similar to the kinetics of their metabolism[16–18]. This would also be expected behaviour if one considers that a relationship has been demonstrated for substrates of these enzymes between their lipid solubility and their ability to be metabolized[19]. The lack of ability to give type II spectral changes by N-nitrosamines is not surprizing inspite of the fact that they are amine derivatives and that it was suggested that type II interactions represent the formation of a ferrihemochrome from the interaction of a basic amine and a ferrihemoprotein[16]. In effect, recent findings support the contention that steric and basic features of nitrogen of amines are of primary importance in type II binding[16]. The strong electron-attracting properties of the nitroso group, as well as its linking to the nitrogen of the amine portion, intensively modify the alkaline nature of the molecule[20] to the extent that it might reduce its ability for interaction with type II binding sites and also could sterically hinder the access to the nitrogen of the ferrihemoprotein as it was previously demonstrated for other molecules[21].

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Changes in brain dopamine levels and aggressive behavior with aging in 2 mouse strains

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Summary. The genetic programming of brain monoamine changes with aging show remarkable differences in 2 mouse strains. A marked increase in dopamine occurred in 32-week-old grouped ICR mice and the males showed intense irritability and aggressive behavior. Brain amines changed only slightly in old C57BL6J mice and behavior remained benign. Old females showed similar amine changes but aggressive behavior did not occur in either strain.

We have previously reported[1] the brain monoamine levels of dopamine (DA), norepinephrine (NE) and serotonin (5HT) for 3 mouse strains: C57BL6J, BALBJ and ICR. There are remarkable biochemical and behavioral differences among these strains. Of particular interest is the high brain level of DA in BALB mice, a strain noted for fighting and aggressive behavior among young adult males in contrast to the benign behavior of young adult C57BL6J and ICR males. The turnover rate of dopamine in BALB males also is higher than in the other strains[2]. In the present study the changes of brain monoamines with age and concomitant behavioral changes were investigated in 2 strains of mice.

Methods. The brain amine levels of DA, NE and 5HT in young adults (4 weeks old) and old adults (28–32 weeks old) of C57bL6J and ICR male and female mice were determined as described previously[3]. The mice were kept in groups of 20 or more in large cages. The strains and sexes were separated. General behavior was observed both in the large home cages and further observations were made in small plastic cages holding 4–6 mice. Reactions to handling were also assessed.

Results. The pertinent observations and brain monoamine levels are summarized in the table. In the young adult mice the brain monoamine levels of both males and females of a given strain are similar. It will be noted that the young adult C57BL6J mice have significantly higher brain levels of all 3 monoamines compared to the ICR strain. The high level of NE in this strain is especially

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Biogenic amines and behavior in young adults and old mice

Strain	Age in weeks	No. of determinations	DA**	Percent change*	NE	Percent change	5HT	Percent change	Aggressive behavior
Males									
ICR	4	10	0.91 ± 0.03		0.53 ± 0.01		0.59 ± 0.01		0 to +
	32	5	1.35 ± 0.05	+48	0.61 ± 0.05	+15	0.76 ± 0.01	+27	+++
C57BL6/J	4	11	1.36 ± 0.02		0.65 ± 0.01		0.69 ± 0.01		0
	28	5	1.45 ± 0.01	+ 7	0.70 ± 0.04	+ 7	0.72 ± 0.04	+ 4	0
Females									
ICR	4	10	0.98 ± 0.02		0.45 ± 0.01		0.61 ± 0.02		0
	32	5	1.60 ± 0.09	+	0.44 ± 0.01	− 4	0.70 ± 0.02	+15	0
C57BL6/J	4	10	1.41 ± 0.01		0.64 ± 0.01		0.80 ± 0.01		0
	32	5	1.76 ± 0.14	+25	0.56 ± 0.01	−13	0.75 ± 0.01	− 6	0

* Percent increase compared to young adults. ** Mean μg/g brain tissue ± SEM.

notable. The general behavior of young adult mice of both strains and both sexes is benign. They show no fighting in either the large home cages or the small observation cages and are also easily picked up and handled.

In striking contrast the 32-week-old ICR male mice show remarkable changes in behavior. Many aggressive fights were observed in the home cage and in the small observation cages. All of these old males showed signs of bites on their tails and bodies. When picked up or handled, they immediately and vigorously attacked with biting, vocalizing and struggling making it necessary to wear heavy leather gloves when working with this group. As can be seen, these old ICR mice show increases in all 3 brain monoamines compared to young adults and particulary a 48% increase in brain DA level. This increased level is also reflected in an increase in DA turnover as well[2].

The old ICR females also show increases in brain DA (63%) but do not show behavioral changes and remain benign. The lack of aggressive behavior in the old ICR females despite comparable increases in brain amines again emphasizes the important permissive role of hormones in patterns of aggressive behavior.

The old C57BL6J male mice showed only small increases in brain monoamine levels when compared to young adults and showed no fighting or changes in behavior in either males or females.

Discussion. These and previous studies[1] show that the levels of brain monoamines in young adults of a given mouse strain are remarkably constant. However, the genetic program of amine changes with aging may show marked strain differences. The increase in aggressive behavior in old ICR males may be related to the marked increase in brain dopamine, compared to the small increases in NE or 5HT. We have previously reported[3] that giving l-DOPA to young adult ICR mice (thus raising brain dopamine) results in aggressive behavior, which is comparable to that observed in the old ICR mice in the present study. As mentioned, the young adult males of the BALB strain show aggressive fighting and have a high level of brain dopamine compared to their NE and 5HT levels[1]. As expected, these modes of aggressive behavior are blocked by small doses of haloperidol and other dopamine blocking agents.

It is possible that these studies may be pertinent to the problems of disruptive behavior seen in some elderly patients and may have a similar biochemical basis. There are clinical reports showing that the tranquilizers are useful in such patients. Basic and clinical studies in the biochemistry of aging and geriatric pharmacology are all too scarce and much needed.

Thymus gland involution induced by lithium chloride

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Summary. Chronic treatment with lithium chloride produced significant involution of the thymus gland with histological evidence of reduced cellularity due to loss of thymic lymphocytes and a significant reduction in the weight of the gland in normal and adrenalectomized mice. Lithium also increased corticosterone levels in normal mice without changes in adrenal weights. The involution of the thymus gland is most likely due to an effect of lithium on the gland, and it is not mediated by adrenocortical mechanisms or stress.

The effectiveness of lithium salts in the treatment of manic-depressive psychosis with mania is now well-documented[2]. In spite of this, the mechanism of action of lithium is not understood. Various studies have suggested an effect of this cation on central neurotransmitter function[3,4]; on endocrine glands, especially the thyroid gland[5], and on adrenal enzymes[6]. In the present study, we report an hitherto unrecognized effect of lithium chloride (LiCl) on the thymus gland in normal and adrenalectomized mice.

Materials and methods. Experiments were carried out in male Swiss (Canadian Breading Farms and Laboratories, Ltd. S.t Constant, Quebec) and CBA (McGill University, McIntyre Medical Science Building) mice weighing approximately 30 g. Mice were caged in groups of 8 under controlled temperature (20 °C) and light (12 h-on, 12 h-off). Standard mice chow (Master Laboratory Cubes, Maple Leaf Mills, Montreal) and water were given ad libitum. Lithium chloride (crystalline powder, Allied Chemical, Morriston, N. J.) was administered i.p. to Swiss and CBA mice in doses of 3 mEq/kg, twice a day for 4 days. In another group of Swiss mice, 4 separate doses of 1, 3, 6 and 9 mEq/kg were given i.p., twice a day for 4 days. Control mice were injected i.p. with normal saline. Another control group was not injected or stressed. Normal saline and LiCl solutions were injected in volumes of 0.2 ml twice daily. Controls and treated mice were sacrificed by cervical dislocation after 4 days. The thorax was opened by 2 incissions parallel to the sternum and the thymus gland was dissected carefully and removed after exposing the upper mediastinum and heart. The thymus glands were weighed individually on an analytical balance (Mettler, model H 31, sensitivity $\pm$ 0.05 mg). Immediately after weighing, the thymus glands were fixed in 10% formalin-saline and embedded in paraffin.

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