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STUDIES ON THE MECHANISM OF NITROGEN STORAGE

PAUL D. BARTLETT

One of the many interesting problems which have attracted investigators in the field of protein metabolism is the mechanism by which a rapidly growing immature organism retains nitrogen and accumulates body protein. For the greater part the author's research program has also been focused upon this problem, and has been guided by the thought that comparative study of nitrogen metabolism in animals in various states of the growth process might reveal certain distinct metabolic differences which would throw some light on the regulatory mechanisms involved. In this connection studies of the metabolic effects of growth hormone in animals in which the growth process has been arrested, either by hypophysectomy or by attainment of the adult state, have been particularly useful.

As is clearly indicated from the titles in the Publication List, the scope of attack on the problem has included studies of amino acids (18, 34), glutathione (134), and plasma protein metabolism (58); muscle, hepatic, and renal transaminase (34, 35); phosphate and pyruvate-activated glutaminase (21, 22); hepatic and renal dehydropeptidase I (52); rates of amino acid catabolism, protein synthesis and degradation; and the size of the nitrogen and urea pools (57, 69, 92, 100). These studies represent an attempt to characterize the growth process, and incidentally also the process of aging, in terms of nitrogen metabolism and enzyme systems involved in the metabolism of nitrogen compounds.

Quite early during the course of studies on the mechanism of action of growth hormone, observations were made by several groups of investigators suggesting that the hormone might function indirectly through regulation of fat metabolism. This is of special interest since accelerated fat catabolism would not only provide the energy requirements for the endergonic process of protein synthesis but also exert a protein-sparing effect during periods of metabolism when carbohydrate was not readily available as an energy source. In considering a number of mechanisms which might explain a regulatory effect of growth hormone on fat metabolism, we were particularly attracted to the hypothesis that control of the concentration of coenzyme A might be the mechanism involved. Initial studies of tissue coenzyme A concentrations, in both normal and induced states of growth, have resulted in the exciting finding of an apparently direct relationship between liver coenzyme A concentration and the growth process in normal rats (116). Currently these studies are being extended to include observations on the short-term effects of growth hormone on concentrations of oxidized and reduced forms of the cofactor in both normal adult and hypophysectomized rats. While it is too soon to adequately assess the significance of our data in relation to the possible effects on fat metabolism, it seems of special interest that in the relatively short period of 5 hours following stimulation with a single dose of growth hormone, in both normal adult and hypophysectomized rats, the balance of reactions requiring or producing liver coenzyme A appears to shift so that the reduced form is significantly increased. In 16 hours this effect has disappeared and the ratio of oxidized to reduced coenzyme A has returned to values similar to those observed in unstimulated rats.
Although indirect evidence appears to support the view that effects of growth hormone on nitrogen metabolism are mediated through alterations produced in fat metabolism, no unequivocal direct effects of the hormone on fatty acid catabolism have been demonstrated. Since the above hypothesis necessarily implies that fat is the preferential source of energy involved in the mechanism by which growth hormone induces nitrogen storage and accumulation of body protein, one might reasonably expect the metabolic pattern of handling a test load of amino acids administered under a condition in which fat is preferentially metabolized to differ from the pattern when carbohydrate metabolism is serving as the energy source. In order to test this supposition, we are presently engaged in a study of the effects of growth hormone on plasma total free alpha-amino acid nitrogen, glutamine nitrogen, and blood urea nitrogen, during the 3 hour period immediately following infusion of a test load of amino acids (10% Amigen) into adult dogs in which either fat or carbohydrate is being metabolized. In experiments in which the effects of fat are being studied, the fat is fed 3 hours prior to intravenous administration of the test load of Amigen. In experiments with carbohydrate, glucose is fed 1 hour prior to infusion of the Amigen.

An increasing interest in the bioenergetics of growth at the subcellular level of organization is shown by studies now in progress in this laboratory in which we are investigating the process of oxidative phosphorylation in liver mitochondria obtained from rats in various states of the growth process.

The opportunity to discuss basic research problems in conjunction with the clinical problems of the Henry Ford Hospital medical staff has proven particularly stimulating. One such discussion has recently emphasized the problems confronting the clinician in the nephrotic syndrome. In considering possible mechanisms which might explain the pathogenesis of glomerular changes and edema in the nephrotic syndrome, several observations suggest that a shift in the metabolism of tryptophane toward the formation of 5-hydroxytryptamine might be an etiological factor. In both the rat and the dog, for example, 5-hydroxytryptamine produces an antidiuretic effect and a decrease in the glomerular filtration rate. The problem, one of mutual interest to the staff of the Pediatrics Clinic and the author, is currently being investigated.1

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ENZYME DIVISION

*Left to right:* Dr. Antonio Giuditta (Fulbright Fellow), Mr. Paul Bernath, Dr. Francisco Lara (Rockefeller Fellow), Dr. Vincent Massey, Dr. Edna B. Kearney, Dr. Thomas P. Singer, Mrs. Joanne Wilberding, Mrs. Lillian Cummings, Mr. Donell Thomas, Miss Maria Warringa (Fulbright Fellow), and Mr. Robert Vukmirovich.