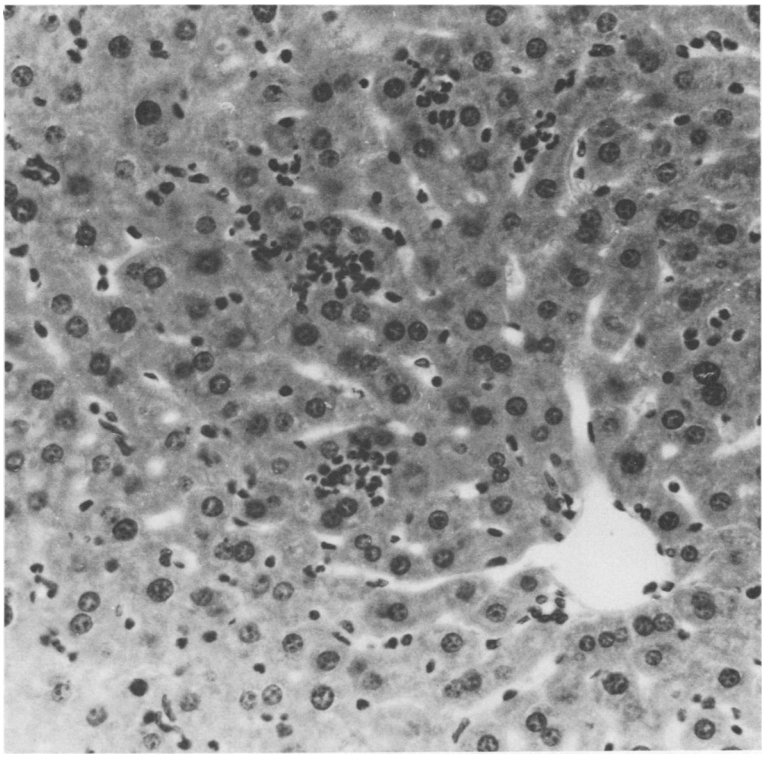

FIG. 8. *Liver lesion 2 days after infection on a BALB/c mouse, showing numerous small foci of infiltrating cells consisting mainly of polymorphs. ×300.*

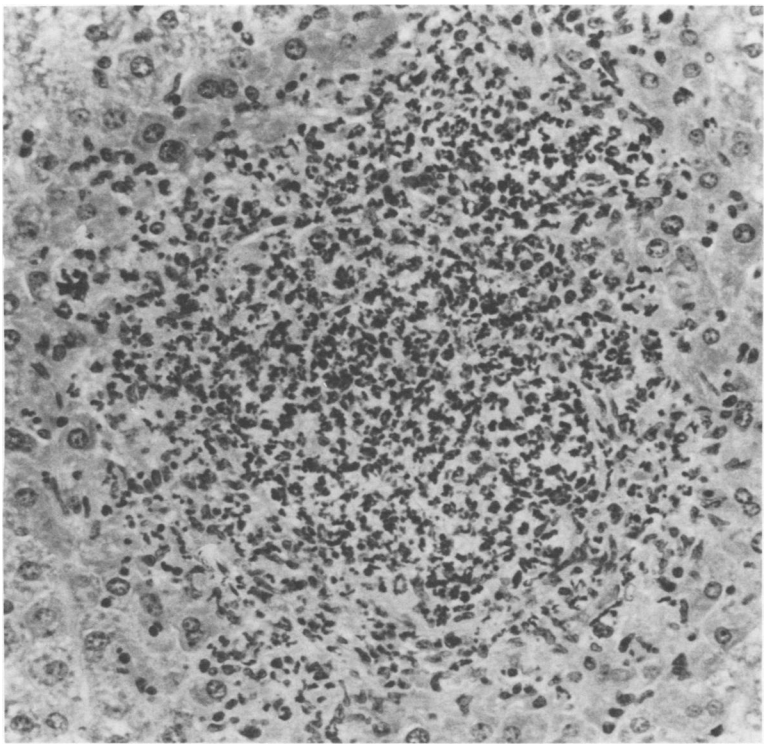

FIG. 9. *Microabscess in liver of a BALB/c mouse 4 days after infection. ×450.*

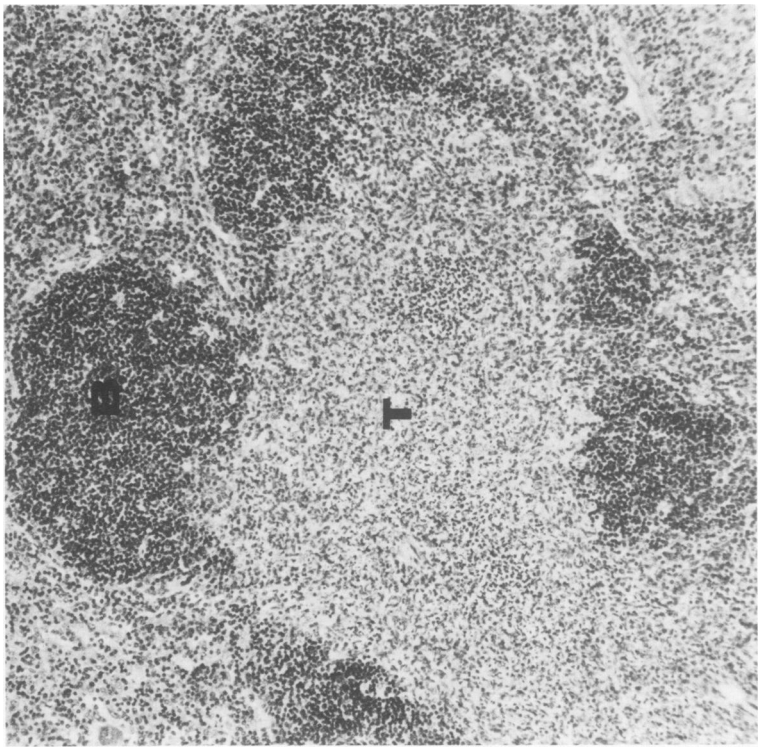

FIG. 10. *Low-power view of the spleen of a C57BL/10 mouse 4 days after infection, showing massive lymphoid depletion of the T-dependent periarteriolar region (T) which contrasts sharply with the lymphoid preservation of the surrounding B-dependent regions (B). ×150.*

present study examined histopathological changes in resistant C57BL/10 and susceptible BALB/c mice for possible correlation with these events.

In terms of differences between the two strains, the liver was perhaps of greatest interest. Initial localization of the bacteria, seen by both light and electron microscopy at 3 h, was similar. Thus, at the high infecting dose used, individual Kupffer cells were multiply infected, indicating that bacterial numbers were not limiting, and equal numbers of Kupffer cells in the two strains were infected, suggesting that each strain had similar numbers of Kupffer cells. By 16 to 24 h, however, there were many more foci of infection in BALB/c than in C57BL/10 mice. In heavily infected animals these foci consisted of central mononuclear cells, with ample cytoplasm and the appearance of Kupffer cells, which were packed with bacteria. It appeared that the number of viable bacteria per liver was related to the number of infected Kupffer cells. It cannot be proven that these were the same Kupffer cells which initially phagocytosed bacteria, since North (18) has shown with radiolabeling studies that incoming monocytes can assume the appearance of Kupffer cells. However, he did not observe these until 2 days after infection in his mice of undefined resistance/susceptibility.

Surrounding infected Kupffer cells were polymorphonuclear neutrophils. In the resistant mice given high doses there were many more bacteria per focus. However, the value of polymorphs in killing *Listeria* organisms is doubtful (2, 23), and it is possible that the scarcity and death of polymorphs in the lesions of high-dosed susceptible mice could be secondary to the large number of foci. Differences between the two strains in the numbers of polymorphs per infective focus were not seen at lower doses, although there were still 10 times more viable bacteria per liver in susceptible then in resistant mice.

Monocytes were not prominent in the early inflammatory response, but small numbers did appear in the livers of resistant mice as early as 2 days postinfection and in susceptible mice by 3 to 4 days. This is consistent with the onset of acquired immunity and downturn in bacterial numbers (18) which occurs at 2 days in C57BL/10 mice and at 3 to 4 days in BALB/c mice. In general, events seen in the livers were similar to those described by others after intravenous (9, 10, 18) or oral (15) infection.

In the spleen, events in the two strains were

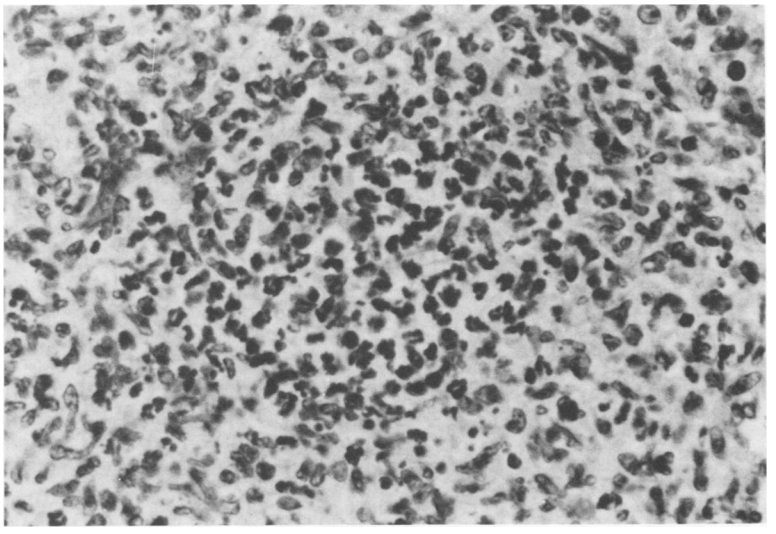

FIG. 11. *Detail of a small microabscess in the T-dependent periarteriolar zone of the spleen in a BALB/c mouse 4 days after infection. ×300.*

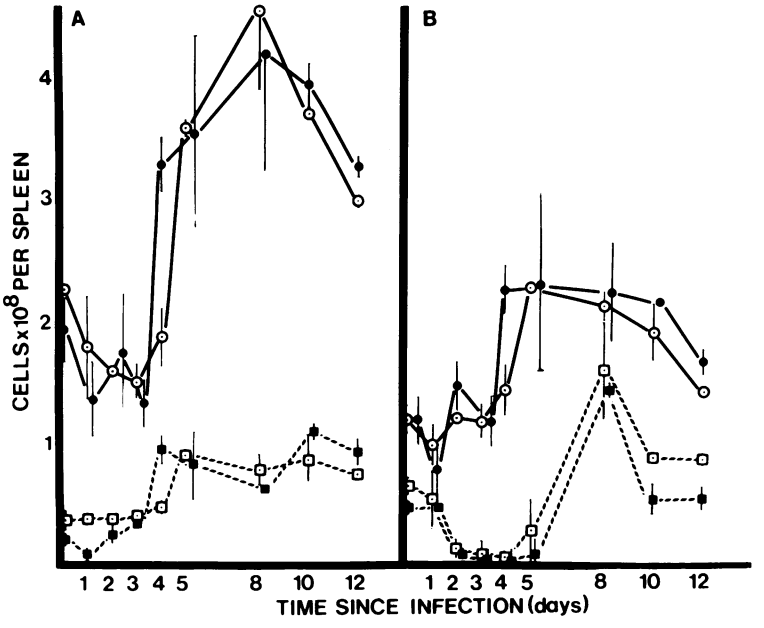

FIG. 12. *Absolute numbers of small mononuclear cells in spleens of C57BL/10 (● and ■) and BALB/c (○ and □) mice infected intravenously with a sublethal dose (10^3 of L. monocytogenes). (A) Total cells (● and ○); Thy-1$^-$ and Ig$^-$ null cells (■ and □). (B) Ig$^+$ lymphocytes (● and ○); Thy-1$^+$ lymphocyte (■ and □).*

remarkably similar. The most striking effect of infection was an almost complete depletion of lymphocytes in the T-dependent periarteriolar regions. When T-lymphocytes in spleen cell suspensions were quantified by using double labeling with anti-Thy-1 and fluoresceinated anti-mouse immunoglobulin sera, it was found that absolute numbers of Thy-1$^+$ cells dropped to 4% of control values at 2 to 4 days, recovering in parallel with histological recovery at 6 to 8 days. Curiously, this striking effect has not been described by others who examined spleen histology (15, 19), possibly because they looked at different times. We found similar T-cell depletion in specific-pathogen-free mice obtained from The Walter and Eliza Hall Institute. Selective deple-

tion of T-cells has also been described in spleens of mice infected with viruses or parasites (1, 22) and is a feature of lymph node pathology and blood in human lepromatous leprosy (6, 24). Slight and delayed T-dependent area depletion has also been described in the spleen of mice given *Mycobacterium bovis* BCG (11).

In contrast to the depletion of T-cells, B-cells and null cells in spleen suspensions rose to levels above normal 3 to 4 days after infection. This rise was more marked in resistant than in susceptible mice and led to an increase in total spleen cells. Since the exact identity of the Thy-1$^-$ immunoglobulin-negative null cells is not established, the significance of this rise is not known. In fact, histological events more closely related to infection are more difficult to define in the spleen than in the liver because of the more heterogeneous splenic population. However, again an initial polymorph response gave way to a monocytic response by days 5 to 8.

Differential blood counts showed an increase in monocytes in the C57BL/10 mice as early as 1 day after infection. Whether monocytes are able to enter the lesions in the liver and spleen at this time was not ascertained, but they were certainly not prominent there (above). The blood response in the BALB/c mice was mostly polymorphonuclear, although a small increase in monocytes was observed on day 4. As in the

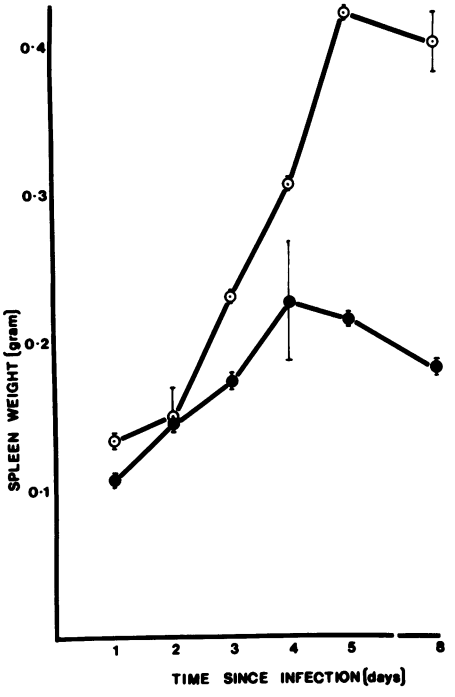

FIG. 13. *Spleen weights of C57BL/10* (●) *or BALB/c* (○) *mice infected intravenously with a sublethal dose (10^3) of L. monocytogenes.*

TABLE 2. *Lymphocytes in the peripheral blood of normal or Listeria-infected mice*

Strain	Cells per ml		
	Thy-1$^+$	Immunoglobulin positive	Null
Uninfected			
BALB/c	3.5×10^6	3.3×10^6	3.5×10^6
C57BL/10	2.1×10^6	4.0×10^6	1.8×10^6
3-day infected[a]			
BALB/c	0.6×10^6	4.2×10^6	3.0×10^6
C57BL/10	0.7×10^6	5.3×10^6	2.0×10^6

[a] Mice infected intravenously with 10^3 *Listeria* and bled from the heart under ether anaesthetic 3 days later. Uninfected mice were similarly bled.

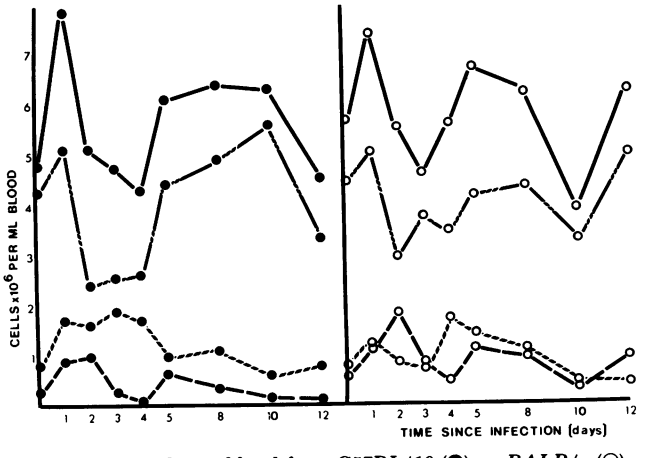

FIG. 14. *Differential cell counts on heart blood from C57BL/10* (●) *or BALB/c* (○) *mice infected intravenously with a sublethal dose (10^3) of L. monocytogenes. Symbols: Total leukocytes* (○——○); *lymphocytes* (○—.—○); *monocytes* (○-----○); *polymorphs* (○— —○).

spleen, there were fluctuations in the lymphocyte population, resulting largely from a decrease in T-lymphocytes on days 2 to 4. Immunoglobulin-positive B-lymphocytes and Thy-1$^-$ immunoglobulin-negative null cells remained roughly constant.

In view of the loss of T-cells in spleen and blood, it is surprising that no corresponding changes were seen in the mesenteric and inguinal lymph nodes. The other organs examined, Peyer's patches, heart, lung, brain, and nonpregnant uterus, showed no changes during infection.

Thymus atrophy, judged by both weight and histology, was seen in the susceptible BALB/c mice, but not in the resistant C57BL/10 mice. Since even with sublethal doses, the BALB/c mice go through a phase of obvious morbidity, this may simply be due to stress.

The mechanism of T-cell depletion remains unknown. However, the histological appearance of the splenic T-dependent areas, with loss of lymphocytes and the appearance of polymorphs and the synchronous loss of T-cells in the peripheral blood, is more suggestive of T-cell death than of migration of T-cells from the spleen. In contrast, it is known that *L. monocytogenes* has a B-cell mitogen (5), and there is indeed an increase in absolute numbers of B-cells in the spleen and peripheral blood. The T-cell depletion we observed in the spleen immediately precedes and includes the period during which it first becomes possible to adoptively transfer immunity to normal syngeneic mice of either strain C57BL/10 or strain BALB/c (4). Therefore, at one stage there must be an enormously enriched population of *Listeria*-specific T-lymphocytes before the general T-cell population recovers. Furthermore, recovery occurs during a period of increased lymphocyte proliferation in the spleen (4, 17), although again we do not know whether recovery depends on this proliferation or on recruitment of T-cells from outside that spleen.

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LITERATURE CITED

1. **Askonas, B. A., A. C. Corsini, C. E. Clayton, and B. M. Ogilvie.** 1979. Functional depletion of T- and B-memory cells and other lymphoid cell subpopulations during trypanosomiasis. Immunology **36**:313-321.
2. **Bennett, M., and E. E. Barker.** 1977. Marrow dependent cell function in early stages of infection with *Listeria monocytogenes*. Cell Immunol. **33**:203-210.
3. **Cheers, C., and I. F. C. McKenzie.** 1978. Resistance and susceptibility of mice to bacterial infection: genetics of listeriosis. Infect. Immun. **19**:755-762.
4. **Cheers, C., I. F. C. McKenzie, H. Pavlov, C. Waid, and J. York.** 1978. Resistance and susceptibility of mice to bacterial infection: course of listeriosis in resistant or susceptible mice. Infect. Immun. **19**:763-770.
5. **Cohen, J. W., G. E. Rodriguez, P. D. Kind, and P. A. Campbell.** 1975. Listeria cell wall antigen: a B cell mitogen. J. Immunol. **114**:1132-1134.
6. **Dwyer, J. U., W. E. Bullock, and J. P. Fields.** 1973. Disturbance of the blood T:B lymphocyte ratio in lepromatous leprosy. N. Engl. J. Med. **288**:1036-1039.
7. **Fowles, R. E., I. M. Fajaro, J. L. Lebowitch, and J. R. David.** 1973. The enhancement of macrophage bacteriostasis by products of activated lymphocytes. J. Exp. Med. **138**:952-964.
8. **Karnovsky, M. J.** 1965. A formaldehyde-glutaraldehyde fixative of high osmobility for use in electron microscopy. J. Cell Biol. **27**:137A.
9. **Lannigan, R., E. Skamene, P. A. L. Kongshavn, and W. P. Duguid.** 1979. Morphology of liver lesions in experimental listeriosis in splenectomised mice. RES J. Reticuloendothel. Soc. **25**:457-461.
10. **Mackaness, G. B.** 1962. Cellular resistance to infection. J. Exp. Med. **116**:381-406.
11. **Meyer, E. M., and E. Grundmann.** 1980. BCG-induced changes in size of thymic cortex and thymus-dependent area in spleen and lymph nodes of mice. Clin. Immunol. **39**:60-65.
12. **Miki, K., and G. B. Mackaness.** 1964. The passive transfer of acquired resistance to *Listeria monocytogenes*. J. Exp. Med. **120**:93-103.
13. **Miles, A. A., and S. S. Misra.** 1938. Estimation of the bactericidal power of blood. J. Hyg. **28**:732-748.
14. **Miller, J. F. A. P., and J. Sprent.** 1971. Cell to cell interaction in the immune response. VI. Contribution of thymus-derived cells and antibody forming cell precursors to immunological memory. J. Exp. Med. **134**: 66-82.
15. **Miller, J. K., and J. Burns.** 1970. Histopathology of *Listeria monocytogenes* after oral feeding in mice. Appl. Microbiol. **19**:772-775.
16. **Nathan, C. F., H. G. Remold, and J. R. David.** 1973. Characterization of a lymphocyte factor which alters macrophage functions. J. Exp. Med. **137**:275-290.
17. **North, R. J.** 1969. Cellular kinetics associated with the development of acquired cellular resistance. J. Exp. Med. **130**:299-314.
18. **North, R. J.** 1970. The relative importance of blood monocytes and fixed macrophages to the expression of cell mediated immunity to infection. J. Exp. Med. **132**: 521-533.
19. **North, R. J.** 1972. The action of cortisone acetate on cell mediated immunity to infection: histogenesis of the lymphoid cell response and selective elimination of committed lymphocytes. Cell. Immunol. **3**:501-515.
20. **North, R. J., and J. F. Deissler.** 1975. Nature of "memory" in T-cell-mediated antibacterial immunity: cellular parameters that distinguish between the active immune response and a state of "memory." Infect. Immun. **12**: 761-767.
21. **Skamene, E., P. A. M. Kongshavn, and D. H. Sachs.** 1979. Resistance to *Listeria monocytogenes* in mice: genetic control by genes that are not linked to the H-2 complex. J. Infect. Dis. **139**:228-231.
22. **Tandon, P., U. C. Chaturvedi, and A. Mather.** 1979. Differential depletion of T-lymphocytes in the spleen of dengue virus infected mice. Immunology **37**:1-6.
23. **Tatsukawa, K., M. Mitsuyama, K. Takeya, and K. Nomoto.** 1979. Differing contribution of polymorphonuclear cells and macrophages to protection of mice against *Listeria monocytogenes* and *Pseudomonas aeruginosa*. J. Gen. Microbiol. **115**:161-166.
24. **Turk, J. L., and M. F. R. Waters.** 1968. Immunological basis for depression of cellular immunity and the delayed allergic response in patients with lepromatous leprosy. Lancet **ii**:436-438.