Peripheral Glucose Uptake during the Oral Glucose-tolerance Test in Normal and Obese Subjects and Borderline and Frank Diabetics

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SUMMARY
Glucose uptake by the forearm muscle tissues has been studied during the 50-g oral glucose-tolerance test in 103 subjects. Thirty-seven were classified as normal (2-h blood-sugars below 120 mg per cent), 28 as borderline diabetics (2-h blood-sugars between 120 and 200 mg per cent), and 38 as diabetics (2-h blood-sugars above 200 mg per cent). The results confirmed earlier observations that glucose uptake is reduced in obesity and diabetes. The normal and borderline groups were indistinguishable. In both, glucose uptake was inversely correlated with the degree of obesity (glucose uptake = 0.898 - 0.193 x skinfold thickness for the normal and 1.055 - 0.255 x skinfold thickness for the borderline group). In the diabetic group this relationship had broken down.

Glucose uptake was not related to age, the peak blood-sugar level, or in the normal and borderline groups to the blood-flow.

INTRODUCTION
The development of the forearm technique over a decade ago has enabled the metabolism of the peripheral tissues to be studied under a variety of circumstances. Harris, Bateman, and Gloster (1962) examined the effects of exercise, Rabinowitz and Zierler (1962a), Häggendal, Kerstell, Steen, and Svanberg (1967), and Zampa, Atilia, Bracchetti, Geminiani, Borgetti, and Odifreddi (1967) studied the effects of small doses of insulin on forearm metabolism and Jackson, Peters, Advani, Rogers, Perry, Day, and Pilkington (1970) studied the reproducibility of forearm metabolism during a glucose-tolerance test. Muscle is the main constituent of the peripheral tissues under investigation and since in the lean man muscle comprises more than half the body mass, its role in metabolic events in the body cannot be overlooked.

We have carried out studies of peripheral glucose metabolism during 50-g oral glucose-tolerance tests in a variety of groups of subjects and found important differences. In previous investigations on 23 subjects glucose uptake after glucose loading was found to be high in the lean non-diabetic subjects and much lower in.
obesity (Butterfield, Hanley, and Whichelow, 1965) and in another study where eight diabetics were compared with four non-diabetics, glucose uptake was found to be reduced in the former (Butterfield and Whichelow, 1965).

Studies of glucose uptake during the oral glucose-tolerance test have now been completed in 103 subjects and we can compare various groups of subjects, normal, obese, and diabetics, to assess the influence of the different measurements involved in our technique—blood-flow, arm volume, arterio-venous glucose difference, skinfold thickness, ponderal index, and blood-sugar levels—on peripheral glucose uptake.

Regarding the segregation of subjects, despite the world-wide use of the glucose-tolerance test, particularly in population surveys for diabetes, it is still not clear which levels of blood-sugar should be taken as diagnostic of diabetes. The British Diabetic Association (Fitzgerald and Keen, 1964) and the World Health Organization (1965) both agree that at 2 h after glucose administration a capillary blood-sugar level above 120 mg per cent should be regarded as suspicious of diabetes. During the Bedford Survey subjects with capillary blood-sugars below 120 mg per cent were classified as normal, those with levels above 200 mg per cent as diabetics, and those with levels between 120 and 200 mg per cent as 'borderline diabetes' (Butterfield, 1964). The last classification will be followed here.

CLINICAL MATERIAL AND METHODS
The details of the groups of subjects studied are shown in Table 1. There were 37 non-diabetics, 28 borderline diabetics, and 38 diabetics.

The preparation of the subjects who volunteered for these investigations and the forearm technique employed have been described in detail elsewhere (Butterfield and Holling, 1959; Butterfield, Hanley, and Whichelow, 1965; Butterfield and Whichelow, 1968). The methods for and timing of blood-sugar estimation and calculation of the mean cell glucose uptake every 15 min for 2 h following glucose administration have been reported previously (Whichelow, Wigglesworth, Cox, Butterfield, and Abrams, 1967; Butterfield, Hanley, and Whichelow, 1965).

Skinfold thickness was measured in triplicate in the sub-scapular region for men and the mid-triceps region for women (Fowler, 1970).

The ponderal index was calculated from the formula

\[ \text{height in in.} \times \sqrt[3]{\text{weight in lb.}} \]

Blood-flow was measured as described previously (Butterfield and Holling, 1959). The arm volume referred to is that volume of arm contained within the plethysmograph, measured by water displacement. The plethysmographs were all between 12.5 and 14.5 cm long, and varied in diameter to accommodate different arm sizes.

RESULTS
In the fasting state cell glucose uptake measured in mg/100 ml forearm/minute, was small and no differences could be discerned between the three groups studied.
<table>
<thead>
<tr>
<th>Subjects</th>
<th>Number</th>
<th>Age</th>
<th>Skinfold thickness (cm)</th>
<th>Ponderal index</th>
<th>Fasting blood-sugar mg%</th>
<th>2-h blood-sugar mg%</th>
<th>Mean blood flow ml/100 ml/min</th>
<th>Cell glucose uptake mg/100 ml/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>37</td>
<td>Mean</td>
<td>43</td>
<td>2.28</td>
<td>12.08</td>
<td>78</td>
<td>93</td>
<td>5.6</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>16-77</td>
<td>0.76-4.30</td>
<td>8.78-14.32</td>
<td>68-90</td>
<td>71-118</td>
<td>2.9-12.4</td>
<td>0.093-1.131</td>
</tr>
<tr>
<td>Borderline</td>
<td>28</td>
<td>Mean</td>
<td>51</td>
<td>1.95</td>
<td>12.25</td>
<td>86</td>
<td>144</td>
<td>5.0</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>27-78</td>
<td>0.56-3.40</td>
<td>9.67-14.44</td>
<td>71-107</td>
<td>121-186</td>
<td>2.5-18.6</td>
<td>0.106-1.183</td>
</tr>
<tr>
<td>Diabetics</td>
<td>38</td>
<td>Mean</td>
<td>52</td>
<td>1.96</td>
<td>12.35</td>
<td>108</td>
<td>292</td>
<td>5.3</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>26-76</td>
<td>0.60-4.23</td>
<td>10.36-14.07</td>
<td>110-426</td>
<td>206-506</td>
<td>2.2-13.0</td>
<td>0.000-0.678</td>
</tr>
</tbody>
</table>
Table 2. Correlations in three groups studied

<table>
<thead>
<tr>
<th></th>
<th>Normal group</th>
<th>Borderline group</th>
<th>Diabetic group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 37</td>
<td>n = 28</td>
<td>n = 38</td>
</tr>
<tr>
<td>Correlation of cell glucose uptake with:</td>
<td>r</td>
<td>P</td>
<td>r</td>
</tr>
<tr>
<td>Skinfold thickness</td>
<td>-0.763</td>
<td>&lt; 0.001</td>
<td>-0.769</td>
</tr>
<tr>
<td>Ponderal index</td>
<td>0.672</td>
<td>&lt; 0.001</td>
<td>0.866</td>
</tr>
<tr>
<td>Arm volume</td>
<td>-0.562</td>
<td>&lt; 0.001</td>
<td>-0.359</td>
</tr>
<tr>
<td>Mean blood-flow</td>
<td>0.308</td>
<td>0.1 &gt; P &gt; 0.05</td>
<td>0.206</td>
</tr>
<tr>
<td>Peak blood-sugar</td>
<td>0.241</td>
<td>N.S.</td>
<td>-0.023</td>
</tr>
<tr>
<td>Mean arterio-venous difference</td>
<td>0.600</td>
<td>&lt; 0.001</td>
<td>0.486</td>
</tr>
<tr>
<td>Age</td>
<td>0.087</td>
<td>N.S.</td>
<td>0.081</td>
</tr>
<tr>
<td>Correlation of skinfold thickness with mean arterio-venous differences</td>
<td>-0.525</td>
<td>&lt; 0.001</td>
<td>-0.486</td>
</tr>
</tbody>
</table>
The mean results with standard deviations were: control group, 0.091 (±0.135), borderline group, 0.133 (±0.082), and diabetic group, 0.082 (±0.135). However, differences did become apparent after glucose loading and the rest of this paper will deal with events during the 2.5 h after the oral administration of 50 g glucose.

Table 2 shows the correlation coefficients of the mean cell glucose uptake (CGU) for the 2.5 h following glucose administration, with skinfold thickness, ponderal index, arm volume, mean blood-flow, peak blood-sugar, mean arterio-venous difference and age for the normal, borderline, and diabetic groups.

Non-diabetic group

The closest correlation of mean cell glucose uptake was a negative one with skinfold thickness, which confirmed earlier observations on a smaller number of subjects (Butterfield, Hanley, and Whichelow, 1965). The correlations with skinfold thickness for men \( (r = -0.732, n = 17, P < 0.001) \) and women \( (r = -0.779, n = 20, P < 0.001) \) separately were also remarkably close, and although the skinfold thickness was measured at different sites in the two sexes, the regression lines were statistically indistinguishable \( (t = 0.019, n = 37, P > 0.1) \), Fig. 1. The two sexes will therefore hereafter be considered together.

There were also statistically significant correlations between cell glucose uptake and ponderal index, as another measure of obesity, and between cell glucose uptake and arm volume. Since the plethysmographs used in this study were of a similar length, and were all carefully placed so that the proximal edge was level with the
insertion of the bicipital aponeurosis, it is not surprising that there is also a correlation between arm volume and fat fold thickness \(r = -0.563, n = 37, P < 0.001\). The arm volume must be related to arm size, and a large arm will be the result of a large muscle or adipose tissue mass.

Forearm blood-flow did not correlate with cell glucose uptake, but the mean arterio-venous difference did, \(r = 0.600, n = 37, P < 0.001\). Furthermore there was a close inverse correlation between skinfold thickness and the mean arterio-venous difference, \(r = -0.525, n = 37, P < 0.001\). For lean subjects (skinfold thickness less than 1.5 cm) the mean arterio-venous difference was 15.3 (±6.2 S.D.) and for obese subjects (skinfold thickness greater than 2.5 cm) the mean arterio-venous difference was 5.8 (±2.6 S.D.). The difference between the means is significant, \(P < 0.01\). This is in agreement with earlier observations of wider arterio-venous differences in leaner subjects than those in more obese ones in a limited series where deep and superficial veins were catheterized (Whichelow, Wigglesworth, Cox, Butterfield, and Abrams, 1967).

There was no correlation of cell glucose uptake with age or with the peak blood-sugar.

**Borderline group**

The correlations of cell glucose uptake with skinfold thickness and ponderal index were also very close in this group (Table 2) and so was that between skinfold thickness and the mean arterio-venous difference. Once again the closest correlation was with skinfold thickness and the regression line for this correlation was indistinguishable from that for the control group \(t = 0.108, n = 65, P > 0.1\), Fig. 2. There was only a poor correlation with arm volume, and none with the mean blood-flow, peak blood-sugar, or age.

**Diabetic group**

The mean cell glucose uptake levels were on average much lower than those of the other two groups (Table 1) and Table 2 shows that the highly statistically significant relationship between glucose uptake and skinfold thickness observed in the other groups had disappeared \(r = -0.043, n = 38, \text{n.s.}\).

Fig. 3 relates glucose uptake and skinfold thickness for the individual diabetics, for comparison with the regression line derived from the normal group. It is immediately apparent that as far as muscle glucose uptake is concerned those diabetics showing the greatest deviation from the normal for their skinfold thickness were the leaner ones. In marked contrast the forearms of the more obese diabetics assimilated similar amounts of glucose to those of the non-diabetics. This was confirmed by finding a close correlation between skinfold thickness and the observed glucose uptake expressed as a percentage of that for a normal person of the same skinfold thickness, \(r = 0.541, n = 38, P < 0.001\). Thus, the fatter the diabetic the more likely he or she is to have an appropriate peripheral glucose metabolism.

The percentage decrease in glucose uptake was not related to the height of the blood-sugar either fasting, peak, or at 2 h after glucose.
Fig. 2. Relationship between mean cell glucose uptake and skinfold thickness for borderline subjects (2-h blood-sugar between 120 and 200 mg per cent). Double circles indicate subjects with 2-h blood-sugar levels above 160 mg per cent.

Fig. 3. Relationship between mean cell glucose uptake and skinfold thickness for diabetic subjects (2-h blood-sugar above 200 mg per cent) and showing regression line and 95 per cent confidence limits for normal group.
The only other significant correlation found in this diabetic group was between the cell glucose uptake and the mean blood flow ($r = 0.442$, $n = 38$, $P < 0.01$), presumably because, when insulin action transporting glucose into the cells is ineffective, the arterio-venous differences, normally wide, are much reduced and consequently variations in blood-flow became the major variable in the calculations of glucose uptake.

### DISCUSSION

#### The technique

Various criticisms can be levelled at the technique employed and the results obtained.

First our investigations are not carried out under the steady-state conditions advocated by Zierler (1961). Even in the fasting state steady-state conditions are not always achieved particularly in the diabetic group, where the systemic blood-sugar level frequently shows wide and rapid fluctuations (Butterfield and Holling, 1959). Furthermore, since peripheral glucose uptake in the fasting state is similar in all three groups, differences only emerge when a stress in the form of a glucose load is applied. Of course in clinical practice the same stress has to be employed for the differentiation between normals and diabetics. We have set out elsewhere our argument for using the present technique when the blood-sugar is changing and have shown that meaningful results can be obtained, mainly because the circulation time through the forearm is so brief (Butterfield, Abrams, St. John, and Whichelow, 1967).

In obesity the large amount of adipose tissue in the large forearms of the obese subjects might affect the results, particularly as the A-V difference in deep veins is greater than in superficial veins draining territory where the adipose tissue is so abundant in obesity (Rabinowitz and Zierler, 1962; Whichelow, Wigglesworth, Cox, Butterfield, and Abrams, 1967). Could blood returning from the adipose tissue contaminate the venous samples we assume to be from muscle? We think not because we take great care to thread our venous catheters through at least one valve into the deep muscle compartment and reduce further the risk of such contamination through the valve by sampling slowly over long time periods—1 min or more.

Does the excess adipose tissue in obesity upset our blood-flow estimations and produce a systematic error? We believe that any such error is small and does not affect the over-all validity of our hypotheses for the following reasons. Glucose uptake is measured in units of mg per 100 ml of total forearm tissue per minute and there is indeed a close inverse correlation between arm volume and glucose uptake (Table 2). The arm volume here is that volume of tissue, measured by water displacement contained in the plethysmograph. Since our plethysmographs are of a similar length, the length of arm studied is comparable from one subject to another. However, since the range of arm volumes was less than threefold (from 440 to 1105 ml) whereas the range of glucose uptake was twelvefold (0.093 to 1.131 mg/100 ml/min) we believe the reduction of peripheral glucose uptake in obesity must be due, for the most part, to a reduction of muscle glucose uptake.
By measuring blood-flow with the venous occlusion plethysmograph the total forearm and not just muscle blood-flow is measured. Unfortunately satisfactory methods for repeated frequent measurements and specifically for muscle blood-flow have not been available. If blood-flow were apparently higher in the lean than the obese subjects due to high muscle and low adipose tissue blood-flow, then glucose uptake would appear higher in the lean subjects. However, as there was no correlation between blood-flow and skinfold thickness and because the mean arterio-venous difference during the test was statistically wider in the lean than the obese subjects (Table 2) glucose uptake must have been greater in lean subjects.

Our finding that in resting limbs glucose uptake remains remarkably independent of blood-flow in the control and borderline groups (Table 2) suggests that when the muscles are at rest, differences in blood-flow may be due to the opening or closing of arterio-venous anastomoses, or to changes of the circulation through tissues with relatively low energy requirements—tendons, muscle septa, etc.

**Obesity**

The very close correlation of increasing skinfold thickness with diminishing cell glucose uptake confirms earlier observations (Butterfield, Hanley, and Whichelow, 1965) and is further substantiated by the highly significant reduction in arterio-venous glucose difference in obesity without any compensating increase in blood-flow. There was also a close correlation between glucose uptake and ponderal index, although it was not so close as that with skinfold thickness. The ponderal index, calculated from a relationship between height and weight, makes no distinction between muscularity and adiposity and may not therefore be such a good reflection of lipid stores as skinfold thickness, which has been shown to correlate well with total body fat as measured by radioisotopic techniques (Steinkamp, Cohen, Gaffey, McKey, Bron, Sin, Sargent, and Isaacs, 1965).

All the evidence points to a real impairment of muscle glucose uptake in obesity, the reason for which is not yet known. It is certainly not an irreversible genetic lesion, since following weight reduction by diet or therapy with fenfluramine, glucose uptake is increased to the amount expected for the new, smaller skinfold thickness (Butterfield and Whichelow, 1968; Whichelow and Butterfield, 1970). It seems probable that in obesity muscles utilize non-esterified fatty acids as their main energy source even after glucose loading, and that by dieting and losing weight the stores of fat are depleted, so that carbohydrate becomes once more an important energy source.

The low glucose uptake in persons with high fat-fold thickness is particularly interesting in view of the high levels of circulating insulin which are now well recognized in obesity. This lack of insulin action in the peripheral tissues could be due to some defect in insulin filtration from the circulation, or insulin resistance in the tissues themselves. The latter possibility seems very likely, particularly as Chlouverakis and White (1969) have found insulin resistance in vitro, that is without an intact circulation, in the muscle tissues of obese hyperglycaemic mice, and observed that this insulin resistance was absent if the animals were kept thin by dietary restriction.
However, the possibility of a circulatory defect as well certainly should not be ruled out. Previous studies when $^{131}$ insulin was injected intra-arterially to perfuse the forearm tissues revealed close correlations in non-diabetic volunteers between (1) the local insulin concentration achieved in the plasma and the insulin fixation by the tissues (the insulin which disappeared from the circulation), and (2) the insulin fixation and the subsequent increase in glucose uptake (Butterfield, Garratt, and Whichelow, 1963). Further analysis of those data has shown that among such subjects there was also a correlation ($r = 0.720, n = 9, P < 0.02$) between the ratio of insulin fixed to the insulin concentration and the ponderal index, Fig. 4. That the more obese subjects showed lower levels of fixation in relation to concentration indicates that insulin filtration from the blood into the tissues is reduced in obesity.

Plasma triglycerides might play a part in the insulin resistance of obesity, possibly by filling the filtration pores for insulin in the capillary basement membrane since Bierman (1970) and Bagdade (1968) have observed correlations between the plasma insulin and triglyceride levels.

**Borderline group: diagnosis of diabetes**

Butterfield (1966) has suggested that the normal range of blood-sugars extends much higher than many workers currently believe but that there is considerable overlap of the normal and diabetic groups so that there are also some diabetics with quite low blood-sugars. Using a ‘Gamblers Ruin’ type of analysis (Butterfield, 1968) of the Bedford Random Sample population he suggested that two groups could be distinguished, with 2-h blood-sugars above and below 200 mg
Glucose Uptake in Normal, Obese, and Diabetic Subjects

The suggestion is that as an individual's 2-h blood-sugar approached and reached the 200 mg per cent level, the more likely he was to be diabetic and presumably to run the risk of diabetic complications. In the present series, 16 of the 28 borderline subjects had 2-h blood sugars below 140 mg per cent and so, on the above hypothesis, are most likely to be normal. Six had 2-h blood sugars between 140 and 160, and six between 160 and 200 mg per cent. The latter six, amongst whom are likely to be the most diabetics, are shown as double circles in Fig. 2. Although five of them fall below the regression line, instead of three which would be predicted on a chance basis they lie well within the ranges of the other members of the group.

The most remarkable finding in the present study was that the borderline group showed the same trends as the normals with respect to glucose uptake and the correlations between glucose uptake and the other variables studied. Moreover, the regression lines for these correlations were very similar to those of the normal group. There was no statistical difference between the regression lines relating cell glucose uptake and skinfold thickness for the two groups $t = 0.108, n = 65, P > 0.1$.

Only one member of this group had been diagnosed as a diabetic previously; he was being treated with tolbutamide. It seems therefore that as far as muscle glucose uptake is concerned this group is mainly composed of normal subjects and that the results as a whole can be taken as additional evidence in support for the suggestion that the 2-h blood-sugar level for the segregation and diagnosis of diabetes can be set at 200 mg per cent.

It is also interesting that there was no correlation in either the normal or borderline group of glucose uptake with peak blood-sugar. The height of the blood-sugar or 'head of pressure of glucose' does not therefore appear to be important in determining glucose uptake. We assume from other studies that it is controlled by the amount of insulin filtered from the circulation into the tissues (Butterfield, Garratt, and Whichelow, 1963). Although there is a tendency for diabetes to develop with advancing age this does not seem to be associated per se with impaired peripheral glucose uptake because there was no correlation in the present series with age.

Diabetes

In the diabetic group with 2-h blood-sugars above 200 mg per cent the relationships of glucose uptake with skinfold thickness, ponderal index, and arm volume are lost. Glucose uptake is low in all subjects, but for their body build this is particularly noticeable in the lean diabetics (Fig. 3 and Results). As is also shown in Fig. 3, most of the juvenile onset insulin-dependent cases were lean (with a skinfold thickness less than 2.0 cm.) and had the greatest impairment of glucose uptake. These diabetics had received no insulin for at least 16 h preceding the test and only soluble insulin for the 30 h previous to that. Thus the absolute deficiency of insulin must be in these cases a prime factor in the impairment of glucose uptake.

However, it has also been found that in the diabetic reduced insulin fixation results in reduced glucose uptake (Butterfield, Garratt, and Whichelow, 1963) and
this may be an important factor in impaired glucose uptake during the oral glucose-tolerance test, particularly with the maturity onset cases, who were not insulin dependent and capable of secreting at least some endogenous insulin in response to glucose stimulation.

Although impaired insulin clearance may also be responsible for the reduced glucose uptake observed in obesity, the results of studies with phenformin therapy in diabetes and obesity have demonstrated that the block to muscle glucose uptake in obesity differs from that in diabetes, the latter being influenced by phenformin but not the former (Butterfield and Whichelow, 1968).

The development of adult onset obesity-diabetes

Carbohydrate is now the major source of nutritional calories in the Western World, reaching about 300 g/day in most adults. We can therefore attempt to trace the development of adult-onset obesity-diabetes in terms of carbohydrate disposal. It can be calculated from the results of the present study that in the normal lean person of any age (muscle mass about 30 kg) of each 50 g glucose consumed, as much as 40 g may find a pathway of disposal in the peripheral muscles, leaving some 10 g for the liver, adipose tissue, brain, etc.

As obesity develops in a member of an affluent, mechanized society, carbohydrate disposal into the resting muscle mass falls, so that eventually the muscles may take up only 5–10 g. So long as there is a suitable rise of plasma insulin, conditions are appropriate for the disposal of some of the remaining carbohydrate into peripheral adipose tissue, the rest probably going to the liver. The well-recognized elevations of plasma insulin and of β-cell hypertrophy associated with obesity probably arise because the adipose tissue is less insulin sensitive than muscle (Rabinowitz and Zierler, 1962b; Whichelow, Wigglesworth, Cox, Butterfield, and Abrams, 1967). The prolonged hyperinsulinaemia seen in obesity may be a reflection of the poor perfusion of the fat-laden adipose tissue in these circumstances.

In due course, either as a result of failure of islet blood-supply to keep pace with demands for insulin transport, or to the β-cells failing to release adequate amounts of insulin to dispose of the glucose in the diet (possibly due to the development of insulin resistance in the liver), hepatic glucose uptake falls and the glucose-tolerance curve, previously low, rises. Although the blood-sugar may fall slowly in the fasting state, after a carbohydrate load glucose cannot be assimilated by the muscles, liver, or adipose tissue fast enough and a new route for disposal is used, namely glycosuria. But although the β-cells cannot meet the increasing needs to satisfy the demands for glucose homeostasis as the liver becomes less insulin sensitive, there is nevertheless enough in the plasma to ensure that lipolysis in the adipose tissue is not too rapid, and that the free fatty acids released do not exceed the level which can be utilised by the liver, heart, and muscles, so ketosis does not develop.

The above processes can be reversed by dieting, though here it should be noted that, in the absence of carbohydrate intake to stimulate insulin production and to stop growth hormone release by the anterior pituitary, the adipose tissue does
undergo lipolysis and circulating NEFA values rise. This is associated, however, with an increased muscle glucose assimilation after a glucose load which seems to run counter to the concept of the fatty-acid glucose cycle hypothesis, that NEFAs are the preferred substrate in muscle and that high levels prevent glucose uptake (Randle, Garland, Hales, and Newsholme, 1963).

It seems, based on our studies in patients, that weight reduction in some way corrects the block to muscle glucose assimilation. In three obese patients who lost 15 to 25 lb in 2 to 13 weeks, the muscles disposed of 14, 10, and 6 g during glucose-tolerance tests before and 26, 24, and 16 g after weight loss respectively (Butterfield and Whichelow, 1968). This increased glucose uptake by muscle must be at least one of the factors operating to bring about the improvement in glucose tolerance observed in obese diabetics who lose weight.

Work now needs to be undertaken to resolve the mechanism whereby muscle glucose uptake is reduced in obesity. The defect we have postulated in the local filtration of insulin and other macromolecules must be confirmed.

REFERENCES

——— 1962b. Ibid., 2191.