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THE EFFECT OF AGE ON HORMONAL-REGULATION OF LIPOLYSIS
IN ISOLATED ADIPOCYTES OF THE RAT

By

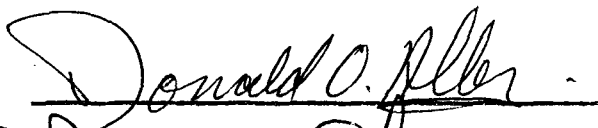
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Submitted to the faculty of the Graduate School
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy in
the Department of Pharmacology,
Indiana University

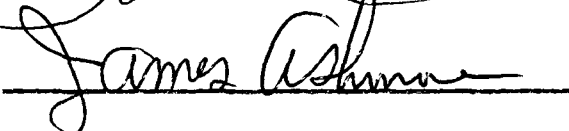
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Accepted by the faculty of the Graduate School, Department of Pharmacology, Indiana University, in partial fulfillment of the requirements for the Doctor of Philosophy degree.

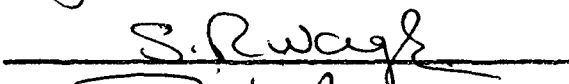
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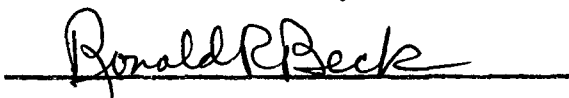
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ABSTRACT

The effect of senescence in the rat, accompanied by increased body weight, on adipose tissue metabolism was studied in isolated fat cells. For most studies, fat cells were obtained from rats either 45 days old or over 14 months in age and glycerol was measured as an index of lipolysis. It was found that aging affected lipolysis but the type of change observed was dependent on the hormone used to stimulate lipolysis. If epinephrine were used, a biphasic lipolytic dose-response curve was produced in fat cells from rats weighing less than 350 g. The two phases were designated LI and LII. In older fat cells a monophasic response was observed. The maximum response was unchanged in the old and young fat cells but a higher concentration of epinephrine was needed to produce a response in old fat cells. Studies were undertaken to demonstrate whether the monophasic response was similar to LI, LII or a combination of both based on the differential sensitivity of LI and LII to the effect of propranolol and the lack of K^+ . The monophasic response was identified as being similar to LII. Determination of the pA_2 values for LI, LII and the monophasic response indicated that LII and the monophasic response were mediated by a receptor distinct from the LI receptor. Insulin had three different effects on epinephrine-stimulated lipolysis depending on the age of the rat, the dose of insulin and the dose of epinephrine used.

Insulin inhibited LI, augmented LII and had no effect on the monophasic response. These studies indicate that aging causes alterations in the cell probably at the receptor which results in a loss of LI and changes the sensitivity of the cell to insulin.

The effect of ACTH, dibutyryl cyclic AMP and theophylline in old and young fat cell was examined. ACTH and dibutyryl cyclic AMP stimulated old fat cells to a significantly lesser degree than young fat cells. The lipolytic dose response curve to theophylline was unaffected by the age of the rat. Aging affects a site prior to the site of action of theophylline, either the receptor or a subsequent step.

Studies were undertaken to examine the activities of adenylate cyclase, phosphodiesterase and cyclic AMP levels in old and young fat cells. Senescence decreased the adenylate cyclase response to ACTH, epinephrine and NaF. It was found that the absolute adenylate cyclase activity was diminished but not the relative degree of absolute activity stimulated by ACTH and epinephrine. Of the two phosphodiesterase enzymes present in adipose tissue, only the high K_m enzyme was decreased in the older animal. The low K_m enzyme was unchanged. Measurement of cyclic AMP levels in old and young fat cells did not reflect the alterations in adenylate cyclase and the high K_m phosphodiesterase. Cyclic AMP dose-response curves to epinephrine were similar to the lipolytic dose-response curves except at basal and $10^{-7}M$ epinephrine where the cyclic AMP levels were elevated in the old fat cells. It was concluded that although alterations do occur in adenylate cyclase and phospho-

diesterase activities, the main site of alteration in the old fat cell is at the receptor and is due mainly to the increased size of the old fat cell.

Measurement of plasma corticosterone and insulin levels demonstrated that old and young rats had different hormonal patterns which could influence the metabolic response. Corticosterone levels were unchanged; the aged rat was hyperinsulinemic as compared to the young rat.

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