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Effect of infection by lactic dehydrogenase virus on expression of intercellular adhesion molecule-1 on vascular endothelial cells of pancreatic islets in streptozotocin-induced insulitis of CD-1 mice

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Summary. Streptozotocin (SZ)-induced insulitis, which is an animal model for insulin-dependent diabetes mellitus, was suppressed by lactic dehydrogenase virus (LDV) infection. There were no differences in degenerative and necrotic changes of islet cells between SZ-treated mice and SZ-treated mice with LDV infection during the pre-insulitis phase. The degree of insulitis was more severe and the plasma glucose levels were higher in SZ-treated mice than in SZ-treated mice with LDV infection. Severe degenerative and necrotic changes of cells with mononuclear cell infiltration into the islets were seen in the SZ-treated mice. Infiltration of these cells into islets was less in SZ-treated mice with LDV infection. During the pre-insulitis phase, there was slight expression of intercellular adhesion molecule-1 (ICAM-1) on the surface of vascular endothelial cells in and/or around islets in both groups. ICAM-1 expression on vascular endothelial cells increased in parallel to the degree of insulitis. The degree of this expression in SZ-treated mice was higher than in SZ-treated mice with LDV infection. These results suggest that expression of ICAM-1 on vascular endothelial cells in SZ-treated mice may be important for the development of insulitis. Also, decreased expression of ICAM-1 in the islets may be responsible for the inhibition of the development of insulitis seen in SZ-treated mice with LDV infection.

Keywords: insulitis, LDV, SZ, ICAM-1, endothelium

Lactic dehydrogenase virus (LDV) is unique as a model for modulation of inflammatory and immune reactions without pathological changes. The host is the mouse, and target cells are subpopulations of macrophages (Rowson & Mahy 1985). LDV infection prevents autoimmune reactions and autoimmune diseases (Hayashi *et al.* 1992; 1993; Inada & Mims 1986a; Oldstone & Dixon 1972; Takei *et al.* 1992) in mice.

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On the other hand, multiple low-dose streptozotocin (SZ)-induced diabetes in mice is considered as a model of insulin dependent diabetes mellitus (IDDM) (Like & Rossini 1976). IDDM may be the result of cell-mediated immunity, because mononuclear cell infiltration is seen in and around islets in SZ-treated mice (Nakamura *et al.* 1984). SZ-induced insulitis is inhibited in mice treated with anti-T cell antibody (Herold *et al.* 1987) or silica (Oschilewski *et al.* 1985). These data suggest that immunologic injury by mononuclear cells may cause damage to islets. However, exact mechanisms are

largely unknown. The cell adhesion molecules play an important role in various inflammatory and immune responses (Altmann *et al.* 1989; Dustin & Springer 1988; Osborn *et al.* 1989). Previously we suggested that intercellular adhesion molecule-1 (ICAM-1) and lymphocyte function-associated antigen-1 (LFA-1) interactions are important for the development of SZ-induced insulitis, since SZ-induced insulitis is inhibited by treatment with anti-ICAM-1 and anti-LFA-1 monoclonal antibodies (Hayashi *et al.* 1994). SZ-induced insulitis is also reduced by LDV-infection. As suggested by our previous observations, LDV-infection may suppress ICAM-1 expression on vascular endothelium in and around islets. Thus, the present study investigates the effect of LDV infection on SZ-induced insulitis in ICR (CD-1) mice with special reference to the expression of ICAM-1 on vascular endothelial cells in and around islets.

Materials and methods

Animals

Eight-week-old male ICR (CD-1) mice were obtained from SLC Co. (Shizuoka, Japan). Autoclaved pellets MF (Oriental Yeast, Tokyo, Japan) and tap water were supplied *ad libitum*. Each set of experiments consisted of ten mice.

Virus

A stock preparation of LDV (Hayashi *et al.* 1988) kindly supplied by Dr A.L. Notkins (National Institute of Dental Research, National Institutes of Health, USA) was used throughout the experiments. Mice were infected with virus at the age of 9 weeks by intraperitoneal injection of $10^{4.5}$ median infectious doses. Mice were infected with LDV just before the first SZ injection (this day is referred to as day 0).

Experimental procedure

Streptozotocin (SZ: Sigma, St Louis, MO, USA) was dissolved in citrate buffer (pH 4.0 ~ 4.5) before use. Dose of injection was adjusted to 40 mg in 0.2 ml citrate buffer per kg. Groups of mice with or without LDV infection were injected intraperitoneally with SZ daily for 5 days (days 0–4). Glucose concentrations in the blood of fasting mice and histopathology were examined at 1, 3, 5, 7, 14 and 28 days.

Pancreas was fixed in Bouin's solution and sections were stained with haematoxylin and eosin (HE), and aldehyde-fuchsin. The incidence of insulitis, including peri-insulitis, was calculated as the percentage of islets with insulitis within one mouse. Also, for histologic score of insulitis, each pancreas was microscopically evaluated for the presence of inflammatory cell infiltration as follows: 0; no insulitis; 1, peri-insulitis; 2, insulitis 25% of islet area; 3 insulitis 25–50% of islet area; and 4, insulitis 50% of islet area. The grade of insulitis in a mouse was expressed as the average score calculated by the following equation: score index = total score/number of islets. About 20 different islets were examined.

Detection of intracellular adhesion molecule-1 (ICAM-1) in and around islets

ICAM-1 in the pancreas was detected by indirect immunofluorescence. In brief, pancreata were frozen in *n*-hexane and stored at −70°C. Cryostat sections were incubated with rat monoclonal antibody (IgG2a) against mouse ICAM-1 (Seikagaku Co., Tokyo, Japan) or rat monoclonal antibody (IgG2b) against mouse lymphocyte function-associated antigen-1 (LFA-1; CD11a, Pharmingen, CA, USA) at a dilution of 1:40 for 30 minutes and then incubated with fluorescein isothiocyanate-conjugated goat anti-rat immunoglobulin G (heavy and light chains; Jackson Immunores. Lab. Inc., PA, USA) at a dilution of 1:70 for 30 minutes. The intensity and distribution of fluorescence (immunofluorescence score for ICAM-1) was graded on a 0–3 scale as follows. 0, faint and limited fluorescence on endothelial cells around islets; 1, the fluorescence for ICAM-1 increased slightly on endothelial cells in and/or around islets; 2–3, the fluorescence increased diffusely on the endothelial cells and staining was acccentuated in and around islets. At least 10 islets were examined for each animal and the index of fluorescence was calculated with the same method as histologic score index. Immunofluorescence for ICAM-1 was examined on day 0 (just before the first day of SZ injection) and on days 3, 7, 14 and 28. Also, frozen sections from pancreas fixed in 10% neutral buffered formalin (pH 7.4) on day 14 were immunostained and bound antibody was visualized. In brief, endogenous peroxidase was inactivated by incubation in 3.5% methanol–hydrogen peroxide for 30 minutes and secondary antibody was blocked by incubation with 5% normal goat serum for 10 minutes. Sections were then incubated with the primary monoclonal antibody (anti-ICAM-1 or anti-LFA-1 described above) at the optimal dilution (1:20) for 3 hours, followed by incubation with peroxidase-conjugated goat anti-rat IgG (heavy and light chains; at a dilution of 1:40; E-Y Lab., CA, USA) for 40 minutes. The chromogen used was diaminobenzidine (DAB; Kanto Chem. Japan, 0.05% DAB, and

0.01% H_2O_2 in 0.05 mol Tris-buffered saline; TBS, pH 7.6). The slides were counterstained with methyl green, dehydrated, and coverslipped. Between all steps, sections were rinsed in 0.05 mol TBS and were incubated at room temperature. Each specimen was run with one negative control in which the primary antibody was substituted by TBS.

Statistics

In all experiments data points are expressed as the mean ± standard error (s.e.). Differences between means with P values less than 0.05 ($P < 0.05$) were considered to be significant.

Results

Effect of LDV infection on plasma glucose concentrations

Plasma glucose concentrations in uninfected and LDV-infected groups of mice without SZ treatment were about 150 mg/dl during the experimental periods (data not shown). As shown in Figure 1a, glucose levels over 200 mg/dl were seen 7–28 days after the first SZ treatment (day 0) in SZ-treated mice (SZ group), whereas only a slight increase in glucose levels was seen in SZ-treated mice with LDV infection (SZ + LDV group). There were statistical differences in glucose concentrations between SZ and SZ + LDV groups ($P < 0.01$; comparison at 14 and 28 days).

Incidence and histologic score of insulitis

As shown in Figure 1b and c, incidence of insulitis and score index (degree of insulitis) increased prominently on day 14, and incidence and high score index persisted until 28 days in the SZ group. Incidence and score index in SZ + LDV group were markedly suppressed ($P < 0.01$; comparison at 14 and 28 days). No insulitis was seen in uninfected or LDV-infected groups without SZ treatment during the experimental periods (data not shown).

Histopathology

There were no histopathological changes in the pancreata of uninfected or LDV-infected groups without SZ treatment. Oedematous changes and a few degenerative and necrotic cells in the islets were detected in both SZ and SZ + LDV groups, respectively (Figure 2a and b) on day 5. Also, decrease in staining intensity by aldehyde-fuchsin was detected in all SZ treated-mice with or without infection. Moderate peri-islet infiltration of macrophages and lymphocytes were seen in both groups on day 7. On day 14 necrotic cells increased in SZ group with severe infiltration of macrophages and lymphocytes into islets (Figure 2c). However, the degree in the SZ + LDV group was less than in the SZ group. The severity of the inflammatory changes varied considerably among animals and within the pancreas with some islets showing little change while others showed moderate to extensive cell infiltration. In some areas of the pancreas, only a portion of the islet was involved. In the

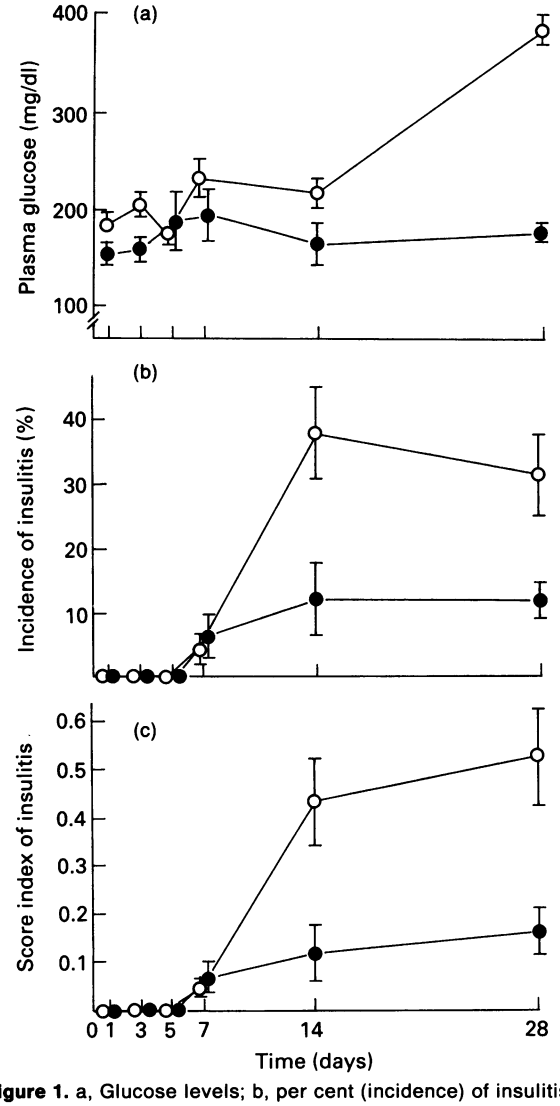

Figure 1. a, Glucose levels; b, per cent (incidence) of insulitis; and c, score index (grade of insulitis) in mice treated with SZ under the condition ●, with or ○, without LDV infection. Each point indicates the mean ± s.e..

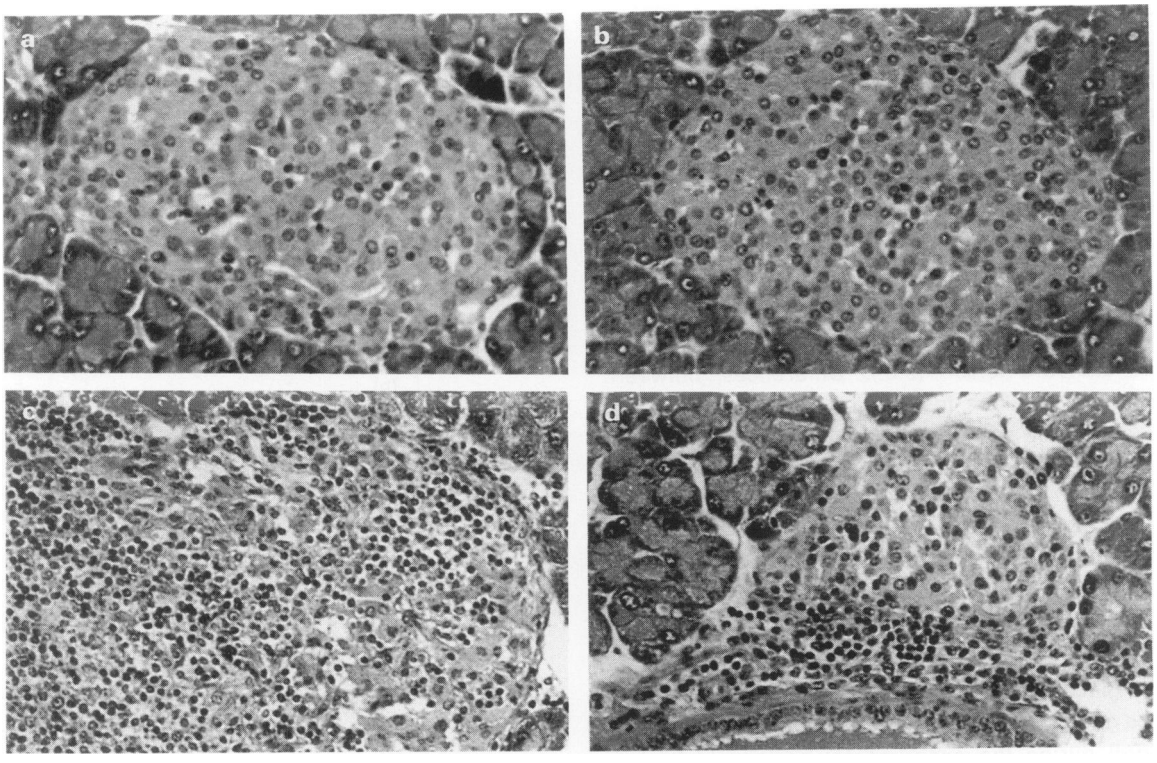

Figure 2. Section of pancreas showing focal necrotic changes of islet cells in a, an uninfected and b, an infected mouse on day 5 after first treatment with SZ. c, Islet cells showing extensive necrosis and infiltration of mononuclear cells in an uninfected mouse, and focal necrosis of islet and mild infiltration of mononuclear cells in an LDV-infected mouse on day 14 after first treatment with SZ. H & E. ×250.

SZ + LDV group, slight necrotic changes with macrophage and lymphocyte infiltration in and around islets (Figure 2d) were seen. Though these changes persisted on day 28, there was an increase in atrophic islets in SZ group as compared to SZ + LDV group.

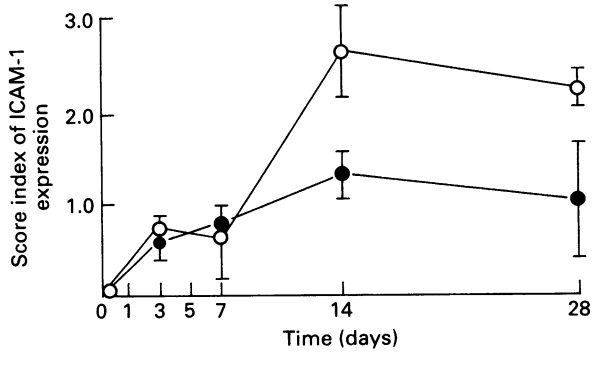

Figure 3. Immunofluorescence evaluation (score index; grade of intensity and distribution) on expression of ICAM-1 on endothelial cells in and/or around islet in ○, uninfected and ●, LDV-infected mice. Each point indicates the mean ± s.e.

Development of expression of ICAM-1 on endothelium

Figure 3 shows score index (the intensity and distribution of ICAM-1 expression) on endothelial cells in and/or around islets of both groups of mice. There was faint and limited expression of ICAM-1 on endothelial cells around islets before the SZ treatment. Slight expression of ICAM-1 on endothelial cells in and/or around islets of both SZ and SZ + LDV groups was seen on days 3 and 7. However, there was no difference in ICAM-1 expression between the two groups of mice (Figure 3). ICAM-1 expression on endocrine cells in islets was not seen in either group of mice at this stage.

On days 14 and 28, in the SZ group most endothelial cells in the islets and peri-islets with or without cell infiltration developed prominent ICAM-1 expression on their surface (Figure 4a). However, ICAM-1 expression of endothelial cells in the SZ + LDV group was weaker (Figure 4b) than in the SZ group (Figure 3, $P < 0.01$). Endocrine cells did not usually express ICAM-1 in either group of mice. Rarely, ICAM-1 was expressed on endocrine cells of islet with marked inflammatory infiltrates. Most of the infiltrated cells also expressed ICAM-1

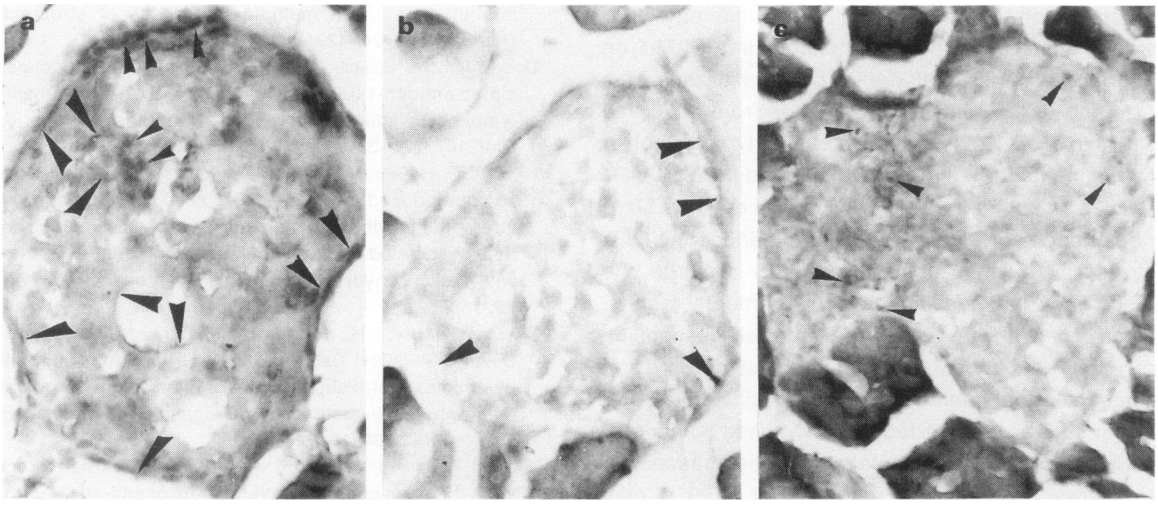

Figure 4. Immunoperoxidase stainings of an islet in a, c, uninfected mice or b, an infected mouse with SZ on day 14. Intense ICAM-1 expression on endothelium in and around an islet (a; large arrow heads) as well as infiltrated cells(a; small arrow heads) and a weak ICAM-1 expression on endothelial cells around an islet (b; large arrow heads). LFA-1 positive mononuclear cells were seen (c; small arrow heads). a And b, ×250; c, ×100.

(Figure 4a). Infiltrated cells in and/or around islets expressed LAF-1 (Figure 4c), though the intensity varied in both groups.

Discussion

The present study shows that SZ-induced insulitis in CD-1 mice is inhibited by infection with LDV. Differences in destructive changes between SZ and SZ+LDV groups were negligible in the early stages (preinsulitis phase) following SZ treatment in both groups. Expression of ICAM-1 on the surface of endothelial cells in and around islets in SZ-treated mice was seen prior to the infiltration of LFA-1 positive mononuclear cells and increased in parallel to the degree of insulitis. The degree of ICAM-1 expression was higher in the SZ group than in the SZ+LDV group. The results suggest that ICAM-1 expression on endothelium may be responsible for the development of SZ-induced insulitis in mice, since adhesion molecules are essential for local inflammation (Osborn *et al.* 1989).

It has been reported that several cytokines induce ICAM-1 expression on endothelial cells (Dustin & Springer 1988). The mechanisms of cytokine production in SZ-treated mice may be as follows. During the pre-insulitis phase the multiple low-dose SZ treatment impairs functionally insulin-producing cells and may cause some lysis due to direct cytotoxic activity (Bonnevie-Nielsen *et al.* 1981). Subsequently a specifically sensitized T-lymphocyte is stimulated with islet antigens and blastogenic responses in lympho-reticular organs may occur, since β cell surface proteins may indeed be immunogenic (Wilson & Leither 1990). Then T cells, especially helper T cells (Prud'homme *et al.* 1984), may release cytokines such as γ-interferon (IFN) (Mossmann & Coffman 1989). Thereafter γ-IFN in the circulation may activate endothelial ICAM-1 expression non-specifically. Endothelial cells in the pancreatic interstitium and pancreatic ducts did show increased expression of ICAM-1 (data not shown). At the same time, SZ may activate intraislet macrophages (Kolb-bachofen *et al.* 1988), resulting in release of cytokines such as interleukin-1 (IL-1) (Snyder & Unanue 1982). These cytokines may cause further increase in ICAM-1 expression on the endothelial cells. Further studies are needed to clarify these points, including the role of tumour necrosis factor-α, which are stimulators of ICAM-1 expression (Picarella *et al.* 1993; Pober *et al.* 1986), in SZ-treated mice. At the insulitis phase, infiltrated cells in and around islets may release cytokines as described above, leading to additional effects on expression of ICAM-1.

The potential for ICAM-1 expression by inflammatory cytokines on isolated mouse pancreatic β cells was recently reported by Prieto *et al.* (1992). However, they could not detect ICAM-1 expression on β cells in cryostat sections of NOD mice by immunohistochemistry. In contrast, the present results demonstrated ICAM-1 on endocrine cells. The explanation for this discrepancy is not clear. Comparison of these studies is difficult because the

pathogenesis on the development of insulitis may differ from each other. Endocrine cells expressing ICAM-1 on their surface were associated with severe infiltration. This may be due to the release of cytokines from infiltrated cells (Prieto *et al.* 1992), leading to efficient expression of ICAM-1 in the infiltrated areas. As reported here, ICAM-1 expression on endocrine cells was usually negative. This may be due to short-lived expression on endocrine cells (Prieto *et al.* 1992). Another possibility may be the influence of certain conditions or environmental factors. Vives *et al.* (1989) have reported that cell suspension preparations and monolayer cultures, but not cryostat sections, of normal human islets were positive for ICAM-1. Further studies are needed to clarify these points.

ICAM-1 expression on isolated β cells induced by inflammatory cytokines (Prieto *et al.* 1992) may enhance the ensuing damage mediated by infiltrating immuno-competent cells (Hutchings *et al.* 1990). Also, Vives *et al.* (1989) suggested that this expression may be important during the initial insulitis process. In addition, ICAM-1 expression on infiltrating mononuclear cells could be important for antigen presentation and induction of cytokine release (Patarroyo 1991).

In the early phase, in SZ-treated mice expression of ICAM-1 on the surface of endothelium in and/or around islets may be induced by systemically produced cytokines as described above. At the same time, islet-derived chemotactic factors, that induce direct migration of leucocytes, are released (Muir *et al.* 1991). As a result, circulating leucocytes may be trapped in the islet. Subsequently, leucocytes trapped in the islets may also produce cytokines which may cause further expression of ICAM-1, resulting in the further development of insulitis. As discussed before (Hayashi *et al.* 1994), in LDV-infected mice each of these steps and/or cytokine production being responsible for ICAM-1 expression may be inhibited by induction of suppressor T cells (Inada & Mims 1986b), suppressed IL-1 production by macrophages (Hayashi *et al.* 1991), decreased chemotactic activity (Stevenson *et al.* 1980) and impaired antigen presenting activity (Isakov *et al.* 1982) of macrophages and selective loss of Ia positive macrophages (Inada & Mims 1985), causing suppression of development of insulitis.

References

Altmann D.M., Hogg N., Trowsdale J. & Wilkinson D. (1989) Cotransfection of ICAM-1 and HLA-DR reconstitutes human antigen-presenting cell function in mouse L cells. *Nature* **338,** 512–514.

Bonnevie-Nielsen V., Steffes M.W. & Lernmark A. (1981) A major loss in islet mass and β-cell function precedes hyperglycemia in mice given multiple low doses of streptozotocin. *Diabetes* **30,** 424–429.

Dustin M.L. & Sringer T.A. (1988) Lymphocyte function-associated antigen-1 (LFA-1) is one of at least 3 mechanisms for T lymphocyte adhesion to cultured endothelial cells. *J. Cell. Biol.* **107,** 321–331.

Hayashi T., Hashimoto S. & Kameyama Y. (1994) Reduced streptozotocin-induced insulitis in CD-1 mice by treatment with anti-intercellular adhesion molecule-1 and anti-lymphocyte function associated antigen-1 monoclonal antibodies together with lactic dehydrogenase virus infected. *Int. J. Exp. Path.* **75,** 117–121.

Hayashi T., Iwata H., Hasegawa T., Ozaki M., Yamamoto H. & Onodera T. (1991) Decrease in neutrophil migration induced by endotoxin and suppression of interleukin-1 production by macrophages in lactic dehydrogenase virus-infected mice. *J. Comp. Path.* **104,** 161–170.

Hayashi T., Mori I. & Yamamoto H. (1992) Lactic dehydrogenase virus infection prevents development of anti-nuclear antibody in (NZB × NZW)F_1 mice; role of prostaglandin E_2 and macrophage Ia antigen expression. *Int. J. Exp. Path.* **73,** 593–601.

Hayashi T., Noguchi T. & Kameyama Y. (1993) Suppression of development of anti-nuclear antibody and glomerulonephritis in NZB × $NZWF_1$ mice by persistent infection of lactic dehydrogenase virus: possible involvement of superoxide anion as a progressive effector. *Int. J. Exp. Path.* **74,** 553–556.

Hayashi T., Salata K., Kingman A. & Notkins A.L. (1988) Regulation of enzyme levels in the blood: influence of environmental and genetic factors on enzyme clearance. *Am. J. Path.* **132,** 503–511.

Herold K.C., Nontag A.G. & Fitci F.W. (1987) Treatment with anti-T lymphocyte antibodies prevents induction of insulitis in mice given multiple dose of streptozotocin. *Diabetes* **36,** 796–801.

Hutchings P.R., Rosen H., O'Reilly L., Simpson E., Gordon S. & Cooke A. (1990) Transfer of diabetes in mice prevented by blockade of adhesion-promoting receptor on macrophages. *Nature* **348,** 639–642.

Inada T. & Mims C.A. (1985) Pattern of infection and selective loss of Ia positive cells in suckling and adult mice inoculated with lactic dehydrogenase virus. *Arch. Virol.* **86,** 151–165.

Inada T. & Mims C.A. (1986a) Infection of mice with lactic dehydrogenase virus prevents development of experimental allergic encephalomyelitis. *J. Neuroimmunol.* **11,** 53–56.

Inada T. & Mims C.A. (1986b) Live lactic dehydrogenase-elevating virus (LDV) induces suppressor T cells that inhibit the development of delayed hypersensitivity to LDV. *J. Gen. Virol.* **67,** 2103–2112.

Isakov N., Feldmann M. & Segal S. (1982) Acute infection of mice with lactic dehydrogenase virus (LDV) impairs the antigen-presenting capacity of their macrophages. *Cell. Immunol.* **66,** 317–332.

Kolb-bachofen V., Epstein S., Kiesel U. & Kolb H. (1988) Low-dose streptozotocin-induced diabetes in mice. Electron microscopy reveals single-cell insulitis before diabetic onset. *Diabetes* **37,** 21–27.

Like A.A. & Rossini A.A. (1976) Streptozotocin-induced pancreatic insulitis: new model of diabetes mellitus. *Science* **193,** 415–417.

Mosmann T.R. & Coffman (1989) Heterogeneity of cytokine secretion patterns and functions of helper T cells. *Adv. Immunol.* **65,** 55–63.

Muir A., Rovin B.H., Lacy P.E. & Schreiner G.F. (1991) Macrophage-specific chemotactic lipid release by in vivo streptozotocin-administered mouse islets. *Diabetes* **40,** 1459–1466.

Nakamura M., Nagahuchi S., Yamaguchi K. & Takaki R. (1984) The role of thymic immunity and insulitis in the development of streptozotocin-induced diabetes in mice. *Diabetes* **33,** 894–900.

Oldstone M.B.A. & Dixon F.J. (1972) Inhibition of antibodies to nuclear antigen and to DNA in New Zealand mice infected with lactate dehydrogenase virus. *Science* **175,** 784–786.

Osborn L., Hessiono C., Tizard R., Vassallo C., Luhowshy J.S., Chi-Rosso G. & Lobb R. (1989) Direct expression cloning of vascular cell adhesion molecule 1, a cytokine-induced endothelial protein that binds to lymphocytes. *Cell* **259,** 1203–1211.

Oschilewski U., Kiesel U. & Kolb H. (1985) Administration of silica prevents diabetes in BB-rats. *Diabetes* **34,** 197–199.

Patarroyo M. (1991) Leukocyte adhesion in host defense and tissue injury. *Clin. Immunol. Immunopath.* **60,** 333–348.

Picarella D.E., Kratz A., Li C-B., Ruddle H. & Flavell R.A. (1993) Transgenic tumor necrosis factor (TNF)-α production in pancreatic islets leads to insulitis, not diabetes. Distinct patterns of inflammation in TNF-α and TNF-β transgenic mice. *J. Immunol* **150,** 4136–4150.

Pober J.S., Gimbrone M.A., Lapierre L.A., Mendrick D.L., Fiers W., Rothlein R. & Springer J.A. (1986) Overlapping patterns of activation of human endothelial cells by interleukin 1, tumor necrosis factor, and immune interferon. *J. Immunol.* **137,** 1893–1896.

Prieto J., Kaata E.F., Juntti-Berggren L., Berggren P-O., Sandler S., Biberfeld P. & Patarroto M. (1992) Induction of intercellular adhesion molecule-1 (CD54) on isolated mouse pancreatic β cells by inflammatory cytokines. *Clin. Immunol. Immunopath.* **65,** 247–253.

Prud'homme G.J., Fuks A., Colle E. & Guttmann R.D. (1984) Isolation of T-lymphocyte lines with specificity for islet cell antigens from spontaneously diabetic (insulin-dependent) rats. *Diabetes* **33,** 801–803.

Rowson K.E.K. & Mahy B.W.J. (1985) Lactate dehydrogenase-elevating virus. *J. Gen. Virol.* **66,** 2297–2312.

Snyder D.S. & Unanue E.R. (1982) Corticosteroids inhibit murine macrophage Ia expression and interleukin-1 production. *J. Immunol.* **129,** 1803–1805.

Stevenson M.M., Rees J.C. & Meltzer M.S. (1980) Macrophage function in tumor bearing mice: evidence of LDV-associated changes. *J. Immunol.* **124,** 2892–2899.

Takei I., Asaba T., Kasatana T., Marutama T., Watanabe K., Yanagawa T., Saruta T. & Isii T. (1992) Suppression of development of diabetes in NOD mice by lactate dehydrogenase virus infection. *J. Autoimmun.* **5,** 665–673.

Vives M., Badenas J., Foz M. & Putol-Borrel R. (1989) Expression of intercellular adhesion molecule-1 (ICAM-1) in human islet cells. *Diabetes* **38 (Suppl. 2),** 186 (abstr.).

Wilson G.L. & Leither E.H.. (1990) Streptozotocin interactions with pancreatic β cells and the induction of insulin-dependent diabetes. *Curr. Topics Microbiol. Immunol.* **156,** 27–54.