Growth Hormone and Carbohydrate Metabolism

R. C. de Bodo, M.D., and M. W. Sinkoff, M.D., New York

The importance of the anterior pituitary gland in the regulation of carbohydrate metabolism has long been recognized. This relationship was shown by experiments[1] in which (1) hypophysectomy ameliorated the diabetes of depancreatized dogs, and (2) diabetes was induced by the administration of anterior pituitary extracts. Of the known anterior pituitary hormones, the part played by the adrenocorticotrophic hormone (ACTH) in carbohydrate metabolism via the adrenal cortex is well established.

The purpose of this paper is to present evidence that (1) an anterior pituitary hormone(s) other than ACTH plays a role in normal carbohydrate metabolism, and (2) most probably, this is growth hormone, or else some factor closely linked with it and as yet not separable.

METHODS

Trained and unanesthetized normal, adrenalectomized, adrenalectomized - gonadectomized, hypophysectomized, and adrenalectomized-hyophysectomized dogs were used. The animals were maintained in good condition on a mixed diet[2]. All adrenalectomized dogs (including those gonadectomized or hypophysectomized) were maintained on daily minimal doses of desoxycorticosterone acetate (DCA) in oil (Schering) 1.5—2.0 mg. per day intramuscularly unless otherwise stated.

All experiments were performed in the postabsorptive state, that is, 17-18 hours after the last food intake. Insulin sensitivity was determined by the response to 0.025 unit per kg. insulin (Lilly) administered intravenously. This has been designated as the "test dose". The glucose tolerance was determined by the response to an intravenous infusion of glucose, 0.075 gm. per kg. per min. for 10 min. In both types of tests, the blood sugar changes were followed at stated intervals over a 4-hour period.

The growth hormone preparations used were Armour preparations: lot Nos. 22KRI, J21609R and GH3; also Squibb preparation lot No. C515 was used. In addition, a growth hormone preparation was supplied by Dr. C. H. Li. The Armour and Squibb preparations were prepared according to the Wilhelmi method. The dosage varied from 0.02 to 2.0 mg. per kg. per day intramuscularly once daily. Growth hormone usually was administered after the afternoon feeding. The adrenocortical steroids, cortisone acetate or hydrocortisone acetate were given in daily dosages of 0.83—1.4 mg. per kg. intramuscularly in two divided doses (9 a.m. and 5 p.m.). Thyroxin (Roche-Organon), 0.25-0.52 mg. per kg. per day intramuscularly was given to hypophysectomized dogs. Some hypophysectomized dogs received whole thyroid, 600 mg. per day.

RESULTS

I. *The Insulin Sensitivity and Glucose Tolerance of Adrenalectomized, Adrenalectomized - Gonadectomized and Adrenalectomized-Hypophysectomized Dogs*

Figure 1 shows the response to the test dose of insulin of adrenalectomized dogs compared with that of normal and adrenalectomized-hypophysectomized dogs. The adrenalectomized dog maintained on DCA responds almost like a normal dog[3,4]. This is true, even when the DCA maintenance is withheld for periods of 8-14 days and signs of adrenal insufficiency supervene, so long as the animal being tested still is in the postabsorptive (17-18 hour fasted) state. Thus, removal of DCA has no effect upon the insulin response of adrenalectomized dogs. In

From the Department of Pharmacology, New York University College of Medicine, New York City.

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Address communications to Dr. de Bodo at New York University Bellevue Medical Center, 477 First Avenue, New York 16, N. Y.

contrast to this, the adrenalectomized-hypophysectomized dogs, on DCA maintenance, develop a precipitous fall in their blood sugar in response to the "test dose" of insulin which is followed in many cases by hypoglycemic convulsions [5,6,7]. This often necessitated a discontinuation of the experiment and institution of emergency treatment to save these dogs.

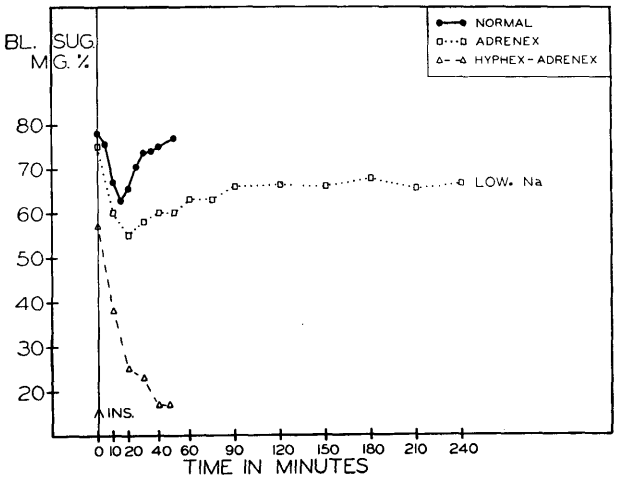

FIGURE 1. Composite blood sugar curves produced by insulin (0.025 u/kg. i.v.) in normal, hypophysectomized-adrenalectomized (hyphex-adrenex) dogs and adrenalectomized (adrenex) dogs, the latter during DCA-free periods. Courtesy of the "Annals of the New York Academy of Sciences."

In response to intravenous glucose the adrenalectomized dog manifests a secondary hypoglycemia, i.e., the blood sugar does not stabilize at the pre-infusion levels as it does in the normal dog, but rather falls below to hypoglycemic levels (Figure 2). Again, as with the insulin test, the adrenalectomized-hypophysectomized dog reacts more severely. The secondary hypoglycemia is more profound and frequently results in convulsions (Figure 2).

With regard to its responses to insulin and glucose, the adrenalectomized-gonadectomized dog reacts no differently than does the adrenalectomized-non-gonadectomized animal [6,7] (Figure 3).

COMMENT

From the above experiments (1) it is evident that an anterior pituitary factor(s) is responsible for the differences in carbohydrate metabolism (as judged by the responses to insulin and glucose) between adrenalectomized and adrenalectomized-gonadectomized dogs, on one hand, and adrenalectomized-hypophysectomized dogs on the other. (2) ACTH is not the factor being sought since it can be ruled out on the basis of its ineffective-

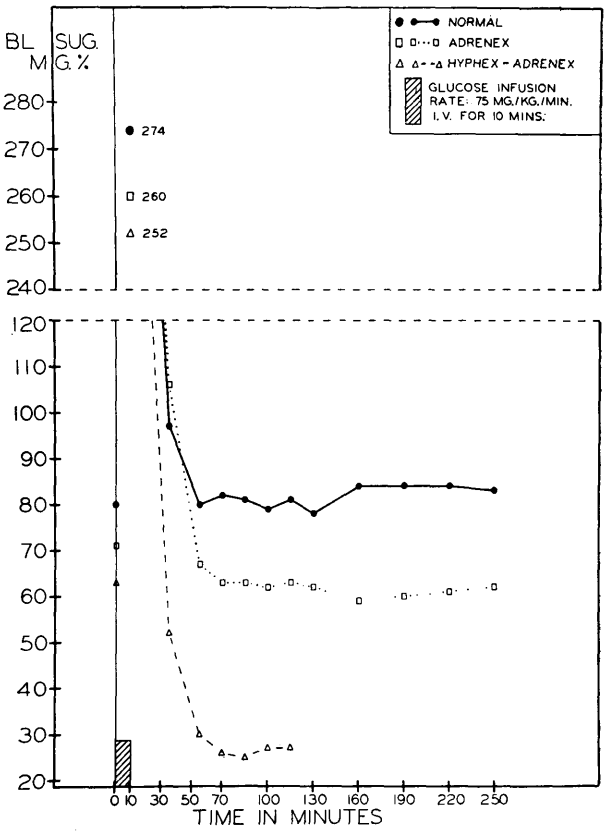

FIGURE 2. Composite blood sugar curves produced by intravenous glucose (0.75 g./kg.) in normal, adrenalectomized (adrenex) and hypophysectomized-adrenalectomized (hyphex-adrenex) dogs. Courtesy of the "Annals of the New York Academy of Sciences."

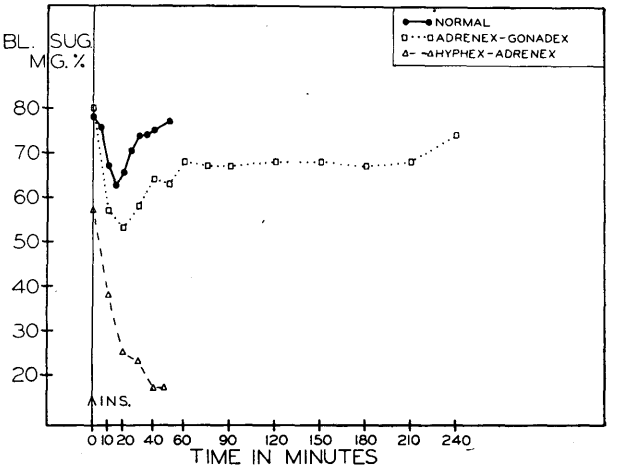

FIGURE 3. Blood sugar curve produced by insulin (0.025 u/kg. i.v.) in adrenalectomized-gonadectomized (adrenex-gonadex) dogs compared with those of normal and hypophysectomized - adrenalectomized (hyphex-adrenex) dogs. Courtesy of the "Annals of the New York Academy of Sciences."

ness in altering the insulin response of adrenalectomized dogs[8]. (3) Furthermore, the gonadotrophins also can be ruled out. (4) Moreover, the anterior pituitary factor in question can exert its action without the intermediation of either the adrenocortical or sex steroids.

II. *The Insulin Sensitivity and Glucose Tolerance of Hypophysectomized Dogs Before and During Cortisone or Hydrocortisone Regimens*

Further indirect evidence in support of the concept that an anterior pituitary hormone other than ACTH exerts an anti-insulin action in the normal animal was obtained from a series of experiments on hypophysectomized dogs treated with adrenocortical steroids. When such dogs received continued administration of either cortisone or hydrocortisone in dosages (0.83—1.4 mg. per kg. per day) sufficient to abolish the disturbances in carbohydrate metabolism of adrenalectomized dogs maintained on DCA, they still exhibited a greater insulin hypersensitivity than normal dogs as well as an abnormal glucose tolerance, that is the secondary hypoglycemia still was present[7,9]. Thus, although the steroids did ameliorate the disturbances in carbohydrate metabolism of the hypophysectomized dogs, they did not restore them to normal as they had in the adrenalectomized dogs. In other words, steroid replacement therapy showed that an anterior pituitary factor still was lacking in the hypophysectomized animals, and it was not ACTH.

III. *Effects of Thyroxin or Thyroid on the Insulin Hypersensitivity of Hypophysectomized Dogs*

The influence which thyrotrophin might have in the control of carbohydrate metabolism was then investigated. Thyrotrophin preparations were not used inasmuch as they contained significant amounts of several other anterior pituitary hormones which might thus have confused the interpretation of any positive results obtained.

With this in mind, whole thyroid or thyroxin was administered to hypophysectomized dogs in dosages which eventually produced signs of clinical hyperthyroidism (increased irritability, increased heart rate, loss of weight, rise in body temperature). However, the effect upon the insulin hypersensitivity of these dogs was slight [6,7]. Thus, thyrotrophin also was ruled out as the possible factor being sought. Of the remaining anterior pituitary hormones, only growth hormone and prolactin had to be considered.

IV. *Effects of Growth Hormone on the Insulin Hypersensitivity and Glucose Tolerance of Hypophysectomized Dogs*

Growth hormone (Armour), when administered in a dose of 1.0 mg. per kg. intramuscularly to the postprandial hypophysectomized dog, will produce a significant diminution in the dog's exaggerated response to insulin; this is in evidence when the animal in the postabsorptive state is tested 17-18 hours after the injection of growth hormone. After 3 or 4 days of such a growth hormone regimen (1.0 mg. per kg. per day), the insulin hypersensitivity usually is completely abolished[2, 10, 11] (Figure 4). However, concomitantly, a diabetic glucose tolerance (Figure 5) and a resistance to even large doses of insulin always develop[2]. No glycosuria or acetonuria has been observed in such a growth hormone-treated hypophysectomized dog, although toxic manifestations (anorexia, nausea, vomiting, lethargy) have appeared during the regimen and, occasionally, death of the animal has occurred. Similarly, growth hormone will produce abolition of the insulin hypersensitivity of adrenalectomized-hypophysectomized dogs[5,6,12], thereby ruling out the possible influence of the ACTH contamination of the growth hormone preparation. In addition, such an action, when obtained in adrenalectomized-hypophysectomized dogs, rules out the essentiality of the adrenocortical steroids for the production of a growth hormone effect.

Although growth hormone has potent effects on carbohydrate metabolism, its diabetogenic action can be of little physiological significance unless it can be shown that growth hormone antagonizes the hypoglycemic action of insulin and thus raises the blood sugar in physiological life without producing diabetes. If this is true,

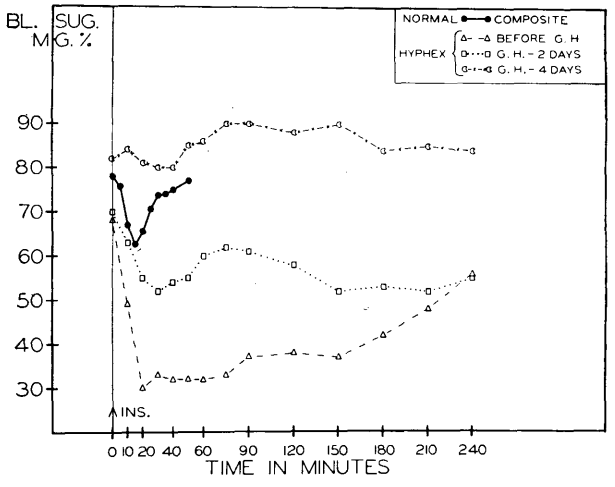

FIGURE 4. Blood sugar curves produced by insulin (0.025 u/kg. i.v.) in a typical hypophysectomized dog before and during growth hormone regimen compared with that of normal dogs. Armour growth hormone #22KRI, 1 mg./kg./day, administered. Insulin tests performed after 2 and 4 doses of growth hormone.

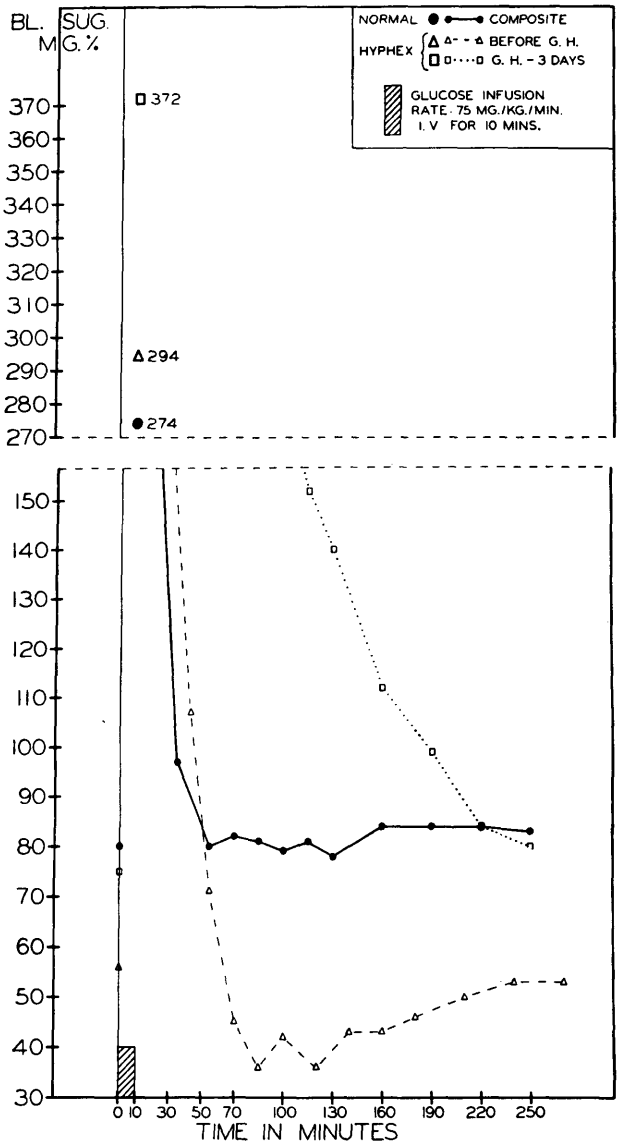

FIGURE 5. Blood sugar curves produced by intravenous glucose (0.75 g./kg.) in a typical hypophysectomized dog before and during growth hormone regimen compared with that of normal dogs. Armour growth hormone #22KR1, 1 mg./kg./day administered. Glucose tolerance test performed after 3 doses of growth hormone.

then it should be possible to demonstrate, with the proper dosages and under the proper conditions, that growth hormone will ameliorate the exaggerated insulin response of hypophysectomized dogs without inducing diabetes. Furthermore, such an effect, when once obtained, should continue indefinitely without incident during the administration of the hormone. Only then could growth hormone be considered to have some physiological importance in carbohydrate metabolism.

With this objective in view and using the same Armour preparation, the growth hormone dosage was reduced from 1.0 to 0.3 mg./kg./day[6]. While this reduction delayed, it nevertheless resulted in the development of diabetes or toxicity. Even when growth hormone was administered in the smallest effective dosages, 0.02 mg./kg./day, a diabetic tendency eventually appeared in about 50 per cent of the dogs[5,6]. These studies were concluded because the animals in time (after 30-40 days administration) became resistant to the growth hormone action. (It should be emphasized that 0.02 mg. per kg. per day is about 1/10 the amount of growth hormone needed to produce measurable growth in hypophysectomized rats).

In another series of experiments, prolonged administration of large doses of growth hormone (1.0-1.5 mg. per kg. per day) to hypophysectomized dogs was made possible without the production of either diabetes, insulin resistance, or toxicity. This was accomplished by combining the growth hormone regimen with an adrenocortical steroid regimen[5,6,13]. Figures 6 and 7 illustrate the responses to insulin and glucose, respectively, of hypophysectomized dogs that first received cortisone or hydrocortisone therapy and subsequently, a combined steroid-growth hormone regimen. It will be noted that the steroid regimens alone only ameliorated the disturbances

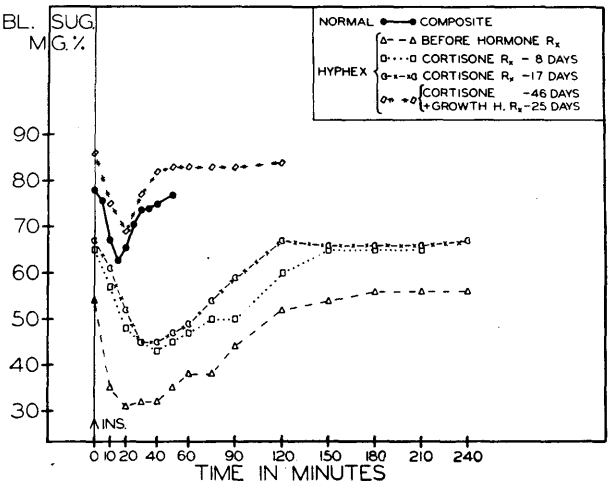

FIGURE 6. Blood sugar curves produced by insulin (0.025 u/kg. i.v.) in (a) normal dogs and in a typical hypophysectomized dog (b) during the untreated state, (c) during cortisone regimen alone and (d) during a combined cortisone-growth hormone regimen. Cortisone, 1.0 — 1.4 mg./kg./day, given for a total of 46 days. Squibb growth hormone #C515, 1.0 — 1.5 mg./kg./day, begun on the 22nd day of cortisone regimen and continued for 25 days.

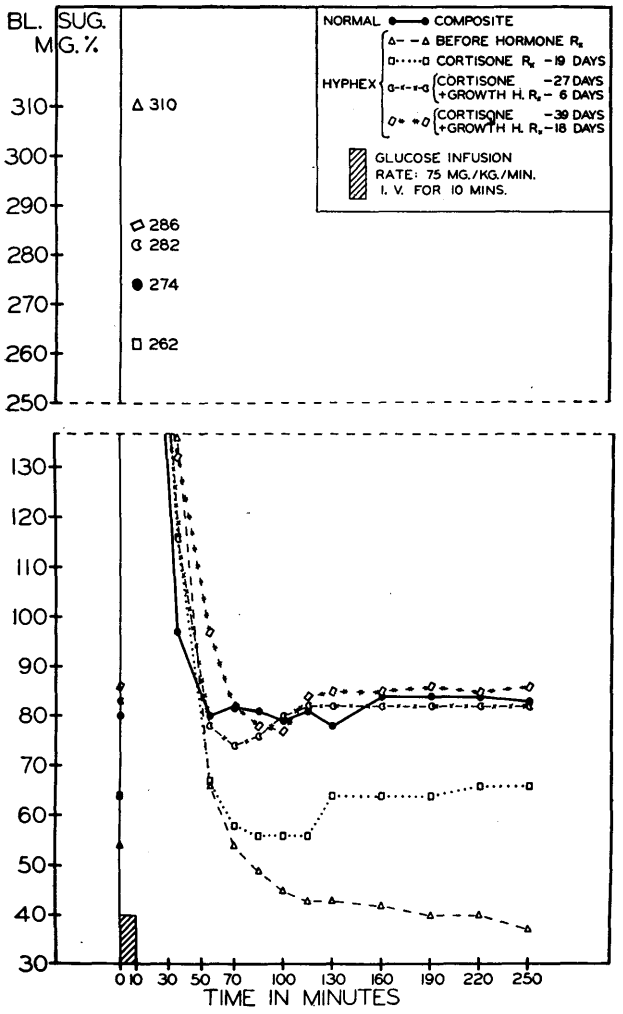

FIGURE 7. Blood sugar curves produced by intravenous glucose (0.75 g./kg.) in (a) normal dogs and in a typical hypophysectomized dog (b) during the untreated state, (c) during cortisone regimen alone and (d) during a combined cortisone-growth hormone regimen. Cortisone, 1.0 — 1.4 mg./kg./day, given for a total of 39 days. Squibb growth hormone #C515, 1.0 mg./kg./day, begun on the 22nd day of cortisone regimen and continued for 18 days.

in carbohydrate metabolism of the hypophysectomized dog[9]. On a combined hormonal regimen, however, the responses both to insulin and glucose became normal and remained so throughout the prolonged therapy[5,6,13]. No toxic manifestations were observed.

Thus far, attempts to administer the growth hormone regimen first and then follow it with a combined growth hormone-steroid regimen have proved to be unsuccessful. With such an order of administration, the hypophysectomized dogs were not able to tolerate the growth hormone (in view of its toxicity) so that several animals died before the adrenocortical steroid therapy could be given in conjunction with the growth hormone.

DISCUSSION

From the above experiments, it is apparent that the adrenalectomized dog has a functioning anterior pituitary hormone (probably growth hormone or some other factor closely linked with it) which exerts an anti-insulin action in the absence of the adrenocortical steroids and does not produce any toxic manifestations. This anti-insulin action is sufficient to protect the adrenalectomized dog against very small doses of insulin (e.g., 0.025 unit/kg.) but not against larger doses (namely 0.25 unit/kg.). Administered growth hormone also produces potent effects (not due to ACTH) in the absence of the adrenocortical steroids as shown by its action in adrenalectomized-hypophysectomized dogs. However, such administration eventually results in the production of diabetes, insulin resistance and/or toxicity. This is true even for the smallest effective dose used, 0.02 mg. per kg. per day intramuscularly. These untoward manifestations of growth hormone administration are eliminated if C-11, 17-oxycorticosteroid therapy precedes and then accompanies the growth hormone regimen in the hypophysectomized dog. Indeed, a normal carbohydrate metabolism results. Under these conditions, large doses of growth hormone (1.0-1.5 mg. per kg. per day intramuscularly) can be administered safely for prolonged periods of time.

Since such optimum effects were achieved with combined growth hormone-adrenocortical steroid regimens, these experiments suggest that a delicate balance exists between these two hormonal factors which enables growth hormone to participate effectively in the regulation of carbohydrate metabolism.

At present, our knowledge of the mechanisms of action of the steroids and growth hormone is insufficient to explain the above findings produced by a combined hormonal regimen. The adrenocortical steroids and growth hormone both antagonize the action of insulin and are either potentially or actually diabetogenic, the former, primarily by enhancing gluconeogenesis[14,15] and possibly interfering with the peripheral utilization of sugar[16,17,18,19] and the latter hormone, by inhibiting peripheral utilization [2,20,21,22]. Yet both, in combination, did not produce a summation or potentiation of their respective effects. It is evident therefore, that the interplay between these two hormonal agents still awaits elucidation.

In addition to growth hormone and its effect on car-

bohydrate metabolism, experiments in progress with adrenalectomized-hypophysectomized dogs have revealed that prolactin can exert an anti-insulin action which is not due to the ACTH contaminant[12,23]. Likewise, heated prolactin can exert an anti-insulin action, thereby ruling out the growth hormone contaminant[12,23]. Thus, the role of prolactin, if any, in carbohydrate metabolism still awaits clarification.

SUMMARY AND CONCLUSIONS

1. An anterior pituitary factor other than ACTH exerts an anti-insulin action in the adrenalectomized dog. It is not thyrotrophin nor the gonadotrophins. 2. It can exert its action in the absence of the C-11, 17-oxycorticosteroids and sex steroids. 3. Most probably this factor is the growth hormone or a hormone intimately linked with it. The ACTH content of growth hormone preparations is not responsible for the actions in carbohydrate metabolism attributed to the growth hormone, nor are the adrenocortical steroids absolutely essential for its action(s). 4. Administered growth hormone exerts a potent anti-insulin action in hypophysectomized dogs, but concomitantly produces diabetes, insulin resistance and toxicity. 5. Administered growth hormone can be given for extended periods of time without producing diabetes, insulin resistance, and/or toxicity when given in conjunction with C-11, 17-oxycorticosteroid regimens. A normal carbohydrate metabolism is produced in hypophysectomized dogs treated with such combined hormonal regimens. 6. Thus, it appears that in physiological life, growth hormone acts in concert with the adrenocortical steroids in the endocrine control of normal carbohydrate metabolism.

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Group discussion of this paper and that by Dr. Ephraim Shorr and his associates follows after the next paper

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The Relation of Chronic Disease to Diet

A challenging problem for the nutritionist is the fact that physicians, who so often ascribe acute illness to a recent dietary mishap, have always hated to accept any theory ascribing chronic disease to bad food. Thus, the causation of scurvy was clearly and convincingly described by Bachstrom in 1743; lemon juice as a preventive and cure, with excellent resistance to storage, was recommended in Lind's treatise in 1754. A critical test was given by the British navy in 1795, the year of Lind's death, and the brilliant success led to the orders which abolished scurvy forever from British ships. Thanks to Lind's work, Nelson's sailors enjoyed unusual health during the decades when his "distant storm-tossed ships" stood between Napoleon and the conquest of the world.

In 1908 Holst and Frohlich found that the guinea pig, alone among domestic or laboratory animals, developed scurvy on diets like those of the sailors before 1800, and could be cured by lemon juice. This test animal later served to control the isolation and synthesis of ascorbic acid (Vitamin C). But all this left the medical profession cold. For a decade after Holst's work, and a century and a quarter after the Lords of the Admiralty accepted Lind's theories, the *Encyclopedia Britannica* and leading medical texts disparaged the dietary theory and spoke favorably of "infection by an unknown microbe." In 1950 a text widely used by English-speaking students of medicine stated that "young men totally deprived of Vitamin C, but leading an active life with outdoor exercise, have not developed any symptoms or signs of scurvy over prolonged periods." Thus two centuries after Bachstrom's studies and twenty years after Szent-Gyorgy identified the chemical nature of the missing substance in scorbutic diets, a distinguished internist found the theory so distasteful that he allowed himself to forget that sailors who died of scurvy had been young men getting 12 to 20 hours daily of "active outdoor exercise" on the decks and in the rigging of their ships and that lemon juice had promptly cured every symptom and sign.

The story of scurvy is now being re-enacted in the history of atherosclerosis and the effect of excessive dietary cholesterol.

Since two centuries of practical and experimental study have failed to convince some physicians that diets of salt pork, beans, and flour may be inadequate for maintaining health, it probably will take a long time to convince the profession that diets rich in eggs, butter and cream cause the disease which now kills nearly one out of every three physicians. The biologist knows that such diets are as alien to adult mammals as those which cause scurvy, beriberi, and pellagra.

The nutritionist may fail to correct this type of abnormal diet, but industry will find it profitable to have those who use these foods add sitosterols or dihydrocholesterol[1] to the diet. These substances block cholesterol absorption, and prevent both hypercholesterolemia and atherosclerosis in the experimental animal.

Thus, by a slight increase in cost of his foods, man may learn to eat cholesterol and not absorb it.

From an editorial entitled "The Reluctance of Physicians to Admit That Chronic Disease May be Due to Faulty Diet," by William Dock, M.D., in *The Journal of Clinical Nutrition,* March-April 1953.

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