Increased Incidence of Lymphomas in Thymectomized Mice - Evidence for an Immunological Theory of Aging[1]

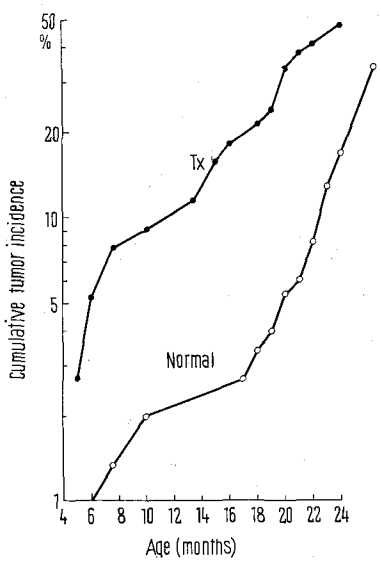
In a recent preliminary communication, I reported an increased incidence of lymphoreticular tumors in aging neonatally thymectomized mice[2]. The present report confirms and extends these findings by observation of such animals over a longer time period. Graphical analysis of the data is also presented.

(C57B1/1XA)F_1 hybrid mice were subjected to neonatal thymectomy. Similar F_1 hybrid mice, not thymectomized, served as controls. All animals were observed twice weekly thereafter, for the duration of the experiment. Tumor incidence was based on clinical examination, corroborated by histologic studies.

One-third of the thymectomized (Tx) mice died of wasting by 4 months. Since few deaths due to wasting occurred subsequently, tumor incidence was based on a study of 77 neonatally thymectomized mice alive at 4 months, and on 149 normal controls.

The cumulative tumor incidence is plotted in the Figure. In the Tx group, tumors were first detected at 5 months of age. After the 7th month, the curve of tumor incidence for this group showed a fairly uniform slope on semi-logarithmic plot. Tumors were also first noted at 5 months in the normal controls. After the 17th month, the slope for this group was also uniform. The slope of this curve was greater than the slope of the curve for the Tx group, so that convergence of the curves of tumor incidence for the Tx and control groups was clearly evident. The incidence of tumor at a given age was significantly higher in the Tx group than in the controls, for all ages plotted in the Figure, as determined by the chi square test. For example, at 10 months tumor incidence in the Tx group was 7/77 (9.0%) compared to 3/149 (2.0%) for the controls ($P < 0.02$). At 24 months the tumor incidence figures were 36/77 (47.0%) and 25/149 (16.8%), respectively ($P < 0.001$). Histologically, the tumours in both groups were lymphoreticular: they were classified as reticulum cell sarcomas, although in some areas they appeared to be lymphomosarcomatous.

Previous reports have recorded an increased incidence of tumors in thymectomized mice following exposure to carcinogenic agents[3], or viruses[4]. Spontaneous polyoma tumors, which are very rare in normal mice, occur more frequently following neonatal thymectomy[5]. However, this is the first demonstration of a highly significant increase in the incidence of lymphoreticular tumors in thymectomized mice not exposed to exogenous agents.



Cumulative tumor incidence in 77 neonatally thymectomized (Tx) (C57B1/1 X A)F_1 hybrid mice, compared to the incidence in 149 normal F_1 hybrid controls.

Persuasive arguments have been advanced in the support of the theory that aging is to a large extent dependent on the immune processes[6,7]. The thymus-dependent system has as its most essential function immunological surveillance, that is the capacity to deal with cellular aberrations arizing during the life of the animal. The manifestations of these aberrations include neoplasms and autoimmune disease. The thymus system undergoes gradual exhaustion with age, in both mouse and man. If then it is assumed that cellular aberrations occur at a constant rate throughout life[7], it would follow that neoplasms and autoimmune phenomena would become increasingly common in old age. The present experiments, by demonstrating an increased incidence of lymphoreticular tumors in thymectomized mice (as well as autoimmune changes[2]), provide experimental proof of these concepts. Additional evidence for these concepts are afforded by the observations of MEWISSEN[6]. He found that age specific incidence rates of spontaneous tumors in C57B1/6 mice fitted a linear Gompertzian regression. The findings supported the concept of 2 interacting components, 1 of phenotypic expression acting at a constant rate, the second of repression gradually losing strength at a constant rate throughout the life span of the animal.

The convergence of the curves of tumor incidence for the Tx and control groups might be explained as follows: Neonatal thymectomy undoubtedly resulted in immunological impairment which was quite variable (since thymectomy was carried out over a period from 1 to 24 h after birth). Those animals most seriously impaired died at an early age of post-thymectomy wasting. The mice which were less seriously deficient immunologically did not waste but soon developed tumors, while those animals which were least impaired developed tumors at an older age. Thus through a selection process, the post-thymectomy group gradually approached the controls in immunological characteristics. In the control mice, the later onset and steeper slope of the cumulative tumor incidence curve probably represents the effects of age-related exhaustion of the thymus-dependent system in normal old mice. Such a loss of the immunological surveillance function could occur rapidly and quite uniformly after a certain age.

Zusammenfassung. Bei einem Mäusestamm mit hoher Rate spontaner Retikulosarkome wird gezeigt, dass die Tumoren bei neonatal thymektomierten Tieren signifikant rascher und häufiger auftreten.

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