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EVIDENCE THAT AUTOIMMUNE RENAL DISEASE AND TUMOUR FORMATION IN NZB/W MICE ARE DUE TO SEPARATE DEFECTS

SUSAN ADAMS AND D. D. ADAMS

Immunopathology Group, New Zealand Medical Research Council, Otago University Medical School, Dunedin, New Zealand

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SUMMARY

The effect of 600 r of γ-radiation on NZB/W and stock mice was studied. In both groups of mice more than 50% of the animals died from thymomas and a small percentage from other tumours. The deaths from thymomas occurred significantly earlier than the deaths from other tumours. The time of onset and incidence of autoimmunity in the NZB/W mice did not appear to be affected by the treatment. The stock mice developed no autoimmunity.

INTRODUCTION

Reports on the incidence of neoplasia in the NZB and NZB/W mice vary from less than 5% (Bielschowsky & Bielschowsky, 1962) to 49·5% (Holmes & Burnet, 1963).

Bielschowsky & Bielschowsky (1962) studied the effect of the carcinogen 2-aminofluorene on NZB, NZC and NZO mice. They found that the tumour incidence was significantly higher in the NZBs, suggesting that as well as autoimmune disease these mice had an increased tendency to undergo neoplastic transformation.

Casey (1967, 1968) found that administration of the immunosuppressive drug azathioprine to NZB mice did not prevent the onset of autoimmune disease, but had a carcinogenic effect, the majority of the mice developing malignant lymphomas.

With NZB/W mice, azathioprine treatment had the same carcinogenic effect, more than 50% of the animals dying of malignant lymphomas. The renal disease was suppressed by the treatment.

In this work the effect of suppressing the immune mechanism with γ-radiation was studied in NZB/W and stock mice.

MATERIALS AND METHODS

Thirty female NZB/W and thirty female stock mice were irradiated at the age of 1–2 months.

Correspondence: Miss Susan Adams, Immunopathology Group, New Zealand Medical Research Council, Medical School, Dunedin, New Zealand.

The stock mice were from The Otago Closed Random Bred Colony, which originated from mice obtained from accredited animal breeders in England. The colony was transferred to New Zealand in 1930. All the mice have light-coloured coats.

The γ-radiation was given, using a Cobalt machine, in four-weekly doses each of 150 r (total 600 r).

The following tests were performed on all the mice every 2 weeks:

(1) *Blood urea nitrogen.* By the method of Searcy (1961) using 20-mm^3 samples of serum. Values of more than 80 mg/100 ml serum were considered to be high.

(2) *Proteinuria.* Protein in the urine was detected by reagent strips (Albustix, Ames Co.). Values of + + + (300 mg protein/100 ml urine) were considered to be raised.

(3) *Body weights.*

Post-mortem examination

At death the weights of liver, spleen, thymus and kidneys were measured and the histology of these organs was studied.

RESULTS

Table 1 shows the life span of the irradiated NZB/W and stock mice and their cause of death as far as could be determined.

TABLE 1. Life-span and cause of death of irradiated NZB/W and stock mice

	Cause of death							
	Thymoma		Other tumours		A.I. renal disease		Unknown	
	NZB/W	Stock	NZB/W	Stock	NZB/W	Stock	NZB/W	Stock
Age at death in lunar months	5·8	6·4	6·1	14·0	8·3	—	4·4	1·4
	5·9	6·8	9·3	17·1	10·4	—	5·2	1·4
	6·0	7·0	15·6	17·9	10·6	—	5·8	1·5
	6·0	7·1	16·8	19·8	11·0	—	—	1·8
	6·6	7·1	19·5	20·0	12·7	—	—	2·3
	6·7	7·3	—	22·1	13·6	—	—	2·6
	7·2	7·3	—	22·6	14·8	—	—	18·1
	7·3	8·8	—	—	22·2	—	—	26·5
	7·5	9·6	—	—	—	—	—	34·0
	7·6	9·8	—	—	—	—	—	34·0
	7·7	11·1	—	—	—	—	—	—
	8·8	13·1	—	—	—	—	—	—
	10·0	16·6	—	—	—	—	—	—
	12·0	—	—	—	—	—	—	—
Number of deaths	14	13	5	7	8	0	3	10
Mean age at death	7·5	9·1	13·5	19·1	13·0	—	5·1	12·4
P for difference		$P<0·01$		$P<0·001$				

In both the NZB/W and stock mice groups nearly 50% of the animals died from thymomas. The slight difference in the mean age at death between these groups is not significant.

The number of deaths from other tumours was also approximately equal in the two groups of mice, and the mean ages at death did not differ significantly. Tumours of organs other than the thymus occurred in the ovary, lung, femur, sternum, abdominal cavity and thoracic cavity.

In both the NZB/Ws and stock mice death from thymomas occurred significantly earlier than death from other tumours.

Eight of the NZB/W mice died from autoimmune renal disease. The majority had life-spans of 8–15 months which is the usual age of greatest frequency of death (Howie & Helyer, 1968). No stock mice developed any signs of autoimmune disease.

A group of six stock mice and three NZB/Ws died under the age of 6 months, probably as a direct result of exposure to radiation. A further three stock mice lived for 1–3 years and died from unknown causes.

DISCUSSION

The irradiation greatly increased thymoma and other tumour formation in the NZB/W mice. However, the treatment did not appear to have any effect on the incidence or time of development of autoimmunity in the NZB/W mice. The stock mice given the same irradiation treatment showed an identically high incidence of thymomas and other tumours but developed no autoimmunity. The finding that tumour formation in both NZB/W and stock mice was greatly increased by the treatment, but that autoimmunity was quite unaffected suggests that tumour formation and autoimmunity in NZB/W mice are due to separate defects.

These results are compatible with the idea that immune surveillance may be defective in NZB/W mice, making them unduly susceptible to mutagenic agents (Bielschowsky & Bielschowsky, 1962; Casey, 1967). The results of our irradiation treatment could mean that when immune surveillance is abolished, the NZB/W and stock mice become equally susceptible to neoplasia.

It has been found that irradiation will induce leukaemia in some strains of mice (Kaplan, 1967). This effect has been ascribed to activation of latent leukaemogenic viruses through depression of the immunity system. Our irradiation treatment may have increased neoplasia by a similar mechanism.

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