hancing drug, also possesses radioprotective effect. (2) This effect is significant for both short and long time.

Zusammenfassung. Magnesium-Pemolin, bekannt als gedächtnisstärkendes Arzeimittel, besitzt eine erhebliche Schutzwirkung gegen ionisierende Strahlen. Dieser strahlentherapeutische Effekt betrifft sowohl kurze, als auch langdauernde Wirkungsperioden.

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Age Dependency of the Primary Immune Response in the Hereditary Pituitary Dwarf and Normal Snell-Bagg Mouse

The experiment reported here was undertaken as part of an investigation dealing with the problem of the possible hormonal control of the primary immune response, using as experimental animals the hereditary recessive pituitary dwarf and normal Snell-Bagg mice. Studies on the immunological responsiveness and on the thymus and the peripheral lymphoid tissues of this strain of mice regardless of the age at the time of sacrifice, were previously reported from this laboratory[1-4]. The immunological defects found in dwarf mice are probably related to a congenital underdevelopment of the thymus[2,3]. It is the purpose of this paper to describe the age dependency of immunological reactivity in this particular strain of mice.

Material and methods. Inbred hereditary recessive pituitary dwarf (genetic symbol *dw*) and normal mice of the Snell-Bagg strain were used. Experimental groups were made up of animals of the same age. Since the immunological responses of males and females were similar[5], the sex of the animals is not reported. Four days before sacrifice, the animals were given i.p. 4×10^7 sheep red cells in 0.1 ml of saline, and 24 h before sacrifice an i.p. injection of thymidine-H^3 (Amersham, specific activity 3000 mc/m*M*) at the dose of 0.8 μc/g of body weight. The animals were then killed at different times between 15 and 60 days of age. At the time of sacrifice, body, thymus and spleen were weighed and individual antibody-plaque-forming cells (APFC) from spleen were detected according to the technique of JERNE et al.[6]. Thymus, peripheral and mesenteric lymph nodes and Peyer's patches were fixed in Carnoy's fluid, and histological sections were stained with methyl-green pyronine. Additional sections of peripheral lymphoid tissues were processed for autoradiographic studies, stained with hematoxylin, and the proportion of labelled nuclei was determined by counting 1000 cells randomly chosen in the cortical germinal centres as well as in the paracortical areas. Only cells with 5 or more grains were scored as labelled.

Results. The primary immune response to sheep red blood cells as measured by the capacity to form APFC, and the total number of spleen cells of normal and pituitary dwarf mice of different ages, is reported in the Table, together with the weight values. Normal animals showed a moderate response at 15 days of age; the number of APFC subsequently increased up to the sixtieth day, with a maximum rate of rise between 20 and 30 days of age. Fifteen-day-old pituitary dwarf mice, on the other hand, showed a very poor response. Between 20 and 45 days of age, an only slightly higher, still definitely subnormal plaque-forming capacity was found. Due to the limited life span of pituitary dwarf mice, the experiment was discontinued at this time. A higher total number of spleen cells was constantly found in the normal than in the dwarf mice, in which, on the contrary, a progressive fall was seen.

In histological sections of peripheral lymphoid tissues, the proportion of pyroninophilic cells was greater in normal than in dwarf animals. Starting from 15 to 60 days of age we found a progressively increasing number of pyroninophilic cells, mainly plasmablasts and immature plasma cells in the germinal centres of the normal animals. In these animals sacrificed between 45 and 60 days of age, we found the highest number of these cells with occasionally scattered mature plasma cells. In contrast to this, a constant lack of pyroninophilic cells was found in the germinal centres of the peripheral lymphoid tissues of the pituitary dwarf mice, regardless of the age at time of sacrifice. It was interesting to note that, while in the normal mice we were able to observe a progressive increase of the number of the germinal centres and of the proportion of the pyroninophilic cells, in the dwarf animals a constant pattern of marked lack of pyroninophilic cells as well as of small lymphocytes in the thymus-dependent paracortical areas were the main histological findings throughout the duration of the experiment. In peripheral lymphoid tissues, a constantly high mean % of labelled nuclei was found regardless of the age at the time of sacrifice; in contrast, a constantly lower proportion of labelled nuclei was recorded for these tissues in the dwarf animals (Table).

Histological study of thymus sections from dwarf animals has given results substantially in agreement with our previously reported observations[1,4], showing a progressive early involution with marked loss of lymphocytes and evident fibrosis. In addition, in thymus of dwarf animals sacrificed at 30 and 45 days of age, patterns of cortical inversion resembling those described by METCALF[7] in preleukemic AKR thymuses, have been noted. This condition is histologically characterized by a variable degree of thickening of the connective capsule and substitution of the medulla with medium and small lymphocytes and scattered reticulum cells.

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Body, thymus and spleen weight, No. of spleen cells and APFC, and proportion of labelled cells in peripheral lymphoid tissues in normal and dwarf mice

Age in days	No. of mice	Body weight (g)	Weight of thymus (% b.w.)	Weight of spleen (% b.w.)	No. of spleen cells × 10^6	No. of APFC/10^6 nucleated spleen cells	Proportion of labelled cells (%) in peripheral lymphoid tissues
Normal							
15	4	10.3 ± 0.3	0.549 ± 0.079	1.094 ± 0.110	120.7 ± 27.3	32.4 ± 10.4	26.6 ± 3.5
20	4	9.2 ± 1.0	0.562 ± 0.054	0.909 ± 0.078	94.0 ± 6.0	65.2 ± 18.7	24.7 ± 3.2
25	4	12.3 ± 1.7	0.461 ± 0.058	1.064 ± 0.132	114.2 ± 22.0	137.8 ± 52.3	27.2 ± 1.5
30	5	14.7 ± 0.9	0.448 ± 0.220	0.997 ± 0.017	139.8 ± 18.7	194.7 ± 51.2	28.6 ± 1.7
45	6	15.9 ± 1.2	0.417 ± 0.048	0.850 ± 0.046	159.3 ± 14.2	246.1 ± 34.5	28.3 ± 1.3
60	6	20.5 ± 1.9	0.267 ± 0.046	0.671 ± 0.052	155.6 ± 10.1	265.8 ± 31.4	23.1 ± 1.4
Dwarf							
15	4	6.1 ± 0.6	0.385 ± 0.012	0.696 ± 0.080	37.9 ± 8.5	6.5 ± 1.9	11.3 ± 1.1
20	4	4.6 ± 0.6	0.300 ± 0.064	0.449 ± 0.054	11.2 ± 0.4	33.2 ± 11.1	6.1 ± 0.2
30	4	3.9 ± 0.4	0.192 ± 0.053	0.311 ± 0.036	4.5 ± 1.2	27.9 ± 5.8	12.6 ± 1.2
45	4	4.6 ± 0.3	0.147 ± 0.023	0.260 ± 0.034	6.5 ± 1.0	42.1 ± 13.3	16.1 ± 2.6

Discussion. Previous studies have clearly shown that the immunological responsiveness related to the primary immune response of an animal tends to increase after birth to adult age[8-12]. The present experiment has shown a rise with age of the primary immune response in the normal Snell-Bagg mouse. In addition, in the normal animals sacrificed between 15 and 30 days of age, there is a more accelerated rise in the hemolysin-forming capacity of spleen cells than in those sacrificed in the following periods up to the sixtieth day. In contrast to this, in the hereditary recessive pituitary dwarfs of the Snell-Bagg strain we have noted a constantly extremely low plaque-forming capacity which showed no significant increase with age.

According to previously reported observation[8,9,11], there is a direct relationship between the rise of immunological reactivity with age and the number of potential antibody-forming cells of the spleen. Our results seem to give support to this concept for the period of life after weaning.

Moreover, during the suckling period our observations also suggest the importance of the host environment[13-16] in the establishment of the immunological reactivity. This fact is illustrated by the parallel fall of the number of spleen cells joined with the rise in immunological reactivity in normal as well as in dwarf mice during the suckling period.

In dwarf animals the number of spleen APFC and the proportion of pyroninophilic cells remains relatively steady after weaning throughout life. This observation can be explained on the basis of a lack of immunological maturation of the precursors of antibody-forming cells during foetal and early life, probably depending on the previously described thymus functional inadequacy of the dwarf mouse of our strain[1,3-4].

Our results also show a rise with age of immunological capacity in animals with normal hypophysis and normal thymus and, conversely, a constant low immunological reactivity in dwarf mice with hypophysis underdevelopment and thymus early involution. This fact suggests an hypophyseal control of the thymus and possibly of the primary immune response, in agreement with other results[17], and with our preliminary unpublished observations. Further experiments are now in progress in order to verify whether the hypophysis may thus, directly or indirectly through the thymus, control the balance of the antibody-producing cell system.

Riassunto. Vengono riportati i dati relativi allo sviluppo in funzione dell'età, della reatività immunologica primaria nel topo con nanismo ereditario preipofisario e nel corrispondente fratello normale. Mentre in quest'ultimo si è notato un graduale incremento della reattività immunitaria di tipo primario soprattutto a partire dalla fine del periodo di allattamento, nel topo nano la reattività immunitaria primaria è rimasta costante nel tempo su bassi livelli anche dopo lo svezzamento. Alla luce dei dati sperimentali riportati viene ipotizzata l'esistenza di un controllo ipofisario della reattività immunitaria primaria.

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