# MINIREVIEW

# Aging: Hypothalamic Catecholamines, Neuroendocrine-Immune Interactions, and Dietary Restriction (43150B)

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*Abstract.* **The decline in hypothalamic catecholamine (CA) activity with age in rats leads to a reduction in hormone secretion by the neuroendocrine system, and results in decreased reproductive function, a reduction in protein synthesis, development of numerous mammary and pituitary tumors, and probably contributes to the decline in immune function. Some of these same effects can be produced in young rats by administration of drugs that lower hypothalamic CA activity. Administration of drugs to old rats that elevate hypothalamic CA activity can inhibit or reverse the reproductive decline, increase protein synthesis, induce regression of mammary and pituitary tumors, decrease disease incidence, probably elevate immune function, and significantly extend the life span. Therefore, hypothalamic CA have a critical role in the development of aging processes.**

**When young or mature rats or mice are fed a caloric restricted diet, aging processes are inhibited and life span is significantly lengthened. These effects are believed to be mediated primarily via the neuroendocrine system, since calorie restriction results in decreased secretion of hypothalamic, pituitary, and target gland hormones. The decline in hormone secretion leads to a reduction in most body functions, lowers whole body metabolism, and reduces gene expression, and thereby results in a decreased rate of aging of body tissues and longer life. These effects of caloric restriction can be counteracted by administration of hormones, providing evidence that the favorable effects on aging are mediated by reducing hormone secretion.** [P.S.E.B.M. 1990, Vol 195]

The late Nathan Shock (1), dean of American gerontologists, expressed the view that "aging, as we see it in the total animal, may be more a function of the breakdown in integrative mechanisms than of changes in individual cells, tissues, or organs." The most important integrative mechanisms in the body are the brain, endocrine glands, and immune tissues which function coordinately as an interdirectional network, and are collectively termed the "neuroendocrinimmune system." The brain, particularly its hypothalamic portion, directly or indirectly regulates hormone secretion by the endocrine glands and influences factors produced by the immune tissues (peptides, cytokines, lymphokines, etc.), which in turn feed back on the brain and endocrine glands to modulate their functions. Recent studies on neuroendocrine and immune actions during aging have begun to uncover their role in development and progression of many aging decrements in body functions. The genome and environment are believed to control aging processes mainly via the neuroendocrinimmune system.

From a physiologic viewpoint, aging can be defined as a decline in the morphologic integrity and functional capacity of organs and tissues, associated with a decrease in ability to maintain homeostasis. Aging decrements occur in many components of the neuroendocrine and immune systems and in the organs and tissues they regulate, but the faults that develop in the hypothalamus appear to be of particular importance. The hypothalamus contains peptide-releasing or release-inhibiting hormones that directly control pituitary hor-

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mone secretion, and neurotransmitters that modulate release of the peptide hormones into the hypothalamo-pituitary portal vessels. Hypothalamic catecholamines (CA) have been shown to be particularly important in regulating pituitary function, and have a significant role in determining the declines in many body functions with age.

In this review, I place major emphasis on recent reports which confirm and extend knowledge of the role of hypothalamic CA on aging changes, discuss some interactions between the neuroendocrine and immune systems during aging, and provide evidence that dietary restriction inhibits aging and prolongs life by reducing secretion of hormones. An attempt will be made to relate some of these findings in the aging rat and mouse to problems in human aging.

**Further Evidence that the Decline in Hypothalamic CA Leads to Aging of Body Functions**

In the aging rat, a decrease develops in secretion by hypothalamic neurons of CA, particularly dopamine (DA) and norepinephrine (NE) (2, 3), which leads to lower hypothalamic release of gonadotropin-releasing hormone (GnRH), growth hormone-releasing hormone, and thyrotropin-releasing hormone (TRH). These result in reduced secretion by the pituitary of gonadotropic hormones, growth hormone (GH), biologically active thyrotropic hormone (TSH), and an increase in secretion of prolactin (PRL) (2–4). The decrease in gonadotropic hormones leads to loss of estrous cycles in female rats and reduced secretion of testosterone in male rats, the decline in GH secretion to lower somatomedin (IGF-1) secretion and reduced protein synthesis, the reduction in biologically active TSH to lower thyroid hormone secretion and a fall in body metabolism, and the elevated PRL to development of numerous mammary and pituitary tumors. The reductions in GH and thyroid hormone secretion are believed to be at least partially responsible for the decrease in immune competence.

We have previously reviewed evidence for the decline in hypothalamic CA activity in aging rats (2, 3). Simpkins (5) observed that DA concentrations were significantly lower in the median eminence (ME), medial basal hypothalamus, preoptic area-anterior hypothalamus, and striatum of 25- to 26-month-old than in 3- to 4-month-old female rats. The concentration of dihydroxyphenyl-acetic acid, the major acid metabolite of DA, was similarly reduced in all four areas. NE concentrations were decreased in the medial basal hypothalamus and preoptic area-anterior hypothalamus but not in the ME or striatum. McIntosh and Westfall (6) compared CA accumulation and release *in vitro* from hypothalamic tissue removed from Fischer F344 rats that were 2–4, 11–14, and 21–26 months of age. Marked decreases in hypothalamic CA levels, uptake, and release in response to high frequency stimulation were apparent even at 12 months of age (6), coinciding with the age when estrous cycles cease and GH secretion is significantly reduced in female rats (2, 3). Gregerson and Selmanoff (7) reported a decrease in release of tritium-labeled DA from synaptosomes from the ME and corpus striatum of old as compared with young rats. Weiland and Wise (8) observed a decrease in $\alpha_1$-adrenergic receptors in the ME and suprachiasmatic nucleus by middle age, and in all regions of the hypothalamus by old age in rats.

Administration of drugs that elevate hypothalamic CA activity have been shown to inhibit or reverse many aging declines in the body. We first reported in 1969 (9) that injections of epinephrine in oil could induce ovulation in old noncycling rats, which suggested that CA may be involved in the reproductive decline. Subsequently we reported that L-dopa, the precursor of CA, delayed loss of estrous cycles in aging rats and reinitiated cycles in old noncycling rats; iproniazid, a monoamine oxidase (MAO) inhibitor which depresses catabolism of CA, also induced resumption of estrous cycles in old rats (10). Huang (11) reported that transplantation of fetal anterior hypothalamus, presumably capable of secreting CA and GnRH, restored estrous cycles in old female rats and elevated luteinizing hormone and testosterone secretion in old male rats.

GH is the most important protein anabolic agent in the body, and its decline during aging is believed to be largely responsible for the decrease in protein synthesis. Twice daily injections of L-dopa for 8 days increased pulsatile GH secretion in old male rats to the same levels as in young male rats, and promoted protein synthesis in diaphragm muscle (12). GH injections for 10 days into old rats and/or mice also significantly increased the weights of the heart, kidneys, liver, thymus, and spleen (12). GH also returned thymic function in old rats to the same level as in young rats (13). Presumably, these same effects would be produced in old animals by administration of drugs that elevate hypothalamic CA. Administration of dopaminergic drugs inhibited PRL secretion and resulted in regression of mammary and pituitary tumors (2, 3). Since hypothalamic NE promotes TRH and TSH secretion (14), its decline probably accounts for the reduced secretion of thyroid hormones in aging rats (15).

Four different laboratories have reported that drugs that elevate hypothalamic CA activity can prolong the life span of mice and/or rats. Cotzias *et al.* (16) observed that chronic administration of L-dopa in the diet increased the life span of Swiss albino mice by about 50% and extended fertility. Clemens *et al.* (17) reported that when female rats were fed lergotrile mesylate, a DA receptor agonist, for 2 years, it significantly reduced the death rate and increased survival. In two studies, only 40–45% of control rats were alive at the end of 2 years,

whereas 70–90% of the ergoline mesylate-treated rats survived. Knoll (18) reported some remarkable effects on male sexual behavior and longevity by injecting *deprenyl*, a MAO-$\beta$ inhibitor, three times weekly to 66 two-year-old male rats. Another 66 two-year-old male rats served as controls and were injected three times weekly with physiologic saline. MAO-$\beta$ is the major enzyme that catabolizes CA, and since deprenyl inhibits the action of MAO-$\beta$, it elevated DA tone and increased DA turnover. Sexual behavior was measured by counting weekly the number of mountings, intromissions, and ejaculations when the old male rats were placed with young females. None of the 2-year-old rats initially showed a full complement of sexual behavior before deprenyl treatment, but 64 of 66 rats showed the full complement of sexual behavior during deprenyl treatment. The average life span of the control rats injected with saline was 147 weeks (2.8 years), and the longest lived rat was 164 weeks old, whereas the deprenyl-treated rats lived to an average of 198 weeks (3.8 years) or 1 year longer. The longest lived rat was 226 weeks old, and the shortest lived rat was 171 weeks old. Knoll (18) stated that this exceeded the maximum life span of these rats. He also found a correlation between sexual activity and life span, with the more sexually active males living longer. The effects of deprenyl on life extension were recently confirmed (19) in 2-year-old Fischer F344 rats, a shorter lived strain of rat than the hybrid strain used by Knoll (18). In a second report (20), this laboratory reported a smaller extension of longevity when Fischer F344 rats 23 to 25 months old were injected with deprenyl, but very significantly found no decrease in body weight as compared with controls. This indicates that the life-prolonging effects of deprenyl were not produced by reducing food intake.

The effects of deprenyl were attributed by Knoll (18) to their action on the corpus striatum, a brain region associated with control of motor function and Parkinson's disease. Since we have previously shown that iproniazid, another MAO inhibitor, can induce resumption of estrous cycles in old noncycling rats (10), and in view of our work with L-dopa and other drugs showing that they can reverse aging changes in old rats, it is probable that the life-prolonging and sex-stimulating effects of deprenyl were mediated mainly via the hypothalamus rather than the corpus striatum. Thus, the CA-induced release of GnRH not only results in increased secretion of pituitary gonadotropins, but GnRH also acts on the brain to stimulate sexual behavior. This does not exclude a role for the corpus striatum in reversal of these aging changes. It was reported that when deprenyl was given in combination with L-dopa and a peripheral inhibitor of L-dopa metabolism to Parkinson patients, it significantly prolonged their life span as compared with treatment with the L-dopa and peripheral inhibitor combination (21).

Walker *et al.* (22) studied the effects of daily administration of *ibopamine,* a CAergic drug, for 2 years on development of disease in male and female rats initially 50 days old. Six neoplastic diseases (adrenal cortical, mammary, and pituitary adenomas, skin papilloma, pheochromocytoma, and mammary adenocarcinoma) and five non-neoplastic diseases (chronic glomerulonephropathy, renal pelvic mineralization, hepatocellular proliferative module, galactoceles, and chronic cardiomyopathy) were examined histologically in all rats that died during treatment and at the end of the 2-year treatment period, when all rats were killed. Both neoplastic and non-neoplastic diseases were significantly reduced in the ibopamine-treated rats as compared with controls. No significant differences in food intake or body weight were found between control and ibopamine-treated rats, except for a small reduction in body weight in the rats given the highest dose of ibopamine. Therefore, the effects of this drug cannot be attributed to a decrease in food intake. Walker *et al.* (22) stated that the ibopamine-treated rats would probably have lived longer if they had not been killed at the end of 2 years.

Can a reduction of hypothalamic CA in young or mature animals produce some of the same aging changes normally observed in old animals? Studies of the effects of chronic administration of central acting drugs or hormones which lower brain CA levels suggest that some of the same aging changes can be produced in young or mature rats. Thus, chronic administration of haloperidol, phenothiazines, or reserpine, neuroleptic drugs that inhibit brain CA activity, reduced gonadotropin secretion and inhibited reproductive functions, increased PRL secretion, and hastened development of spontaneous mammary tumors in rats (23). These drugs also inhibit GH secretion (14). Chronic administration of estrogen to rats or mice also reduces hypothalamic CA, inhibits gonadotropic hormone secretion and reproductive functions, and increases PRL secretion which promotes development of mammary and pituitary tumors (23, 24). These observations further emphasize the important role of hypothalamic CA on the onset of aging changes, and suggest that decreased hypothalamic function rather than chronologic age may be the critical factor involved in development of some aging changes in rats and mice.

What is responsible for the decline in hypothalamic CA with time? Damage and loss of neurons may result from catabolism of the CA, leading to formation of hydrogen peroxide, superoxide anions, hydroxyl radicals, and highly reactive quinones (25). The destructive effects of these agents over a lengthy period of life can lead to a progressive loss of neurons in the hypothalamus. A significant decrease of neurons has been observed in the arcuate nucleus, medial preoptic area, and ventromedial and lateral hypothalamic nuclei of old

rats (26). The continuous action of some hormones on neurons may also damage or destroy them. Prolonged exposure to estrogen in young rats was observed to injure neurons in the arcuate nucleus and medial basal hypothalamus (27, 28), similar to that seen in the hypothalamus of untreated old rats. Ovariectomy, by removing the major source of estrogen, was observed to extend the life of hypothalamic neurons involved in reproductive processes. Thus, removal of the ovaries from rats and mice early in life, followed by grafting of fresh ovaries many months later, resulted in reinitiation of estrous cycles that continued for many months beyond the period when intact animals ceased to cycle (29, 30). Chronic elevation of circulating PRL levels also was reported to damage hypothalamic neurons (28). Since estrogen stimulates PRL secretion, it is possible that some of the harmful effects of chronic estrogen action on neurons are mediated via PRL or in conjunction with PRL. Glucocorticoid hormones were shown to damage neurons in the hippocampus (31), a brain region that has input to the hypothalamus and thus may indirectly affect hypothalamic function.

There is evidence that tyrosine hydroxylase, the rate-limiting enzyme for the synthesis of CA, is reduced in old rats, whereas MAO which catabolizes CA, is increased (25). Similar changes in these enzymes have been reported in the nigrostriatal brain area of elderly human subjects (21). A decrease in brain dopamine-$\beta$-hydroxylase, which converts DA to NE, has also been reported in old mice (32). The causes for these enzyme changes with age remain to be investigated.

### Neuroendocrine-Immune Interactions during Aging

There is now substantial evidence that the neuroendocrine and immune systems interact to regulate each other's functions. In general, GH, PRL, and thyroid hormones have been reported to promote immune functions, whereas gonadal and adrenal glucocorticoid hormones inhibit immune functions (33). Electrolytic lesions placed in the hypothalamus or reticular formation induced severe involution of the thymus, the chief component of the immune system (34), perhaps by reducing secretion of hormones that promote thymic activity. The thymus secretes peptides that can stimulate secretion of GnRH, ACTH and adrenal cortical hormones (35), and thymosin fraction 5 was reported to inhibit secretion of TSH in young but not in old rats (36). Activated lymphocytes were reported to be capable of secreting ACTH, TSH, and $\beta$-endorphin (37). In mice, neonatal thymectomy resulted in derangement of reproductive functions and reduced pituitary hormone secretion, which was remedied by implantation of fetal thymic tissue (35).

Both neuroendocrine and immune functions decrease with age, but relatively little is known of the extent to which each is responsible for the decline of the other. The thymus shows a marked loss in size and function at the time of puberty, due to the rise in secretion of gonadal hormones. This is followed by a progressive decline with age in secretion of thymic peptides such as thymosin $\alpha_1$, thymopoietin, and thymulin, which are essential for production of mature T cells and other cells of the lymphopoietic system (35). When $T_4$ was given to old mice, the thymus assumed a youthful-like histologic appearance and resumed secretion of thymulin. Transplantation of the thymus from old $T_4$-treated mice to young thymectomized mice resulted in as much secretion of thymulin as by the young thymus. Hypopituitary dwarf mice exhibit very low secretion of GH, PRL, ACTH, and TSH, associated with continuous involution of the immune tissues, accelerated graying of hair, general weakness, occasional cataracts, and die at 3–5 months of age. All of these effects were prevented by injecting GH and $T_4$ for 30 days (35).

Our laboratory reported that administration of GH significantly increased the weight of the thymus and spleen in old rats and/or mice (2, 3). Kelley *et al.* (13) observed that implantation of GH-secreting tumor cells into old rats not only restored thymus weight but full function as well as measured by five tests. Administration of GH also was reported to increase thymus size and function in adult dogs (38). In a recent study (Brooks *et al.*, unpublished data), we observed a correlation between the decrease in GH and $T_4$ secretion and the decline in thymic and spleen function in old rats. It appears probable, therefore, that the decrease in GH and thyroid hormone secretion contributes importantly to the aging decline in immune function. Little information is yet available on the role of the immune system on the decrease in neuroendocrine function in old animals.

### Relation of the Neuroendocrine System to the Inhibitory Effects of Dietary Restriction (DR) on Aging Processes

Many investigators have reported that DR (total calories are usually reduced by 40 or 50%), when initiated in young or mature rats, mice, and other species, can retard aging of organs and tissues, reduce the decline in immune function, delay development of pathology including tumors, and prolong the life span by 50% or more (39, 40). It has been stated that this constitutes the only method by which life can be significantly extended beyond the *maximum* life span for these species. Not all of the effects of DR can be considered to be beneficial, since it also produces significant decreases in many if not most body functions. In young rats and mice, DR leads to a slowdown in body development and growth and a delay in onset of puberty, in mature animals to a loss of body weight and a decline or cessation of reproductive functions, to a

decrease in whole body metabolism, a reduction in body temperature, lower blood glucose levels, decreased capacity to perform muscular work, reduced ability to withstand severe stress, and some indications of persistent hunger. Therefore, the beneficial effects of DR are achieved at the cost of a prolonged depression in most body functions.

Much attention has focused recently on the mechanisms by which DR inhibits aging changes and prolongs life. In view of the current emphasis on cellular and molecular mechanisms, many investigators have stressed reduced damage by free radicals and toxins, altered protein turnover, decreased gene expression, lower cell division, less damage to DNA, and so forth (39, 40). We have emphasized the effects of DR on hormone secretion by the neuroendocrine system, since it is well established that DR results in a general decrease in secretion of hormones (41, 42). The sole exception is that when DR is severe, ACTH and glucocorticoid hormone secretion may increase due to the resulting stress. DR was shown to reduce GnRH, growth hormone-releasing hormone, and TRH in the hypothalamus (43) and to lower circulating levels of luteinizing hormone, follicule-stimulating hormone, TSH, PRL, and GH (42). DR was also found to reduce CA in the hypothalamus and other regions of the brain (44), which may explain why pituitary hormone secretion is decreased (42). The hormone-reducing effects of DR have been shown to be mediated via the hypothalamus, and not directly on the pituitary since the pituitary response to hypothalamic hormones is not reduced in DR rats (42). More recently we observed that a 50% reduction in food intake for a period of even 2.5 months resulted in a chronic depression of GH, $T_3$, and $T_4$ secretion in young, middle-aged, and old rats (45). Merry and Holehan (46) found that even at the end of 457 days of 50% food restriction, thyroid hormones remained depressed in rats. Insulin levels also remained low during long-term underfeeding (39). Since DR experiments involve long periods of food reduction, these observations indicate that hormone secretion remains low.

If DR inhibits aging processes mainly by reducing hormone secretion, then administration of hormones to DR animals should counteract the effects of DR. Several short-term studies indicate that administration of hormones to underfed rats or mice can overcome the effects of underfeeding on specific organ systems. Injections of gonadotropic hormones were reported to overcome the depressing effects of DR on gonadal function in guinea pigs and mice (47, 48). Stimuli which promote gonadotropic hormone secretion also overcame the effects of underfeeding. Thus, when rats were fed 50% of normal food intake and ceased to undergo estrous cycles, they were placed under continuous light or injected with epinephrine in oil. They came into proestrus or estrus and their ovarian and uterine weights were significantly increased (49), demonstrating that the inhibitory effects of DR on gonadal function were the result of reduced secretion of gonadotropic hormones.

Since DR is known to inhibit development and growth of tumors, it was of interest to determine whether administration of hormones could counteract regression of mammary tumors in DR rats. Female rats with carcinogen-induced mammary adenocarcinomas were restricted to 50% normal food intake for a period of several weeks, resulting in a significant reduction in the size of these tumors. When PRl and estrogen, the two hormones known to be essential for mammary tumor development and growth in rats (23), were elevated in the underfed rats, the mammary tumors grew as well or better than in the *ad libitum*-fed controls (50). This study shows that regression of mammary adenocarcinomas by DR was due primarily to a reduction in secretion of hormones essential for mammary tumor growth.

Can a decrease in hormone secretion in *ad libitum*-fed rats produce the same anti-aging effects as DR? When chronic hypothyroidism was induced early in the life of *ad libitum*-fed rats, it resulted in a significant extension of life span, whereas chronic administration of thyroxine shortened the life span (51, 52). Since hypothyroidism may also reduce secretion of GH, ACTH-adrenal cortical hormones, and gonadotropins (14), it probably results in a general reduction in body functions, similar to the effects of DR. Therefore, these studies, although limited in scope, support the view that DR prolongs the life span mainly by reducing hormone secretion. The lower hormone secretion depresses whole body metabolism, decreases gene expression, and lowers "wear and tear" on neuroendocrine, immune, and other body tissues, thereby preserving their morphologic and functional integrity, inhibiting aging processes, and prolonging life.

## Conclusions

Primary emphasis was placed in this review on the role of hypothalamic CA in many well-recognized aging changes in the rat and mouse. The decrease in hypothalamic CA activity with age was shown to be largely responsible for the decline in reproductive functions, the decrease in protein synthesis, development of numerous mammary and pituitary tumors, and probably for the reduction in immune function. The ability of central acting drugs that elevate CAergic tone to inhibit or reverse these declines in body functions is evidence of their critical role in aging processes. When drugs such as L-dopa, iproniazid, ergot drugs, deprenyl, or ibopamine were given to old rats and/or mice, they inhibited or reversed loss of estrous cycles in female rats, increased testosterone secretion and promoted sex-

ual behavior in male rats, elevated GH secretion and increased protein synthesis, lowered PRL secretion and thereby induced regression of mammary and pituitary tumors, decreased the incidence of neoplastic and non-neoplastic diseases, and significantly lengthened the average life span as reported by four independent laboratories. The latter is of major interest, since only DR has previously been reported to significantly extend the life span of rats and mice. However, the effects of DR are not strictly comparable to the effects of these drugs, since DR must be initiated when the animals are either young or mature, and most body functions are depressed during DR. By contrast, the effects of drugs that elevate hypothalamic CA activity are not mediated by reducing food intake, are most effective when administered to old animals, and stimulate rather than depress body functions. Prolongation of life span by these drugs may be effected by increasing immune competence, by inhibiting development of disease and tumors, and probably by improving the functions of the liver, kidneys, cardiovascular system, and other organs and tissues. It remains to be confirmed that any of these drugs can extend *maximum* life span.

Hypothalamic neurotransmitters other than CA may also participate in aging developments, since they can also influence pituitary hormone secretion, but little is presently known of their possible role. Serotonin is considered to be a major modulator of pituitary hormone secretion in the rat, but no significant changes in hypothalamic serotonin levels have been found in old as compared with young rats (5). The capacity of hypothalamic neurons to secrete releasing or release-inhibiting hormonal peptides may also be depressed with age, but no information is presently available on this question. Reduced responsiveness of the pituitary, its target glands, and tissues to certain hormones has been observed in old rats. We have reported that GnRH, growth hormone-releasing hormone, TRH, and corticotropin-releasing hormone are less effective in inducing release of pituitary hormones in old than in young rats (3), probably due to loss of receptors or to postreceptor changes in pituitary cells. Although such decrements are secondary to the decline in hypothalamic CA as causative factors in aging, they are important.

The decrease in immune competence with age is associated with greater susceptibility to infections, development of autoimmune diseases, increased occurrence of some tumors, and so forth (39). The present evidence suggests that the decline in GH and thyroid hormone secretion are at least partly responsible for the decrease in immune competence, since administration of GH and/or thyroid hormone reversed the decline in thymic function in old mice, rats, and mature dogs (13, 35, 38). Little is presently known of the possible contribution of the immune system to the decline in neuroendocrine function during aging.

Evidence was reviewed here showing that DR results in reduced hormone secretion by the hypothalamus, pituitary, and target glands (41, 42). DR does not decrease the responsiveness of the pituitary to hypothalamic hormones or of target glands to pituitary hormones (42), indicating that its major site of action is on the hypothalamus. In short-term studies, it was demonstrated that administration of appropriate hormones could overcome the depressing effects of DR on gonadal function and growth of carcinogen-induced mammary tumors. It remains to be seen whether chronic administration of hormones during prolonged periods of DR can continue to counteract the effects of DR. The report that early induction of hypothyroidism in *ad libitum*-fed rats resulted in lengthening the life span (51) supports the view that DR exerts its effects on aging by decreasing hormone secretion. It is likely that DR also has direct effects on body tissues in addition to those on the neuroendocrine and immune systems.

The relation of the work reviewed here in rats and mice to problems in human aging is not clear at present. Relatively few studies on man have focused on neuroendocrinimmune aspects or have tested the effects of prolonged DR on aging processes. Interestingly, hypothalamic CA have been reported to be decreased in elderly man (53) as in old rats, but their relation to changes in neuroendocrinimmune functions have not been established. The closest parallel to a change in hormone secretion in the rat is the similar decrease in GH and somatomedin secretion in aging man. The large pulses of GH normally released during deep sleep in young or mature individuals are either attenuated or completely absent in old people (54). Also, less GH is released in response to administration of L-dopa, exercise, or insulin-induced hypoglycemia in old than in young individuals (12), indicating that major faults have developed in the hypothalamo-pituitary system. The reduction in GH secretion may be related to the reduced hypothalamic CA activity as in old rats. Their importance in man is clearly indicated by reports that both DAergic and NEergic drugs stimulate GH secretion, as in animals (14). The effects of low secretion of GH in elderly human subjects has recently received emphasis in the report that injections of human GH for 6 months into men 60–80 years of age increased lean body mass, decreased adipose tissue mass, increased skin thickness, and produced a small increase in density of lumbar vertebral bone (55). It is possible that administration of appropriate CAergic drugs could produce similar effects in elderly man.

The decline in reproductive functions in men and women has been attributed mainly to deficiencies that develop in gonadal capacity to secrete steroid hor-

mones, resulting in elevated secretion of gonadotropic hormones. However, recent studies indicate that there is also a decrease in GnRH release by the hypothalamus and reduced responsiveness of the pituitary to GnRH stimulation, as in old rats (56). Whether the decrease in secretion of hypothalamic CA has any role in the reproductive decline in man is unknown at present.

It is debatable whether DR can be viewed as a practical or even desirable procedure for inhibiting aging processes in man. DR decreases secretion of hormones in man as in animals (14), but it remains to be demonstrated that this results in extension of life span. Based on the many animal studies and on a very limited number of observations in human populations, Weindruch and Walford (39) concluded that DR begun in early adulthood may be a worthy regimen to follow for retarding aging and prolonging life. Others have raised doubts about such an approach. There is some evidence that mortality is greater in underweight people and lower in slightly overweight persons (57), although these data have been questioned (39). A more promising approach is indicated by the studies reviewed here on the effects of central acting drugs on brain CA activity in old rats and/or mice. It is possible that safe drugs with minimal side effects can be developed that will improve body and brain functions in elderly men and women, and perhaps even prolong the life span.

## Addendum

Two sympathomimetic drugs, ephedrine and phenylephrine, were reported to increase survival and decrease occurrence of leukemia and pheochromocytoma in Fischer 344/N rats and B6C3F$_1$ mice (58, 59). In addition, clonidine, a norepinephrine agonist, was reported to improve memory retention in old C57BL/6N nia mice (60). This study suggested a role for the noradrenergic system in the age-related recline in memory function.

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