EDITORIALS

THE INFLUENCE OF INSULIN ON PROTEIN METABOLISM

Since various opinions have been expressed about the part played by insulin in protein metabolism, it is fitting to review some of the literature to see how these different conclusions may be explained. Table 1 presents a summary of selected articles of which some are old and often quoted, and others permit one to think of the most recent methods and results in this field. The table indicates some of the main headings although no such simplified arrangement does justice to such a variety of experimental detail.

It is clear that the exaggerated protein metabolism of pancreatectomy or severe diabetes mellitus and the control of this accelerated protein catabolism by insulin have been consistently observed[1-5] since the epoch-making works of von Mering and Minkowski[6] and Banting and Best[7]. There is no question about the fact that, when used to replace severe insulin deficiency, insulin has a powerful protein anabolic action within certain limits. "Within limits" means that protein metabolism is restored to normal, but that (except for the transitory restoration of the protein deficit) there is no sustained anabolism above and beyond the normal level of protein balance.

In contrast to the depancreatized animal, the results in Houssay animals may be noted. The actual fasting nitrogen excretion is the same in the normal animal and in the Houssay animal which lacks both pituitary and pancreas. One would conclude from this that insulin does not influence protein metabolism in any primary or direct manner, a conclusion which would be quite at variance with the striking effect of insulin in the diabetic animal. Both phenomena force one to think of the metabolic situation in which insulin is acting. In any case, the tendency of insulin to restore the protein balance of diabetic animals to, but not beyond, the normal equilibrium has been further examined by the use of insulin in normal animals and man. It is here, i.e., in the normal animal, that some difference of opinion has arisen. Without analyzing all of the experiments, one may note certain features of the experiments listed in Table 1 under the heading, "Investigators who failed to observe protein anabolism."

In the first place, some of these experiments were conducted in fasted animals. There seems to be complete agreement that the administration of insulin does not cause demonstrable protein anabolism in the fasted animal [1, 8, 9, 10]. This is compatible with other observations on protein anabolism. Thus, Munro[11] reviews the caloric requirements for protein storage under various conditions and concludes that the addition of extra energy to an adequate diet usually leads to nitrogen retention whether this energy is provided by carbohydrate or fat. Moreover, the feeding of carbohydrate to fasting animals reduces the nitrogen output, but the feeding of fat does not have this effect until the fat stores are exhausted. If these things are so in normal animals with ample endogenous insulin, one would not expect protein anabolism to take place when insulin was added during the fasting state. Even insulin cannot make bricks without straw. These comments on protein metabolism during fasting may be concluded by noting an important difference between insulin and growth hormone. Growth hormone has a nitrogen sparing action in the fasting normal animal[12, 13]. With this effect on protein there is a mobilization of fat, which is manifested by increased ketonuria and also[14, 15] by a diminution in body fat.

Another point about these experiments (Table I, II, A) is that in some of them[9, 16, 17] one dose of regular insulin was given daily, sometimes followed by the observation of urinary nitrogen for a few hours only. It now seems, from many studies on nitrogen excretion, from studies with repeated doses of insulin or protamine insulin, and from current knowledge of the cumulative action of growth hormone[18, 19] that the conditions which lead to protein anabolism are the ones in which there

TABLE 1

Selected studies of the influence of insulin on protein metabolism

I. Pancreatectomy results in an increased catabolism of endogenous protein (increased N excretion during fasting)[6].
Insulin treatment of depancreatized animal, or of severe diabetic patient, prevents this "secondary" acceleration of protein catabolism[1–5].

II. Insulin given to normal animals

A. Investigators who failed to observe protein anabolism:
No increased growth of rabbits[16].
No effect on fasting N balance of rats[8].
No effect on growth or N excretion of normal rats, with or without control of diet[9].
No change or an increase in N excretion[17].
Increased N excretion of fasting dogs[1].
No effect on growth of rats[25–27].
No effect on protein depletion or repletion[10].

B. Investigators who concluded that insulin promotes protein anabolism:
Glucose and insulin spare more protein than glucose alone in normal subjects[20].
Insulin causes positive N balance in fed normal dogs[1].
Insulin causes nitrogen retention in normal rats, with or without constant diet[21].
Positive N balance in patients given insulin (appetite increased)[22].
Insulin reduces accumulation of blood NPN in nephrectomized dogs[23].
Liver and diaphragm incorporate more labeled amino acid under influence of insulin if glucose is present[24].

III. Relation of insulin to the action of other hormones on protein metabolism

A. Testosterone (T)
No effect of T on blood NPN in depancreatized dogs[29].
Anabolic effect of T occurs in alloxan diabetic rat[30].
Ability of T to increase arginase activity of kidney was not impaired in alloxan diabetes[31].
T causes N retention in hypophysectomized rats on constant diet[32,33].

B. Growth Hormone (GH)
Action is impaired in insulin deficiency[34].
Nitrogen retention in fasting rats[12,13].
Lability of nitrogen of different muscles varies under influence of GH or inanition[45].
Effect of GH on special tissues[46].
Part of defective growth of hypophysectomized rats was restored by forced feeding[38].
GH caused N retention in diabetic rats, but no N retention in Houssay cats[35–37].
Insulin causes growth in hypophysectomized rats[28].
Extended protein repletion in rats[10].

C. Adrenal Cortical Hormones
Effect of cortisone on protein of different tissues[47].
Insulin does not prevent the increased N excretion caused by cortisone or ACTH[40-41].
Increased insulin seemed to prevent or reduce increased N excretion in diabetics receiving ACTH[42].

D. Excess catabolism of hyperthyroidism and growth promoting action of thyroid hormone in cretinism both occur in presence of ample insulin (the thyroid is not discussed herein).

is a fairly sustained action of the anabolic influence.

The next group of experiments (Table I, II, B) provides definite evidence that in the fed animal or man, insulin tends to cause protein anabolism as measured by nitrogen balance[1, 20, 21, 22] or by other methods [23, 24]. The tendency of insulin to produce a positive nitrogen balance has not led to growth in normal animals[25–27] and with the exception of the report of Salter and Best[28] which will be discussed later, there is no evidence that insulin influences growth as shown by the tibia test. Probably the physician has seen the most striking failure of insulin to produce growth in the case of patients with islet cell adenomas. Some of these people have had hypoglycemia for years before operation; some are thin, many slightly obese; but none have ever had excessive growth of the type seen in acromegaly. Whatever the reason for this may be, these patients show us that the anabolic influence of insulin does not of itself suffice for body growth, however important it may be as a synergist to growth hormone.

It is probable that a study of the relation of insulin to the action of other hormones which promote protein anabolism is essential to an understanding of the action of insulin itself (Table I, III). In the case of testosterone, more information is required to define its relation to other anabolic agents. The evidence of Sirek and Best[29] indicates that insulin is required for the anabolic action of testosterone, since there was no alteration of the blood NPN by testosterone in depancreatized dogs deprived of insulin. The studies of Kochakian[30, 31] do not contradict this because the presence of insulin is not excluded by our present methods of producing diabetes in rats. For the moment, one must conclude that the presence of insulin, but not necessarily its increased secretion, is required for the action of testosterone on protein metabolism. In contrast to this, testosterone causes nitrogen retention in the absence of growth hormone, i.e., in the hypophysectomized animal[32, 33]. Although this is a concise statement, the biochemical sites of action of all hormones which regulate protein metabolism are quite obscure.

The relation of insulin to anterior pituitary growth hormone has been studied for years by the use of crude and later of highly purified preparations with growth-promoting activity. Thus, it has been determined that in depancreatized dogs and cats maintained on fixed doses of insulin, the action of growth hormone on nitrogen balance is present but greatly reduced[34, 35]. Nitrogen retention also takes place when growth hormone is given to alloxan diabetic rats whose available

insulin is obviously reduced[36, 37]. More recently, the effect of one hormone in the absence of the other has been examined. Milman *et al.*[35], using metabolic periods in hypophysectomized-depancreatized (Houssay) cats found that in the absence of insulin, growth hormone caused no retention of nitrogen. Since growth hormone is most accurately tested in hypophysectomized animals, this result cannot be due to the pituitary deficiency, and the essential part played by insulin in the anabolic action of growth hormone is apparent.

On the other hand, the determination of the effect of insulin on protein metabolism in the absence of growth hormone is only beginning to receive attention. The absence of growth hormone means the use of the hypophysectomized animal which, as is well known, is extremely sensitive to insulin. Nevertheless, Salter and Best[28] have described growth in hypophysectomized rats treated with protamine insulin. The tendency of hypophysectomized rats to continue growing up to 40 days of age was duly controlled. Growth was measured by body weight, body length and the tibia test, and there is no doubt about the fact that growth occurred. However, there is still doubt about the mechanism by which this growth was produced. The impaired growth after hypophysectomy is observed in the presence of ample insulin and of insulin sensitivity but on a reduced food intake. The protamine insulin which was used increased the appetite of the treated rats which were also given additional food or glucose to prevent or treat insulin reactions. Samuels *et al.*[38] restored part of the defective growth of hypophysectomized rats by forced feeding. For this reason it is uncertain whether the results of Salter and Best[28] were due to some primary action of insulin or to the secondary effect of the increased food intake.

During the past year Doctor McCann and I have done preliminary experiments related to this problem. On a constant diet of meat, the nitrogen excretion of cats was recorded. When 5 to 10 grams of glucose were added daily to the meat diet, the usual protein sparing action of carbohydrate was observed, as nitrogen retention, in the normal animals (Tables 2 and 3). *In hypophysectomized cats treated in a similar manner, there was no protein sparing effect of carbohydrate.* These experiments were designed to test the effect of the endogenous insulin which is presumably secreted in response to the added glucose and, at the same time, to avoid the hazard of insulin reaction. The results in cats differ from those in rats in which Bancroft, Geiger and Hagerty[37] found that the nitrogen sparing action of sugar was of the same magnitude in normal and in hypophysectomized animals. This indicates that one must reckon with a striking species difference in such experiments.

TABLE 2

The effect of operative procedures on pancreatic diabetes in the cat[39]

Type and No. of Cats	Urine			Liver fatty acids
	Glucose g/k/d*	Nitrogen g/k/d*	Ketones mg/k/d*	per cent
Normal (7)	0	0.6	15	5
Depancreatized (10)	3.2	1.4	133	24
Hypox-depan. (6)	0.7	0.7	8	9
Adrex-depan. (14)	0.5	0.7	10	7

* Fasting values—gm. or mg. per kilo per day.

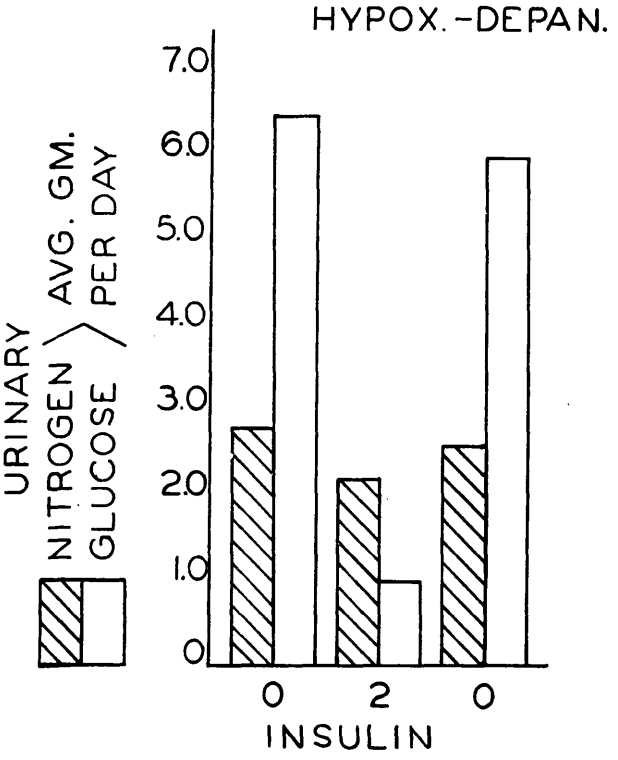

FIGURE 1. Cat 6-53. Hypophysectomized March 4; depancreatized, April 6, 1953. Diet of 50 gm. of meat and pancreatic extract (Viokase) was constant throughout the periods charted. These periods were consecutive and consisted of a control period of 5 days, a middle period of 5 days when 2 units of protamine insulin was given daily, and an after-period of 4 days without insulin. The effect of insulin on the glycosuria is obvious; the effect on the nitrogen excretion is significant. The difference between the nitrogen excretion of the second control period and the insulin period is 0.38 gm. per day. This corresponds to the average nitrogen retention observed when 5 gm. of glucose was added to the diet of the normal cat (cf. Table 3).

TABLE 3
Protein sparing action of carbohydrate in cats

Cats Type	No.	Average Urinary Nitrogen: Meat[1] only gm/day	Meat plus glucose gm/day	Average nitrogen retained gm/day
Normal	10	3.55±0.11	3.16±0.13	—0.39±0.06
Hypox.	5	2.89±0.26	2.97±0.26	+0.08±0.12

[1] The amount of meat (100 gm. daily) was constant throughout all periods.

We have tested the effect of insulin in a single Houssay animal (Figure 1). Compared to control periods before and afterward on a constant diet, insulin brought about the utilization of 5 gm. of urinary glucose. This was accompanied by a significant diminution in nitrogen excretion. If this single experiment is confirmed, the situation will be as follows. Glucose spares protein in the normal cat; glucose fails to spare protein in the hypophysectomized cat; glucose utilized by administered insulin spares protein in the Houssay animal. This means that glucose and insulin may or may not spare protein when the pituitary is absent. Such a result suggests that better methods of assay are needed.

Little is known of the relation between insulin and the adrenal cortical hormones, yet this is a large component of the subject of insulin and protein metabolism. Long and Lukens[39] showed that adrenalectomy abolished the protein catabolic response to pancreatectomy and many investigators (e.g.[40, 41]) have demonstrated the protein catabolic action of ACTH and cortisone under various conditions. However, the effect of insulin on the protein catabolic action of the adrenal cortical hormones has received less attention. Ingle *et al.*[40] and Conn *et al.*[41] found that in the rat and in man large doses of insulin which reduced the glycosuria did not control the increased nitrogen excretion produced by cortisone or ACTH. On the other hand, increased doses of insulin appeared to prevent or reduce the increased N excretion in diabetic patients who were receiving ACTH[42] but here the picture is complicated by the simultaneous relief of the complicating rheumatic disease. All these possibilities are well discussed in the study of Burns *et al.*[49] who found that cortisone did not alter the response to insulin in the fasting state but strikingly altered the glucose-insulin test.

The failure of insulin to produce growth in normal animals or in patients with islet cell tumors might be due to the antagonistic action of the adrenals. If this were so, it might explain why, in spite of these results in the normal animal, Salter and Best[28] observed growth in their hypophysectomized rats which lacked the normal degree of adrenal cortical function.

It is with an eye to the future that certain studies on protein metabolism should be particularly noted. The importance of the quantity and quality of the protein intake, the relation between caloric intake and protein storage and the need for differentiating the effects of the anabolic hormones which may be acting simultaneously are fairly well recognized. In addition, there are features of protein metabolism which may point the way to the development of better methods.

The procedures most commonly used to study protein metabolism have included the measurement of dietary, urinary and fecal nitrogen; body growth; changes in the protein or nitrogen content of the carcass; changes in the rate of accumulation of the nitrogenous constituents of the blood in nephrectomized animals. All of these record the systemic equilibrium or response and all are affected by both dietary and hormonal factors. If, in agreement with Handler[50], one calls growth hormone, testosterone, thyroxine and insulin the anabolic hormones, it is already clear that they act in different ways even if considerable synergism is involved. How are we to identify more accurately these sites of action on protein metabolism? First, we should make more use of the response of individual tissues with the hope of selecting the most significant site of action of the metabolic hormones. In 1936, Addis, Poo and Lew[43] examined the rate of protein formation in numerous tissues of the body after depletion and re-feeding. They concluded that, "each organ and tissue has its own individual characteristics with respect to the degree and rate of the rebuilding of protein when casein is given after a period of protein loss" (see Figure 2) and recorded appropriate details. Munro and Naismith[44] have made similar observations relevant to the influence of energy intake on protein metabolism, and they call attention to "the bodily distribution of changes in nitrogen balance." Geiger *et al.*[45] found no effect of insulin, growth hormone or cortisone on the gain in body weight during repletion.

This provides an interesting background to the current reports of Greenbaum and Young[46] and Scow[47]. The former[46] compared the loss of nitrogen in various tissues during inanition and the gain in tissue nitrogen during treatment with purified growth hormone. In particular, the striking lability of the nitrogen content of certain muscles and the relative stability of other

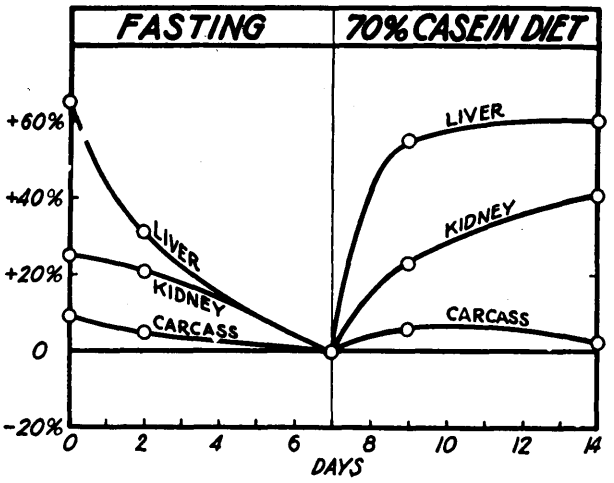

FIGURE 2. Changes in protein content from levels at 7-day fast. From: Addis, Poo and Lew: J. Biol. Chem. 116:343, 1936

muscles was noted. Scow[47] observed the effect of growth hormone on various protein fractions in the muscles of thyroidectomized and hypophysectomized rats. As an example of his results, growth hormone promoted a marked weight increase in the thigh muscle, accompanied by a significant increase in the myosin fraction. This agrees with Greenbaum and Young's[46] finding that the quadriceps was a most active and "labile" muscle in regard to changing its nitrogen content. The individual characteristics of different tissues has also been demonstrated in the response of rats to cortisone which caused a wastage of nitrogen from carcass fractions other than structural protein (i.e. collagen and elastin)[48]. The protein of the liver was increased by this so-called catabolic hormone, indicating that a re-distribution of protein may take place within the overall protein balance. The sites and nature of protein anabolism induced by testosterone have also been described[49]. In summary, if the tissues and the particular proteins which are influenced by the hormones can be identified, there should be better methods of assaying their action.

SUMMARY

Insulin promotes protein anabolism secondarily by its action on the utilization of carbohydrate in the presence of other anabolic hormones. The following facts appear to support this concept.

(a) Insulin does not cause nitrogen retention in the fasting animal (in contrast to growth hormone).

(b) The protein sparing power of carbohydrate.

(c) The quantitative relations between caloric intake and protein anabolism in normal animals.

(d) Additional insulin, administered or from a secreting islet cell tumor, does not cause growth, in spite of a definite tendency to nitrogen retention.

(e) Insulin, *as replacement therapy,* prevents or improves diabetic dwarfism and prevents the catabolic response to pancreatectomy.

(f) Since the protein catabolic response of pancreatic diabetes is abolished by removing the pituitary or adrenal glands to the same degree as when insulin is given, insulin would not appear to have a primary or direct action on protein metabolism.

(g) As noted, in all of these conditions other anabolic hormones, notably growth hormone, are present.

(h) The failure of normal growth in the hypophysectomized animal takes place in the presence of endogenous insulin which may cause added fat formation. It is in part corrected by forced feeding. Such added factors as age and possibly species which influence the degree to which hypophysectomized animals may grow, must be considered.

Possibly discrepant facts are: (1) the administration of insulin causes true growth in rats (certain questions of diet and species behavior may need elucidation) and (2) the nitrogen retaining effect of insulin in the Houssay animal (one experiment only).

In conclusion, a review of these studies on the influence of insulin in protein metabolism suggests that we should examine the effects of anabolic hormones on specific tissues, on particular proteins of those tissues and probably on the accelerated incorporation of labelled amino acids into such selected proteins in the hope of improving methods of assay which at present permit considerable discrepancies to appear.

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NUTRITIONAL ADEQUACY OF THE DIABETIC DIET

Advances in medicine have enabled the physician to reduce the mortality rate from diabetes mellitus. The introduction of insulin therapy, the understanding of fluid and electrolyte balance in the treatment of ketotic acidotic coma and the use of sulfa drugs and antibiotics were the contributing factors to this increased longevity. One of the major problems that remains is the avoidance of chronic invalidism of those whose lives have been extended. The treatment of a chronic disease should be designed to allow the individual to make his full contribution to society. The mere prolongation of life without health or happiness is short of the desired goal.

In the maintenance of good health and a sense of well-being, the *adequacy of the nutrition* of the individual is a very important factor. The term "adequate" is relative and its interpretation very variable. A diet adequate for a healthy young, vigorous adult male is excessive for a female or an elderly male. At the same time, it may be inadequate for a growing boy or in the rehabilitation convalescent period of the young adult. The problem is to define a set of nutritional requirements for the diabetic and teach the physician to calculate the diets accordingly.

A great many dietary standards have been promulgated for population groups and even for individuals. In 1940 the Food and Nutrition Board of the National Research Council accepted the responsibility for developing a dietary standard for the people of the United States. The philosophy of their recommendations was based on *allowances suitable for the achievement of good nutrition in the whole population* rather than filling the minimal needs of the average individual. These were published in 1943, and revised in 1945 and again in 1948. They are at present undergoing further revisions in certain detail.

It is universally accepted that diet therapy is the keystone to modern treatment of diabetes mellitus. The accent of the diet therapy has been on the control of one very obvious phase of the condition, that is carbohydrate utilization and prevention of hyperglycemia and glycosuria. This emphasis at times has distracted attention from the over-all nutritional adequacy of the diet. In the published literature in this field, frequent reference is made in the text of an article to the importance of nutrition. Examination of the tables and figures of diets actually prescribed not infrequently fail to substantiate the text. The statement, "If the weight is maintained, the diet is adequate in calories," is commonly quoted. An analysis of this statement proves its incompleteness. The statement should read "If the *ideal or optimum* weight is maintained, the diet is adequate in calories." Reduced caloric intakes result in adaptative mechanisms with associated lowering of metabolic requirements and slowing down of metabolic processes. Caloric equilibrium can be reached and body weight maintained at a 1200 to 1500-caloric intake for a young adult whose optimum calorie requirement may be 2600 calories. At the lower equilibrium, he is incapable of a full active, healthy life and will show easy fatigibility, decreased resistance to infection, loss of vigor, and even apathy and mental depression. At the higher level of a caloric equilibration, he can be a normal adult with a sense of well-being.

The most commonly prescribed diets for diabetic adults today (Table 1) provide approximately 1600 to 2100 calories.