# Decreased Response to Intra-arterial Insulin in Acromegaly

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The direct peripheral action of insulin and its fixation in healthy tissues has been demonstrated in both animals[1] and man,[2-4] after injection of the hormone into the brachial or femoral artery. The intra-arterial administration of insulin results in a fall in venous glucose concentration which is much greater in the blood draining the injected than the contralateral limb. An increase in the arteriovenous glucose difference is apparent in the injected limb within five minutes and persists for over an hour. Such effects were observed in the absence of any significant change in the blood flow through skin or muscle,[4] and hence indicate that a proportion of the insulin administered was immediately fixed in the tissues of the injected arm. The changes in arteriovenous glucose concentration can therefore be used as a measure of the effect of insulin on peripheral glucose uptake in the living subject in various conditions.

In the present study, peripheral responses to insulin in patients with acromegaly and in subjects after an infusion of human growth hormone were compared with those previously observed in healthy adults.

## SUBJECTS AND METHODS

Subjects were tested at rest under standard conditions in the laboratory after a fast of six to sixteen hours. Indwelling needles were inserted under local anesthesia into the brachial artery and an antecubital vein of one arm, and into an antecubital vein of the opposite arm. Blood glucose was estimated by a modified Shaffer-Hartman method[5] in samples taken simultaneously from the three vessels.

Duplicate control samples were taken initially; two units of soluble insulin contained in 2 ml. of isotonic saline were then rapidly injected into the brachial artery and further samples taken at 5, 15, 30, 45 and 60 minutes after the injection.

Ten patients with acromegaly were studied in detail (cases 1 to 10, table 1); less complete data were obtained in three other patients (cases 11 to 13). Two patients (cases 1 and 2) were relatively early examples of the condition with classical features of activity; the disease was apparently progressing slowly in one other patient (case 11), but in the remainder, the advance of the disorder appeared to have been arrested either spontaneously (cases 3 to 6, 9 and 12) or after treatment (cases 7, 8, 10 and 13). None was receiving hormone or other specific therapy at the time of the investigation. One patient (case 10) was a frank though mild diabetic who was not receiving insulin. Glucose tolerance tests had been done at some time during the course of their disease in nine of the other patients; three cases (cases 2 to 4) had normal curves and four (cases 1, 7, 8 and 11) showed some degree of carbohydrate intolerance short of the true diabetic pattern which had been demonstrated in cases 5 and 13. Impairment of insulin sensitivity, as shown by insulin-glucose tolerance tests,[6] was present in cases 1, 4 and 7 but not in the two other patients so examined (cases 3 and 13).

The effect of human growth hormone on the response to intra-arterial insulin was investigated in three healthy adults. In two, 2 mg. of growth hormone, diluted to a volume of 60 ml., were infused intravenously over thirty minutes. Insulin (two units) was then injected into the brachial artery and samples taken as in previous experiments for a further hour. In the third subject 6 mg. of growth hormone, diluted in 45 ml., were given intravenously over fifteen minutes, and the test dose of insulin was given after a further twenty-five minutes.

Limb blood flow was measured by venous occlusion plethysmography[7] during two of the infusions of growth hormone and in some of the studies both in normal subjects and in patients with acromegaly.

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TABLE 1

Clinical details of thirteen acromegalic patients

| Case No. | Sex | Age | Approximate duration (years) | Clinical activity | Carbohydrate tolerance* | Insulin sensitivity† |
|---|---|---|---|---|---|---|
| 1 | F | 58 | 2 | ++ | Impaired | Impaired |
| 2 | F | 27 | 4 | ++ | Normal | — |
| 3 | M | 19 | 9 | 0 | Normal | Normal |
| 4 | M | 44 | 30 | 0 | Normal | Impaired |
| 5 | M | 61 | 35 | 0 | Diabetic | — |
| 6 | M | 44 | 30 | 0 | — | — |
| 7 | F | 47 | 10 | 0 | Impaired | Impaired |
| 8 | M | 48 | 8 | 0 | Impaired | — |
| 9 | M | 60 | 25 | 0 | — | — |
| 10 | M | 46 | 15 | 0 | Diabetic | — |
| 11 | M | 36 | 15 | + | Impaired | — |
| 12 | F | 33 | 11 | 0 | — | — |
| 13 | F | 64 | 22 | 0 | Diabetic | Normal |

*50 gm. glucose.
†Method of Himsworth (1936).

## ANALYSIS OF RESULTS

The uptake of glucose at any time, in either forearm, is given by the expression F(A—V):

Where F = blood flow
A = arterial glucose concentration
V = venous glucose concentration

In the initial series of experiments,[4,8] there was no general or selective change in peripheral blood flow after the intra-arterial injection of two units of insulin. Under standard conditions at rest in the laboratory, forearm blood flow remains remarkably constant for one to two hours.[9] Since, in the present study, the effect of insulin was assessed by the simultaneous comparison of glucose uptake in both forearms and since random changes in flow were only slight and approximately equal and synchronous on the two sides, the value for F in the expression F(A—V) was considered to be constant. A measure of glucose uptake in either forearm in these circumstances could therefore be obtained by calculation of the arteriovenous glucose difference.

Peripheral glucose uptake is, however, a linear function of the arterial concentration of glucose,[10] and it has been shown that a more accurate indication of the changes in glucose uptake mediated, for example, by insulin, can be obtained by calculating the value of $\frac{A-V}{A}$ (where A = arterial glucose concentration and V = venous glucose concentration), provided that there is no change in blood flow.[11]

The factors $\frac{A-Vi}{A}$ and $\frac{A-Vc}{A}$ (where Vi = glucose concentration in the vein draining the injected forearm and Vc = glucose concentration in the vein draining the opposite forearm) may therefore be used as measures of glucose uptake in the injected and in the contralateral forearm respectively.

The value of $\frac{A-Vi}{A}$ however, represents not only the effect of "immediately fixed" insulin, but also that of insulin which was not fixed on its first passage through the capillaries of the injected limb and which has circulated through the lungs and possibly other tissues. The effect of this "circulated" insulin is indicated by the changes in glucose uptake in the contralateral, noninjected forearm and can be assessed by the factor $\frac{A-Vc}{A}$. The effect of the "immediately fixed" insulin on glucose uptake can thus be calculated from the expression:

$$\left(\frac{A-Vi}{A}\right) - \left(\frac{A-Vc}{A}\right)$$

i.e. $$\left(\frac{Vc-Vi}{A}\right)$$

The results of detailed studies in thirteen healthy adults[4] were analyzed in this way, and compared with the values obtained in the present study of patients with acromegaly.

## RESULTS

1. *Response to intra-arterial insulin in acromegaly.* The mean pattern of response to intra-arterial insulin in euglycemic acromegalics, i.e., those patients whose fasting blood sugar was less than 100 mg. per ml. (cases 1 to 8, tables 1 and 2) differed from that

TABLE 2

Effect of intra-arterial insulin on blood sugar (mg. per 100 ml.) of eight euglycemic acromegalics

| Case No. | Time (minutes after insulin) | Arterial (A) 0 | 5 | 15 | 30 | 45 | 60 | Ipsilateral Venous (Vi) 0 | 5 | 15 | 30 | 45 | 60 | Contralateral Venous (Vc) 0 | 5 | 15 | 30 | 45 | 60 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | | 90 | 92 | 83 | 83 | 89 | 82 | 94 | 92 | 65 | 76 | 88 | 85 | 91 | 91 | 73 | 81 | 84 | 90 |
| 2 | | 92 | 89 | 67 | 74 | 90 | 70 | 76 | 71 | 38 | 41 | 57 | — | 87 | 76 | 61 | 57 | 74 | 74 |
| 3 | | 80 | 75 | 63 | 57 | 77 | 78 | 72 | 68 | 64 | 57 | 78 | 76 | 80 | 72 | 62 | 63 | 69 | 82 |
| 4 | | 100 | 93 | 79 | 80 | 87 | 92 | 93 | 74 | 83 | 83 | 83 | 82 | 87 | 83 | 81 | 83 | 82 | 80 |
| 5 | | 94 | 97 | 81 | 78 | 80 | 77 | 99 | 83 | 83 | 80 | 75 | 66 | 98 | 89 | 80 | 72 | 72 | 73 |
| 6 | | 93 | 90 | 81 | 85 | 88 | 83 | 90 | 75 | 56 | 61 | 63 | 73 | 88 | 86 | 78 | 70 | 75 | 73 |
| 7 | | 94 | 91 | 87 | 90 | 90 | 89 | 87 | 74 | 71 | 49 | 70 | 80 | 89 | 88 | 83 | 78 | 81 | 81 |
| 8 | | 90 | 88 | 69 | 76 | 90 | 80 | 88 | 75 | 72 | 76 | 83 | 80 | 84 | 87 | 70 | 81 | 78 | 86 |
| Mean | | 92 | 89 | 76 | 78 | 86 | 81 | 87 | 76 | 67 | 65 | 75 | 77 | 88 | 84 | 73 | 73 | 77 | 80 |
| Mean levels in thirteen normal subjects | | 84 | 81 | 56 | 60 | 75 | 80 | 77 | 65 | 37 | 35 | 51 | 59 | 75 | 72 | 46 | 44 | 59 | 69 |

observed in healthy adults (table 2 and figure 1). After the injection of two units of insulin into the brachial artery, the arteriovenous glucose difference in the ipsilateral arm was much less in acromegalic subjects than in healthy adults. Similarly, there was a smaller fall in arterial glucose concentration and in the venous glucose concentration of the opposite arm. The mean effect of "immediately fixed" insulin, calculated from the expression $\frac{Vc-Vi}{A}$, is shown in figure 2. In healthy subjects there was a significant rise in uptake after the injection of insulin, at 5, 15, 30 and 60 minutes.*

In acromegalic patients, however, a significant increase in uptake was only recorded at five minutes ($t = 2.466$, $P<0.05$) and even this increase was significantly less than that observed in the control group

* ($t = 4.329$, $P<0.001$ at five minutes; $t = 2.678$, $P<0.05$ at fifteen minutes; $t = 2.911$, $P<0.05$ at thirty minutes; $t = 4.571$, $P<0.001$ at sixty minutes).

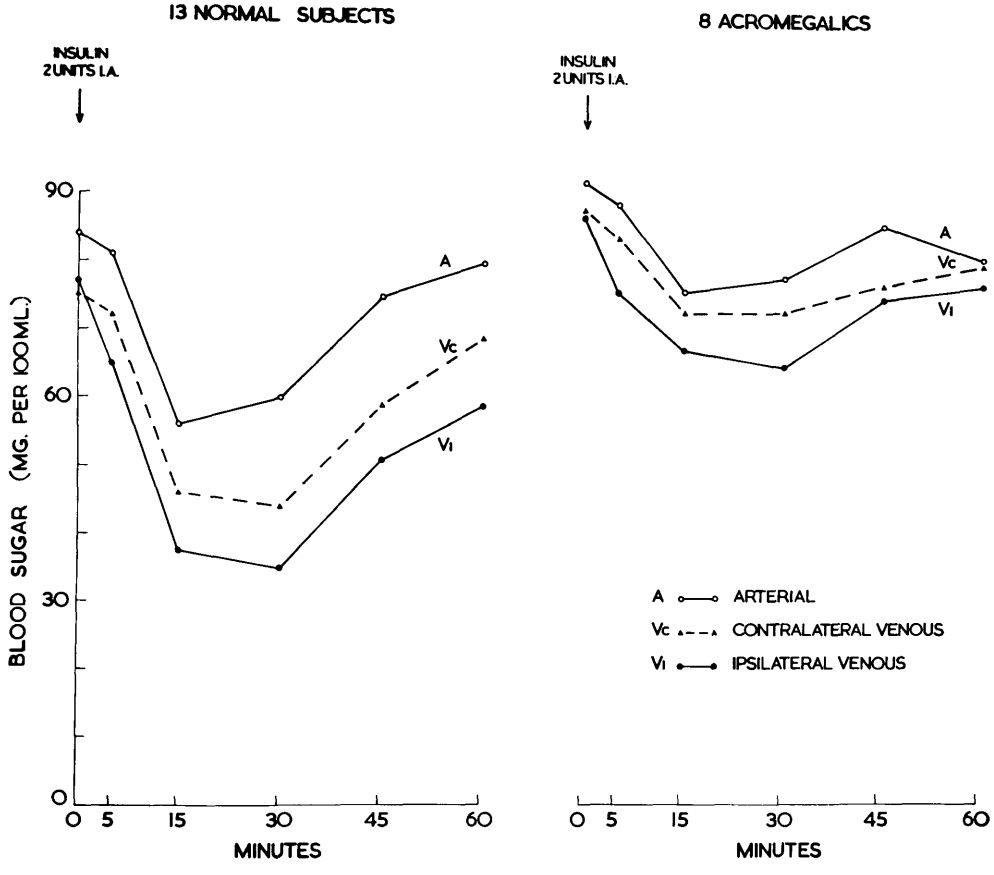


FIG. 1. Mean blood sugar levels after intra-arterial injection of two units of insulin in (a) thirteen normal subjects and (b) eight euglycemic acromegalics.

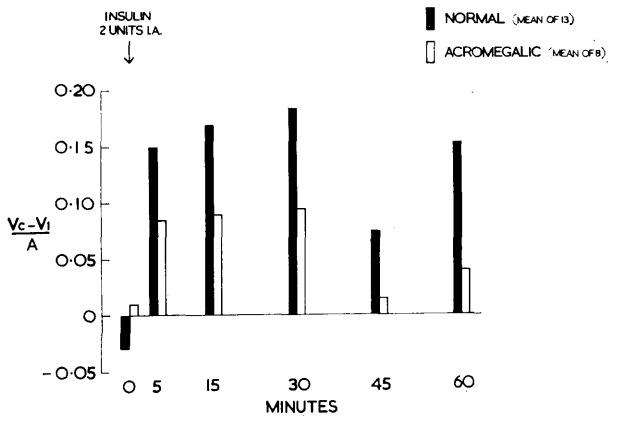


FIG. 2. Effect of "immediately-fixed" insulin $\left(\frac{Vc-Vi}{A}\right)$ in normal and acromegalic subjects.

($t = 12.8$, $P<0.001$). Thus, in acromegalic subjects, there appears to be an impairment of the action of "immediately fixed" insulin.

The changes in glucose uptake which occur in the contralateral arm are illustrated in figure 3. Significant differences between the mean response in acromegalic subjects and healthy individuals were recorded at 15, 30, 45 and 60 minutes.*

The mean effect of intra-arterial insulin was undoubtedly reduced in patients with acromegaly, and some impairment of the response was apparent in nine (70 per cent) of the thirteen subjects. Four (cases 2, 6, 9 and 12), however, showed a pattern of response resembling that observed in the control group. There was no relation between individual responses to insulin and the activity, duration or degree of the disorder, the age or sex of the patient, or the response to the glucose tolerance test.

2. *Response to intra-arterial insulin in normal subjects after infusion of human growth hormone.*

In the subject who received an infusion of 6 mg. human growth hormone twenty-five minutes before the test dose of insulin, the response was reduced compared with that seen in the control study (figure 4). This modified response was similar in pattern to that seen in the majority of the acromegalics. In one of the subjects given 2 mg. of growth hormone, the peripheral response to insulin was less than that seen normally, while the remaining subject showed no impairment of response. There was no change in blood flow during or after the infusion of 2 mg. of growth hormone.

## DISCUSSION

The method of analysis in the present study is based on the fact that when insulin is given into a peripheral artery, its action is, in the first instance, confined to the tissues supplied by that vascular bed. A widening of the arteriovenous glucose difference in the injected limb after the intra-arterial administration of insulin was first demonstrated in rabbits and depancreatized dogs.[1,12] Similarly, when insulin was injected into the femoral artery of healthy men, the fall in glucose concentration was much greater in venous blood draining the injected leg than on the opposite side.[2] The direct peripheral effect of insulin was subsequently studied in more detail in the human forearm.[4] After the intra-arterial injection of two units of insulin, there was a rapid fall in glucose concentration of venous blood from the injected forearm, which was sustained for at least two hours. Changes in venous glucose concentration in the opposite forearm were slight and only temporary. These findings were interpreted as evidence of the immediate fixation of insulin in healthy tissues. The insulin fixed in this way during its first passage through the capillaries of the injected arm avoids the risk of modification or inactivation by visceral mechanisms. Moreover, the time during which the hormone is exposed to any modifying influences in the plasma is reduced to a minimum.

The immediate localization of insulin in significant amounts in the tissues in vivo is not unexpected when previous in vitro studies are considered. Stadie and his colleagues[13] showed that exposure of isolated rat diaphragm to an insulin-containing medium for as short a time as ten seconds led to increased glycogen synthesis; they subsequently demonstrated that insulin was irreversibly fixed in a similar way by other tissues.[14]

* ($t = 2.264$, $P<0.05$ at fifteen minutes; $t = 2.105$, $P<0.05$ at thirty minutes; $t = 2.332$, $P<0.05$ at forty-five minutes; $t = 2.245$, $P<0.05$ at sixty minutes.

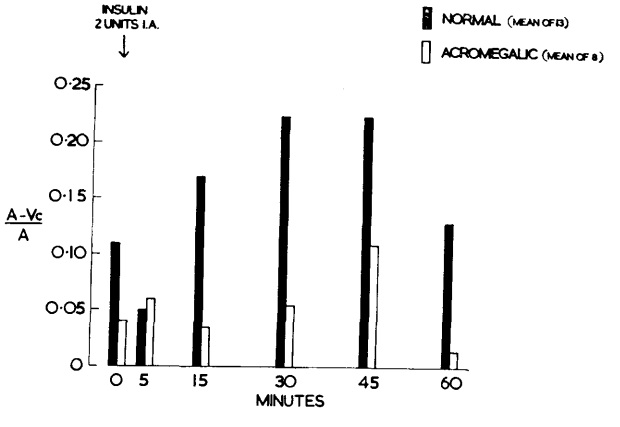


FIG. 3. Effect of "circulated" insulin $\left(\frac{A-Vc}{A}\right)$ in normal and and acromegalic subjects.

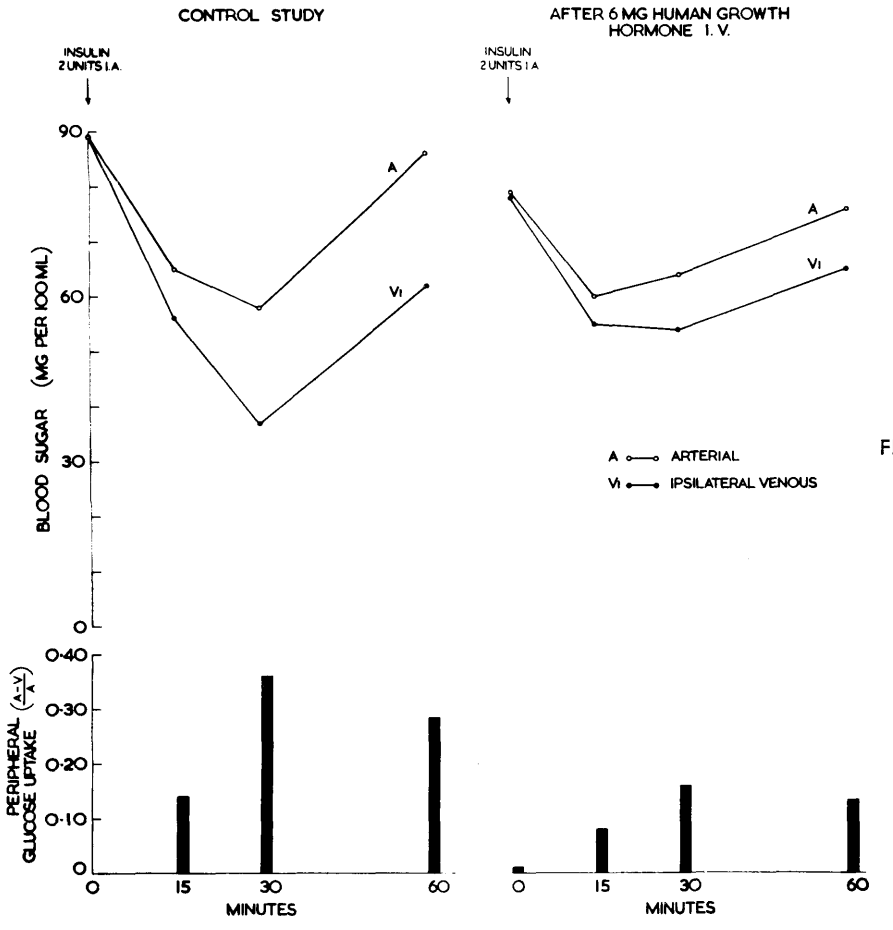


FIG. 4. Response to intra-arterial insulin in a healthy subject. Comparison of (a) control study with (b) study twenty-five minutes after an intravenous infusion of 6 mg. of human growth hormone.

The present findings suggest that there may be two separate types of abnormality of insulin activity in acromegaly. Firstly, there is an impairment of the immediate action of the hormone during its initial passage through the tissues of the injected arm. This reduction in the effect of "immediately fixed" insulin might be due either to interference with the normal, instantaneous fixation in peripheral tissues, or to inhibition of peripheral action after fixation has taken place. A further possibility is that there is a qualitative change in peripheral glucose metabolism in this condition.

Secondly, there would seem to be impairment of the peripheral response to the insulin which has circulated through the lungs and possibly other viscera. Although this abnormality may be due to a mechanism identical with that causing the altered response to "immediately fixed" insulin, the degree of impairment of peripheral glucose uptake appears to be greater in the case of "circulated" insulin. In particular, two acromegalics (cases 7 and 10) showed a definite response to insulin in the injected limb but only a very slight effect in the contralateral limb. This may mean that, in addition to the disturbance of insulin action in the peripheral tissues, there is some other site of antagonism in the plasma or in the lungs or other viscera. The "immediately fixed" insulin may be less susceptible to inactivation in the plasma because of the very short period of exposure before local fixation in the tissues.

Wright,[15] noting a discrepancy between the plasma insulin levels in normal subjects as recorded by himself and by Vallance-Owen and Hurlock[16] and the higher levels recorded by a technic involving dilution of the plasma,[17] suggested that dilution might liberate insulin from some inactive form or might inactivate a circulating insulin antagonist. The discrepancy between results obtained by the two methods is much greater with plasma from acromegalic patients[15,18] suggesting the presence of a correspondingly greater concentration of the insulin antagonist or inactivator. Insulin inhibitors associated with various fractions of the serum proteins have also been found in the plasma of diabetics who have never been treated with insulin.[19,20] In healthy

adults, insulin antagonists have been demonstrated in association with plasma albumin[21] and α-2 globulin fractions.[22] These factors are not found after hypophysectomy[23,24] but reappear after the administration of growth hormone.[23] These various anti-insulin factors, although humoral in origin, probably act at the periphery and not directly in the circulation. However, Marsh and Haugaard[25] have demonstrated an insulin-neutralizing substance in the serum of normal and of diabetic subjects which is apparently effective in the bloodstream.

The diabetogenic effect of anterior pituitary extracts and of growth hormone is well established[26-28] although diabetes mellitus is not an inevitable complication of acromegaly, the reported incidence being less than 30 per cent.[29,30] A much higher incidence of disturbed carbohydrate metabolism was, however, apparent in the present series, an impairment of insulin action at the periphery being revealed in 70 per cent of the acromegalics. It is interesting to note that such impairment was often demonstrated in the absence of clinical or biochemical evidence of diabetes. It is possible that this may reflect the functional integrity of the pancreatic islets, since diabetes is more likely to occur in those acromegalics who have a familial predisposition to the former disease.[29] It may also be relevant that a similar abnormality of the response to insulin has been observed in nondiabetic subjects during prolonged treatment with adrenocortical steroids.[31]

The finding that previous administration of human growth hormone can apparently reproduce this abnormality of peripheral response in healthy adults is of considerable interest and supports the suggestion that resistance to insulin in acromegaly is dependent on excess growth hormone. In the present experiments, however, there was no correlation between impairment of the response to insulin and clinical activity of the disease. Moreover, although crude preparations of the anterior pituitary inhibit glucose uptake in the isolated rat diaphragm, whether injected in vivo or applied in vitro during incubation, purified growth hormone inhibits glucose uptake only when injected in vivo and at least three hours before sacrifice.[32,33] It would appear, therefore, that although growth hormone is not a direct inhibitor of peripheral glucose uptake, it may alter in some way the metabolic activity of the tissues. Since the response to insulin was impaired in the absence of other evidence of activity of the acromegalic process, it is possible that this metabolic abnormality, once induced, is permanent, the situation being analogous to that occurring in the skeleton. The precise relationship between these physical and biochemical changes and the concentration or activity of growth hormone is, however, still not clear. In any case, it seems likely that the abnormality of carbohydrate metabolism in acromegaly is complex, and does not bear a simple relationship to excessive production of growth hormone.

## SUMMARY

Peripheral glucose uptake was measured in the forearm of healthy adults and of patients with acromegaly, after the intra-arterial injection of two units soluble insulin. Peripheral glucose uptake was significantly reduced in 70 per cent of the acromegalic subjects. There was no correlation between the reduction in response to insulin and clinical activity of the disease.

Peripheral glucose uptake was reduced in normal subjects by the previous administration of human growth hormone, in a manner comparable with that seen in acromegaly.

The mechanism of antagonism to insulin in acromegaly is discussed and it is suggested that both tissue and serum factors may be involved.

## SUMMARIO IN INTERLINGUA

*Reducite Responsa a Insulina Intra-Arterial in Acromegalia*

Le captation peripheric de glucosa esseva mesurate in le antebracio de adultos normal e de patientes con acromegalia, post le injection intra-arterial de duo unitates de insulina de forma solubile. Le captation peripheric de glucosa esseva reducite significativemente in 70 pro cento del subjectos acromegalic. Non esseva constatate un correlation inter le reduction del responsa a insulina e le activitate clinic del morbo.

Le captation peripheric de glucosa esseva reducite in subjectos normal per le previe administration de hormon de crescentia human. Iste reduction esseva simile a illo notate in acromegalia.

Es discutite le question del mechanismo del antagonismo contra insulina in acromegalia. Es presentate le conception que le factores responsabile es de character tanto tissular como etiam seral.

## ACKNOWLEDGMENT

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A partial explanation for the failure to find an increase in total corticosteroid excretion in the face of high plasma levels was provided by C. J. Migeon, J. Bertrand and B. E. Wall (*J. Clin. Invest. 36*: 1350, 1957). These investigators demonstrated that the rate of disappearance of cortisol-4-C-14 from the blood was greatly delayed in pregnancy. This observation was subsequently confirmed by M. Cohen, M. Stiefel, W. J. Reddy and J. C. Laidlaw (*J. Clin. Endocrinol. & Metab. 18*:1076, 1958). The additional observation has been made by N. P. Christy, E. Z. Wallace, W. E. L. Gordon, and J. W. Jailer (*J. Clin. Invest. 38*:299, 1959) that tetrahydrocortisol as well as cortisol has a prolonged half life in the blood of pregnant women. The impaired metabolism of cortisol differs from the impairment which occurs in cirrhosis of the liver, in which the metabolism of the reduced hormone is apparently unaffected.

Although the reported decrease in the rate of metabolism of cortisol helps to explain the pattern of the urinary excretion of corticosteroids, it fails to account for the elevation of the plasma level of cortisol and the absence of signs of hyperadrenalcorticism which would be expected with elevations of the plasma cortisol level.

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