Influence of Physiologic Fluctuations in Plasma Growth Hormone on Glucose Tolerance

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SUMMARY

In oral glucose tolerance tests (GTT) performed three, four, or six hours after a previous GTT, six hours after a combined protein-glucose tolerance test or two and one-half hours after intravenous insulin, impairment in tolerance could be closely correlated with the magnitude of the growth hormone secretory response in the previous procedure. These observations support the physiologic role of growth hormone in determining glucose tolerance.

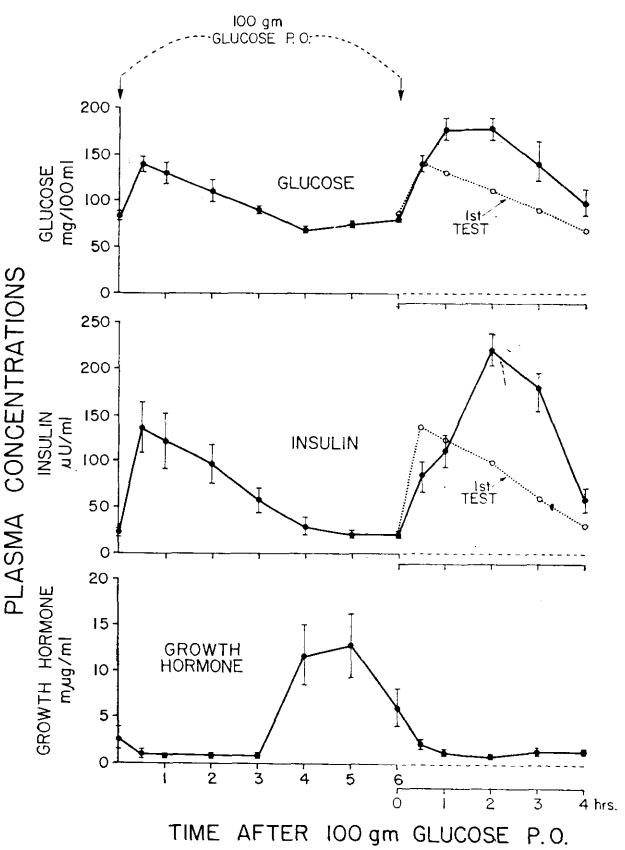
Impairment in glucose tolerance was generally associated with an augmented integrated plasma insulin response and improvement in glucose tolerance was frequently seen in association with a lesser plasma insulin response. These observations support the view that plasma insulin follows blood glucose but that the rate of glucose disposal is determined by factors other than the level of plasma insulin alone. DIABETES *18*:402-08, June, 1969.

Although the deleterious effect of excess growth hormone on glucose tolerance has been appreciated since the early work of Houssay, Evans, Young and their collaborators, and a relatively high incidence of diabetes mellitus in acromegalic subjects is generally recognized, the influence of physiologic fluctuations in plasma growth hormone on glucose tolerance in man has not been established.

In an earlier study[1] it was shown that hypoglycemia provides a potent stimulus to growth hormone secretion and, furthermore, that a rapidly falling blood sugar, even without frank hypoglycemia, is also followed by a rise in plasma growth hormone,[2] a phenomenon that may account for the rebound rise in plasma growth hormone late during an oral glucose tolerance test.[2,3] It was suggested[1,4] that the effect of hypoglycemia on growth hormone secretion[1] might contribute to the Somoygi effect.[5] In a recent study, Mintz et al.[6] have come to a similar conclusion.

In the present study the influence of physiologic fluctuations in plasma growth hormone has been evaluated by performing glucose tolerance tests at various in-

FIG. 1. **Plasma glucose, insulin, and growth hormone concentrations during oral glucose tolerance tests carried out at about 8:30 a.m. and again six hours later.**



1a. **Six nonobese and one moderately obese (24 per cent overweight) nondiabetic subjects showing a peak growth hormone concentration of at least 10 mμg./ml. at the fourth or fifth hour in the first test. The vertical bars represent ± 1 S.E.M.**

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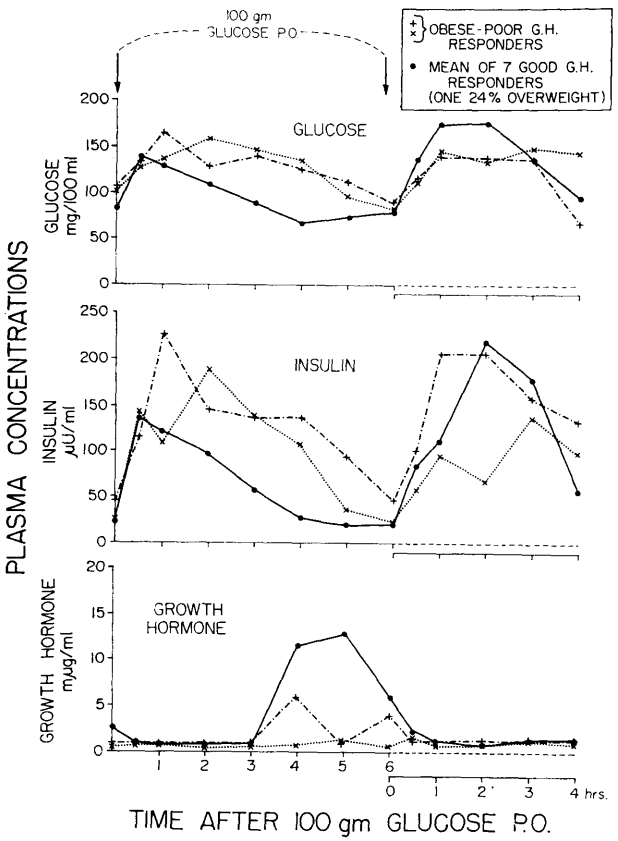
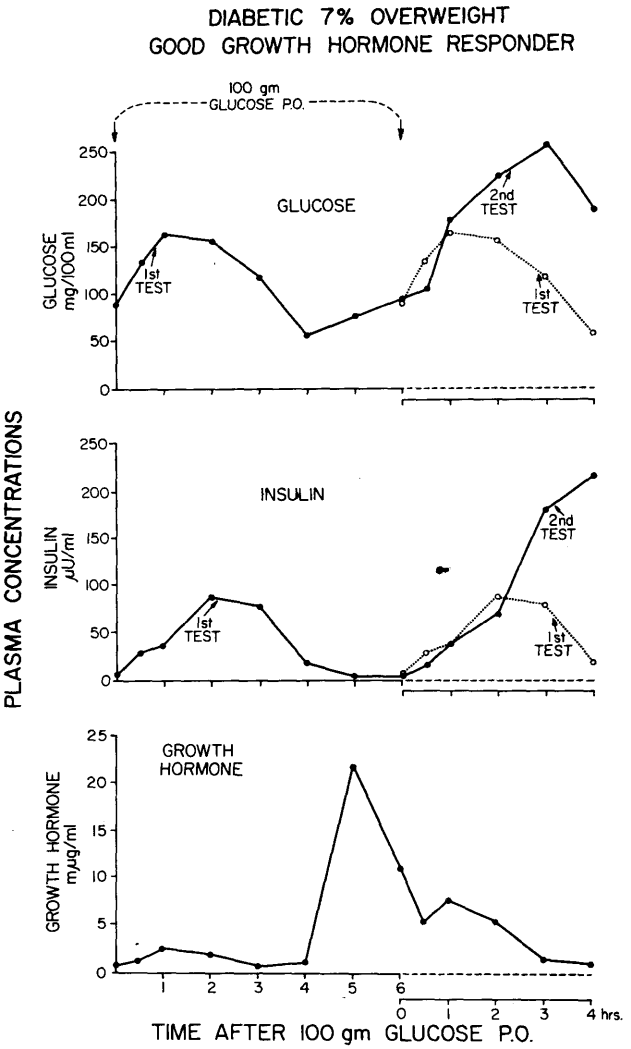


1b. Two obese subjects showing peak growth hormone responses not exceeding 6 mμg./ml. during the first test. The mean curves of figure 1a are reproduced for comparison.



1c. Nonobese mild diabetic subject. Although in this study the highest plasma glucose concentration during the first test was only 163 mg./100 ml. frankly diabetic glucose tolerance tests had been obtained on several previous occasions.

tervals after procedures designed to alter the concentration of plasma growth hormone were carried out. In the selection of these procedures we were guided by the knowledge that it takes about two hours following the exogenous administration of growth hormone before impairment of glucose tolerance is evident.[7]

METHODS

Plasma insulin and growth hormone concentrations were determined by radioimmunoassay.[8,9] The methods previously described were modified in that talc tablets were used to effect separation of antibody-bound and free hormone[10] and I-125-labeled hormones were used as tracers.[11] Plasma glucose was measured by the method of Hoffman[12] as adapted for use in the AutoAnalyzer.

Following an overnight fast of fourteen hours, 100 gm. oral glucose tolerance tests were carried out starting at about 8:30 a.m. Tests were repeated three, four, or six hours later. In one group of eight subjects, 100 gm. oral glucose tolerance tests were performed six hours after a combined feeding of 100 gm. glucose and 60 gm. protein in the form of broiled beef. In other experiments oral glucose tolerance tests were performed two and one-half hours after initiation of an intravenous insulin tolerance test (0.1 U./kg.). Subjects who had peak concentrations of plasma growth hormone equal to or greater than 10 mμg./ml., during the first glucose tolerance test or during the insulin tolerance test are described as "good growth hormone responders," those exhibiting peak plasma growth hormone concentrations less than 6 mμg./ml. as "poor growth hor-

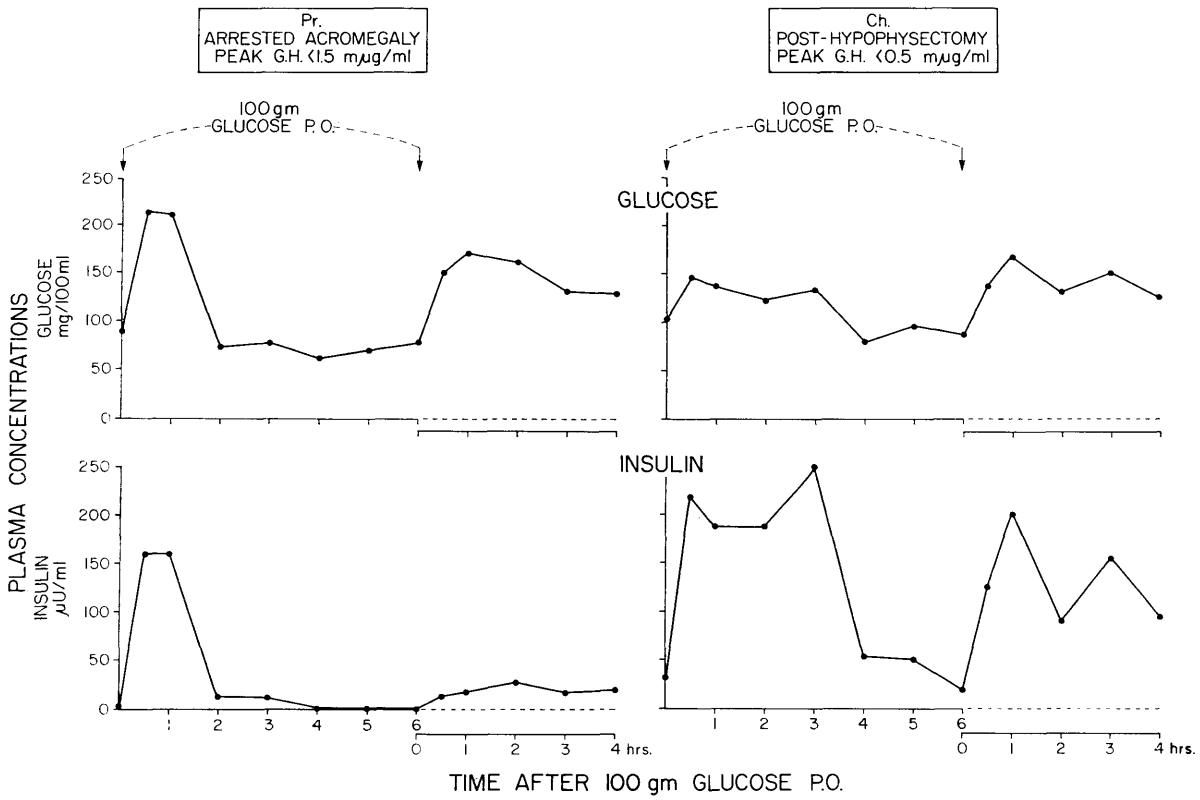


FIG. 2. Conditions as in figure 1 in two patients with consistently absent growth hormone response to provocative stimuli.

mone responders."

Two patients with absent growth hormone responses to provocative stimuli were studied. One had been subjected to surgical hypophysectomy for a chromophobe adenoma in 1954 and has since been on adequate replacement therapy with desiccated thyroid and corticosteroids. The second patient showed arrested acromegaly after a well-documented episode of pituitary apoplexy in December 1963. In earlier studies[13] he had failed to show adequate growth hormone responses to hypoglycemia but there was never any suggestion of either thyroidal or adrenal cortical insufficiency and he required no therapy with thyroidal or steroidal hormones; in 1966, PBI was 5.6 μg./100 ml. and plasma cortisol 18 μg./100 ml.

RESULTS

When glucose tolerance tests were repeated six hours following the morning test a significant worsening of tolerance was exhibited by all subjects (seven nondiabetic and one diabetic) who were good growth hormone responders (figure 1a, c), but two obese poor growth hormone responders showed no impairment of glucose tolerance in the repeat test (figure 1b). In all

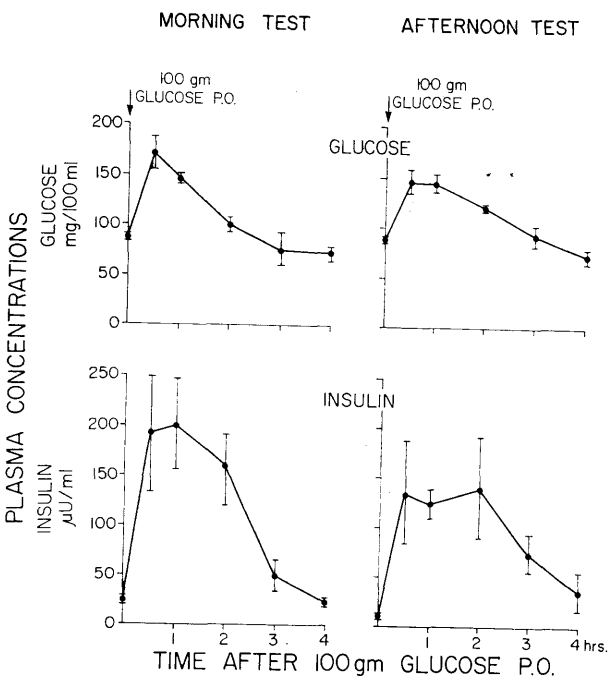


FIG. 3. Plasma glucose and insulin concentrations during oral glucose tolerance tests performed in the fasting state at 8:30 a.m. after a fourteen-hour fast (left) and on another day at 1:30 p.m. after a fourteen-hour fast (right).

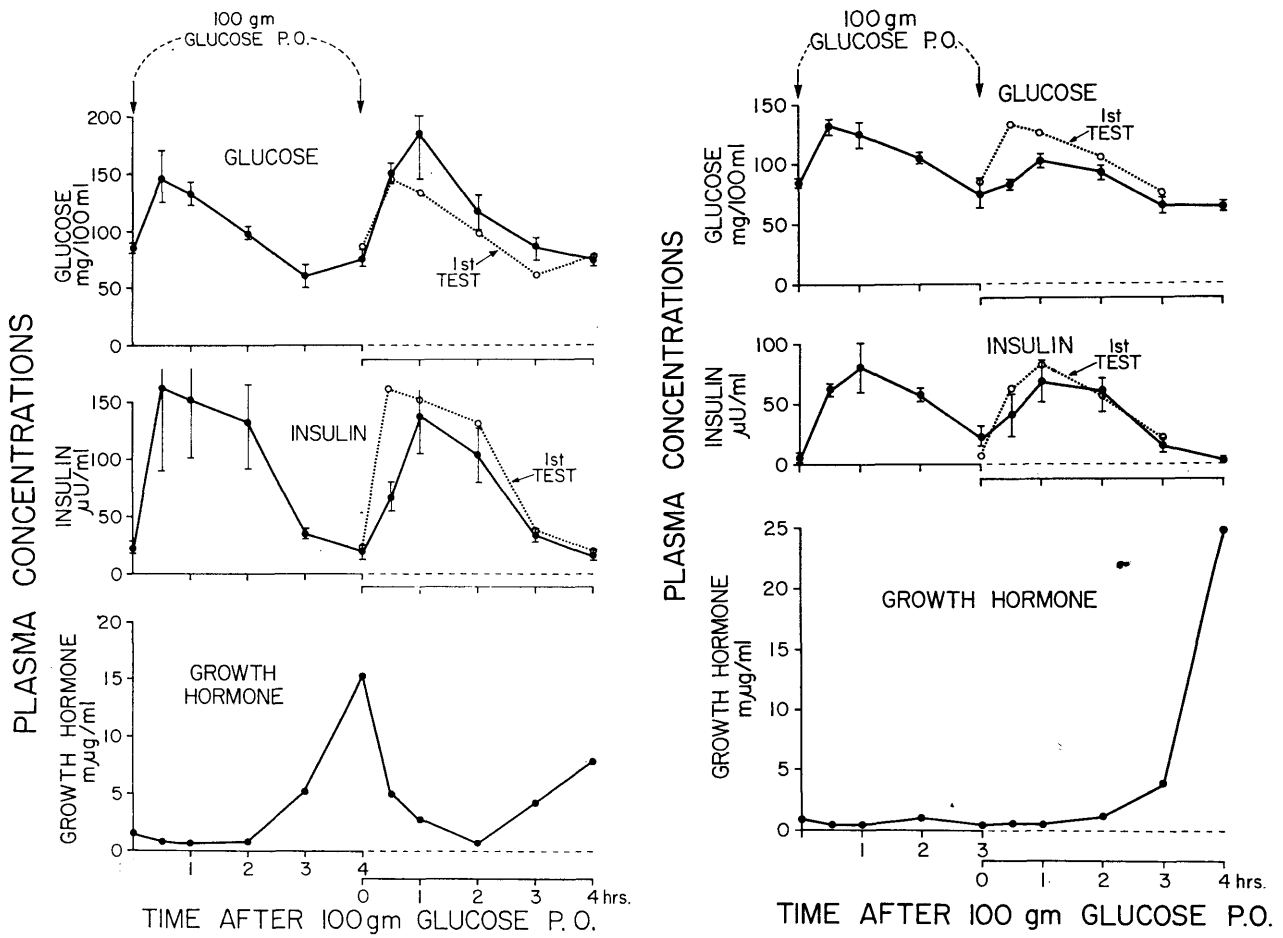


FIG. 4. Plasma glucose, insulin and growth hormone concentrations during oral glucose tolerance tests carried out at about 8:30 a.m. and again (a, left) four hours later (three subjects) or (b, right) three hours later (three subjects).

ten subjects the initial rise in plasma insulin was delayed in the second test but, in the eight good responders showing impaired glucose tolerance, the total integrated area under the plasma insulin curve was greater in the second test than in the first (figure 1). Plasma growth hormone concentrations had not risen by four hours after the second administration of glucose even in subjects showing a rise during the first test.

In the hypophysectomized subject and in the arrested acromegalic patient, who both showed very low plasma growth hormone levels (less than 0.5 mμg./ml. and 1.5 mμg./ml. respectively) during the first glucose tolerance test, there was no significant impairment of glucose tolerance in the test repeated at six hours (figure 2). The high glucose curve in the arrested acromegalic during the first test and anomalously high plasma insulin curves in the hypophysectomized subject were unexpected and are not readily explained.

In control experiments in three subjects, glucose tolerance tests performed at about 1:30 p.m. after a fourteen-hour fast (subjects having been fed just before midnight) revealed a lower integrated plasma glucose curve than on a morning test performed on another day so that the differences described above could not be attributed to diurnal variability (figure 3).

When the second glucose load was administered four hours after the first test (coincident with the time of the peak growth hormone response) glucose tolerance was only slightly impaired and there was no augmentation of insulin secretion (figure 4a).

When the repeat oral glucose tolerance test was started three hours after the first, there was an *improvement* in tolerance in spite of a delay of the initial rise in the plasma insulin concentration and a smaller total integrated insulin-secretory response (figure 4b).

In glucose tolerance tests performed after insulin-

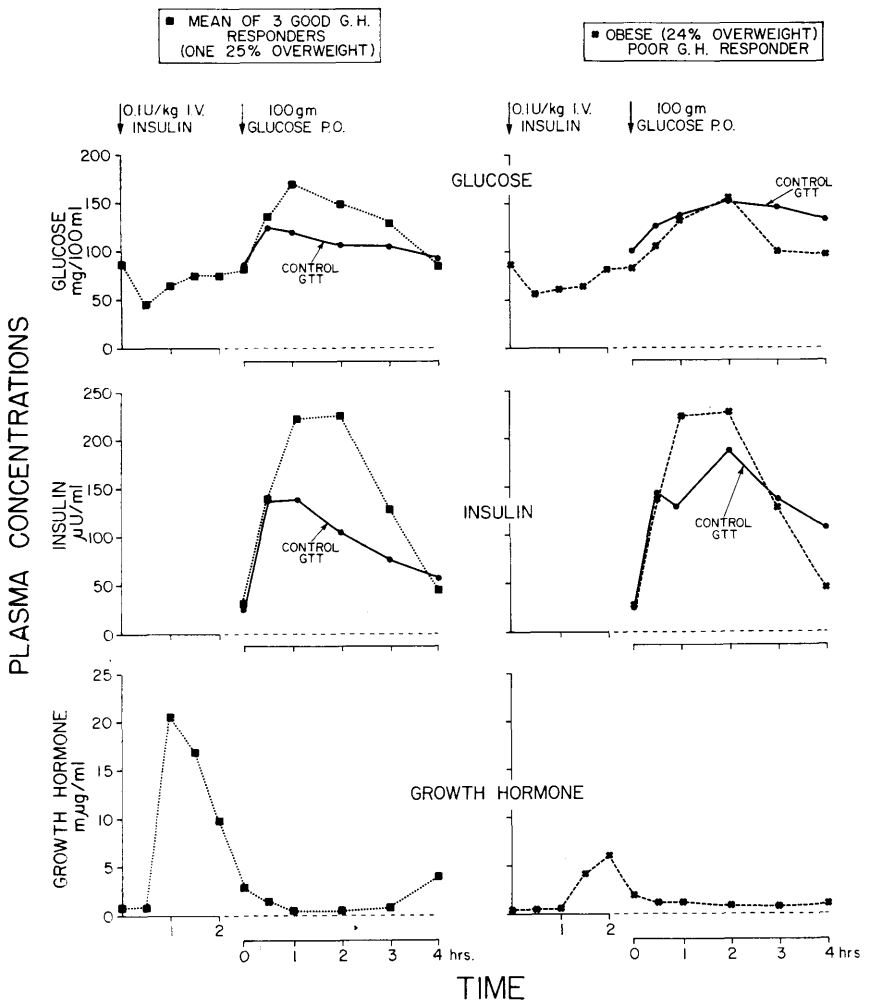


FIG. 5. Plasma glucose and growth hormone concentrations during insulin tolerance test and plasma glucose, insulin and growth hormone concentrations during subsequent glucose tolerance tests in three good growth hormone responders and in one poor responder (peak growth hormone concentration was 6.2 mμg./ml. during hypoglycemia). Curves marked "control GTT" were obtained in the same subjects on another day in the fasting state without a preceding injection of insulin.

induced hypoglycemia, impaired glucose tolerance associated with rather marked hyperinsulinism was observed in three good growth hormone responders but glucose tolerance was not diminished in one poor growth hormone responder (figure 5). There was no delay in the initial insulin-secretory response as compared to control tests performed on another day in the same individuals.

In six subjects given a combined feeding of glucose and protein, the peak growth hormone response averaged only about one half the level seen after glucose alone but four of the subjects showed peak levels above 6.5 mμg./ml. and in the remaining two subjects, peak levels of 4.3 mμg./ml. and 5.0 mμg./ml. respectively were observed (figure 6). Slight impairment of glucose tolerance observed in repeat tests was associated with a significantly greater integrated plasma insulin response compared to control tests performed on another day. Two subjects showing negligible increases in plasma growth hormone during the first test showed no impairment of glucose tolerance but rather somewhat better glucose tolerance and lower plasma insulin curves than were obtained in control studies (figure 6). These subjects are good responders in straight glucose tolerance tests (see four-hour growth hormone level in second test, figure 6).

DISCUSSION

The experiments described herein were designed to test the relationship between physiologically induced enhancement of growth hormone secretion and the state of glucose tolerance shortly afterwards. It had previously been observed that obese patients generally show obtunded growth hormone-secretory responses to such stimuli as fasting, exercise, and the fall in blood sugar late during the course of a glucose tolerance test.[2] In the present study, relatively poor responses were again observed in several obese patients and in these, no diminu-

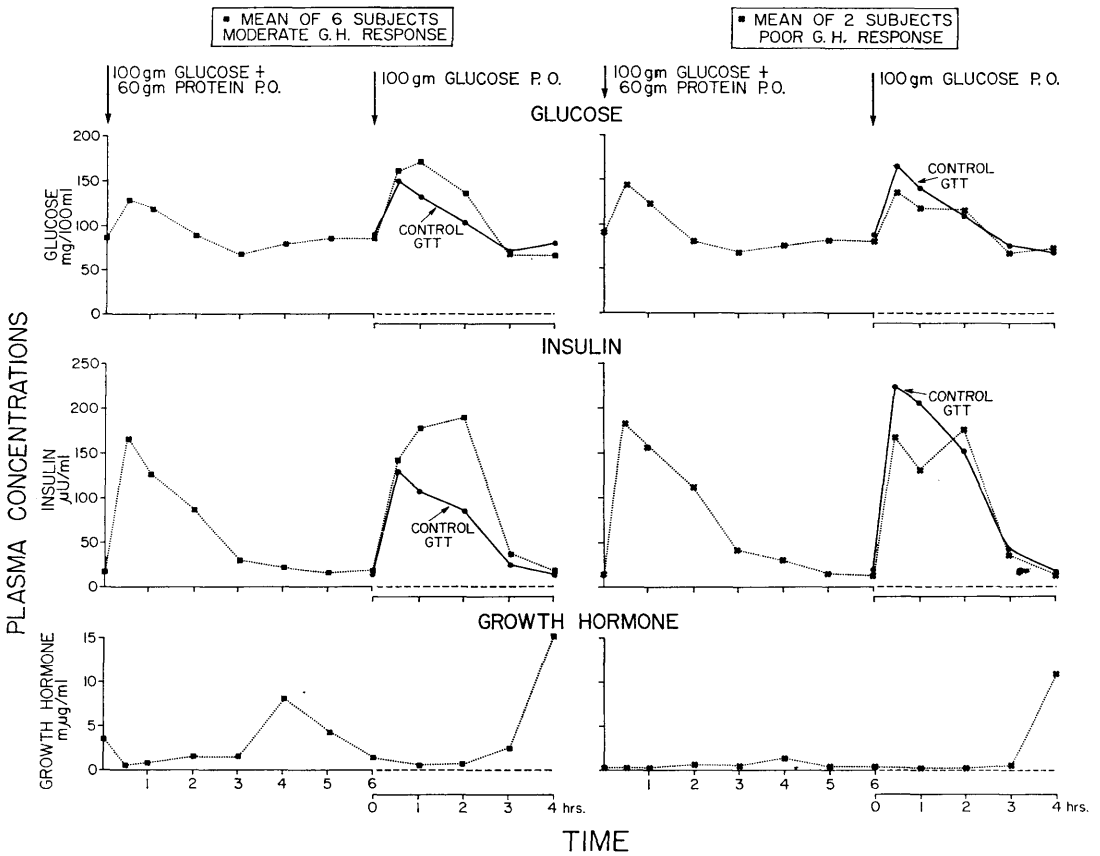


FIG. 6. Plasma glucose, insulin and growth hormone concentrations during a combined glucose-protein tolerance test carried out at about 8:30 a.m. and during a glucose tolerance test performed six hours later in six subjects showing peak growth hormone levels of at least 4.3 mμg./ml. in the first test (left) and in two subjects showing virtually no increase in plasma hormone during the first test (right). Three of the six moderate growth hormone responders shown on the left were 19 to 35 per cent overweight. The poor growth hormone responders shown on the right were nonobese (< 10 per cent overweight).

tion in glucose tolerance was observed in tests performed after hypoglycemia or after a previous glucose feeding. Obese patients showing a good growth hormone response behaved like nonobese patients in showing impairment of glucose tolerance two to three hours after the rise in plasma growth hormone concentration.

Tests of glucose tolerance six hours after a preliminary feeding of glucose plus protein were undertaken because of the finding of others[14,15] that the combined feeding is associated with a markedly enhanced insulin secretion and a significantly lower and flatter glucose curve compared to that obtained after carbohydrate alone. Presumably as a consequence of the lesser fall in blood sugar, the late rise in plasma growth hormone is markedly blunted. In the present study only a moderate reduction in the four-hour growth hormone level was observed in six patients and this was associated with a lesser impairment in the glucose tolerance tested six hours after the combined feeding. In two patients, however, the rise in plasma growth hormone at four hours was virtually abolished and glucose tolerance was not impaired.

In all types of experiments there was an almost constant association of good growth hormone responses with subsequent impairment of glucose tolerance and of poor growth hormone responses with subsequent unimpaired glucose tolerance. Furthermore, in almost all experiments in which an anticipated growth hormone response was obtunded or pre-empted, glucose tolerance in the second test was usually improved, even though the integrated insulin-secretory response was diminished. For the present, these results can be considered highly suggestive of a cause and effect relationship which, however, remains to be conclusively established. Counter-regulatory mechanisms following hypoglycemia and a falling blood sugar involve so many other hormonal

responses that growth hormone cannot be unequivocally indicted as the sole culprit in the later impairment of glucose tolerance. Although the results in the two hypopituitary subjects (in whom neither thyroid deficiency nor adrenal cortical insufficiency could be considered contributory) offer further support for the role of growth hormone in this phenomenon, the lack of other pituitary factors cannot be excluded from consideration and the anomalous plasma insulin and glucose curves observed in these patients are a bit disconcerting. It is therefore desirable to consider that a more crucial test of the relationship of endogenous growth hormone to glucose tolerance would be afforded by similar studies in patients with proved isolated growth hormone deficiency. We have not had the opportunity to study such subjects.

There are several incidental observations of interest that deserve comment. A delayed insulin secretory response was uniformly observed during the second glucose tolerance test performed three, four or six hours after the first test. This delay did not produce impairment of glucose tolerance in the three-hour repeat test; indeed, glucose tolerance was significantly improved in spite of a slightly lower total integrated plasma insulin concentration. This combination of events would seem to reflect improvement in tissue sensitivity induced by the first test. The association of improved glucose tolerance and a smaller insulin response was observed also in the comparison of control tests performed at 8:30 a.m. and 1:30 p.m. without previous glucose administration. The marked impairment of glucose tolerance in the six-hour repeat test was associated with a significantly greater integrated insulin concentration, and similar observations were made following the combined glucose-protein feedings and following hypoglycemia. Only in the experiments involving glucose tolerance tests four hours apart was there any suggestion of an association of lower plasma insulin concentrations with higher glucose concentrations but the overlap observed was such that the results were without statistical significance.

We feel that these observations, demonstrating that enhanced glucose tolerance can coexist with a lessened output of insulin and vice versa in one and the same individual must force a re-examination of our views regarding the relationship between blood glucose and plasma insulin. In short, the indications are that the insulin-secretory response to the level of blood glucose is more impressive than the blood glucose response to the level of plasma insulin in a given individual studied under varying physiologic conditions. Excluding the extremes of severe insulin deficiency or marked insulin excesses, the plasma insulin level may not be the most important determinant in the disposition of blood glucose. The results of the present study offer support to the thesis that physiologic changes in plasma growth hormone are also of importance.

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