Experimental Steroid Diabetes

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The list of natural and synthetic compounds which are diabetogenic is already large and continues to grow apace. Steroids of the adrenal cortex are among the several hormones which are diabetogenic when given in excess. Evidence of this was first seen in patients having adrenal hypercorticism,[1] but the relationship between adrenal cortical functions and diabetes was not appreciated prior to the classical studies of Long and Lukens[2] and of Long, Katzin and Fry.[3] In these studies it was shown that diabetes is ameliorated by removal of the adrenal cortices and exacerbated by the administration of large amounts of the 11-oxygenated steroids. In related studies[4] it was shown that the diabetogenicity of cortisone and hydrocortisone is much greater than that of 11-desoxycorticosterone.

The production of severe hyperglycemia and glycosuria in the normal rat by the injection of cortisone was reported fifteen years ago.[5] In a further study[6] steroid diabetes was induced in normal rats by the injection of large amounts of either cortisone or hydrocortisone. A comparison was made between adrenal steroid diabetes and pancreatic diabetes in the rat. Among the features of adrenal steroid diabetes are the following: (1) a tendency toward insulin resistance which becomes remarkably severe in some individual animals; (2) a severe negative nitrogen balance; (3) absence of glycosuria during fasting; and (4) reversibility of the diabetes when the administration of hormone is stopped.

The question as to whether the adrenal cortices of the normal rat have the capacity to secrete diabetogenic amounts of steroids was easily answered. Ingle et al.[7,8] demonstrated steroid diabetes in normal rats given frequent injections of corticotropin. This hormone was found to be without a diabetogenic effect in adrenalectomized rats.[9]

Steroid diabetes has been demonstrated in other rodents.[10] The cat and dog are relatively resistant to steroid diabetes, although they are much more susceptible to the diabetogenicity of growth hormone than is the rodent. In 1949 Sprague et al.[11] described steroid diabetes in a 14-year-old boy with Cushing's syndrome. The diabetes was of unusual severity and was insensitive to insulin. Hydrocortisone was excreted in the urine in considerable quantities. Hyperplastic adrenal cortices were found at autopsy. In addition to its occurrence in some patients with Cushing's syndrome, steroid diabetes is known to develop in some patients who are given large amounts of either corticotropin or hydrocortisone and chemically related compounds.[12–14] Actually when these hormonal therapeutic agents are used judiciously, the incidence of steroid diabetes among patients is very small. Impairment in glucose tolerance can be demonstrated in some patients receiving large doses of these hormones. Changes in insulin tolerance are even less frequent.[15]

RECENT STUDIES

Conditions required for the development of steroid diabetes in the rat. The smallest dose of steroid which we have found to induce temporary glycosuria in any individual rat is 3 mg. of cortisone per day and 2 mg. of hydrocortisone per day. A daily dose of 10 mg. per rat causes at least a temporary glycosuria in almost all of the animals tested. The rat is more likely to develop steroid diabetes when it is force fed, than when it eats an equivalent amount of food ad libitum. The twice-daily force-feeding of a fluid diet represents a greater dietary load per unit time than does ad libitum eating. However, normal animals can tolerate at least twice the normal caloric requirement of a high carbohydrate fluid diet without the development of alimentary glycosuria.[16]

In our initial studies on steroid diabetes the rats were maintained on a high carbohydrate diet. Subsequent studies demonstrated that rats can be made to excrete glucose on any diet representing a normal caloric intake. Figures 1 and 2 illustrate the development of glycosuria in normal rats maintained on a high fat, low carbohydrate diet and given large doses of corticotropin[17] or of cortisone acetate.[18] Steroid diabetes cannot be induced in the fasting rat by the daily injection of up to 50 mg. of either cortisone or hydrocortisone per rat per day.

Duration of steroid diabetes in the rat. There is a latent period of at least three days between the beginning

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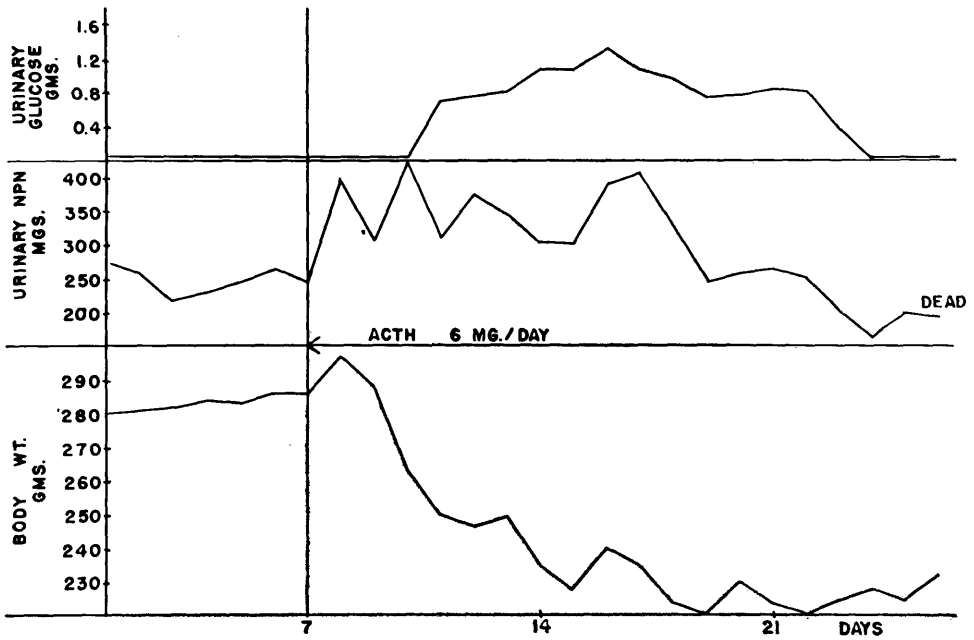

FIG. 1. Continuous injection of ACTH (Li) to a normal male rat force-fed a high fat diet.[17]

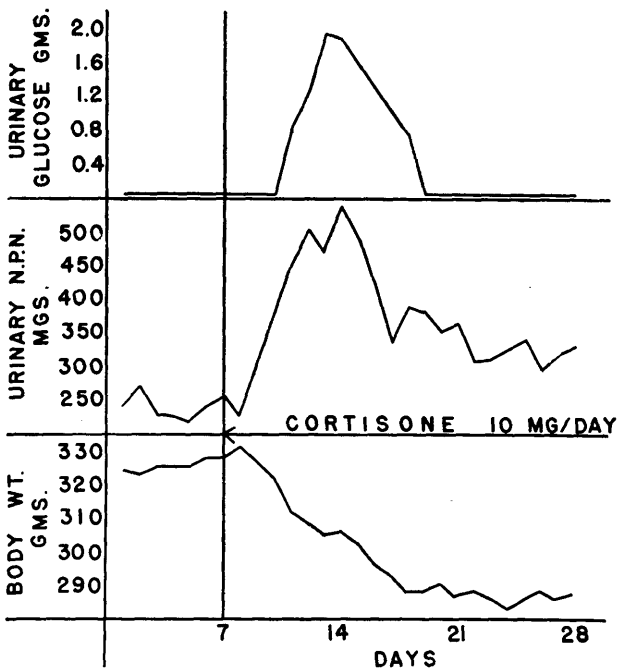

FIG. 2. Normal male rat force-fed a high fat, low carbohydrate diet.[18]

of administration of the steroid and the appearance of glycosuria. In earlier days I came to the possibly incorrect conclusion that steroid diabetes cannot be sustained in the normal rat. It is true that in most rats the diabetes may wax and wane, but with doses of 10 mg. of cortisone acetate per rat per day we have not seen the glycosuria disappear during periods up to six weeks. We have not studied such animals for longer periods due to the development of generalized infections in rats with severe hypercorticism. This complication could probably be prevented by treatment with antibiotics. In the rat the diabetes always disappears when the administration of the steroid is stopped.

Steroid diabetes in rats given cortisone and diethylstilbestrol. Estrogens are diabetogenic in the force fed rat. Cortisone and diethylstilbestrol were administered separately and in combination for fourteen days to normal rats which were force fed a medium carbohydrate diet. Doses of these drugs that failed to cause glycosuria when given separately did cause glycosuria when given simultaneously.[19] These results are illustrated in figure 3.

In similar experiments Engel et al. have shown additive diabetogenic effects of growth hormone and either corticotropin[30] or cortisone acetate.[31]

Level of liver glycogen in rats having steroid diabetes. The results of studies on levels of liver glycogen in animals having either alloxan or pancreatic diabetes have been highly variable. We find a very high level of liver glycogen in rats having steroid diabetes.[25] Male rats force fed a medium carbohydrate diet were injected with cortisone for seven days and the liver excised at the end of a 24-hour fast. The results are shown in figure 4.

Normalizing effects of adrenal steroids. Although the fasting "adrenally insufficient" animal is prone to develop hypoglycemia, the tolerance of such animals for carbohydrate can be shown to be less than normal if the

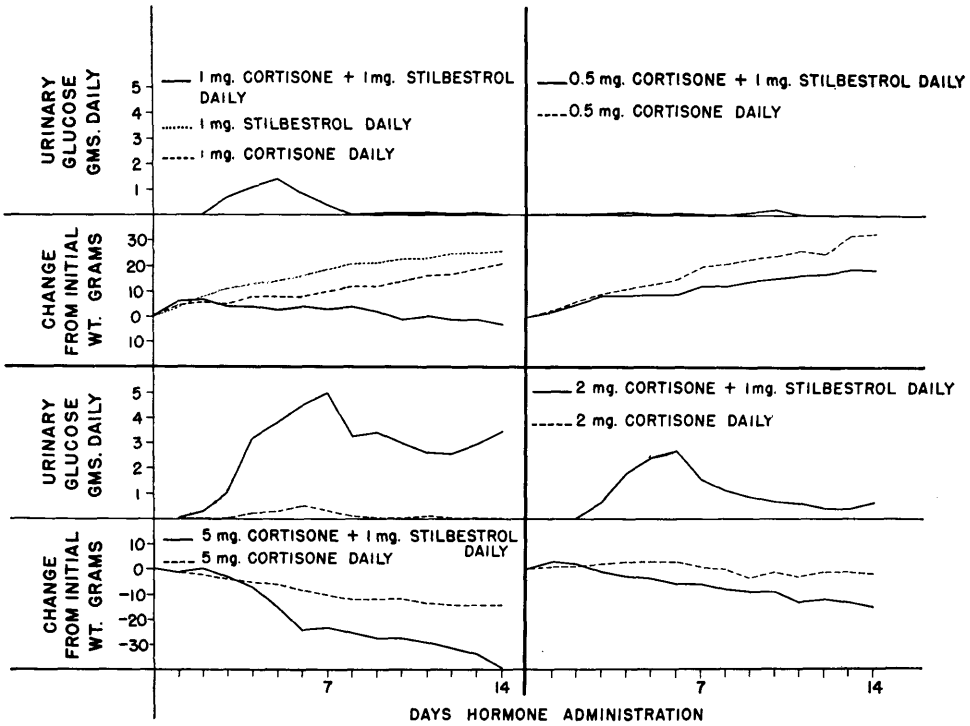

FIG. 3. Effects of diethylstilbestrol and of cortisone acetate given separately and in combination upon the glycosuria of normal force-fed rats. Averages, 6 to 12 rats per group.[19]

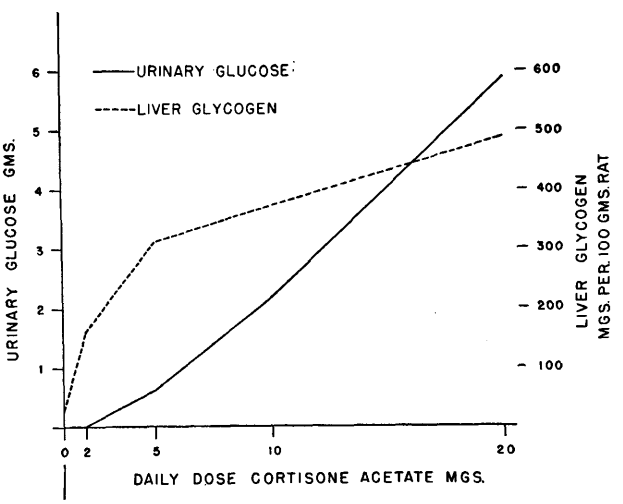

FIG. 4. Levels of urinary glucose and of liver glycogen as related to the dose of cortisone acetate. Averages, 6 to 16 rats per group.[25]

ability of the animal to assimilate an abnormally high load of carbohydrate is fully tested.[22, 23] In such cases treatment with adrenal cortical extract or steroid in physiological or normalizing amounts will improve the ability of the animal to adapt to carbohydrate excess. Only states of hypercorticism cause steroid diabetes. De Bodo and associates[24] have shown that the diabetes caused by the administration of growth hormone to hypophysectomized dogs is ameliorated by treatment with normalizing doses of adrenal steroids.

Suppression of experimental diabetes with adrenal steroids. The prolonged administration of small doses of 11-oxygenated steroids to partially depancreatized rats caused a marked decrease in the number showing glycosuria at the end of six months.[26] This protective action is associated with marked hypertrophy and hyperplasia of the pancreatic islets.

MECHANISMS OF STEROID DIABETES

Gluconeogenesis. The well-known effect of the 11-oxygenated adrenal steroids in stimulating gluconeogenesis from noncarbohydrate sources is an important factor in causing steroid diabetes. Some investigators believe that the accelerated formation of carbohydrate is solely responsible for steroid diabetes. I do not believe that an increase in gluconeogenesis can account for all of the glucose wasted during the diabetic state. Welt et al.[27] gave continuous intravenous infusions of solutions of C^{14} glucose into anesthetized fasted rats until constant levels of specific activity of urinary glucose were obtained in normal and cortisone-treated rats. From the specific activities of injected and excreted glucose and the known rate of injection, the rate of gluconeogenesis from sources not derived from the infused glucose was calculated. Rats having steroid diabetes induced by cortisone showed an approximately sevenfold increase over normal in the rate of gluconeogenesis. The rate of oxidation of glu-

cose to carbon dioxide did not appear to be significantly affected by treatment with cortisone. However, just prior to the experiment the magnitude of the glycosuria of the active fed animals represented an average of 262 mg. of glucose per rat per hour which is too great to be accounted for on the basis of the calculated rate of glucose production of 113 to 133 mg. per rat per hour. Values for glucose excretion up to 540 mg. per rat per hour have been observed[6] in steroid diabetic animals fed a high carbohydrate diet. On the basis of simultaneous nitrogen excretion data this degree of glycosuria was too great to be attributed solely to gluconeogenesis from protein. When these data are considered together with the finding that normal active rats can be adapted to utilize as much as 1,000 mg. of glucose per hour, it seems plausible that in the fed active rats having steroid diabetes there is contribution to the glycosuria from impairment in utilization of carbohydrate.

The evidence[27] that the rate of conversion of protein to carbohydrate is greater in steroid diabetes than in alloxan diabetes should be critically re-examined. Our rats having diabetes caused by cortisone were studied after the diabetes had existed for only a few days. They were still well nourished, and nitrogen loss had just reached its peak. The rats treated with alloxan had been diabetic for several weeks and were somewhat protein depleted although still vigorous. It is known that rats with steroid diabetes tend to re-establish nitrogen balance, or at least the rate of nitrogen loss declines. We have unpublished data to show that when the alloxan diabetic rat is treated with insulin until its proteins are repleted there is much greater gluconeogenesis from protein when insulin is withdrawn.

Inhibition of carbohydrate utilization. In addition to the failure of the known changes in gluconeogenesis to account for all of the glucose wasted into the urine in steroid diabetes, there are several lines of evidence that the 11-oxygenated steroids inhibit some phase of carbohydrate utilization. The studies of Price et al.[28] have shown that adrenal cortical extract can modify the hexokinase reaction by intensifying the inhibitory effect of anterior pituitary extract upon the action of insulin. An action at this level would not explain all of the effects of adrenal steroids upon carbohydrate metabolism, for these hormones act in the absence of the pituitary hormones and in the absence of insulin. There are other studies contributed to and reviewed by Bacila and Barron[29] showing that the metabolism of isolated tissues, especially anaerobic glycolysis, is modified by the adrenal steroids.

A decrease in respiratory quotient following the administration of adrenal steroids to patients with Addison's disease[30] may be due to suppression of carbohydrate utilization, but such effects have been infrequently reported. Boutwell and Chang[31] studied the utilization of radioactive glucose in normal and cortisone-treated mice. The amount of glucose utilized by the mice within four to six hours following the injection of cortisone was 65 per cent of normal. The reduction of glucose utilization was attributed to a depression in glucose oxidation as well as to the quantity of glucose lost to other metabolic pools.

Frawley[32] has noted an elevation of pyruvic acid without accompanying changes in glucose tolerance in patients with Cushing's syndrome and in patients receiving prolonged corticotropin or 11-oxygenated therapy.

Since the liver is the prinicipal site of gluconeogenesis we have studied the effect of cortisone, hydrocortisone, and adrenal cortical extract upon the glucose tolerance of the eviscerate rat.[33] Adrenal cortical extract caused a significant elevation of blood glucose above the average value for control animals during a period of 24 hours, but the two steroids were relatively ineffective. When large doses of either cortisone or hydrocortisone are given to the adrenalectomized-eviscerate rat without insulin there is suppression of glucose tolerance.

COMMENT

Steroid diabetes apparently involves both overproduction and under-utilization of carbohydrate. How are these effects related? Is one secondary to the other, or are both effects secondary to a more basic action? There is no apparent reason why acceleration of gluconeogenesis would cause suppression of carbohydrate utilization, although this order of causal relationship cannot be excluded. We[6, 35] have tested the possibility that control of steroid-induced glycosuria by insulin will suppress the accompanying rise in urinary nonprotein nitrogen. The reduction of glycosuria during insulin therapy did not suppress the nitrogen loss. Although very large doses of steroid cause insulin resistance, something more than inhibition of insulin action is involved since the diabetogenicity of these steroids is manifest in the absence of insulin.

Since the secretory activity of the adrenal cortices is increased during severe stress it has been imagined that any severe nonspecific stress should cause exacerbation of a diabetic state. Insofar as this problem has been studied there is little supporting evidence. Some stressors such as aspirin,[36] cold,[37] exercise,[38] and injections of dilute formaldehyde[39] cause a decrease in the glycosuria of diabetic rats. Infections may cause insulin resistance in diabetic patients,[40] and ethylenediamine causes exacerbation of the diabetes of partially depancreatized rats.[41] Some of our experiments[42–44] can be interpreted as evidence

that activation of the adrenal cortices during stress serves to meet an increased need for cortical steroids and does not cause hypercorticism.

The question as to whether the steroids of the adrenal cortex play an active etiologic role in diabetes mellitus has not been answered to the satisfaction of all clinical and laboratory investigators in the field. It is my opinion that the question will probably be answered in the negative for the following reasons: (1) There is little evidence of hypercorticism among patients with diabetes mellitus; (2) steroid diabetes is rare among the large population of patients now treated with larger than physiological doses of adrenal steroids or corticotropin; (3) steroid diabetes does not simulate diabetes mellitus in several important respects; and (4) steroid diabetes is reversible, i.e., it disappears when treatment with exogenous steroid or corticotropin is withdrawn.

SUMMARIO IN INTERLINGUA

Diabete Steroide Experimental

Diabete steroide involve apparentemente (1) hyperproduction e (2) hypoutilisation de hydratos de carbon. Que es le relation de iste effectos? Es le un secundari al altere, o es ambes secundari a un action plus fundamental? Nos vide nulle ration proque le acceleration del gluconeogenese causarea un suppression del utilisation de hydratos de carbon, sed il non es possibile excluder categoricamente un tal nexo causal. Nos ha studiate le possibilitate[6, 35] que le controlo insulinic de glycosuria a induction steroide supprime le accompaniante augmento del nonproteinic nitrogeno urinari. Le reduction del glycosuria durante le therapia a insulina non supprimeva le perdita de nitrogeno. Ben que grandissime doses steroide causa un resistentia a insulina, un factor in ultra del inhibition del action de insulina es involvite in iste situation, proque le diabetogenicitate de iste steroides es manifeste in le absentia de insulina.

Proque le activitate secretori del cortices adrenal es augmentate sub conditiones de sever stress, on ha speculate que omne nonspecific stress deberea causar un exacerbation del stato diabetic. In tanto que iste problema ha essite studiate, il non existe multe datos a supportar ille speculation. Certe stressantes—per exemplo aspirina,[36] rheuma,[37] exercitio,[38] e injectiones de dilutiones de formaldehydo—causa un reduction del glycosuria de rattos diabetic. Infectiones pote causar resistentia a insulina in patientes diabetic,[40] e ethylenediamina causa un exacerbation del diabete de partialmente pancreatectomisate rattos.[41] Certes inter nostre experimentos[42–44] pote esser interpretate como prova que le activation del cortices adrenal sub conditiones de stress servi a satisfacer le augmentate requirimentos de steroides cortical e non produce hypercorticismo.

Le question de saper si le steroides del cortice adrenal ha un active rolo etiologic in diabete mellite ha non ancora recipite un responsa que satisface omne le investigatores clinic e laboratorial in le campo. In mi opinion il es probabile que le responsa va esser negative. Mi rationes es le sequentes: (1) Il non ha multe datos indicante le presentia de hypercorticismo in patientes con diabete mellite. (2) Diabete steroide es rar inter le numerose patientes qui es hodie tractate con doses plus que physiologic de steroides adrenal o de corticotropina. (3) Diabete steroide non simula diabete mellite in certe aspectos importante. E (4) diabete steroide es reversibile, i.e., illo dispare quando le tractamento con steroide exogene o con corticotropina es supprimite.

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DISCUSSION

JOSEPH W. JAILER, M.D., (*New York*): Dr. Ingle will be the first to admit that we must not blindly fall into the trap of transferring data obtained in one species to another. I should like to discuss superficially, at least, what is known of the role of adrenal steroids in diabetes mellitus in man. The steroids which have been commonly used, of course, have been cortisone, hydrocortisone, and prednisone.

We do know, for example, that diabetes exists in hyperadrenalism and that 85 per cent of patients with Cushing's syndrome have at least decreased glucose tolerance. However, only about 25 per cent of patients with Cushing's syndrome have overt diabetes. When these patients are treated, the glucose tolerance may revert to normal in some cases but not in others, and those patients with overt diabetes, who may need some steroid replacement therapy, still may require insulin. Of course, the insulin requirement is greatly decreased. Consequently, one may readily conclude that the steroids play an important role in the diabetes of Cushing's syndrome.

Another interesting phenomenon in which the steroids may play a part in changing the course of diabetes is in pregnancy. As you know, many patients with diabetes show an exacerbation of their disease during pregnancy. Others have been known to develop diabetes during the course of pregnancy. There is circumstantial evidence that these manifestations may be due to increased corticoid secretion from the adrenals and perhaps even from the placenta. Increased urinary and plasma corticoids have been found during pregnancy, as determined by various methods. The adrenals also show an exaggerated response to ACTH during pregnancy, as determined by the response of plasma corticoids. This is in contrast to the normal. In addition, we have studied two pregnant Addisonian patients and have found a rise in plasma corticoids during pregnancy. That this rise is not due to the adrenals has been shown by the administration of ACTH, which causes no further rise in the plasma corticoids.

There is one more point I should like to make, and that concerns the role of adrenal steroids in diabetic acidosis or in coma. MacArthur and her collaborators have found excessive amounts of corticoids in the urine of patients in diabetic coma or severe acidosis, and we have had the experience of finding elevated plasma corticoid levels in just such patients. This might possibly explain the phenomenon of insulin resistance in these patients at that time. That this is in all probability the effect and not the cause is shown by the following data. When the blood sugar is brought down to normal and the acidosis corrected, the plasma corticoids are normal. In addition, MacArthur had withheld insulin from such patients and has shown that the development of acidosis precedes the increase in urinary corticoids. Consequently, one must conclude that acidosis is probably a stress which activates the pituitary-adrenal system and results in increased adrenocortical secretion.

The Influence of Heredity

The interest in hereditary bulimia which began with Danforth's work on yellow mice in 1927 has greatly increased with new work on other mammals.[1]

While studies of heredity in human obesity cannot be pursued under as rigorous conditions as in laboratory animals, there are a number of careful projects which reinforce the thesis that the constitution or the physical characteristics (shape and size) of the body are inherited but the amount of adipose tissue is not. The more convincing of these human studies are on identical (monozygotic) twins, because it is believed that such pairs are identical for all body traits. If there is a bodyweight variation, it is presumably due to environmental, including psychological, factors. It was, in fact, found by von Verschuer in 1927 and Newman et al. in 1937 that the weight of identical twins varied more significantly than any other anthropologic measurements.[2, 3]

The differences in weight tended to be two to three times as great as the other trait variations. This was especially true for identical twins living apart under dissimilar conditions.

So again we find that the evidence from human genetics compels us to examine in closer detail the nature of environmental factors influencing appetite and habits of eating.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "The Psychology of Appetite" by Henry W. Brosin, M.D., p. 77.

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