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# Pituitary Growth Hormone as a Metabolic Hormone

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The removal of the pituitary from young growing animals induces atrophy of the adrenals, thyroid, and gonads, as well as stoppage of general body growth. The development, growth, and secretory activity of these endocrine glands are controlled by the hormones of the anterior pituitary. In this capacity, the pituitary hormones function as growth-promoting substances; all are specific with respect to their growth-promoting effects, with the exception of growth hormone, which affects the growth of the body as a whole (*1*). For example, adrenocorticotropic hormone (corticotropin, ACTH) causes hypertrophy of the adrenal cortex and induces the hypertrophied gland to secrete cortical hormones into the blood circulation. Without ACTH, the adrenal glands of hypophysectomized animals are forever atrophied, and no further growth of the gland can occur.

## Growth and the Anterior Pituitary

However, it should be pointed out that the anterior pituitary is only one of the many agents that determine the ultimate size and form of the whole animal and its component organs. There is also good reason to believe that the presence of a pituitary factor is not always essential for growth.

Although it is known that hypophysectomy of very young rats does not lead to an immediate cessation of growth (*2, 3*), growth does cease when the young hypophysectomized rats reach an age of about 30 days (*4*). When rats are hypophysectomized at a very early age, their life span becomes extremely limited; such animals survive for less than 75 days (*5*). For instance, among several hundred rats hypophysectomized at 6 days of age, there was a mortality of 86 percent in the period immediately following operation (the first 10 postoperative days). During the next 13 days (up to 28 days of age) no deaths occurred; starting immediately thereafter (at 29 days of age), deaths in the 43 remaining untreated rats were frequent, until by 74 days of age all of them had died.

These deaths have been attributed to brain damage; the brain had continued to grow to normal size within a cranium that had become dwarfed through the premature arrest of its growth in both length and width. The chief factor in this arrest appeared to be the cessation of endochondral osteogenesis at the base of the skull. Before death, these animals were characterized by distinct abnormalities, which appeared in some cases as early as 20 days of age; virtually all of these abnormalities could be related to the nervous system. However, when these young hypophysectomized animals were treated with growth hormone, they survived, and furthermore, they manifested no evidence of neural damage. Apparently, the arrest of their cranial growth, both longitudinal and lateral, was counteracted by the growth hormone, so that the crania of the treated animals could attain normal size, adequately accommodating the brain.

This remarkable effect of growth hormone furnishes one of the best illustrations of its influence on the growth of bony tissue. In fact, the most sensitive and reliable method for the bioassay of growth hormone is based on its stimulation of the proximal epiphyseal cartilage of the tibia in young hypophysectomized rats (*6*). It should be mentioned that growth hormone does not cause skeletal maturation but is concerned chiefly in the process of osteogenesis (*7*).

When normal adult rats, maintained on a constant dietary intake, were injected with growth hormone, an increase in body weight with an accompanying decrease of urinary nitrogen was observed (*8*). Furthermore, it has been shown that the protein content in the bodies of hypophysectomized rats increases when the animals have received treatment with growth hormone (*9*). That growth hormone is a powerful protein anabolic agent gains additional support from experiments with sulfur-35-labeled albumin, in which the effect of growth hormone on the metabolism of plasma albumin was studied. It was found that treatment of the adult hypophysectomized rat with growth hormone results in a great acceleration of albumin synthesis, so that the replacement rate is increased twofold or more (*10*).

Adrenocorticotropic hormone is now well established as a growth inhibitor (*11*); administered to young normal rats, it retards their rate of growth, and it induces a similar stunting in young hypophysectomized rats (*12*). It has also been reported that ACTH injections inhibit hair growth (*13*). Furthermore, in experiments with normal rats, treatment with ACTH resulted in a retardation of both chondrogenesis and osteogenesis in the region of the proximal epiphysis of the tibia (*14*). Since growth hormone is a promoter of growth, it is not surprising that it can counteract the growth-inhibiting effect of ACTH; for example, the decrease in body weight and in the width of the epiphyseal cartilage that are usually induced by ACTH were halted completely, or almost completely, by the simultaneous administration of growth hormone (*15*). A similar antagonism between these two hormones has also been observed in the osseous system in hypophysectomized rats (*16*). Furthermore, it was found that growth hormone reverses the weight loss produced by the administration of ACTH or cortisone, without affecting the ability of the latter hormones to inhibit the growth of transplanted mammary adenocarcinomas in C3H mice (*17*).

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## Extra-"Somatotropic" Effects

Since the demonstration of growth-promoting activity in pituitary extracts by H. M. Evans and J. A. Long in 1921 (*18*), the chief function of growth hormone has been thought to be the promotion of somatic growth. However, the frequent failure of growth hormone to produce growth in human dwarfs has been a great disappointment to clinical endocrinologists in recent years, although Shorr *et al* (*19*) have recently reported enhanced storage of nitrogen, calcium, and phosphorus during the course of the administration of the hormone to two female subjects of abnormally small stature. It may be that growth hormone can exercise biological functions other than just the promotion of body growth. Indeed, recent studies from this laboratory (*20*) have demonstrated, in normal rats, the ability of growth hormone to effectively counteract the depression of resistance to *Pasteurella pestis* that is induced by relatively high doses of ACTH. In the same study it was shown that growth hormone, when administered simultaneously with ACTH, prevents the lowering of serum antibody levels that results from the administration of the latter hormone, following a single injection of a soluble protein antigen. Other investigators (*21*) have also obtained evidence of the beneficial effect of growth hormone on animals that have been sensitized by cortisone to tuberculosis infection.

There have been other indications of extra-"somatotropic"—in the restricted sense now generally accepted for this term—effects exercised by the growth hormone. After treatment of hypophysectomized female rats with growth hormone, an increase was noted in the weight of the uterus, and tall columnar mucous cells were discernible in the vagina; similar stimulation was observed in hypophysectomized-ovariectomized or hypophysectomized-adrenalectomized animals that had been treated with the hormone (*22*). It has also been demonstrated that growth hormone possesses an ability to effect partial restoration of the atrophied secondary sex organs of hypophysectomized-castrated male rats (*23*).

There is now much evidence to the effect that growth hormone administered to experimental animals produces typical signs of diabetes and causes various changes in carbohydrate metabolism (*24*) while recent data strongly suggest that growth hormone accelerates the mobilization and oxidation of depot fat (*25*). In view of these observations of the strong influence exercised by the growth hormone on the general processes of metabolism, it is not surprising that this hormone has been found to be galactopoietic in the cow (*26*) and that it has been further demonstrated to be essential for the induction of milk secretion in hypophysectomized rats (*27*).

## Growth Hormone as a Biological Synergist

When growth hormone is administered concurrently with testosterone to young hypophysectomized-castrated male rats, the two hormones operate synergistically to promote the growth of the accessory sex glands (*28*). A similar synergism between ACTH and growth hormone with respect to the development and function of the adrenal glands of hypophysectomized animals has also been observed (*23*).

Regression of the mammary glands of hypophysectomized-castrated rats was apparent when the animals received either growth hormone or estrone alone. However, if these two hormones were injected together, synergistic effects were clearly evident in the remarkable end-bulb proliferation (*27*). In the absence of growth hormone, estrone exercises no biological action on the development of the mammary gland; the presence of growth hormone seems to bring out what may be the true physiological function of estrone. Does this ability to act as a synergist mean that growth hormone plays a permissive or supporting role in the biological action of a hormone or of a biological agent? It is not unreasonable to assume that growth hormone creates the necessary and sufficient environment for other biological agents to exercise the full scope of their functions.

## Growth Hormone and Cancer

To further illustrate the supporting role played by growth hormone in biological phenomena, we may recall the early studies on the influence of growth hormone on the development of tumors in normal and hypophysectomized rats. When normal rats were treated with growth hormone for a period of 485 days, many neoplasms developed in the organs of all these animals (*29*). These lesions occurred most frequently in the lungs, adrenal medulla, and reproductive organs. However, no neoplastic response was noted in hypophysectomized animals that were similarly treated (*30*). It would appear that growth hormone is not in itself the cause of the development of tumors; in the presence of excessive growth-hormone stimulation, an unidentified substance becomes active and induces abnormal growth in the body of the animal.

It is known that hypophysectomy results in a marked suppression of the response of animals to carcinogens. Recent studies with 9,10-dimethyl-1,2-dibenzanthracene in rats indicate that this alteration of response produced by hypophysectomy manifests itself in delayed appearance of the neoplasms as well as in their lowered incidence (*31*). It was found, for example, that in rats with intact pituitaries, 50 percent of the animals developed tumors within 60 days after injection of the carcinogenic agent, whereas in hypophysectomized rats, 156 days elapsed before a 50-percent incidence of tumor development was reached. When the hypophysectomized rats were treated with growth hormone, the interval again approximated that encountered with the intact animals. Thus, it is evident that growth hormone plays a supporting role in connection with the carcinogenic action of dimethyl-dibenzanthracene in hypophysectomized rats; in the absence of growth hormone, the production of sarcomas by the carcinogenic agent is markedly delayed.

## Concluding Remarks

This article (*32*) is not intended to be a summary of the biological properties of the growth hormone, nor is its purpose to present new data from our unpublished work. I wish primarily to call attention to the way in which the name of this hormone, adopted because of the first experimental observations on its action, has led to a misleading expectation about its biological activity and sometimes to a mistaken evaluation of its biological usefulness. When for many years the pituitary growth hormone was thought to possess only general body-growth-promoting activity, as its name indicates, any observed biological effects other than the promotion of growth were attributed to some contaminating factor or factors. At one time or another, the existence of glycotropic, pancreatropic, glycostatic, diabetogenic, and ketogenic principles in purified pituitary preparations that were also rich in growth-promoting activity was postulated. We now know that these effects can be attributed to the action of the growth hormone itself (*33*).

It should be borne in mind that a hormone known to be pure, and whose chemical structure has been elucidated —ACTH (*34*), for example—can exercise more than one biological function. Conversely, it should be borne in mind that molecules of differing chemical composition may possess similar biological activities. It is therefore not surprising that the growth hormone protein, which behaves as a homogeneous substance (*35*), exhibits a variety of metabolic effects.

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32. The work reported here has been supported in part by grants from the Albert and Mary Lasker Foundation and by the American Cancer Society on recommendation of the committee of Growth of the National Research Council.
33. Since so many effects involving various tissues and organs have now been ascribed to the pituitary "growth hormone," it might be more appropriate to designate the hormone *somatotropin*, if, avoiding the restrictive distinctions between somatic tissue and the visceral or generative organs that have led to confusion in recent years, we understand the term in its broad sense as implying something that nourishes or affects the whole body (*soma*).
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# Fallout Dosages at Washington, D.C.

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The ground-level concentration of fission products in the air has been measured daily for several years. Fission product activity at Washington, D.C., although it is readily detectable, has generally remained less than the natural background due to radium and thorium products that are normally present in the atmosphere. However, even with low air concentrations of long-lived activities, material deposited on the ground may conceivably lead to appreciable dosages for long exposures.

In this report, a calculation of the radiation dosage received by an unshielded man for all biologically significant time (here referred to as the "infinity dose") is therefore attempted from the measured air concentration of fission products and the estimated rate of fallout (*1, 2*). Detailed calculations, to be sure, are not feasible on account of the many unknowns such as particle size, meteorological parameters, and so forth; but in view of the general lack of information on the subject, even a crude calculation based on experimental data is of interest.

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## Data and Analysis

It will be assumed that the fission products are distributed in the lower atmosphere in the concentrations measured by our air filtration equipment (*2*). Our experimental data consisted of daily measurements of the atmospheric radioactivity collected by an efficient filter device. The collected radioactivity was measured with a thin-window Geiger counter, and the activity due to fission products was calculated from decay measurements. The estimated over-all accuracy of this determination is ± 20 percent. Figure 1 is an example of the raw filtration data obtained during 1953 and 1954. The earlier and most prominent responses observed during 1953 were due to United States tests in Nevada, while those later in the year followed tests in the Soviet Union. Subsequent to the Pacific thermonuclear tests of 1954, the atmospheric fission product concentration increased gradually from June to September, when much larger activities from Soviet tests appeared.

If $a(t)\ dt$ represents the number of fission product disintegrations at time $t$ in time interval $dt$ per unit volume, the total number $n(t)$ of disintegrations that take place per unit volume after a time $t$ will be

$$n(t) = \int_t^\infty a(t_1)\,dt_1. \qquad (1)$$

(This is also the number of radioactive atoms contained in a unit volume at time $t$.) According to Way and Wigner (*3*), the time dependence after 1 day is given by

$$a(t_1) = ct_1^{-1.2} \qquad (2)$$

where $c$ is a constant. One measurement at $t_1 = t$ suffices to determine the constant $c$. Evaluating Eq. 1 by means of Eq. 2, we obtain

$$n(t) = \int_t^\infty a(t)\,(t/t_1)^{1.2}dt_1 = 5a(t)t. \qquad (3)$$

If $V_1$ is the velocity of fallout, the total number of radioactive particles that will fall on a unit of area (and later disintegrate there) is then simply $5\ V_1 a(t)t$. The total number of radioactive atoms $N$ that fall on a unit area due to deposition from the entire volume directly above is then

$$N = 5\int_0^\infty V_1 a(t)\,t\,dt. \qquad (4)$$

(This is also the total number of disintegrations that will occur per unit area for all time.)

Although Eq. 2 is not valid at $t = 0$, the lower limit of Eq. 4 causes no difficulty since, at some distance from the explosion, $a(t)$ usually remains zero for the first few days after detonation. Under the assumption that each measured beta disintegration corresponds to one gamma