ADVANCES IN

# *Metabolic Disorders*

Volume 7

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# *Metabolic Disorders*

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# Growth Hormone and Somatomedin



## I. Introduction

One of the classical discoveries in the field of endocrinology is the growth-promoting activity of the anterior part of the pituitary gland.

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It goes back to the demonstration by Evans and Long in 1921 that crude extracts from the anterior lobe of beef pituitary glands produced gigantism in normal plateaued rats by repeated intraperitoneal injections. Later, Smith in 1930 produced dwarfism and sexual infantilism in rats by hypophysectomy, and demonstrated the restoration of growth following the injection of crude pituitary extracts. A period of intense scientific activity followed these observations, concentrating on the different metabolic aspects of growth hormone. Some of the studies were directed toward the different aspects of the growth process itself. Out of the vast number of data in the literature, one may pick the following major findings: that chronic treatment of adult rats with purified growth hormone resulted in an increase in the protein content of the animals (Li and Evans, 1949); that urinary nitrogen excretion diminished and, thus, nitrogen was retained in dogs during treatment with growth hormone; that the primary effect of growth hormone *in vivo* was to stimulate the uptake of amino acids by tissue and their incorporation into protein (Russel, 1955, 1957).

All these effects of growth hormone *in vivo* have one thing in common: they are similar to the *in vivo* and *in vitro* effect of insulin. This similarity between growth hormone and insulin was noted already in 1945 by Young, who then concluded: "There must exist in the body a pituitary-stimulatory mechanism which enhances protein anabolism. The secretion of insulin is capable of fulfilling such a mechanism provided that, under its influence, the blood sugar is not allowed to fall to hypoglycemic levels but is maintained or even elevated." Evidence against the idea that growth hormone acts on protein metabolism by triggering insulin secretion was provided by Manchester and Young (1959), who found that administration of antibodies to insulin did not inhibit the protein stimulation induced by growth hormone.

Since then growth hormone from pituitary glands both from animals and man has been purified, and its chemical structure determined (Li and Evans, 1944; Li *et al.*, 1962; Li and Dixon, 1971). By the use of such preparations it has been well established that growth hormone *in vivo* promotes skeletal growth and protein synthesis. The mechanism involved in these processes have been only partly elucidated (see reviews by Astwood, 1955; Knobil and Greep, 1959; Raben, 1959; Engel and Kostyo, 1964; Knobil and Hotchkiss, 1964; Sonnenberg, 1968; Tata, 1969; Korner, 1970; Kostyo and Nutting, 1973). The present review will consider the hypothesis that growth hormone promotes protein synthesis by stimulating the appearance in the tissues of a secondary factor, sulfation factor or somatomedin, which transfers the action of the hormone to the tissues.

## II. Sulfation Factor—Somatomedin

The epiphysial plate of the long bones of the rat declines after hypophysectomy and increases after treatment with growth hormone. This increase in width of the epiphysial plate of the proximal end of the tibia of hypophysectomized rats accompanying the administration of growth hormone *in vivo* has also been used for quantitative measurements of the hormone (Evans *et al.*, 1943; Greenspan *et al.*, 1949). The incorporation of labeled sulfate into cartilage as chondroitin sulfate provides a useful index of cartilage metabolism. Nearly all the sulfate incorporated by cartilage enters the glucosaminoglycans (Ebert and Prockop, 1967).

The rate of the *in vivo* uptake of sulfate into different cartilaginous tissues of the rat has been shown to decrease after hypophysectomy, and to be restored to normal after parenteral administration of growth hormone (Ellis *et al.*, 1953; Denko and Bergenstal, 1955; Daughaday *et al.*, 1955; Murphy *et al.*, 1956; Collins and Baker, 1960, 1961; Chesley, 1963). Furthermore, the sulfate incorporation *in vivo* into costal cartilage from mice after correction for the size of the exchangeable inorganic sulfate pool of the animal decreased by 30% after hypophysectomy; the following administration of porcine or ovine growth hormone induced a dose-dependant increase (Herbai, 1970, 1971).

The effect of various vitamins and hormones *in vitro* on the uptake of labeled sulfate has been studied extensively. An important observation by Salmon and Daughaday (1957) was that the stimulatory effect on cartilage obtained by growth hormone treatment *in vivo* could not be reproduced by adding growth hormone *in vitro*. Growth hormone had to be added in very high concentrations to the incubation medium before any effect could be detected. In 1956 Salmon, working in the laboratory of Daughaday, made the critical observation that normal serum but not serum from hypophysectomized rats could stimulate the *in vitro* incorporation of labeled sulfate into cartilage of hypophysectomized rats (Salmon and Daughaday, 1956, 1957). Administration of growth hormone to hypophysectomized rats restored the stimulatory activity of their serum. Salmon and Daughaday (1957) concluded that serum contains a factor dependent on growth hormone, and that this factor has a direct effect on cartilage. They termed it *sulfation factor*.

The occurrence in serum of a growth hormone-dependent sulfation factor has been amply confirmed. This factor is not selectively concerned with the introduction of sulfate into glucosaminoglycans but has a more general effect on cartilage. The effects of serum from normal or growth-