membrane immunofluorescence test. In contrast, only a few or no leukemic cells were found to be positive for surface membrane immunoglobulin (SmIg). The number of leukemic cells having E-receptors varied from 8 to 41.5%. The number of leukemic cells having EA(Fcγ) receptors also varied from 2.5 to 73.5%, whereas a few EAC receptor-positive cells were found in all cases. It is speculated that the finding of various percentage of Fcγ-positive cells in the various cases suggests, in turn, the presence of Fcμ-positive cells, and that PNU-induced leukemia will be the consequence of malignant transformation of a heterogeneous T-cell subset. As intracellular markers, cytoplasmic immunoglobulin (CIg) M and G, which are found in pre-B cells and plasma cells, could not be found in the cytoplasm of leukemic cells by the direct immunofluorescence test. TdT-positive cells, which are usually seen in thymus cortex[8], were found to be 9–32% of the leukemic cells by cytoplasmic immunofluorescence.

Taking these facts into consideration, it was concluded that all of the PNU-induced leukemias tested were T-cell leukemia, which is considered to be similar to T-cell malignancies found in human disorders.

Furthermore, the presence of oncorna virus-related antigens in these T-cell leukemia was examined by the cytotoxicity test using anti-Gross tumor serum[9] and anti-rat erythroblastosis virus serum[10]. None of the leukemic cases gave positive results whereas, in sharp contrast, 50% of the leukemic cells induced by the viruses were killed by the anti-Gross tumor serum with a dilution of 1:32 and by the anti-erythroblastosis serum with a dilution of 1:1024, respectively. It is again stressed that even in rat T-cell leukemia, where there is a possibility of viral implication, there is no association of oncorna virus with leukemogenesis in rats[9].

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Effect of lithium on normal and chronic granulocytic leukemia colony forming cells (CFU-GM)

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Summary. The effect of lithium on normal and chronic granulocytic leukemia (CGL) granulo-monocytic precursors (CFU-GM) has been studied. Lithium slightly increases normal CFU-GM growth whereas it is withouth effect or moderately inhibitory for CGL CFU-GM. It is suggested that it is unlikely that lithium therapy enhances the proliferation of a silent leukemic clone.

Lithium, due to its stimulatory effect on granulopoiesis[2,3], has been used to treat granulocytopenias both idiopathic and secondary to cytostatic treatment[4,5]. Extensive in vitro investigation has thrown some light on the mode of action of lithium on normal hemopoietic cells, showing that its stimulatory effect depends on an enhancement of the production of colony stimulating activity as well as on a direct stimulation of hemopoietic stem cells[6–8]. On the other hand nothing is known of the effect of lithium on leukemic cells. Such information appears to be of some relevance because of recent reports of cases of leukemia during or subsequent to treatment with lithium; it has been suggested that these resulted from a transformation of a normal cell, or a stimulation of a silent malignant clone, induced by lithium[9–11]. While there is evidence against a mutagenic effect of lithium[12] it is not known whether lithium can accelerate leukemic cell proliferation[13]. For this reason we undertook studies on the in vitro effect of lithium on normal and CGL CFU-GM.

Increasing concentrations of lithium chloride (dissolved in distilled water) were added to 1×10^5 cells from 10 normal bone marrow samples and from peripheral blood of 8 CGL patients. All samples were prepared as previously described[14] in McCoys 5A supplemented medium with 15% foetal calf serum (FCS, Seromed, Munich, FRG) in agar 0.3% and plated over feeder layers prepared, according to Pike and Robinson[15], in McCoys 5A supplemented medium with 15% FCS in 0.5% agar. After 8 days' incubation in a fully humidified atmosphere with 5% CO_2 the dishes were scored and all aggregates of more than 40 cells were counted as colonies.

The table shows that lithium slightly increased normal CFU-GM growth, confirming the results of Tisman et al.[6] while no effect or a slight inhibition was observed in CGL cultures. At lithium concentrations between 1 and 5 mM the difference in response between normal and CGL CFU-GM was statistically significant ($p < 0.05$).

Effect of increasing concentrations of lithium on normal and CGL CFU-GM. In each experiment mean CFU-GM colony number of 3 dishes per point was determined and expressed as a percentage of control colony number. Results are means ± SD of these percentages. Colony number range in control dishes/10^5 cells plated: normal = 68–172; CGL = 42–184.

	Lithium (10^{-3} M) 0	0.5	1.0	2.5	5.0	10.0
Normal	100	116 ± 13	118 ± 11	119 ± 15	128 ± 18	98 ± 26
CGL	100	94 ± 16	82 ± 18	79 ± 19	75 ± 23	71 ± 28

Our data indicate significantly different effects of lithium on normal and CGL CFU-GM. The reason for this difference is unknown, but it is not surprising considering the multiple defects in the response to regulatory factors observed in CGL cells[16,17].

The hypothesis that the action of lithium that we observed on CFU-GM is not direct, but mediated by other cells is unlikely in view of the low number of cells plated; at this density no endogenous production of Colony Stimulating Activity (CSA) is detectable (15).

In conclusion, considering the caution required in view of the limitations of in vitro systems for studying in vivo phenomena, our data do not seem to support the hypothesis that lithium can enhance the proliferation of a silent leukemic clone. However, caution in the use of lithium to treat granulocytopenias is warranted until the relevance in humans of the late depletion of stem cells, observed in mouse continuous cultures of hemopoietic stem cells[7] is established.

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Pathological changes in inbred strains of mice following early thymectomy and irradiation[1]

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Summary. Mice subjected to thymectomy and irradiation were found to develop a range of pathological change in various organs. These changes were accompanied by antibodies to a variety of self-components. The pattern of pathological and autoimmune change was found to vary with the strain. This strain-related expression did not appear to be associated with the major histocompatibility complex (H-2).

Autoimmune disease presents a continuing problem both in clinical terms and also in understanding the basic mechanisms of aetiology and pathogenesis. Efforts to study the fundamental aspects of such diseases have to a large extent depended upon attempts to induce similar states in laboratory animals by immunization with appropriate self components and complex adjuvants[3,4]. However, such procedures often lead to failure or inconsistent reproduction of autoimmune changes which in any case tend to differ from the clinical condition in many basic respects.

Evidence accumulated over the last decade, indicating that thymus-derived cells and their products play an important role in the regulation of the immune response, including reactions of the autoimmune type, has enabled a different approach to be made to the development of relevant experimental models of autoimmunity[5,6]. In this study we describe the induction of a wide spectrum of pathological changes with some evidence for autoimmune origin in inbred mice strains, following interference with immune regulatory function by early thymectomy and irradiation without the requirement for autoimmunisation. This particular approach affords a new opportunity to investigate the basic pathogenic mechanisms underlying a number of autoimmune lesions in a variety of organs, and to investi-

Summary of changes in mice observed after early thymectomy (21 days of age) and sub-lethal irradiation (4 × 250 rad)

Strain	H-2 Type	No. of animals	Incidence of autoantibodies (%)					Incidence of changes in solid organs (%)		
			Erythrocytes	Nuclear components	Parietal cell*	Thyroid	Smooth muscle	Thyroid	Liver	Kidney
CBA/H	k	22	27	0	20	0	0	0	0	0
AKR	k	8	38	25	0	12	0	0	0	0
BALB/c	d	20	30	0	20	15	0	10	0	0
DBA/2	d	6	17	17	60	0	0	0	0	0
C57BL/10	b	14	21	8	0	0	7	0	28	14
SJL/J	s	15	0	34	20	7	6	7	33	20
SWR/J	q	9	0	11	20	22	0	11	0	0

* 5 animals per strain were tested. No changes were observed in normal control mice of the above strains with the exception of two mice of SJL/J (8%) and DBA/2 (7%) strains which had weak ANA.