Amyloidosis in Strain BL/LyDe Mice. (30106)

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Infiltration of amyloid into corpora lutea of the ovaries in breeding females of strain BL/LyDe mice has previously been reported (1). This observation suggested a study of the distribution of amyloid in various organs of female and male mice of this strain.

Materials and methods. Strain BL/LyDe originated from mice of the Bagg stock, obtained from Strong, that were maintained from 1921 on by Dr. Clara J. Lynch, Rockefeller Institute for Medical Research(2). Animals from which the colony at the National Cancer Institute was established were obtained from Dr. Lynch in June 1951, at the 46th generation of inbreeding. They have been inbred by brother $\times$ sister mating since then, and are now in the 87th generation.

Mice of both sexes were set aside, in separate cages, at weaning. They were housed in 8 $\times$ 11 $\times$ 5 inch plastic cages, 7 animals to a cage, and were given NCI pellets(3) and tap water *ad libitum*. They were autopsied at 15 months of age and tissues were fixed in Fekete's modification of Tellyesniczky's fixative (70% ethyl alcohol, 20 parts; formalin, 2 parts; glacial acetic acid, 1 part), sectioned, and stained with hematoxylin and eosin. A few representative sections from both sexes were stained with crystal violet. Sections of the following organs were made—spleen, duodenum, ileum, liver, kidney, heart, adrenal, lung, pancreas, salivary glands, and bladder in both sexes; uterus, vagina, and ovaries in females; and testis and vesicular gland in males. Sections of the tongue were made in a small number of animals. It should be pointed out that in most cases no more than 3 sections of each organ were available for study.

Results. Data on infiltration of amyloid in the organs sectioned are presented in Table I. Infiltration occurred frequently in the spleen, duodenum, ileum, liver, kidney, ovaries, and uterus. Infiltration in these organs was slight at times (figures in parentheses in the table indicate the number of such cases).

Infiltration of amyloid occurred less frequently in the heart, vaginal wall, adrenal cortex, lung, and tongue. In approximately one-third of the instances in the lung, the amyloid occurred in pulmonary tumors. Pulmonary tumors were observed in 9 of 69 females and in 5 of 29 males. Lynch(4,5) has recorded an incidence of 37% for pulmonary tumors in strain BL over 12 months of age (and 26% for all ages).

Amyloid was observed occasionally in the pancreas, salivary glands, bladder, and testis; and never in the vesicular gland. A section of the superficial cervical lymph node was often included with that of the salivary glands. Frequently this node was infiltrated with amyloid (Table I).

Renal disease [described by Dunn(6) as resulting from infiltration of amyloid into the intertubular interstitial tissue and termed papillonephritis in strain A] was observed in 50 of 67 females and in 27 of 29 males of strain BL. This finding was anticipated as both strains trace their origin to Bagg albino mice.

Arteritis was observed occasionally in vessels of the intestine, adrenal, uterus, pancreas, liver, salivary gland, and ovary. It had been seen previously in strain BL(1), in vessels of the ovary, perirenal adipose tissue, uterus, and mesentery.

Discussion. This brief report of amyloid infiltration in organs of strain BL mice will not include any discussion of literature on the induction of amyloidosis since this has been done in several recent papers [Christensen and Rask-Nielsen(7)]. Only the occurrence of amyloid in untreated mice of various strains will be noted.

Fekete(8) described the occurrence of amyloid in corpora lutea of ovaries of strain dba as hyalinization. Thung, Boot, and Mühlbock(9) observed amyloid infiltration in ovaries of strain DBAf, and in this labora-

TABLE I. Infiltration of Amyloid in Organs of Strain BL/LyDe Mice.

Organ	Females		Males	
	No. of organs sectioned	No. with amyloid	No. of organs sectioned	No. with amyloid
Spleen	69	44 (2)*	28	21 (1)
Duodenum	67	64 (1)	29	28 (3)
Ileum	68	66 (2)	29	29
Cervical lymph node	50	45 (26)	18	15 (6)
Liver	69	45 (27)	29	23 (13)
Kidney	67	53 (5)	29	28 (5)
Ovary	69	66 (1)		
Uterus	67	49 (15)		
Heart	68	26 (26)	29	14 (14)
Vagina	61	24 (13)		
Adrenal	60	14 (11)	26	23 (14)
Lung	68	16 (16)†	29	16 (16)‡
Tongue	3	2	5	5 (1)
Pancreas	69	6 (6)	29	7 (4)
Salivary glands	69	4 (4)	29	1 (1)
Bladder	30	1 (1)	22	
Testis			29	4 (4)
Vesicular gland			25	

* Figures in parentheses indicate number of organs in which infiltration was slight.
† Amyloid in pulmonary tumor only in 6.
‡ Amyloid in pulmonary tumor only in 1, in pulmonary tumor and lung in 4.

tory the same observation has been made on substrain DBA2eB(10). Richardson(11) observed amyloid in ovaries of strain CBA. It is interesting to note that strain CBA originated from a cross between a Bagg albino female and a DBA male.

Dunn(6) has described the infiltration of amyloid, in addition to that already mentioned for the kidney of strain A, in the duodenum, limiting ridge of forestomach, colon, heart, lung, pulmonary tumor, ovaries, testicles, adrenal, endometrial stroma, and skin. West and Murphy(12), in an extensive study of amyloidosis in strain A mice of various ages, have described the occurrence of amyloid in additional organs. These were tongue, cervical and mesenteric lymph nodes, urinary bladder, and salivary glands.

Thung(13) has described infiltration of amyloid in mice of strains 020, DBAf, and C57BL, and of hybrids (020 × DBAf)F_1 and (C57BL × DBAf)F_1. Amyloid infiltration was observed in additional organs to those already mentioned, such as pancreas, thyroid, uterus, vagina, ileum, and fatty tissues. There were differences in incidence and in distribution of amyloid among the 3 strains and the 2 F_1 hybrids.

It has been shown that the occurrence of amyloidosis and the resulting nephritis in mice has a genetic basis. Heston and Deringer(14) observed primary amyloidosis in the F_1 hybrids resulting from crossing strains A and YBR, both of which develop amyloidosis, but not in F_1 hybrids resulting from outcrossing strain A to strain C57L, that does not develop primary amyloidosis. This indicated recessive inheritance, and segregation ratios in the F_2 and backcross generations suggested a single recessive gene as the causation of the primary trait. Dunn(6) observed marked differences in the occurrence of amyloidosis in 2 strains of mice and in one group of hybrids and Thung(13) observed differences in 3 inbred strains and their F_1 hybrids. The present study has added further evidence and it is of interest that not only does the frequency vary in different strains but the site of greatest deposition often appears to be strain-determined. In strain BL/LyDe described here, amyloid replacement of the corpora lutea was notable.

Summary. Infiltration of amyloid in various organs of female and male mice of strain BL has been recorded. It was observed to occur frequently in spleen, duodenum, ileum, cervical lymph node, liver, kidney, ovaries, and uterus; less frequently in heart, vagina, adrenal, lung, and tongue; and only occasionally in pancreas, salivary glands, bladder, and testis.

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Control of Cell Multiplication in Epidermis.* (30107)

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Experiments on wound healing have provided considerable data on the mechanisms of cell replication and tissue renewal(1). The repair of a mechanical injury to the skin consists of restoration of the epidermis by multiplication and migration of epithelial cells, accompanied by a non-specific reaction of the connective tissue. Following a wound, the rate of mitotic activity in the adjacent epidermis increases 5- to 10-fold until continuity and full thickness are restored. The experiments of Bullough and Laurence(2) on the response of mouse ear epidermis to superficial wounds have strongly suggested that the proliferative response observed is due to a release of the uninjured tissues from inhibition that is normally present. Their data support the concept of Mazia(3) that "the stimulation of division in multicellular systems is the removal of a block . . . the stimulus is no more than permission of the cell to do what it would have done if it had been left alone in the first place."

Bullough and Laurence showed that the gradient of augmented mitotic activity adjacent to a wound extended for about one millimeter, with the highest activity adjacent to the wound. In the mouse ear, which is only 0.15 mm thick, the gradient of increased mitotic activity extended to the epidermis on the uninjured surface opposite the wound. That is, removal of the epidermis and superficial dermis from the dorsum of the ear resulted in the appearance of a high mitotic count in the ventral epidermis opposite the wound as well as in the adjacent 1 mm perimeter of dorsal epidermis. When the dorsal wound was 3 mm square, a difference in mitotic rate was found opposite the center of the square rather than opposite the wound margins, with the highest activity being opposite the center. Since the wound was 3 mm square and the gradient of increased mitotic activity extended for only 1 mm, this observation cannot be explained by the release of a stimulatory substance or "wound hormone" from the injured marginal cells, but can be readily accounted for in terms of the removal of inhibition of mitotic activity normally present in the epidermis.

In the experiments to be described, additional evidence for the inhibitory action of normal epidermis on epidermal cell replication will be presented. It will be shown that replacement of the resected tissue by a graft of intact epidermis results in suppression of proliferative activity in the nearby epidermis.

Materials and methods. Adult male Syrian hamsters weighing 90-120 g were used. Their ears measure approximately 0.6 mm in thickness and consist of a continuous layer of superficial epidermis supported by thin layers of dermal connective tissue containing hair follicles and sebaceous glands and a central core of cartilage measuring about 0.1 mm thick. Under barbiturate anesthesia, identical wounds measuring 5 mm square were made in the dorsum of each ear using a scalpel and fine forceps. With the aid of magnifying lenses, the epidermis and upper portion of the dermis were excised, leaving the lower half of the dorsal dermis, cartilage, ventral dermis and epidermis intact. One ear served

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