

# (SWR × SJL)<sub>F1</sub> Mice: A New Model of Lupus-like Disease

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## Summary

During the study of autoimmune models we found that (SWR × SJL)<sub>F1</sub> mice (both parental strains with the Vβ<sup>a</sup> phenotype) spontaneously produced immunoglobulin G (IgG) antibodies directed against Sm/U1 small nuclear ribonucleoproteins (snRNPs). In some of these females, the presence of these autoantibodies was found as early as 10 wk of age. Their frequency increased with age i.e., 70% at 40 wk. At that time, only 10% of males developed anti-Sm/U1snRNP antibodies. Anti-Sm/U1snRNP antibodies from positive mice generally recognized the peptides BB', D, 70 kD, and A from RNPs. These polypeptides are known to bear the autoantigenic epitopes that are recognized by human sera containing anti-Sm and anti-U1snRNP antibodies. Reactivity of IgG antibodies with the octapeptide sequence PPPGMRPP was also found in 30% of anti-Sm/U1snRNP positive (SWR × SJL)<sub>F1</sub> mice that precipitated BB' peptides. This octapeptide has been described as the most immunoreactive linear epitope in systemic lupus erythematosus (SLE) patients with anti-Sm and anti-U1snRNP antibodies. Approximately 30% of anti-Sm/U1snRNP positive females, later produced anti-dsDNA antibodies. This fact was accompanied by the development of proteinuria due to glomerulonephritis mediated by immunocomplexes. In addition to the specific autoimmune response, (SWR × SJL)<sub>F1</sub> females also showed other immunologic abnormalities such as hypergammaglobulinemia, and an approximately twofold increase in spleen cell number compared with control mice. These results indicate that (SWR × SJL)<sub>F1</sub> females develop clinical and serological abnormalities similar to those observed in human SLE and constitute a novel model for the study of the genetic mechanisms that result in autoimmunity.

The etiopathogenesis of autoimmune diseases cannot readily be analyzed without appropriate animal models. With regard to experimental autoimmune connective tissue diseases, we can divide these models into two wide groups: (a) inbred mice that spontaneously develop a disease similar to human SLE (1); and (b) chronic GVHD induced in hybrid F<sub>1</sub> mice injected with lymphoid parental cells (2). In the latter, autoantibodies against different antigenic specificities and aspects of different autoimmune connective diseases are developed when different strains of mice are employed (3, 4).

In the studies on GVHD performed in our laboratory (3, 4), we have employed F<sub>1</sub> hybrids generated by crosses between different strains of mice. SWR and SJL were selected because both are deficient in nearly 50% of Vβ genes (Vβ<sup>a</sup> haplotype). In addition they lack I-E expression and carry a functional gene for Vβ17 (Vβ17a) (5). We wanted to explore the effect of their reduced Vβ repertoire on the clinical and biological expression of GVHD induced by the injection of lymphoid cells from either parental strain.

In the course of control experiments aimed at characterizing the control hybrid mice, we found that many (SWR ×

SJL)<sub>F1</sub> mice spontaneously developed antinuclear antibodies in their serum.

This study was undertaken to characterize the clinical and serologic aspects of the autoimmune disease that (SWR × SJL)<sub>F1</sub> mice spontaneously develop.

## Materials and Methods

### Mice

SWR (H-2q), SJL/J (H-2s), (SWR × SJL)<sub>F1</sub> (SJL × SWR)<sub>F1</sub>, BALB/c (H-2d), A/J (H-2a), MRL lpr/lpr (H-2k), and C57BL/6 (H-2b) mice were purchased from The Jackson Laboratory (Bar Harbor, ME), and housed in the animal facilities of the Hospital de Sant Pau. 30 females and 25 males were 8-wk-old at the beginning of the study. Animals were bled from the retro-orbital sinus and the sera were stored frozen at -20°C.

### Clinical Studies

At weekly intervals, mice were inspected for any external signs of pathology (alopecia, skin sclerosis, ascitis, and joint swelling). Combur's test was used to study urine samples for elevated levels

of proteinuria. When the animals were killed, kidneys were processed for immunohistologic studies.

### Serologic Studies

**Indirect Immunofluorescence.** Sera were screened for antinuclear antibodies (ANA) using the indirect immunofluorescence technique. Hep-2 cells grown on glass slides were fixed and used as substrate. The fluorescein-labeled anti-mouse conjugate was purchased from Sera-Lab Limited (Crawl Down, Sussex, UK) and used at a dilution of 1:20.

**Analysis of Immunoprecipitated RNAs.** To identify ANAs capable of binding specific small nuclear ribonucleoproteins (snRNPs)<sup>1</sup>, sera were tested for their ability to immunoprecipitate subsets of small RNAs from extracts of murine Friend erythroleukemia cells, as described previously (3).

**Analysis of Immunoprecipitated Proteins.** A procedure based on that of Matter et al. (6) was used. Briefly, HeLa cells growing in log phase at  $2 \times 10^5$  cells/ml were allowed to incorporate [<sup>35</sup>S]methionine (5  $\mu$ Ci/ml) for 16–18 h. For protein immunoprecipitation, we used protein A-Sepharose particles previously reacted with an IgG class rabbit anti-mouse IgG. The immunoprecipitated proteins were separated and analyzed by electrophoresis on 12% polyacrylamide-SDS gels, as described by Laemmli (7). After electrophoresis, the gel was soaked in 0.5 M sodium salicylate. The gels were dried and exposed to x-ray film with an intensifying screen at  $-70^\circ\text{C}$ .

**Immunoblots.** Immunoblot analysis was performed as described (4). Briefly, HeLa cell extracts, or U1-U6 snRNP-enriched extracts consisting of the eluates from a human anti-U1snRNP and anti-Sm immunoaffinity columns charged with whole extracts of HeLa cells, were subjected to gel electrophoresis and the proteins were transferred to nitrocellulose. The membrane was blocked with 3% (wt/vol) dry skim dry milk in PBS for 4 h and then incubated overnight with serum (1:100 dilution) in the same buffer. The nitrocellulose strips were washed with PBS and PBS/0.1% Tween 20 and then incubated for 30 min with <sup>125</sup>I-labeled rabbit anti-mouse IgG (0.1  $\mu$ Ci/ml; Du Pont de Nemours, Brussels, Belgium). After four washes with PBS, the strips were air-dried and subjected to autoradiography.

**Autoantibodies Reacting with the Octapeptide Sequence (PPPGMR-PP).** A peptide corresponding to the sequence PPPGMRPP was synthesized in solid-phase using an automatic synthesizer (model 430A; Applied Biosystems Inc., Foster City, CA). It was conjugated to BSA by the MBS method of Cys COOH-terminal (10.33 mol peptide/mol BSA). To detect serum autoantibodies against this octapeptide, the conjugate was coated onto polystyrene plates (5  $\mu$ g/well) and ELISA was performed as previously described (3). Anti-Sm and anti-U1snRNP control sera were obtained from five SLE patients. Other control sera included in this study were: 8 MRL/lpr sera (three of them presented anti-Sm antibodies) and 10 sera from mice of each of the following strains: BALB/c, C57BL/6, SJL, and SWR.

**Antibodies to Native DNA.** Antibodies to double-stranded DNA were measured by ELISA as described elsewhere (3). Briefly, pBR322 DNA (Boehringer Mannheim, Indianapolis, IN) was added at 5  $\mu$ g/ml to microtiter plates previously coated with poly-L-lysine (50  $\mu$ g/ml; Sigma Chemical Co., St. Louis, MO). After a 1-h incubation with blocking buffer (10% FCS in 0.01 M Tris-HCl, 0.05% Tween-20, pH 7.4), sera were added (1:100 diluted) and bound antibodies detected with peroxidase-conjugated goat anti-mouse IgG.

If the results exceeded the mean +  $2\sigma$  of 20 normal control sera, they were considered positive.

**Determination of IgG, IgM, and IgA Concentrations in Sera.** IgG, IgM, and IgA levels were measured from sera by a commercial radial immunodiffusion assay (The Binding Site, Birmingham, UK).

### Lymphoid Cell Phenotype

Lymph nodes and spleens were aseptically removed from 40-wk-old mice, and the tissues minced in sterile PBS and pressed through a fine screen to form single cell suspensions. Spleen cell suspensions were treated briefly with an ammonium chloride buffer to lyse erythrocytes.

Absolute lymphocyte count and lymphocyte subsets were studied by flow cytometry analysis. mAbs against Thy1 (Sera Lab), Ly1 (Becton Dickinson, San Diego, CA), CD4 (Becton Dickinson), CD8 (Sera Lab), B220 (American Type Culture Collection, Rockville, MD) were either FITC labeled or used as biotin-conjugated reagents and developed by means of streptavidin-PE. Cells were stained following standard protocols and fluorescence was measured using a flow cytometer (Epics Profile; Coulter Cytometry, Hialeah, FL). Background values were defined by using isotype-matched irrelevant antibodies as negative controls.

## Results

### Clinical Course of (SWR $\times$ SJL)F<sub>1</sub> Mice

All mice remained healthy until they were 20-wk-old. At 20 wk of age, 10% of females but none of the males had developed proteinuria (1 mg/ml). At 40 wk, 26% of females and none of the males had developed proteinuria.

10 females, 4 of them with proteinuria, were killed when they were 40-wk-old, and their kidneys were examined histologically. The immunofluorescence studies showed that the four animals with proteinuria presented granular deposits of IgG and C3 of variable intensity (Fig. 1) and another three mice showed mesangial deposits of IgG. No signs of alopecia, vasculitis, or arthritis were observed in mice during the 40-wk study.

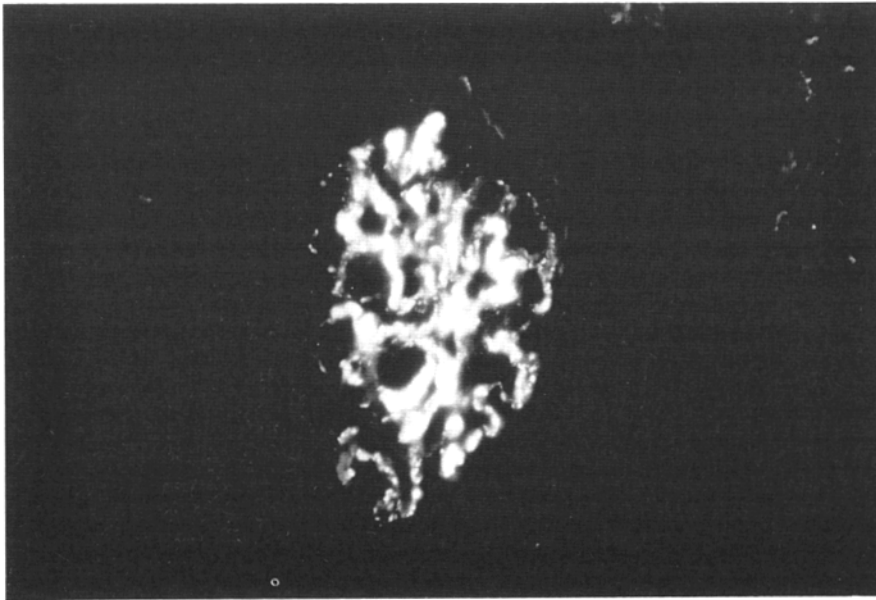
A marked splenic and lymph node hyperplasia was observed in (SWR  $\times$  SJL)F<sub>1</sub> mice as well as in both parental strains. The degree of splenic and lymph node hyperplasia resulted in sizes ranging from two to three times the size of spleen

**Table 1.** Number of Mononuclear Spleen Cells

Strain	No. mononuclear spleen cells ( $\times 10^6$ cells)
SWR	133 $\pm$ 5
SJL	128 $\pm$ 6
(SWR $\times$ SJL) F <sub>1</sub>	145 $\pm$ 10
BALB/c	87 $\pm$ 3
A/J	79 $\pm$ 2

Results are expressed as the mean  $\pm$  SD of the number of mononuclear cells from the spleens of 10 mice.

<sup>1</sup> Abbreviation used in this paper: RNP, ribonucleoprotein.



**Figure 1.** Direct immunofluorescence analysis of kidney sections using fluoresceinated sheep anti-mouse IgG. Granular deposits along the glomerular capillary walls and mesangium are present.

**Table 2.** Phenotype of Spleen Lymphocytes

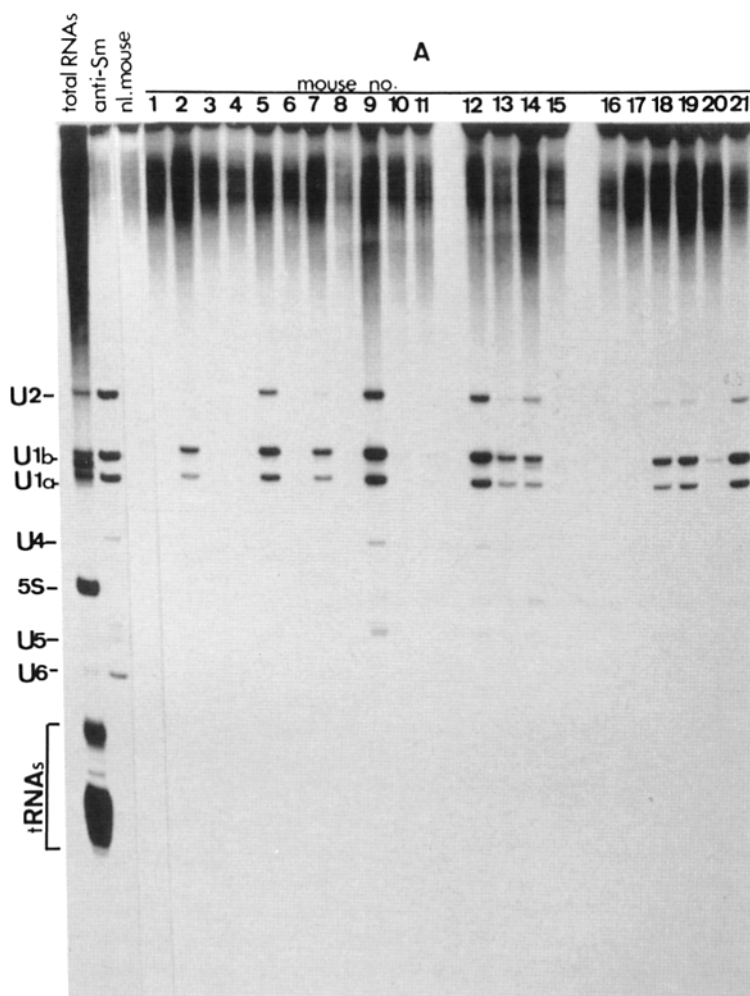
Marker	BALB/c	SJL	SWR	WXJF <sub>1</sub>
B220	44.3 ± 4	41.4 ± 2	54 ± 4	50.1 ± 2
Thy1	38.3 ± 3	37.2 ± 0.9	33.7 ± 4	29.5 ± 1
CD8	15.1 ± 0.7	13.4 ± 0.4	8.5 ± 2	7.4 ± 2
CD4	30.1 ± 1.2	32.3 ± 2	26.6 ± 0.4	26.1 ± 3
Ly1	43 ± 5	41.3 ± 1	32.2 ± 4	40 ± 3

Values represent the mean ± SD of the relative frequency of positively stained cells from 10 BALB/c, 5 SJL, 5 SWR, and 10 (SWR X SJL)F<sub>1</sub> mice.

**Table 3.** Serum Ig Levels in Several Strains of Mice

Age	IgG		IgM		IgA	
	<20 wk	>30 wk	<20 wk	>30 wk	<20 wk	>30 wk
	<i>μg/ml</i>					
BALB/c	2,190	4,068	390	410	400	1,100
B6	1,590	2,920	210	240	ND	ND
MRL + ♀	1,500	6,900	310	405	ND	ND
MRL 1pr	19,000	30,150	600	1,600	1,525	4,950
SWR ♀	ND	9,400	ND	254	ND	5,332
SJL ♀	ND	11,000	ND	250	ND	1,020
WXJF1 ♀	5,177	10,100	344	425	1,000	4,772
WXJF1 ♂	1,819	7,100	190	400	350	1,110

The concentration of the mouse Ig (IgG, IgM, and IgA) was determined by radial immunodiffusion assay (The Binding Site).



**Figure 2.** Small RNAs immunoprecipitated from  $^{32}\text{P}$ -labeled Friend leukemia cell extracts. (A) Lanes 1–21 show the precipitates with sera from 20-wk-old (SWR  $\times$  SJL) $F_1$  females. (B) Lanes 1–5 show the precipitates with sera from 40-wk-old SWR females and lanes 6–10 to SJL females. (C) Corresponds to a representative experiment including the two positive sera (lanes 6 and 7) from 40-wk-old (SWR  $\times$  SJL) $F_1$  males. The total RNA lane contains 1  $\mu\text{ml}$  of whole cell extract. Sera from a human patient known to have anti-Sm antibodies and sera from a normal mouse are included as controls. Small RNAs were identified from their characteristic electrophoretic mobilities.

and lymph nodes from control mice (BALB/c, A/J, and C57BL/6).

The splenic hyperplasia matched with the increased number of mononuclear spleen cells (Table 1).

#### Lymphocyte Markers

Data obtained by flow cytometry showed that the percentage of spleen cell was approximately half in the spleen of (SWR  $\times$  SJL) $F_1$  and SWR mice as compared with control mice (Table 2). Moreover, SWR and (SWR  $\times$  SJL) $F_1$  spleens presented an increase in the percentage of B220 $^+$  and (SWR  $\times$  SJL) $F_1$  spleens a decrease in the percentage of Thy1 $^+$ .

#### Serologic Manifestations

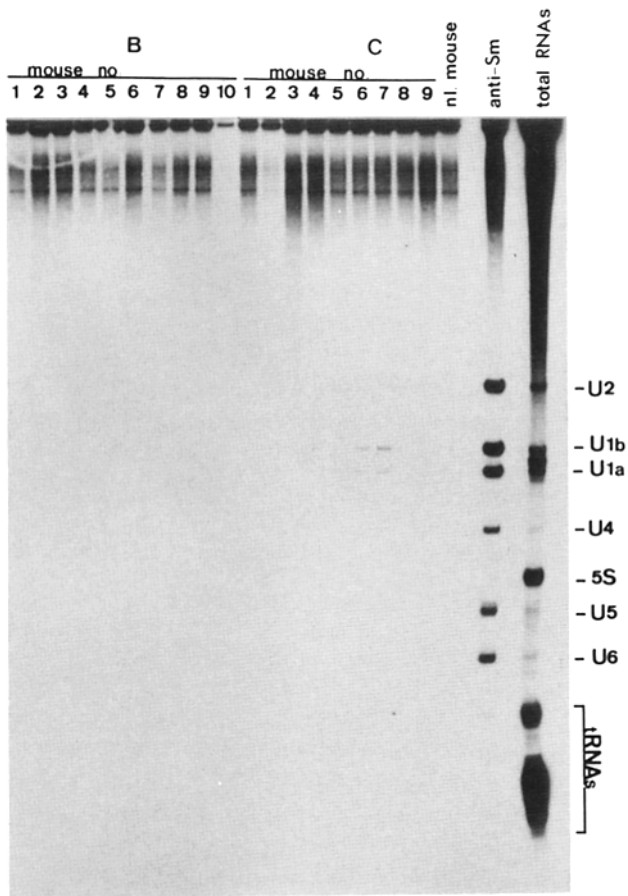
**Serum Ig Levels.** IgM, IgA, and IgG levels in serum from young adults (<20 wk) and older SWR, SJL, and (SWR  $\times$  SJL) $F_1$  mice were compared with those observed in normal and autoimmune strains of mice (Table 3). The three Ig isotypes increased significantly with the age of the (SWR  $\times$  SJL) $F_1$  mice.

Serologic analysis indicated that serum IgG levels in young

adult and 30-wk-old (SWR  $\times$  SJL) $F_1$  females as well as 30-wk-old SWR and SJL mice were increased two and five times compared with control sex- and age-matched BALB/c and C57BL/6 mice, respectively. No difference in serum IgM levels was observed. IgA levels were four- to fivefold higher in SWR and (SWR  $\times$  SJL) $F_1$  females as compared with control females.

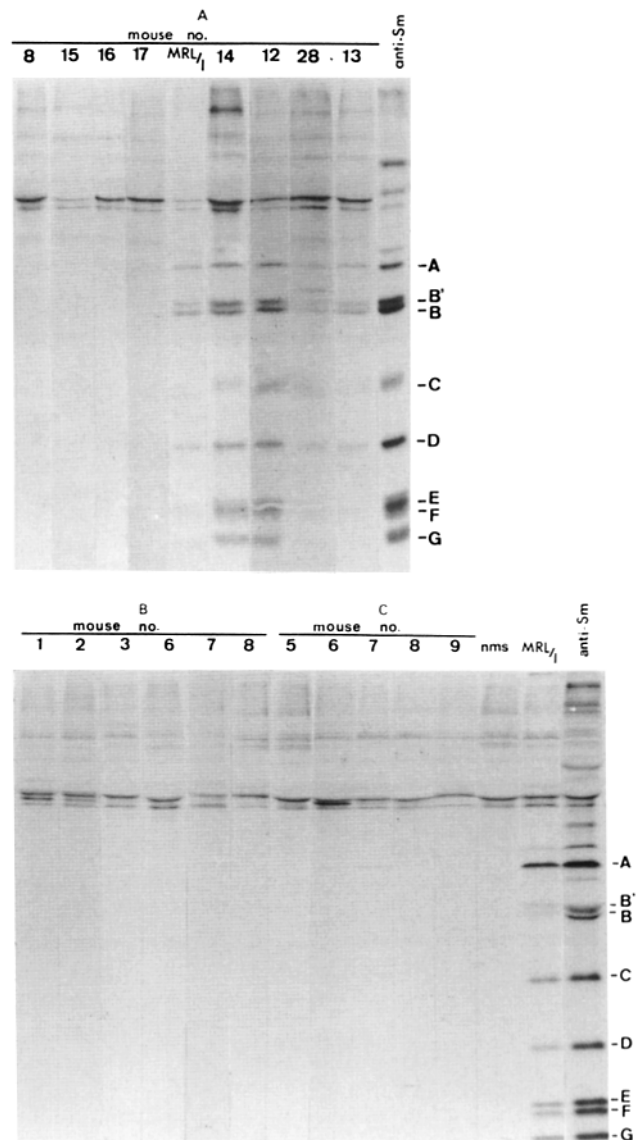
**IgG Class Antibodies to Nuclear Antigens.** IgG antibodies against nuclear components were detected by IIF in the sera of 30% of 10-wk-old females. The titers ranged between 1/160 and 1/640 and speckled patterns were commonly found. Among 40-wk-old mice, the frequency of ANAs rose to 70% of (SWR  $\times$  SJL) $F_1$  females. During the evolution in eight animals the speckled patterns were changed or hidden by a homogeneous one. Only 20% of 40-wk-old males were ANA positive with titers between 1/40 and 1/80. In no cases did the titer decrease or become negative.

**Anti-Sm/U1snRNP Antibodies.** The presence of anti-Sm/U1snRNP autoantibodies in sequential serum samples of control and (SWR  $\times$  SJL) $F_1$  mice was assessed by immunoprecipitation and analysis of small RNAs. 30 (SWR  $\times$  SJL) $F_1$  females, 25 (SWR  $\times$  SJL) $F_1$  males, as well as 30



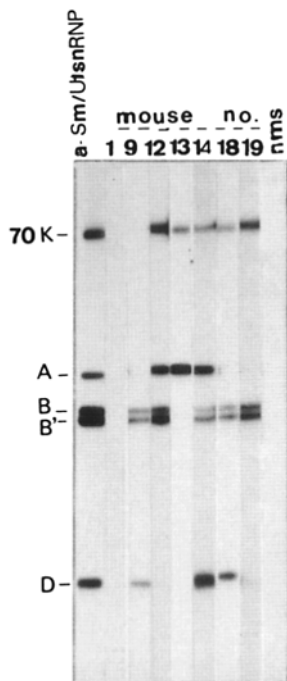
40-wk-old female mice from the parental strains (15 SWR and 15 SJL) were studied. Immunoprecipitated UsnRNAs appeared in 10% of (SWR × SJL)<sub>F1</sub> females at ~10 wk of age, progressing thereafter to 50% at 20 wk and 70% at 40 wk of age. Fig. 2 shows a representative experiment in which sera from 21 (SWR × SJL)<sub>F1</sub> 20-wk-old females were examined (A). None of the sera from parental SWR and SJL strains precipitated UsnRNAs. At 10 wk of age, none of the (SWR × SJL)<sub>F1</sub> males presented anti-Sm/U1snRNP antibodies, and only 10% of them showed this antibody specificity at 40 wk. A representative experiment that included sera of the two positive and seven negative (SWR × SJL)<sub>F1</sub> males, as well as five sera of SJL and five SWR mice is shown (Fig. 2, B and C). Significantly, as the image reveals, the precipitate of the (SWR × SJL)<sub>F1</sub> male positive sera are extremely weak.

(SWR × SJL)<sub>F1</sub> sera that precipitated UsnRNAs, precipitated from HeLa cell extracts a set of polypeptides with molecular weights compatible with those described for the components of Sm particles. The major proteins found included A, B'/B, C, D, E, F, and G. None of the sera from parental SWR and SJL strains precipitated the polypeptide components of the Sm/U1RNP particles. Male (SWR × SJL)<sub>F1</sub> mice sera that showed this antibody specificity weakly precipitated the components of Sm particles (Fig. 3). Only



**Figure 3.** Proteins immunoprecipitated from <sup>35</sup>S-labeled HeLa cell extracts. (A) The precipitate with eight representative (SWR × SJL)<sub>F1</sub> female sera, four of them anti-Sm positive (mouse no. 14, 12, 28, and 13) and four of them anti-Sm negative (mouse no. 8, 15, 16, and 17). (B) The precipitate with sera from three 40-wk-old SWR female mice (mouse nos. 1–3) and three 40-wk-old SJL mice (mouse no. 6–8). (C) The precipitate with 40-wk-old (SWR × SJL)<sub>F1</sub> male sera, including the two anti-Sm positive sera (mouse no. 6 and 7). Sera from a MRL/lpr mouse (lane MRL/1) and from a SLE patient (lane anti-Sm) both with anti-Sm antibodies, were used as positive controls. Sera from a normal mouse (nms) is included as a control. The precipitates were separated by electrophoresis on 12% polyacrylamide-SDS gel and visualized by fluorography.

the A protein appeared in the image because of the small amount of antibody in their sera. To identify the antigenic polypeptides recognized by anti-Sm/U1snRNP antibodies, sera from 16 (SWR × SJL)<sub>F1</sub> females were tested in immunoblots using HeLa extracts. The peptides 70 kD (15 of 16 mice), B'/B (13 of 16), A (3 of 16), and D (3 of 16) were



**Figure 4.** Identification of Sm/U1snRNP polypeptides that are recognized by sera from six (SWR × SJL)<sub>F1</sub> female sera that immunoprecipitated snRNPs (mouse no. 9, 12, 13, 14, 18, and 19). Immunoaffinity purified Sm/U1snRNP particles were fractionated electrophoretically and transferred to nitrocellulose paper. The snRNP polypeptides are identified by their electrophoretic mobility and recognized by a serum known to contain anti-Sm/U1 snRNP antibodies. Sera from a (SWR × SJL)<sub>F1</sub> mouse that did not precipitate snRNA (mouse no. 1) and a normal mouse serum (*nms*) are included as controls.

the main targets of these sera. Fig. 4 shows a representative immunoblotting experiment.

Other unidentified peptides were observed by the analysis of immunoprecipitated proteins of HeLa cell extracts as well as by immunoblot assay.

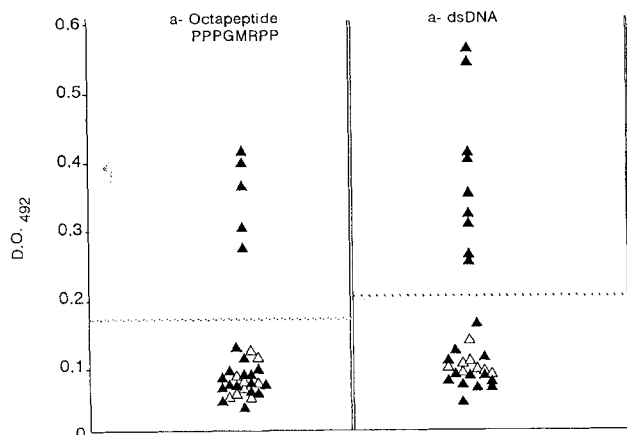
30% of female sera that recognized B/B' peptides were reactive with the synthetic octapeptide PPPGMRPP, the most immunoreactive linear epitope that has been described in SLE patients with anti-Sm/U1snRNP antibodies (8). None of the anti-Sm/U1snRNP negative sera were reactive with this peptide (Fig. 5).

**Anti-dsDNA Antibodies.** Anti-dsDNA antibodies were first detected in 20-wk-old females (2 of 30), progressing thereafter to 9 positive out of 30 mice when they were 40-wk-old (Fig. 5).

The presence of anti-dsDNA antibodies was associated with glomerulonephritis mediated by immunocomplexes. It is interesting to note that glomerular deposits of IgG involving the mesangium but not the glomerular capillary walls were observed in mice that developed exclusively anti-Sm antibodies.

## Discussion

In this paper we demonstrate that the hybrid (SWR × SJL)<sub>F1</sub> as well as (SJL × SWR)<sub>F1</sub> female mice present hypergammaglobulinemia and lymphoid hyperplasia and frequently develop proteinuria and anti-Sm and anti-U1snRNP antibodies. The latter are not present in any of the autoimmune strains of mice described previously. The spontaneous production of specific anti-Sm antibody (9) had been found exclusively in SLE patients and the autoimmune MRL strains. The target peptides of these autoantibodies are the B'/B and D, that have been described previously in the MRL mice and in SLE patients with anti-Sm antibodies, and the A and 70-kD polypeptides, described previously in mixed connective



**Figure 5.** Levels of anti-octapeptide PPPGMRPP and anti-dsDNA antibodies in sera from (SWR × SJL)<sub>F1</sub> mice with anti-Sm/U1 snRNP antibodies (▲) or without anti-Sm/U1 snRNP antibodies (△). OD values were determined by an enzyme-linked immunoassay. Horizontal lines show the mean plus 2 SD value in 20 normal mouse sera (10 BALB/c and 10 C57BL/6).

tissue disease (MCTD) and SLE patients with anti-U1snRNP antibodies. These data and the high restriction of anti-Sm antibodies for SLE suggested that factors similar to those that operate in human SLE and MRL mice are driving the response against these antigenic specificities. However, the response to the linear epitope described as the main target of all the human anti-B'/B Sm antibodies is only detected in the 30% of anti-Sm/U1snRNP positive (SWR × SJL)<sub>F1</sub> mice, suggesting that stochastic mechanisms such as V gene rearrangement or V gene somatic mutations may be involved in the heterogeneity of this response.

Although the frequency of anti-Sm antibodies in (SWR × SJL)<sub>F1</sub> females is similar to that described in MRL/*n* females (10), MRL/*n* males developed anti-Sm antibodies with a higher frequency than (SWR × SJL)<sub>F1</sub> males. Moreover, 40-wk-old (SWR × SJL)<sub>F1</sub> males presented a significant low incidence, low titer, and a later development of anti-Sm antibodies than females. Sexual hormones in (SWR × SJL)<sub>F1</sub> females may be operating as possible enhancing factors in the induction of anti-Sm and anti-U1snRNP autoantibodies.

Anti-dsDNA is another autoantibody specificity frequently present in the sera of SLE patients and in other SLE strains of mice. This specificity is also detected in 30% of the (SWR × SJL)<sub>F1</sub> females, all of them with anti-Sm/U1snRNP antibodies. None of the mice developed antihistones, antierythrocyte antibodies, or rheumatoid factors (data not shown). A relationship between anti-Sm and anti-dsDNA antibodies has been described in MRL *lpr/lpr*: (a) anti-Sm and anti-DNA overlapping responses have been demonstrated in this strain of mice. The isolation of Sm/DNA-specific hybridomas may indicate a common origin of both autoantibodies (11); and (b) parallel sets of autoantibodies have been reported in which Id-H130 is selected against DNA. However other molecules with the same idiotype did not bind to DNA, but did bind to Sm antigens (12). Similar studies in the (SWR × SJL)<sub>F1</sub> mice may be suitable for explaining this relationship.

Anti-dsDNA autoantibodies correlate with the presence of proteinuria and immunocomplex nephropathy. All the animals with proteinuria had anti-dsDNA. Furthermore, mice with anti-Sm/U1snRNP antibodies without anti-DNA antibodies did not show any pathologic disorder during the follow up. A relationship between anti-dsDNA autoantibodies and nephropathy by immunocomplexes has already been described in SLE patients as well as in SLE autoimmune strains of mice (13).

SWR mice are free of autoimmune disease and autoantibodies, although when the SWR strain of mice was crossed with NZB mice, the F<sub>1</sub> progeny developed a severe lupus with glomerulonephritis. However, when the NZB mice were crossed with other normal mice strains such as C57BL/6 and AKR no autoimmune diseases were developed in their F<sub>1</sub> progeny (14). These observations indicate that genes inherited from SWR strongly influence the expression of autoimmune disease in NZB crosses. Some immunologic alterations (IgA levels and lymphocyte subpopulation percentages in spleen

in SWR mice are similar to those observed in (SWR × SJL)F<sub>1</sub> mice, suggesting that SWR genes dominantly influence the immunologic constitution of the hybrid mice.

Furthermore SJL mice spontaneously developed neither autoimmune disease nor autoantibodies (15), although SJL mice have been employed to develop experimental autoimmune encephalitis by immunization with myelin basic protein or peptides derived from this protein. In addition, some immunologic abnormalities have been described such as a quantitative deficit of Ly1<sup>+</sup> B cells and a relative resistance to tolerance induction (16).

Several lines of evidence suggest that the production of a mixed haplotype class II molecule, I-E $\alpha^d$  × I-E $\beta^z$ , plays a key role in development of autoimmunity in (NZB × NZW)F<sub>1</sub> mice (17). The absence of I-E molecules in (SWR × SJL)F<sub>1</sub> mice excludes this possibility in this model. However SJL and SWR strains of mice might genetically complement each other in order to develop the SLE-like disease described in this paper.

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