Spontaneous Lymphomas in Mice Genetically Selected for High or Low Phytohemagglutinin Responsiveness [1,2,3]

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ABSTRACT—Biozzi mice selected for high (Hi) or low (Lo) responsiveness to phytohemagglutinin (PHA) have been followed for their entire life-span to examine their pathology at death. Spontaneous lymphomas were found to exhibit higher incidence and faster development in Lo/PHA than in Hi/PHA females, whereas a similar difference between the two lines did not attain the level of statistical significance in male mice. The incidence of solid tumors was higher in Lo/PHA than in Hi/PHA males but the same in females of the two lines, yet the probability of dying from solid tumors was slightly increased in Lo/PHA mice of both sexes. All these results indicate that T-cell-mediated immunity influences mainly the spontaneous incidence of lymphomas and, to a lesser degree, the appearance of other solid tumors.—JNCI 75:1083-1090.

Different effector mechanisms mediated by the immune system are implicated in the protection against tumor development.

Among them, natural defense mechanisms involving macrophages, natural killer cells, natural cytotoxic cells, as well as tumor-induced immunity mediated by T-cells and antibodies appear to influence the development and growth of tumors. Since the enunciation of the immune surveillance theory (*1, 2*), the relevance and role of these effector mechanisms in the control of tumor growth have been the subject of extensive experimental work indicating that some form of immune surveillance may operate for certain types of tumors.

Thymus-dependent immune responses clearly play a central role in tumors with strong tumor-associated transplantation antigens, particularly tumors induced by oncogenic viruses (*3*), but the absence of thymus has not been associated with increased susceptibility to these and other types of tumors (*4*); the inability to detect tumor-associated transplantation antigens on most spontaneous rodent tumors suggests a restricted role for the antitumor activity of T-cell-mediated immunity.

To test the overall influence of T-cells in the control of tumor development and growth, we have examined the incidence of spontaneous tumors in mice genetically selected for Hi or Lo T-lymphocyte responsiveness to PHA.

Genetic selection by bidirectional breeding for the intensity of T-lymphocyte mitotic response to PHA has led to the development of two lines of mice characterized by Hi/PHA or Lo/PHA response (*5*). At the selection limit, mice from these two lines exhibit not only a difference, about twentyfold, in their in vitro T-cell responsiveness to PHA but also differences as marked in the development of other T-cell-mediated responses both in vivo and in vitro. Thus lymphocyte responsiveness to concanavalin A (*6*), mixed lymphocyte reaction (*7*), and graft-versus-host reactivity (*8*) were shown to be much stronger in mice of the Hi/PHA line, as compared to the responses obtained in mice from the Lo/PHA line.

Conversely, the proliferative response to *Escherichia coli* lipopolysaccharide and the antibody response to injection of ovalbumin emulsified in complete Freund's adjuvant were comparable in Hi/PHA and Lo/PHA lines, indicating that B-cell function was not directly affected by the selection procedure. Analysis of the antibody response to SRBC has demonstrated that peak titers of total anti-SRBC antibodies are similar in the two lines for any antigen dose tested, but mercaptoethanol-resistant antibodies are threefold lower and the total antibody response declines faster in the Lo/PHA line. All these results suggest a marginal defect in helper T-cell activity in mice of the Lo/PHA line (*6*).

Previous work from our laboratory has examined the life-span and pathology of death of mice selected for Hi or Lo antibody responsiveness to natural antigens. In mice selected for antibody responsiveness to heterologous erythrocytes, shorter life-span and higher lymphoma incidence were observed in Lo-responder mice than in Hi-responder mice. Conversely, in mice selected for antibody responsiveness to *Salmonella* flagellar antigens, similar life-span and similar lymphoma incidence were found in Hi- and Lo-responder mice (*9, 10*). Thus in these studies no consistent correlation could be found between lymphoma incidence and antibody responsiveness.

Data reported in the present paper demonstrate that Lo/PHA females exhibit, as compared to Hi/PHA females, a tenfold higher incidence, earlier onset, and faster development of lymphomas. However, a clear-cut difference in frequency and development of lymphomas between the two lines could not be assessed in male mice. The incidence of solid tumors was higher in Lo/PHA than in Hi/PHA males but the same in females of the two lines, yet the probability of dying

ABBREVIATIONS USED: FCC = follicular center cell(s); H & E = hematoxylin and eosin; Hi = high, Lo = low, PHA = phytohemagglutinin; SRBC = sheep red blood cells.

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from this cause was slightly increased in Lo/PHA mice of both sexes. Therefore, T-cell-mediated immunity appears to influence mainly the expression of lymphomas and to a lower degree the incidence of other solid tumors.

MATERIALS AND METHODS

Hi/PHA and Lo/PHA responder mice are lines obtained by bidirectional selective breeding from outbred Swiss albino mice. Assortative breeding was performed between Hi/PHA or Lo/PHA responder mice at each generation by mating several pairs issued from different families within each line, thus avoiding brother-sister mating, to slow the increase of inbreeding. The two lines diverged progressively in PHA responsiveness until the 10th generation when the interline difference attained a maximum value that was maintained throughout the subsequent selective generations (*5*).

Mice of each line at the 16th generation were provided by Dr. G. Biozzi, Fondation Curie, Paris, and were randomly bred in our animal facilities for two generations before experimental use. After a total of 18 generations, mice of each line can be considered homozygote at all loci controlling the selected character (the interline difference already attained at the 10th generation remained unmodified during the subsequent selective generations) while homozygote at about 50% of the other loci (Biozzi G: Personal communication). Mice of either sex were randomized and housed 3 to a cage. Mice were given pelleted food and chlorinated water (10–20 ppm free chlorine; pH 2.5) ad libitum. The animal quarters were kept at 20°C and 60% relative humidity. Mice were inspected daily for their entire life-span. In a few cases moribund animals were killed.

Pathology.—Soon after spontaneous death, a complete autopsy was performed on 295 (97%) of the 303 mice under observation. The necropsy included a complete external and internal gross examination. Tissue masses as well as sections of the major organs were taken and processed for histologic examination. Tissues routinely examined were gross lesions, superficial lymph nodes, lungs, thymus, heart, liver, kidneys, stomach, small intestine, ovaries, uterus, testes, spleen, and sternum. The brain was examined grossly, but it was not processed routinely for histopathologic examination. Tissues were fixed in Bouin's fluid and processed for paraffin embedding and sectioning. Sections were stained with H & E.

The microscopic examination of coded slides was made by the pathologist (V. C.) who recorded his diagnoses on a special form. The collected information was then coded and entered into a computer program for statistical analysis. Tumor diagnoses that appeared doubtful were discussed within the Pathology Standardization Committee of the European Late Effect Project Group (*11*).

Statistical analysis of mortality and pathology data.—The occurrence of diseases was evaluated in terms of final incidence, the significance of the differences being tested by corrected chi-square analysis. Since this procedure may not be informative in all situations, particularly when large differences in mean survival time would bias the comparison among groups or when the small numbers of observed tumors in a group would limit the analysis of latency, age-related death rates with standard error for specific diseases were computed and plotted as cumulated probabilities as a function of time according to a model described in detail elsewhere (*12*). In essence, the model used estimates the probability of death for any specific cause (bronchopneumonia, lymphomas, and solid tumors) within arbitrarily predetermined nonoverlapping time intervals of equal length. Within each time interval the number of animals at risk n' was computed according to the relationship $n' = n - 0.5\ (z+w)$, where n is the number of mice alive at the beginning of the interval, z is the number of mice that died from other causes during the interval, and w is the number of animals withdrawn from the experiment during the interval. In our calculation, w represents the few animals for which no diagnosis was available due to advanced tissue autolysis. The death rate from any specific cause associated with each time interval is then given by the ratio of the number of mice that died from either one specific cause to the number of animals at risk and is therefore corrected for other causes of death and for accidental losses. In summary, the method analyzes both the frequency of lethal diseases and their time of appearance by a single set of statistics that takes competing risks and losses into account and is particularly useful for comparison between Hi and Lo responder lines.

RESULTS

Mean life-span for Hi/PHA and Lo/PHA mice are reported in table 1. The variability is remarkably high in both sexes of the Hi/PHA line, mostly in males.

No difference was found in longevity between Hi/-PHA and Lo/PHA female mice, whereas the life-span of male mice is significantly ($P<.001$) shorter in the Hi/PHA line than in the Lo/PHA line. Curves of cumulative mortality from all causes of death are shown in text-figure 1 for male and female mice. The decrease in mean life-span and the great variability in time of death in Hi/PHA males is apparent from the curves showing a faster initial rise followed by a parallel increase and a final lower rate of mortality in Hi/PHA as compared to Lo/PHA mice. Mortality curves for Hi/PHA and Lo/PHA females overlap completely.

A large spectrum of neoplastic and nonneoplastic diseases was observed at death in Hi/PHA and Lo/PHA mice, and a complete synopsis of the data is reported in table 1.

The frequency of bronchopneumonia is higher in Hi/PHA than in Lo/PHA mice of both sexes. This inflammatory disease was randomly distributed during the life-span of the affected mice, and there was no evidence of peak frequency at any given time.

TABLE 1.—*Neoplastic and nonneoplastic diseases in mice selected for Hi or Lo responsiveness to PHA*

Specification	Tumor type	Hi/PHA		Lo/PHA	
		Males	Females	Males	Females
No. of mice per group		57	86	80	80
Mean life-span, days ± SD		414±225	538±203	649±200	510±175
No. of autopsied mice		55	84	76	80
Inflammatory diseases					
Bronchopneumonia (%)		16 (29)	28 (33)	6 (8)	1 (1)
Lymphoid neoplasms					
FCC lymphoma[a]		1	2	7	14
Lymphoblastic lymphoma[b]				1	4
Total (%)		1 (2)	2 (2)	8 (11)	18 (23)
Solid tumors					
Lung	Alveolar adenoma	2	2	3	1
	Alveolar adenocarcinoma	1	7	23	5
Liver	Hepatocellular adenoma	1	4	4	1
Adrenal	Cortical carcinoma			1	3
GI tract	Adenocarcinoma			2	1
Testis	Leydig's cell tumor			8	
Skin	Carcinoma		1	1	
	Fibrosarcoma		7	5	
Vascular system	Hemangioendothelioma		7	4	
Mammary gland	Adenocarcinoma		3		16
	Tubular adenoma				3
Ovary	Luteoma		1		2
	Granulosa cell tumor		3		3
Uterus	Adenocarcinoma		2		2
	Leiomyofibroma		7		1
Total (%)		4 (7)	44 (52)	51 (67)	38 (48)

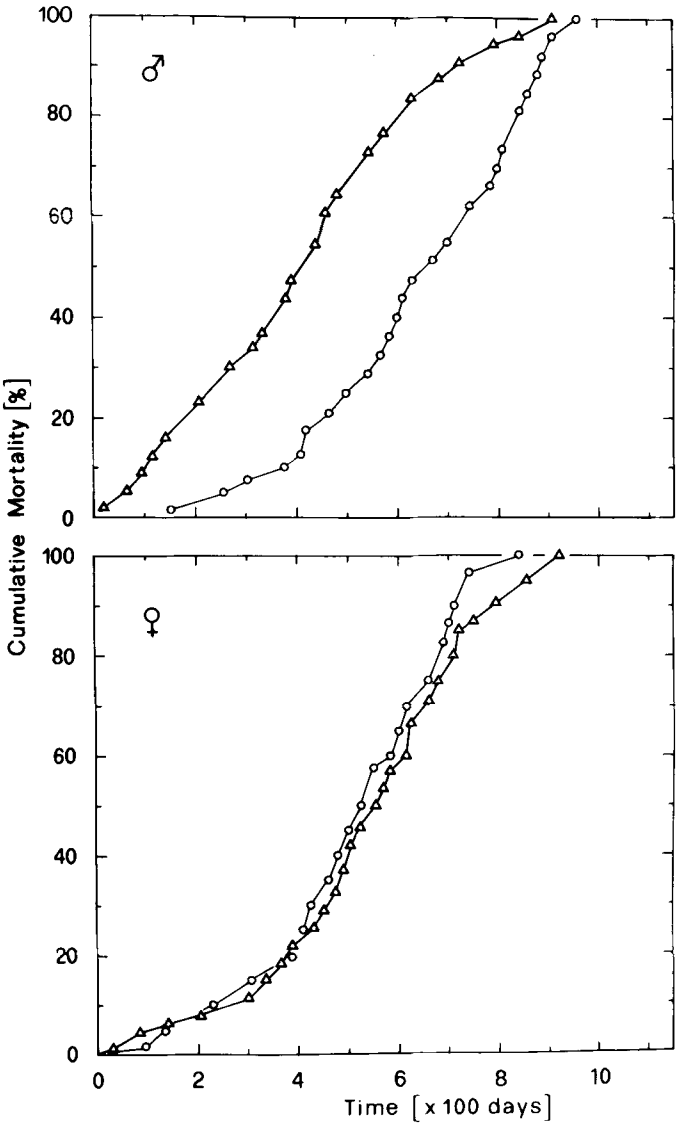
[a] Malignant lymphoma, FCC type.
[b] Lymphoblastic lymphoma, T-cell type.

Among neoplastic lesions the nonthymic malignant lymphoma is the only type of lymphoid tumor observed in Hi/PHA mice. This tumor is a lymphoma with a nodular or diffuse distribution constantly associated with gross involvement of the spleen, liver, and mesenteric lymph node (fig. 1A). In some cases other deep and superficial lymph nodes and Peyer's patches are also involved. Morphologically, the tumor is predominantly composed of moderately pleomorphic cells with cleaved nuclei. Larger cells may also be present with round nuclei containing one or two prominent nucleoli (fig. 1B, 1C). Lymphoblastic T-cell-type lymphomas developed only in Lo/PHA mice of both sexes. At necropsy, mice dying from T-cell-type lymphoma show a large, white, soft mass that occupies the mediastinum. The lungs are often atelectasic. Invasion of the spleen and lymph nodes may occur when the tumor becomes generalized. Morphologically, the thymus is entirely replaced by highly immature lymphocytes, uniform in size with scanty cytoplasm and abundant nuclear chromatin (fig. 2A, 2B). All lymphoid neoplasms are more frequent in Lo/PHA mice than in Hi/PHA mice of both sexes, although the difference is statistically significant ($P<.001$) only in females. The cell origin of lymphomas was not assessed by immunologic methods. According to the Pattengale-Taylor classification, based on anatomical location and cytomorphology (*13, 14*), the majority of lymphomas observed in the present study are of B-cell type, derived from FCC (FCC lymphoma), whereas only a small proportion are of lymphoblastic T-cell type.

Benign and malignant solid tumors of several types were also observed in lungs, skin, and mammary gland. Tumors of other tissues are less frequent and irregularly distributed among groups. The incidence of solid tumors is higher ($P<.001$) in females than in males of the Hi/PHA line, whereas no statistical difference is observed between sexes of the Lo/PHA line. Moreover, the incidence of solid tumors is much higher ($P<.001$) in Lo/PHA than in Hi/PHA males, whereas no significant difference is found between females of the two lines.

The pathology data in table 1 can account to a large extent for the differences in mean life-span observed between the two lines of mice. The shorter life-span in Hi/PHA than in Lo/PHA males may result from the higher incidence of bronchopneumonia in spite of the lower frequencies of lymphomas and solid tumors found in Hi/PHA male mice. Bronchopneumonia as a cause of death in Hi/PHA mice is further stressed by the similar life-span observed in females of the two lines, although lymphoma incidence is tenfold lower in Hi/PHA female mice. Solid tumors seem to play no major role as a differential cause of death in females, since these tumors are equally frequent in the Hi/PHA and Lo/PHA lines. It appears, therefore, from the pathology data in table 1 that the shorter life-span of Hi/PHA males may reflect their high sensitivity to bronchopneumonia, which, being randomly distributed during the life-span, could also account for the great variability in mean survival time observed in these mice.

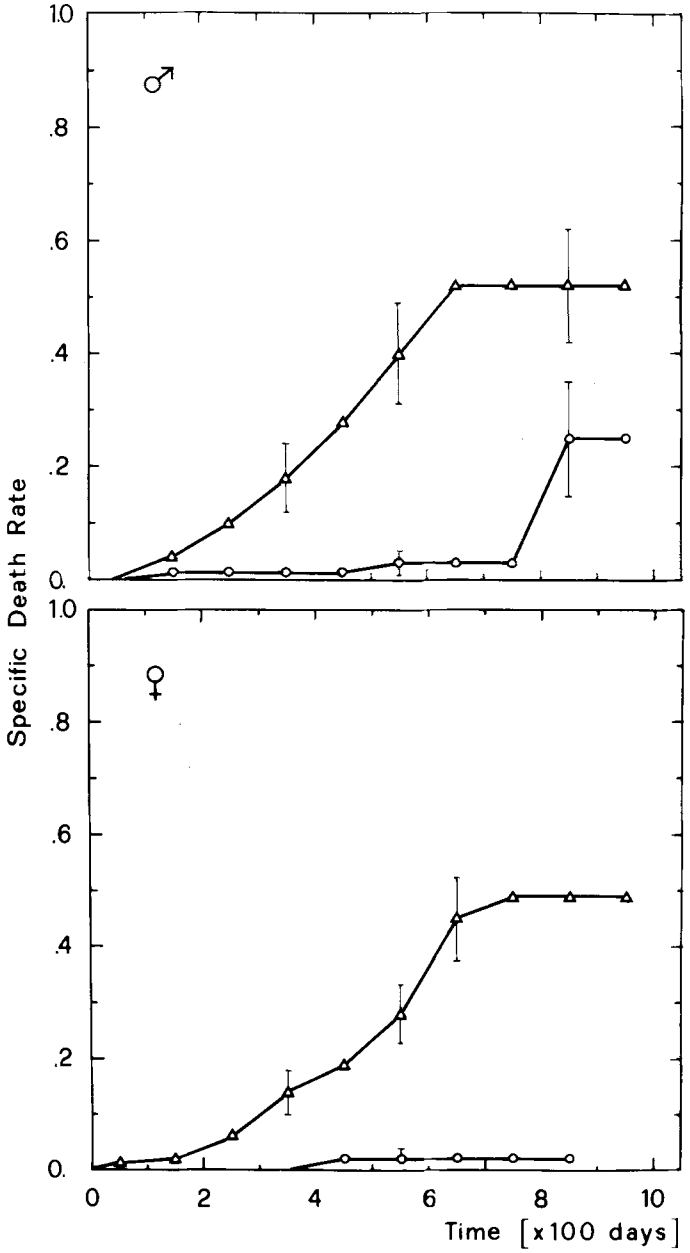
The analysis of age-related death rates for specific causes is most critical to correlate life-span and pathol-



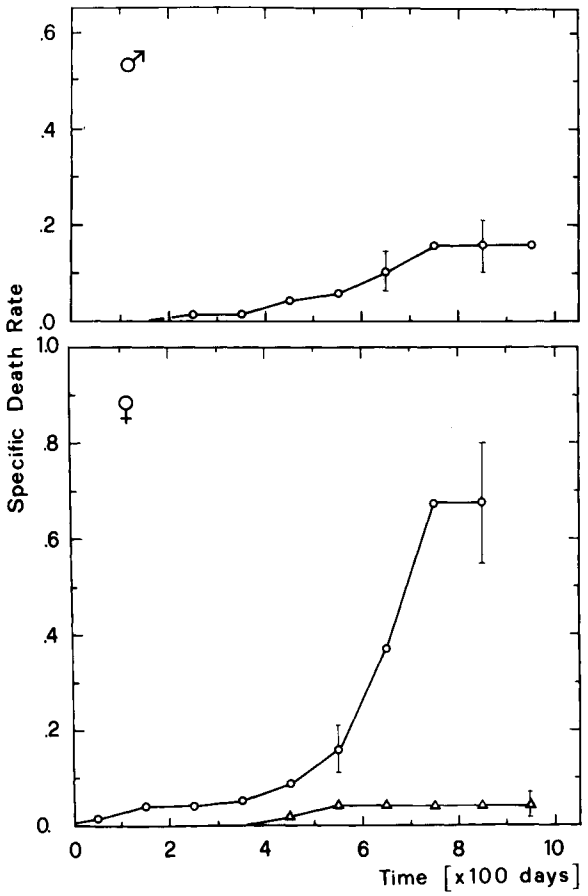
TEXT-FIGURE 1.—Cumulative mortality curves for Hi/PHA (△) and Lo/PHA (○) male and female mice.

ogy data. As reported in text-figure 2, the onset of bronchopneumonia occurs earlier and its development is faster in Hi/PHA mice than in Lo/PHA mice of both sexes. The role of lymphomas as differential cause of death in males cannot be evaluated in terms of specific death rate because only 1 case was found in the Hi/PHA line. However, the probability of dying from lymphomas attained at 800 days in the Lo/PHA line is lower than 20%. In females the risk of dying from lymphomas increases exponentially with age and reaches 70% at 800 days in Lo/PHA mice, whereas it remains at a negligible level in Hi/PHA mice (text-fig. 3). The overall incidence of lymphoid neoplasms is 2% in Hi/PHA mice and 17% in Lo/PHA mice. The reported incidence of lymphoid neoplasms in unselected albino mice, as presumed from an extensive literature survey, is about 7% (*15*). Thus it appears that genetic selection for PHA responsiveness has induced decreased incidence of spontaneous lymphoid tumors in Hi/PHA mice and increased incidence in Lo/PHA mice.

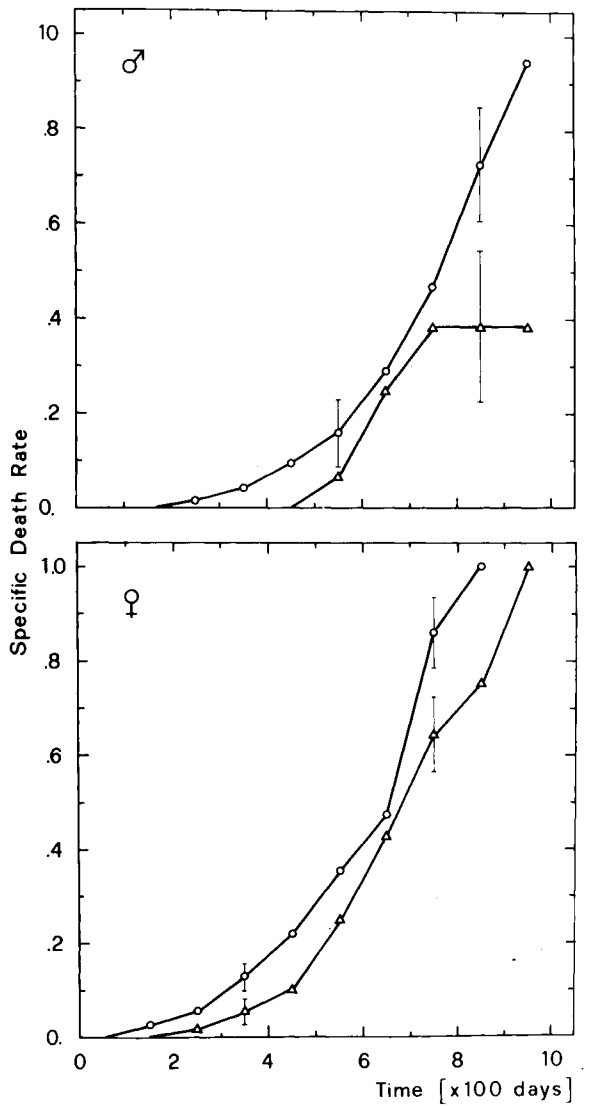
Comparison of text-figures 2 and 3 suggests that the same life-span in females of the two lines is mainly the result of the mutually exclusive risks of dying from bronchopneumonia or lymphomas. As shown in text-figure 4, mice of both sexes exhibit a slightly higher probability of dying from solid tumors in the Lo/PHA line than in the Hi/PHA line, yet the rate for this specific cause of death levels off at about 800 days in



TEXT-FIGURE 2.—Cumulative death rate specific for bronchopneumonia in Hi/PHA (△) and Lo/PHA (○) responder male and female mice as a function of time (consecutive nonoverlapping periods of 100 days). The rate is corrected for other causes of death and accidental losses.



TEXT-FIGURE 3.—Cumulative death rate specific for lymphoid neoplasms in Hi/PHA (△) and Lo/PHA (○) responder male and female mice as a function of time. Death rate in Hi/PHA males was not calculated because only 1 case was observed. *See* text-fig. 2.



TEXT-FIGURE 4.—Cumulative death rate specific for solid tumors in Hi/PHA (△) and Lo/PHA (○) responder male and female mice as a function of time. *See* text-fig. 2.

Hi/PHA males because a large portion of these mice have already died from bronchopneumonia (text-fig. 2).

DISCUSSION

The two lines of mice genetically selected from an outbred population of Swiss albino mice by bidirectional breeding for Hi or Lo T-cell responsiveness to PHA displayed different life-span and cumulative mortality curves in male mice but not in female mice. Longevity of males, indeed, was significantly shorter in the Hi/PHA than in the Lo/PHA line. This difference appears as a result of the higher incidence of bronchopneumonia in Hi/PHA mice in spite of the lower frequencies of lymphomas and solid tumors found in males of this line. The relevance of bronchopneumonia as a cause of death in Hi/PHA mice is also supported by the same life-span of females of the two lines, although lymphoma incidence was tenfold higher in Lo/PHA than in Hi/PHA mice. Analysis of death rate from bronchopneumonia revealed that this inflammatory disease appears earlier and develops faster in Hi/PHA mice than in Lo/PHA mice of both sexes. Bronchopneumonia-inducing microorganisms are usually eliminated by phagocytosis of antibody-coated bacteria, and these processes are considerably enhanced by T-cell-mediated responses. Mice of the Hi/PHA line need to be immunized with a tenfold higher antigen dose to develop delayed-type hypersensitivity and migration-inhibition responses comparable to those induced in Lo/PHA mice (*16*). This observation may therefore contribute to explain the higher incidence of bronchopneumonia in Hi/PHA mice.

At 3 months of age the mean body weight of the 57 Hi/PHA males (30.41±0.43 g) was lower ($P<.001$) than that of the 80 Lo/PHA males (32.49±0.25 g), whereas no difference in mean body weight was observed between the 86 females of the Hi/PHA line (26.02±0.40 g) and the 80 females of the Lo/PHA line (26.62±0.20 g). These considerations are consistent with the mortality curves of text-figure 1, suggesting that genetic selection may have accumulated genes negatively affecting the longev-

ity of Hi/PHA male mice. It is possible that during selection for high T-cell responsiveness to PHA, alleles at other loci that negatively affect longevity have been randomly drifted and have subsequently become fixed. Conversely, positive effect alleles selected for responsiveness to PHA may have pleiotropic negative effects on longevity or may be preferentially associated (linkage disequilibrium) with alleles at other loci with negative effects on longevity. These speculations entertain the possibility that negative genes for longevity increase the susceptibility to inflammatory diseases such as bronchopneumonia.

The main finding of this study is the correlation between high T-cell responsiveness to PHA and low incidence of lymphomas in mice of both sexes. Owing to the detection of only 1 lymphoma in Hi/PHA males, death rates of the two lines cannot be compared in males. Comparison between females of the two lines reveals that the risk of dying from lymphoma appears earlier and increases faster to reach a much higher level in Lo/PHA mice than in Hi/PHA mice. As previously recalled, Hi/PHA and Lo/PHA lines were developed from a parental population of outbred Swiss albino mice (*5*). Since the overall incidence of lymphoid neoplasms observed in the present study is 2% in Hi/PHA mice and 17% in Lo/PHA mice, whereas the reported incidence in unselected albino mice is about 7% (*15*), it appears that genetic selection for high responsiveness to PHA decreases lymphoma incidence in Hi/PHA mice. The relevance of T-cell responsiveness in immune surveillance is further stressed by the higher lymphoma incidence observed in Lo/PHA mice.

The majority of these lymphomas morphologically seems to be derived from B-cells rather than from T-cells (*13, 14*), suggesting that genetic selection against T-cell responsiveness to PHA may bring about alterations in the T-cell compartment which lead more often to impairment of antitumor immunity than to T-cell malignant transformation. Furthermore, the much higher incidence of nonlymphoid solid tumors in Lo/-PHA than in Hi/PHA males as well as the slightly higher risk of dying from these tumors in Lo/PHA than in Hi/PHA mice of both sexes also support the possibility that mice genetically selected for low responsiveness to PHA exhibit a marked impairment in T-cell-mediated responses against spontaneous tumors.

It cannot be excluded that positive effect alleles selected for T-cell responsiveness in Hi/PHA mice have a pleiotropic negative effect on tumor incidence or are preferentially linked to alleles at other loci which reduce tumor incidence. However, the marked differences between Hi/PHA and Lo/PHA mice not only in responsiveness to PHA but also in other T-cell-mediated responses (*6-8*) strongly support the conclusion that genetic selection has accumulated genes that control high or low T-cell-mediated immunity against the appearance and development of spontaneous lymphomas and other solid tumors. The lack of consistent correlation between spontaneous tumor development and antibody responsiveness (*9, 10*) further stresses the importance of T-cell immunity in antitumor responses.

Current studies in our laboratory are addressed to the identification of mechanisms counteracting tumor development by segregation analysis of the selected immune parameter and tumor incidence. This type of analysis is done on the progenies from crosses, intercrosses, and backcrosses between the two selected lines and should establish for each population the percent of mice in each of which high immune responsiveness is associated with lack of tumors and low responsiveness is associated with tumor development. Consistent data obtained by this approach may exclude that heterozygosis at loci other than those controlling the selected character might have affected tumor incidence at the population level.

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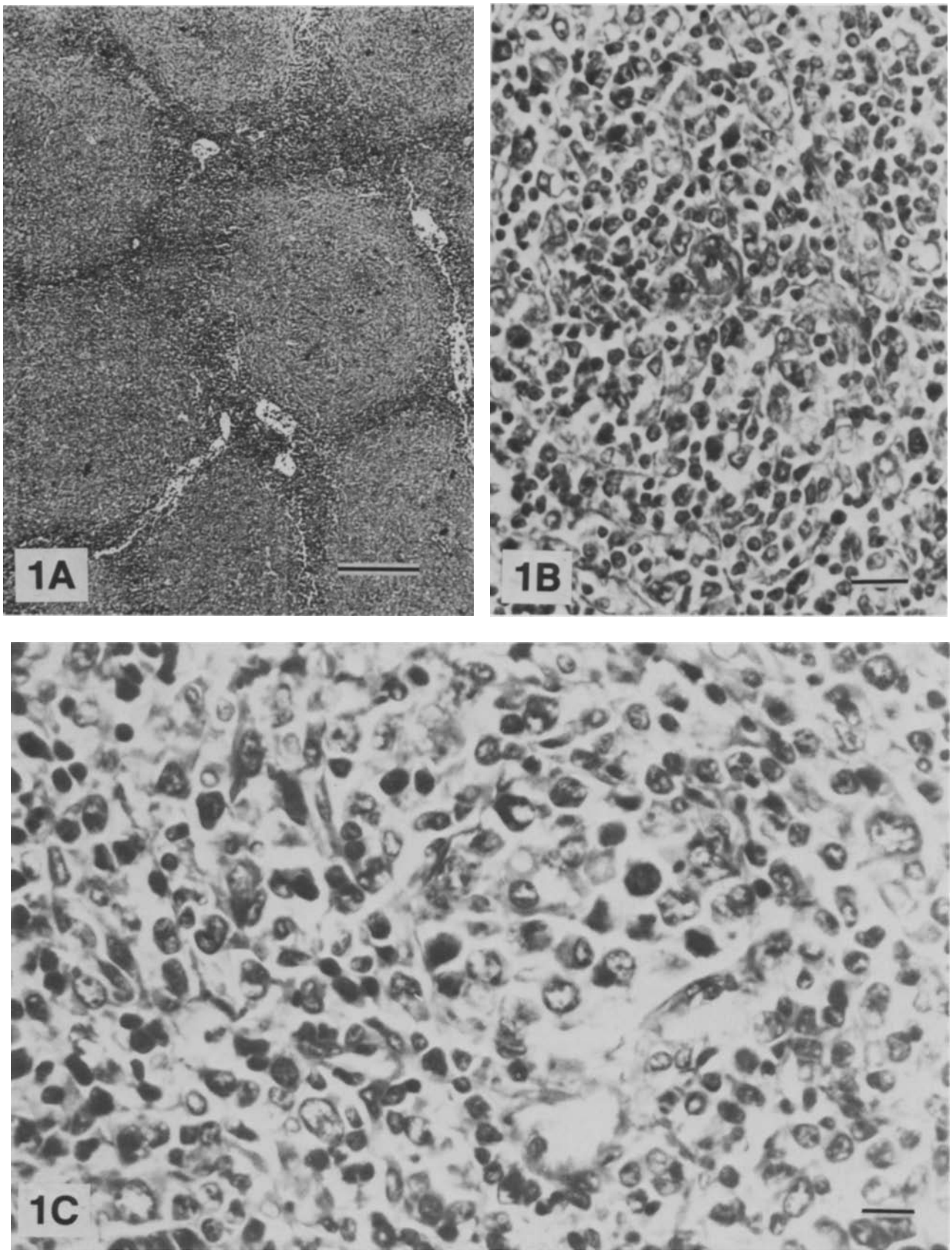

FIGURE 1.—Malignant lymphoma of FCC: 1A) Spleen showing, at low power, the follicular-like pattern. H & E. *Bar*=200 μm. × 70. 1B) Splenic periarteriolar area with lymphoid cells. H & E. *Bar* = 50 μm. × 200. 1C) High-power view of splenic white pulp showing similar proportion of large and small FCC with irregular nuclei (cleaved). FCC lymphoma small and large cell (mixed) type. H & E. *Bar* = 10 μm. × 900

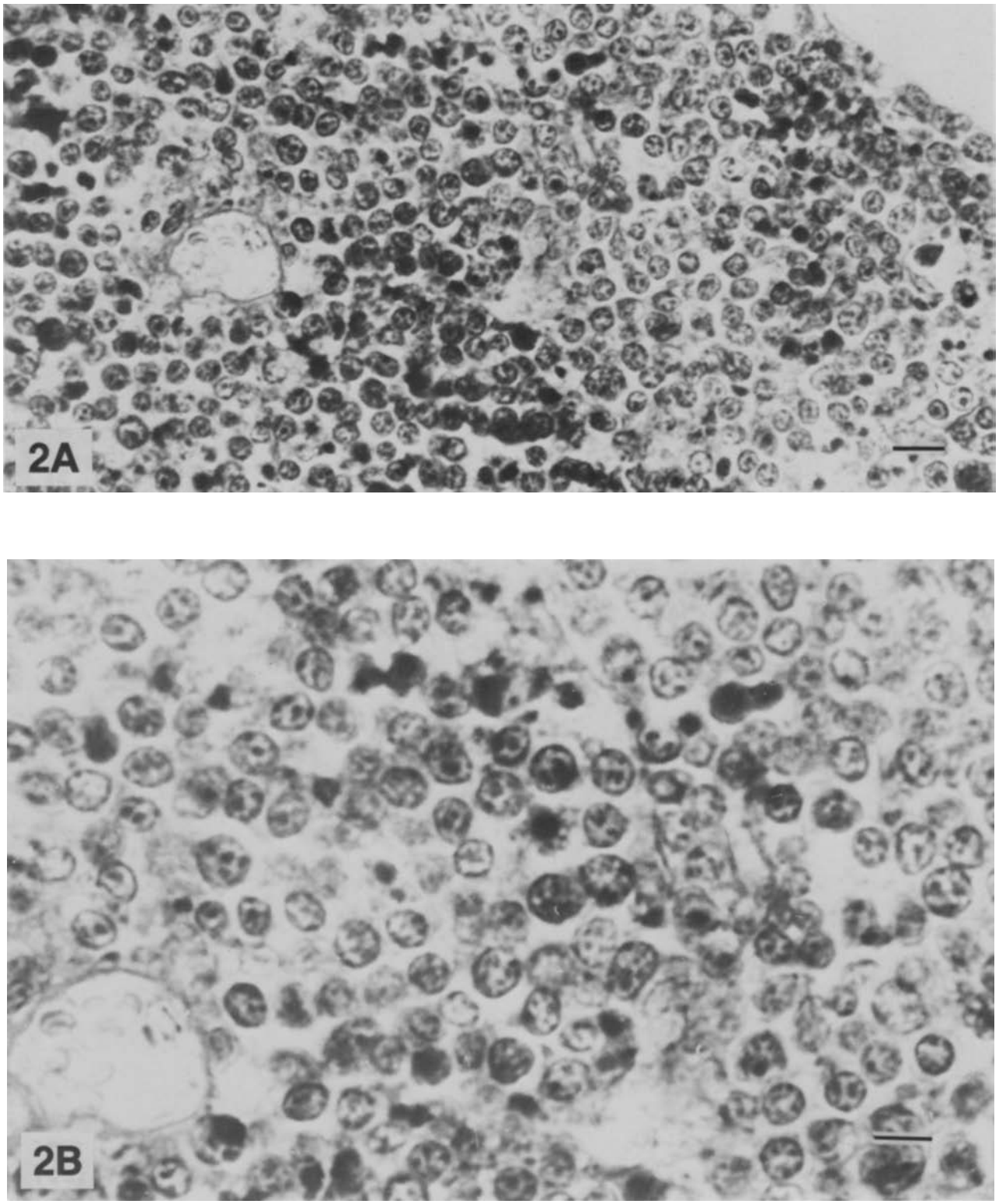

FIGURE 2.—Lymphoblastic lymphoma, T-cell type: 2A) Thymus, sheet of monomorphous lymphoid cells. H & E. *Bar* = 30 μm. × 300. 2B) High-power view of several lymphoid cells with scant cytoplasm, round nucleus, and prominent nucleoli often centrally placed. H & E. *Bar* = 10 μm. × 1,000