Autoimmune Disease in NZB/Bl Mice
II. Autoimmunity and Malignant Lymphoma

By ROBERT C. MELLORS

With the assistance of Dolores A. Landy and David Bard-II

IT IS A matter of much theoretical and practical importance to establish for experimental animals—as have Dameshek and Schwartz,1 Waldenström2 and others for man—the existence of malignant lymphoma (and lymphatic leukemia) accompanied by autoimmune manifestations and gammopathies. It is also important to inquire whether cancers of this type can arise in preexisting autoimmune diseases, such as autoimmune hemolytic anemia, in which the proliferation of immunologically competent cells (basophilic stem cells, lymphocytes, plasma cells) is a central feature. The present study deals with new and relevant findings in NZB/Bl mice,3 an inbred strain which spontaneously develops autoimmune hemolytic anemia4-5-6 and chronic membranous glomerulonephritis, almost certainly induced by immunological and autoimmune mechanisms.5,6,15,16

MATERIALS AND METHODS

These have been described elsewhere,6 to which is added direct platelet counts and serum total cholesterol determinations by the ultramicromethod (adapted from Zak). Our colony of NZB/Bl mice, derived from breeding stock provided by Dr. Marianne Bielschowsky, is now in the 64th generation of brother-sister matings and numbers more than 1400 mice. This study is presented in a perspective gained by 312 laboratory examinations (Table 1) and many more not here recorded, and 20 complete but selected autopsies (with the histologic examination of every organ) of adult NZB/Bl mice, among which were 4 mice with malignant neoplasms arising in lymphatic tissue of spleen and lymph nodes. The immunopathologic findings in these latter mice are the main subject of this report.

RESULTS

Healthy NZB/Bl Mice: Average values and statistical variations of blood constituents in healthy NZB/Bl mice of both sexes are given in Table 1. The results are similar to those obtained by the same methods on hybrid Swiss-Webster albino mice of comparable age, except for Wbc/mm.3 (twice as high in the albino mice) and platelets (more variation in NZB/Bl mice). Urinanalysis for protein yields (—) or at most (++) proteinuria. The direct

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Table 1.—Laboratory Examinations of Healthy NZB/Bl Mice*

<table>
<thead>
<tr>
<th>Determination</th>
<th>AV</th>
<th>AV±SE or Range</th>
<th>SD</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit %</td>
<td>49</td>
<td>48 50</td>
<td>2.5</td>
<td>47</td>
</tr>
<tr>
<td>Reticulocytes %</td>
<td>3.1</td>
<td>2.2 4.0</td>
<td>2.1</td>
<td>46</td>
</tr>
<tr>
<td>Platelets/mm³</td>
<td>1,500,000</td>
<td>300,000 4,200,000</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Wbc/mm³</td>
<td>5200</td>
<td>3200 7800</td>
<td>–</td>
<td>44</td>
</tr>
<tr>
<td>Lymphs. %</td>
<td>70</td>
<td>50 80</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Monos. %</td>
<td>6</td>
<td>2 15</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Polys. %</td>
<td>20</td>
<td>10 50</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Eos. %</td>
<td>3</td>
<td>1 6</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Other %</td>
<td>1</td>
<td>1 10</td>
<td>–</td>
<td>27</td>
</tr>
<tr>
<td>Serum Urea Nitrogen (mg./100 ml.)</td>
<td>24</td>
<td>22 26</td>
<td>4.3</td>
<td>54</td>
</tr>
<tr>
<td>Serum Cholesterol (mg./100 ml.)</td>
<td>150</td>
<td>133 167</td>
<td>34</td>
<td>38</td>
</tr>
<tr>
<td>Total Serum Proteins (Gm./100 ml.)</td>
<td>5.7</td>
<td>5.6 5.8</td>
<td>0.3</td>
<td>39</td>
</tr>
</tbody>
</table>

*The results were obtained on mice mainly between 2 to 3 months of age, except for platelet counts and total cholesterol determinations, 6 to 8 months of age. Symbols: AV, average; SD, standard deviation; SE, standard error; N, number of determinations.

antiglobulin (Coombs) test for incomplete antibodies localized on red cells is usually negative in NZB/Bl mice less than 4 months of age.

Autoimmune Hemolytic Disease in NZB/Bl Mice: At about 3 to 4 months of age the first positive reactions in the direct antiglobulin test are seen; at 6 to 7 months about 50 per cent of mice are positive; and at 10 months nearly 100 per cent of mice are positive.3-5 The indirect antiglobulin tests for incomplete antibodies in serum are usually positive when the direct tests are positive; warm saline agglutinins for papain-treated mouse red cells are also then usually demonstrable (at low titers, up to 1:20). Eluates prepared from saline-washed, Coombs-positive NZB/Bl red cells3-5 and from frozen sections of the spleen of NZB/Bl mice with autoimmune hemolytic anemia contain incomplete antibodies with affinity for papain-treated mouse red cells of NZB/Bl or other strains.

Almost all of the older NZB/Bl mice show evidence of autoimmune hemolytic disease.3-5 Autoantibodies to red cells are eventually demonstrable in virtually all of them. Diffuse hypergammaglobulinemia is common: the serum gammaglobulins, exceeding 16 per cent of the total serum proteins by the sixth month, rise by the eighth month to relative and absolute concentrations that are twice the normal values. Reticulocytosis occurs: the average reticulocyte per cent exceeds 5 at the sixth or seventh month and 20 by the tenth month, and some individual values approach 100. Anemia develops: the average hematocrit per cent is 40 or less by the seventh or eighth month and continues...
to fall thereafter, sometimes to very low levels. The total leukocyte and the
platelet counts and the proportion of lymphocytes, monocytes, neutrophils
and eosinophils in the peripheral blood smear usually remain within normal
limits, but leukopenia and thrombocytopenia are sometimes seen.

The spleen is usually enlarged and weighs on the average about 0.5 Gm.
(2 to 4 times the normal weight). The bulk of it is red pulp containing an
abundance of hematopoietic tissue, a normal finding in the mouse, similar to
that seen in the corresponding bone marrow and comprising erythropoietic
and granulopoietic foci together with numerous megakaryocytes (about 14
per high power field). Macrophages containing hemosiderin are abundant in
the red pulp (imparting a dark brown color) and appear to concentrate near
its junction with white pulp. The latter contain: reticulum cells, lymphocytes
and germinal centers. Numerous plasma cells of immature, mature and
Russell-body types are present in the red pulp and distributed along the
margins of the white pulp. Some of the plasma cells and germinal centers
form immunoglobulins (fig. 1) identifiable by immunofluorescence, extractable
from frozen sections, and thereafter demonstrable at least in part as auto-
antibodies to red cells. The lymph nodes, the thymus and sometimes other
organs such as the kidneys contain immunocytes of diverse form—large
primitive cells, lymphocytes and plasma cells of blast, immature, mature and
Russell-body types—in some instances associated with extramedullary hematopoietic tissue. The bone marrow shows normoblastic and granulocytic
hyperplasia together with many megakaryocytes.

Chronic Membranous Glomerulonephritis in NZB/Bl Mice: The pathology
and the pathogenesis of chronic membranous and lobular glomerulonephritis
in NZB/Bl mice are described elsewhere. This disease has spontaneous and
insidious onset, progresses through chronic stages, bears a remarkable similarity
to a spectrum of human nephrotic renal diseases, and is almost certainly
induced by immunologic and autoimmune mechanisms. Virtually all NZB/Bl
mice develop glomerulonephritis. The full picture of the nephrotic syndrome
occurs in some of them, including edema, ascites, proteinuria (+ + +),
hypoalbuminemia (14 per cent of total serum proteins) with elevated
$\alpha_2$-globulins (36 per cent of the total), cylinduria without hematuria, hyper-
cholesterolemia (320 mg./100 ml.), and—late in the course of events—
azotemia (70 mg./100 ml.).

Plasmacytoma in NZB/Bl Mice: In a few NZB/Bl mice with the usual manifesta-
tions of autoimmune disease (just described) there are also tumor-like
aggregations of plasma cells and less mature immunocytes in various organs,
such as the lungs; viewed in the perspective of human pathology these cor-
respond to localized plasmacytomas. Laboratory data obtained on one such
animal in the present series, a female 13 months of age and with plasmacytoma
of lung, are given in Table 2. The status of such lesions, whether hyperplasia
or neoplasia or transitional between benign and malignant neoplasms (next
to be discussed), is not presently clear.

Malignant Lymphoma in NZB Bl Mice: Malignant lymphoma was found
in four females among 20 selected NZB/Bl mice of both sexes in the 61st generation, sacrificed at 9 to 11 months of age. Laboratory data are given in Table 2. Attention was drawn to the occurrence of neoplastic disease in two of these mice by rapidly growing local tumors; of these, one arose in cervical lymph node (fig. 2) and the other in axillary lymph node, the tumors attaining diameters of 2.5 cm. or more within an observation period of 1 to 2 weeks. Palpable splenomegaly with gross weights about 10 times the normal and well in excess of that occurring in uncomplicated autoimmune hemolytic disease and, in one instance, hypergammaglobulinemia of unusual quantity and quality (figs. 3 and 4) drew attention to the possibility of lymphomatous disease in two animals. Spleen weights at autopsy were 1.78 and 1.35 Gm., respectively; hepatomegaly accompanied splenomegaly. The thymus gland was small (0.01-0.03 Gm.) in 3 mice and weighed 0.3 Gm. in a fourth.

In each example of malignant lymphoma, warm hemagglutinins (to papain-treated mouse red cells) were demonstrable in serum; in 2 of 3 examinations the direct antiglobulin (Coombs) test was positive. Autoimmune hemolytic disease and chronic membranous glomerulonephritis, both common occurrences in NZB Bl mice of comparable age, were present in each instance, with the renal disease structurally evaluated as of moderate severity in two instances and maximal in two others.

The malignant lymphomas were of two histologic types, those composed

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**Fig. 1.—NZB/Bl spleen in autoimmune hemolytic disease.** Germinal center (left) and plasma cells (right) forming mouse immunoglobulins. Frozen section. Immunofluorescence. Left, 425×; right, 1100×.
### Table 2.—Laboratory Examinations of 5 NZB/Bl Mice with Autoimmune Hemolytic Disease and either Plasmacytoma or Malignant Lymphoma

<table>
<thead>
<tr>
<th>Determination</th>
<th>Plasmacytoma</th>
<th>Pleomorphic Type</th>
<th>Reticulum Cell Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit %</td>
<td>40</td>
<td>41</td>
<td>25</td>
</tr>
<tr>
<td>Reticulocytes %</td>
<td>60</td>
<td>31</td>
<td>23</td>
</tr>
<tr>
<td>Platelets/mm³</td>
<td>30,000</td>
<td>1,176,000</td>
<td>1,870,000</td>
</tr>
<tr>
<td>Wbc/mm³</td>
<td>8,250</td>
<td>4,900</td>
<td>5,950</td>
</tr>
<tr>
<td>Lymphs. %</td>
<td>42</td>
<td>38</td>
<td>24</td>
</tr>
<tr>
<td>Monos. %</td>
<td>9</td>
<td>18</td>
<td>64</td>
</tr>
<tr>
<td>Polys. %</td>
<td>44</td>
<td>30</td>
<td>11</td>
</tr>
<tr>
<td>Eos. %</td>
<td>4</td>
<td>9</td>
<td>0</td>
</tr>
<tr>
<td>Other %</td>
<td>1</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Serum Urea Nitrogen</td>
<td>28</td>
<td>32</td>
<td>21</td>
</tr>
<tr>
<td>Serum Cholesterol</td>
<td>190</td>
<td>72</td>
<td>129</td>
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<tr>
<td>Total Serum Proteins</td>
<td>6.4</td>
<td>11.7</td>
<td>7.0</td>
</tr>
<tr>
<td>A%</td>
<td>27</td>
<td>5</td>
<td>19</td>
</tr>
<tr>
<td>a₁%</td>
<td>7</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>a₂%</td>
<td>21</td>
<td>4</td>
<td>16</td>
</tr>
<tr>
<td>β%</td>
<td>20</td>
<td>37</td>
<td>15</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Direct Antiglobulin Test</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
<tr>
<td>Serum Hemagglutins</td>
<td>+</td>
<td>+</td>
<td>ND</td>
</tr>
</tbody>
</table>

*For papain-treated mouse erythrocytes. Symbol: ND, not done.

essentially of malignant reticulum cells and accordingly classified as reticulum cell sarcoma (fig. 5) and others comprising malignant mesenchymal cells of diverse appearance—large primitive (stem) cells with basophilic cytoplasm, plasma cells of blast, immature, mature and Russell-body types, reticulum cells, and lymphocytes of large and small size (fig. 6). Malignant tumors of the second type were herein designated pleomorphic malignant lymphomas, in keeping with their histogenetic similarity to lymphoid neoplasms encountered in somewhat similar settings in human pathology.\(^{10}\) However, pleomorphic malignant lymphoma has not heretofore been described in mice.\(^{11,12}\) It bears a kinship to plasma-cell leukemia of mice\(^{13}\) in respect to the prominence of malignant plasma cells, the cancer-cell origin and distribution in lymphatic tissues (spleen, lymph nodes, thymus), their mode of dissemination (probably hematogenous) and pattern of infiltration of other organs (such as kidney and liver) (fig. 7) and their tendency to spare bone marrow. Pleomorphic malignant lymphoma is readily distinguished from extramedullary hematopoiesis\(^{14}\) in NZB/Bl mice but only difficultly separated from the benign and "prelymphomatous" proliferations of immunologically competent cells in autoimmune disease. In this regard, polyclonal (diffuse) hypergammaglobul-
Fig. 2.—NZB/Bl mouse, 9 months of age, with reticulum cell sarcoma arising in lymph nodes of left cervical region.

linemia becoming monoclonal (narrow-banded), as in the studies of Waldenström and suggested by figure 3, may be one decisive objective criterion of neoplastic transformation.

The reticulum cell sarcoma of primary origin in cervical lymph nodes was minced, transplanted (as 1 mm. cubes), and thereafter grew readily in the subcutaneous tissues of NZB Bl mice; and when also injected intraperitoneally as a tumour cell suspension, it spread widely to various intra-abdominal sites, especially mesenteric lymph nodes (fig. 8) and caused death in several weeks. No attempt was made to transplant malignant lymphoma of pleomorphic type, but this will be undertaken in future studies. Splenic tissue obtained from a mouse with autoimmune hemolytic disease (but without malignant lymphoma) and transplanted into the subcutaneous tissues of other NZB Bl mice produced only a temporary local growth without spread to other sites, and by 4 weeks it had regressed to a tiny (3 mm.) red nodule composed mainly of blood encapsulated by fibrous tissue.

**DISCUSSION**

Mice of the inbred NZB Bl strain, developed by Marianne Bielschowsky, spontaneously develop autoimmune hemolytic disease and chronic membranous glomerulonephritis. The occurrence of spontaneous neoplasms (thymoma, lymphatic leukemia and reticulum cell sarcoma) of the lymphatic
system in NZB Bl mice, then in the 52nd generation of brother-sister matings, was first described by Bielschowsky and Bielschowsky. Moreover, they found that after the administration of the carcinogen 2-aminofluorene the incidence of these tumors was increased five-fold, to 19 per cent, and some of the tumors were transplantable. Holmes and Burnet observed examples of plasmacytoma and what was labeled reticulum cell tumor or leukemia and estimated the incidence of “lymphoid hyperplasia or tumor” to be 33 per cent in NZB/Bl males and 50 per cent in females dying at 400 days or older. We have found both autoimmune disease and malignant lymphoma in 4 of 20 NZB/Bl mice of the 61st generation sacrificed on a selective basis at 9 to 11 months of age. In each example of malignant lymphoma, autoantibodies to red cells and autoimmune diseases (autoimmune hemolytic disease and chronic membranous glomerulonephritis) were also present; in one instance there was
hypergammaglobulinemia of exceptional magnitude. The fundamental question is whether the serologic and pathologic manifestations of autoimmunity preceded, followed or occurred simultaneously with the development of malignant lymphoma in NZB/Bl mice. The following observations favor the view that in the majority of instances the autoimmune diseases preceded the malignant lymphomas. Upon reaching 9 to 11 months of age nearly all NZB/Bl mice already have autoimmune hemolytic disease and chronic membranous glomerulonephritis of various degrees of severity; in some of these mice "pre-lymphomatous" infiltrations of immunologically competent cells are seen in the spleen and other organs. Both autoimmune hemolytic disease and chronic membranous glomerulonephritis were well established in the lymphomatous mice and were generally comparable in severity to those seen at a corresponding age in the absence of malignant lymphoma. Moreover, in two examples of primary malignant lymphoma arising in superficial lymph nodes and showing limited spread, the local tumor growth was so rapid that the accompanying autoimmune hemolytic disease and chronic membranous glomerulonephritis could scarcely have evolved in a comparably short period of time. Lastly, whereas all NZB/Bl mice with primary malignant lymphoma had serum hemagglutinins (for papain-treated mouse erythrocytes), tumor transplants of reticulum cell sarcoma with progressive growth in young NZB/Bl recipients did not, within a period of a few weeks, induce or accelerate in them a serologic conversion to Coombs positivity or hypergammaglobulinemia. However, further transplantation studies will be undertaken, especially with malignant lymphomas of the pleomorphic type.

Autoimmune hemolytic anemia occurs in human malignant lymphoma and lymphatic leukemia, in the latter disease sometime during its course in about
20 per cent of patients. In the studies of Rosenthal et al. dealing with 24 patients with malignant lymphocytic disease (20 with chronic lymphatic leukemia, 4 with lymphosarcoma) and autoimmune hemolytic anemia, the direct antiglobulin test was positive in each of the 20 cases in which it was performed, and serum hemagglutinins (for trypsin-treated erythrocytes) were demonstrable in 19. The diagnosis of malignant lymphocytic disease was made before the onset of anemia in 11 of 20 patients with chronic lymphatic leukemia, but in 3 of 4 patients with lymphosarcoma it was made after the full picture of autoimmune hemolytic anemia had developed, and then only with some difficulty.

Waldenström in his extensive work has called attention to human malignant lymphomas with gammopathies and antibody-rich serology and to seemingly benign proliferative and autoimmune disorders which sometimes appeared to eventuate in malignant lymphoma. Other relevant observations include malignant lymphoma arising in thyroid gland in Hashimoto's thyroiditis, and in salivary gland during the course of Sjögren's disease and perhaps also the well-known association of thymoma and myasthenia gravis or of cancer, including malignant lymphoma, and dermatomyositis.

While the coexistence of autoimmunity and lymphoid neoplasia in NZB/Bl mice and in man conceivably reflects nothing more than a chance occurrence, other interpretations can be offered:
Fig. 6.—NZB/Bl lung. Pleomorphic malignant lymphoma composed of tumor cells of diverse appearance including many plasma cells with compact nucleus, dark (basophilic) cytoplasm, and distinct cell outline, and two Russell-body plasma cells (upper left corner), reticulum cells with indistinct cell outline, mitotic figure (lower right), and large and small lymphocytes (in lymphatic vessel). Hematoxylin-eosin. 960×.

1. The proliferation of immunologically competent cells is central to the pathogenesis of autoimmune disease; the proliferative advantage thus engendered may be a step (mutation) in the direction of lymphoid neoplasia.

2. In some instances, however, autoantibodies may be produced by the neoplastic lymphoid cells or in response to them or their products.

In some other respects immunoproliferative disorders in mice also bear remarkable similarity to those occurring in man: transplantable plasma cell neoplasms are associated with 7S gammopathies, and transplantable leukemias, composed of cells resembling the “plasmacytoid” lymphocytes of Waldenström’s macroglobulinemia in man, are associated with 19S gammopathies.

**SUMMARY AND CONCLUSIONS**

Malignant lymphoma was found in 4 of 20 NZB Bl mice (of the 61st generation) selected for laboratory examinations and autopsy at 9 to 11 months of age. The malignant lymphomas were of two histologic types, reticulum cell sarcoma and pleomorphic malignant lymphoma, the latter term being used to designate malignant neoplasms arising in lymphatic tissue, composed of mesenchymal cells of diverse appearance—mainly plasma cells of blast, immature, mature and Russell-body types but also large primitive (stem) cells, reticulum cells, and lymphocytes of large and small size—and fre-
Fig. 7.—NZB/Bl kidney. Pleomorphic malignant lymphoma infiltrating renal cortex and surrounding 4 glomerular tufts, the site of chronic membranous glomerulonephritis. Hematoxylin-eosin. 144 x.

Fig. 8.—NZB/Bl mouse with extensive intra-abdominal spread of reticulum cell sarcoma, seen mainly in mesenteric lymph nodes, at 6 weeks after receiving a primary transplant of this tumor subcutaneously and intraperitoneally.
quentely associated with gammopathies. One of the reticulum cell sarcomas was transplantable to, and produced lethal disseminated growth in, other NZB/B1 mice.

In each example of malignant lymphoma, warm hemagglutinins (to papain-treated mouse red cells) were demonstrable in serum. Autoimmune hemolytic disease and chronic membranous glomerulonephritis, both of common occurrence in NZB/B1 mice of comparable age, were also present. In one instance of pleomorphic malignant lymphoma, hypergammaglobulinemia of unusual quantity and quality drew attention to the possibility of lymphomatous disease.

Some evidence was brought forth indicating that in the majority of instances the autoimmune diseases preceded the malignant lymphomas. While the coexistence of autoimmunity and lymphoid neoplasia conceivably reflects nothing more than chance occurrence, other interpretations were considered: the proliferative advantage engendered in immunologically competent cells in autoimmune disease may be a step in the direction of lymphoid neoplasia; or, in some instances autoantibodies may be produced by, or in response to, the neoplastic lymphoid cells.

**Summario in Interlingua**

Lymphoma maligne esseva constatat in 4 de 20 muses NZB/Bl (del sexanta-prime generation) seligite pro examine laboratorial e necroptic a etates de inter 9 e 11 menses. Le lymphomas maligne esseva de duo typos histologic, i.e., sarcoma de cellulas reticular e lymphoma maligne pleomorphic, con iste secunde termino usate pro neoplasmas maligne originari de tissu lymphatic, composite de cellulas mesenchymal de diverse apparentias—principalmente plasmocytos de typos blastic, immatur, matur, e a corpore de Russell sed etiam grande cellulas primordial, cellulas reticular, e lymphocytos de grande e micre dimensiones—e frequentemente associate con gammopathias. Un del sarcomas de cellulas reticular esseva transplantabile a altere muses MZB/Bl in le quales illo produceva un disseminate crescentia letal.

In omne le casos de lymphoma maligne, thermohemagglutininas (contra papaino-tractate erythrocytos murin) esseva demonstrabile in le sero. Esseva etiam presente autoimmun morbo hemolytic e chronic glomerulonephritis membranose. Ambe iste conditiones es de occurrientia commun in muses NZB/Bl de etate comparabile. In un caso de pleomorphic lymphoma maligne, hypergammaglobulinemia de quantitate e qualitate inusual suggestionava le possibilitate del presentia de morbo lymphomatose.

Esseva obtenite certe pecias de evidentia a indicar que in le majoritate del casos le morbo autoimmun precedeva le lymphoma maligne. Ben que le coexistentia de autoimmunitate con neoplasia lymphoide reflecte possibilemente non plus que un occurrientia coincidental, altere interpretationes esseva prendite in consideration. Le avantage proliferative generate in immunologicamente competent cellulas in morbo autoimmun es fors an passo in le direction de neoplasia lymphoide. Del altere latere, in certe casos auto-
ACKNOWLEDGMENTS

I am indebted to Dr. Marianne Bielschowsky for her generosity in sending us a breeding nucleus of NZB/Bl mice, to Dr. Leon J. Kutner for his participation in the transplantation study, to Miss Elinore Abravanel for histologic preparations, to Mr. Louis Dienes for assistance in photomicrography, and to Miss Vera Jacusiel for biochemical work.

REFERENCES


Autoimmune Disease in NZB/Bl Mice: II. Autoimmunity and Malignant Lymphoma

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