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# METABOLIC EFFECTS OF GROWTH HORMONE, CORTICOTROPIN, AND VARIOUS STEROIDS

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During 1954 and 1955, the writer participated in arrangements for two International Symposia (102, 125). Research activity took the form of exploratory experiments which provided the basis for resumption of a more active program on completion of these assignments. Mr. Trieste Vitti, Mrs. Rachel Glovinsky, and Dr. Helen Lees, collaborated in developing such a program. Generous support for its inception has been provided by the Michigan Chapter, Arthritis and Rheumatism Foundation, and, for its expansion, by the Division of Research Grants, National Institutes of Health. Several lines of investigation, all requiring similar experimental procedures and instrumentation, are under way.

## 1. *Metabolism of Nitrogen-15 from Various Sources, During Induced Nitrogen Storage or Loss.*

Earlier studies, briefly summarized at a symposium (85), acquainted us with changes in the nitrogen balance and nitrogen partition which growth hormone elicits. Curiosity arose as to whether induced storage of nitrogen is general, involving nitrogen from all amino acids, or whether it has selective characteristics. Even if the name "growth hormone" is valid, present knowledge of transfer of amino groups makes it unsafe to assume that the nitrogen required for growth necessarily comes from each of the amino acids in the proportion that average amino acid composition of total body protein dictates. A less orthodox arrangement, though introducing an element of complexity, might supply one of control. Moreover, studies on changes in transaminase activity, initiated by Bartlett (34, 35) and extended by Zuchlewski (90), suggested the desirability of studying the metabolism of N-15 originating from ammonia, alanine, glutamic acid, and aspartic acid. Some observations on ammonia output in normal dogs receiving growth hormone, and in depancreatized ones receiving growth hormone with or without additional insulin, indicated that effects on ammonia formation, as well as on transamination, might profitably be studied by this approach. These experiments also include observations on incorporation of nitrogen-15 from the various sources into fibrinogen, during nitrogen storage induced with growth hormone, and during nitrogen loss induced with corticotropin. Anatomical distribution of the N-15 is also being studied.

## 2. *Characteristics of the Action of Corticotropin and Various Steroids on Nitrogen and Water Balances*

When growth hormone is injected into normal adult bitches, there is an increase in water intake that exceeds the rise in urine volume. An overnight increase in weight occurs; nitrogen storage begins at once and reaches a maximum in a few days. The entire process reverses quickly after cessation of therapy. After corticotropin (20 units daily), water intake rises less than urine volume, marked losses of weight and nitrogen occur, and, while the losses stop soon after cessation of therapy, restoration

of initial weight may require weeks, or may not occur until the diet is increased. To date, simultaneous observations have not been made on metabolic rate in these experiments. Effects of hydrocortisone acetate (15 mg. daily, intramuscularly), prednisone (10 mg. daily per os), and hydrocortisone ointment applied to affected areas in a metabolism dog which occasionally developed dermatitis, were similar.

### 3. *Certain Interrelationships of Pituitary, Pancreas and Adrenals*

It has long been established that adrenalectomy, in depancreatized cats and dogs, minimizes the accentuation of diabetes by growth hormone. We, therefore, attempted to reproduce these untoward effects by administering corticotropin or hydrocortisone to a fed depancreatized dog receiving a constant dose of insulin. Corticotropin (20 units daily), caused slight nitrogen loss but no increase in glucosuria. Hydrocortisone (15 mg. daily) caused neither nitrogen loss nor glucosuria, although the same dose, in normal dogs, caused marked nitrogen loss. Hydrocortisone (30 mg. daily) increased output of nitrogen, but not of glucose, which was drastically affected by growth hormone under the same dietary conditions. When the diet was altered by addition of 50 gm. of sucrose daily, some increase in glucosuria followed administration of corticotropin or hydrocortisone, but the situation was not alarming, as in experiments with growth hormone. Since the smaller dose of hydrocortisone caused marked nitrogen loss in normal dogs, the intriguing, if remote possibility, that insulin is involved in mobilization, as well as in storage of nitrogen, will be studied later.

### 4. *Toxicity of Growth Hormone*

In depancreatized dogs receiving constant amounts of food and insulin, small daily doses of growth hormone appear to be more dangerous than large single ones. We lost one animal during the second experiment, and considered anaphylaxis, but a second one was lost during the very first course of treatment. Other depancreatized dogs, like the normal ones, tolerate a series of 6 daily doses of 2.5 to 5 mg. of growth hormone without responses that are inconsistent with metabolic studies. Neither insulin nor hydrocortisone is of much avail when the situation has become dangerous to life. While we are in the descriptive stage of this induced upset, studies of its nature and possible prevention or reversal will be continud.