

FOREARM METABOLISM IN OBESITY AND ITS RESPONSE TO INTRA-  
ARTERIAL INSULIN. CHARACTERIZATION OF INSULIN RE-  
SISTANCE AND EVIDENCE FOR ADAPTIVE  
HYPERINSULINISM \*

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(Submitted for publication June 22, 1962; accepted August 15, 1962)

Obesity is considered ordinarily to be a consequence of overeating by an otherwise normal person, but the notion persists that there may be some underlying metabolic defect. The man of 70 kg, on becoming 20 per cent overweight, doubles his adipose organ mass (3). If obesity is viewed as a state of chronic substrate excess necessitating increase in fat storage of this magnitude, one might indeed predict that certain metabolic adjustments would occur, resulting in alterations in, but not implying a primary disturbance of, intermediary metabolism.

Metabolism of obese subjects has been examined by measuring metabolic events in the forearm, which is predominantly skeletal muscle and adipose tissue, in the search for answers to the following questions. 1) What departures from normal take place in basal forearm metabolism of obese subjects and what light do these differences shed on adaptation to chronic substrate excess? 2) Is "simple" obesity related to maturity onset diabetes mellitus, in which obesity is common? Because resistance to exogenous insulin occurs in untreated maturity onset diabetes (4), response to intra-arterial insulin was examined in simple obesity. From the observations it became clear that there are a number of similarities in metabo-

lism between patients with simple obesity and those with diabetes mellitus.

METHODS

Six young subjects were studied, four men and two women, all approximately 20 per cent overweight but otherwise healthy. All had been actively gaining weight in the 6 to 12 months preceding the test, and in none was there a family history of diabetes. Results of oral glucose tolerance tests with 100 g glucose, performed in five of the six subjects, were normal. Subjects were given a 200-g carbohydrate diet for the 3 days before the test. No food was permitted after 8:00 p.m. the previous night. The test was performed between 9:00 a.m. and 1:00 p.m., that is, 13 to 17 hours after the last meal.

A brachial artery, an ipsilateral antecubital vein draining mostly muscle, and a superficial vein draining mostly forearm adipose tissue and skin were cannulated by techniques described previously (5). Blood flow was measured by the indicator-dilution method, based on continuous injection of T-1824 (Evans' blue) dye at constant rate. Circulation to the wrist and hand was excluded during experimental periods by a sphygmomanometer cuff inflated to at least 100 mm Hg beyond systolic pressure.

Uptake or production of a metabolite by the forearm is given by the equation  $\dot{Q} = F(A - DV)$ , where  $F$  is blood or plasma flow in milliliters per minute per 100 ml of forearm,  $A$  is concentration of metabolite in arterial blood or plasma, and  $DV$  is its concentration in deep venous blood. This  $\dot{Q}$  will be referred to as "forearm muscle metabolic rate" even though it underestimates true muscle metabolism. To obtain  $\dot{Q}$  per 100 g muscle, it is necessary to know the fraction of total flow that perfuses muscle and the fraction of total forearm that is muscle mass. With representative figures of 0.82 and 0.6, respectively, for these fractions in normal subjects (5),  $\dot{Q}$  per 100 g of muscle is obtained by multiplying the experimental value of  $\dot{Q}$  (shown later in Tables I and II) by a factor,  $f$ , of 1.37. The greater proportion of adipose tissue in the forearm of subjects who are 20 per cent overweight may reduce the fraction of total forearm volume occupied by muscle to about 0.5. The fraction of total flow that perfuses muscle in the obese forearm is probably less than 0.82, but probably not as low as 0.67,

\* Aided in part by Contract Nonr-248(34) (NR 101-241) between the Office of Naval Research, Department of the Navy, and The Johns Hopkins University, Baltimore; by U. S. Public Health Service Research Grants A-750 and A-5524 and Graduate Training Grant 2A-5232, National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.; and by a grant-in-aid from the Muscular Dystrophy Associations of America, Inc. Presented in part at the 80th meeting of the American Physiological Society (1); a preliminary communication has appeared in *The Lancet* (2). Reproduction in whole or in part is permitted by the authors for any purpose of the United States Government; permission of publisher required.

TABLE I  
*Arterial concentrations, arterio-deep venous differences in forearm blood and uptake (or production) by forearm muscle of glucose, potassium, and FFA in obese subjects\**

Subject	Glucose			Potassium			FFA	
	A	A-DV	$\dot{Q}$	A	A-DV	$\dot{Q}$	A	A-DV
	$\mu\text{mole/ml}$	$\mu\text{mole/ml}$	$\mu\text{mole/min}/100\text{ ml arm}$	$\mu\text{mole/ml}$	$\mu\text{mole/ml}$	$\mu\text{mole/min}/100\text{ ml arm}$	$\mu\text{mole/ml}$	$\mu\text{mole/ml}$
Z	4.92	0.11	0.61	3.92	+0.06	+0.19	0.60	+0.08
G	5.31	0.35	1.08	3.85	+0.04	+0.07	0.58	+0.02
L	5.47	0.18	0.44	3.83	+0.03	+0.04	1.26	0.00
W	4.56	0.22	0.91	3.82	+0.05	+0.12	0.90	-0.06
P	5.31	0.06	0.57	4.10	-0.05	-0.20	0.74	-0.01
F	5.25	0.34	0.72	4.17	-0.08	-0.09	0.67	+0.07
Mean	5.10	0.21	0.72	3.95	+0.01	+0.02	0.79	+0.02
$\pm$ SEM	0.142	0.048	0.132	0.048	0.007	0.058	0.107	0.021
Controls†	4.96	0.14	0.52	4.02	-0.19	-0.43	0.71	+0.02
$\pm$ SEM	0.051	0.017	0.075	0.026	0.027	0.076	0.052	0.034
p	NS	<0.05	<0.05	NS	<0.001	<0.001	NS	NS

\* Abbreviations: A = arterial concentration, A-DV = arterio-deep venous concentration difference,  $\dot{Q}$  = forearm muscle metabolic rate, and p is probability that difference between mean in control and in obese group might occur by chance, estimated by *t* test. NS applied to p > 0.05.

† See reference (8).

for this is the figure at which *f* in obese subjects is equal to that for controls. For values of forearm muscle flow between 0.67 and 0.82 of total forearm flow, *f* varies between 1.37 and 1.6 in subjects who are 20 per cent overweight; that is, *f* is greater in obese subjects than in controls. Therefore, wherever experimental values for forearm metabolism are greater in obese subjects than in controls (for example,  $\dot{Q}$  glucose, Table I), the differences from controls ought to be revised upward.

At least two sets of arterial, deep venous, and superficial venous blood samples were collected under basal conditions, and all values for basal metabolism have been expressed as their means. To shed further light on previous observations (6) that obese subjects show resistance to the hypoglycemic effects of intravenously administered insulin, we have examined the response of the forearm of these six obese subjects to a dose of intra-arterial insulin, standardized previously in normal subjects (7). Glucagon-free insulin<sup>1</sup> was injected, along with Evans' blue dye, into the brachial artery in a dose of 100  $\mu$ U per kg body weight per minute for 26 minutes. When this dose is diluted by brachial arterial plasma flowing by the injection site, the concentration of insulin in forearm arterial plasma is approximately 300  $\mu$ U per ml, the exact concentration depending upon forearm blood flow during the experimental period. Circulation to the wrist and hand was occluded during the full period of insulin administration. Blood samples were drawn 12, 18, and 26 minutes from commencement of the insulin infusion, and for periods up to an hour thereafter.

The technique lends itself nicely to examination of local effects of hormones, since the hormone—insulin in the present experiments—can be injected into the ipsilateral brachial artery at constant rate in amounts large

<sup>1</sup> Lot no. W 3606, Eli Lilly and Company, Indianapolis, Ind.

enough to give measurable effects on the forearm, but small enough to give none in the general circulation. Thus, one observes as far as possible only the effects of the hormone on forearm tissues; the response is not, as in the case of the more conventional intravenous insulin tolerance tests, complicated by counter-regulatory measures the body may institute.

## RESULTS AND DISCUSSION

### Basal forearm muscle metabolism

Results appear in Tables I and II. Control values, which represent mean values of more than 60 experiments, are listed for comparison (8).

*Arterial concentrations.* There were no significant differences in the mean arterial concentrations of the metabolites studied in the obese group compared to the control values. The mean arterial concentration of FFA was 0.79 mEq per L in the obese subjects; while there have been reports of increased venous FFA levels in obese subjects (9), we have not, in a small series, demonstrated consistent arterial hyperlipacidemia.

*Blood flow.* Total forearm blood flow in obese subjects did not differ from control subjects. We are unable to estimate what the fractional flow is through muscle and through subcutaneous adipose tissue and skin.

*Potassium uptake.* Net movement of potassium out of resting muscle into plasma, characteristic in control subjects under the conditions of

these experiments (8, 10), was absent in the obese subjects, who had no net movement of potassium.

**Glucose uptake.** Mean glucose A-DV concentration difference and mean glucose uptake by forearm muscle were both significantly greater than those of controls.

**Lactate production.** Mean lactate A-DV concentration difference and mean lactate production by forearm muscle in obese subjects did not differ significantly from those of control subjects.

**O<sub>2</sub> uptake, CO<sub>2</sub> production, and respiratory quotient (RQ).** No differences from controls were apparent in O<sub>2</sub> consumption or CO<sub>2</sub> production by forearm muscle in obese subjects. The RQ of 0.7, as in normal muscle, is compatible with lipid oxidation.

**A-DV FFA difference.** Mean FFA A-DV concentration difference in obese subjects was +0.02  $\mu$ Eq per ml, which does not differ from the mean value in control subjects (8). Direct demonstration that this fraction of plasma lipid serves as a major substrate for forearm muscle in obese subjects has not been possible. The anatomical factors believed to underly this have been discussed in detail elsewhere (8). In brief, it is probable that release into deep venous blood of FFA from adipose tissue surrounding muscle masks the positive A-V FFA concentration difference across forearm muscle proper. Since there

is undoubtedly a greater mass of adipose tissue in the obese forearm, it is of some interest that A-DV FFA differences were not more negative in the obese subject than in controls.

**The probable metabolic fate of glucose.** The L/G ratio—which, as explained in a footnote to Table II, defines the fraction of glucose uptake accounted for by lactate production—was significantly lower in forearm muscle of obese subjects (0.24) than in controls (0.42). Seventy-five per cent of glucose abstracted from blood, therefore, remains unaccounted for and theoretically available for complete oxidation. This yields a G - L/O<sub>2</sub> ratio (see footnote to Table II)—which defines the fraction of oxygen uptake theoretically accountable for by glucose oxidation—of 0.34, or approximately twice that of controls.

Since, however, forearm muscle in obese subjects takes up more glucose than controls without any rise in RQ, it is probable that the glucose taken up in excess of that abstracted by controls is not oxidized but stored, presumably largely as muscle glycogen.

#### Forearm skin and subcutaneous tissue metabolism

Mean values for basal arterio-superficial venous (A-SV) concentration differences of glucose, lactate, potassium, and FFA in the six obese subjects appear in Table III, along with control val-

TABLE II  
Blood flow and metabolism of forearm muscle in obese subjects\*

	Controls	Obese subjects	P
Forearm blood flow, ml/min/100 ml	3.7 $\pm$ 0.17	4.3 $\pm$ 1.03	NS
A-DV lactate, $\mu$ moles/ml	-0.12 $\pm$ 0.012	-0.10 $\pm$ 0.014	NS
Q <sub>lactate</sub> , $\mu$ moles/min/100 ml arm	-0.44 $\pm$ 0.060	-0.35 $\pm$ 0.074	NS
A-DV oxygen, $\mu$ moles/ml	3.02 $\pm$ 0.168	2.88 $\pm$ 0.336	NS
Q <sub>O<sub>2</sub></sub> , $\mu$ moles/min/100 ml arm	11.6 $\pm$ 0.97	11.0 $\pm$ 1.43	NS
A-DV CO <sub>2</sub> , $\mu$ moles/ml	-2.4 $\pm$ 0.20	-2.0 $\pm$ 0.245	NS
Q <sub>CO<sub>2</sub></sub> , $\mu$ moles/min/100 ml arm	-8.7 $\pm$ 0.94	-6.9 $\pm$ 1.03	NS
Respiratory quotient	0.76 $\pm$ 0.020	0.70 $\pm$ 0.045	NS
L/G†, %	42.3 $\pm$ 8.3	24.3 $\pm$ 6.7	<0.05
G - L/O <sub>2</sub> ‡, %	16.1 $\pm$ 4.6	33.3 $\pm$ 7.5	<0.05

\* Abbreviations as in Table I. All values are means  $\pm$  SE of means.

† L/G = 100 ( $\frac{1}{2}$  lactate A-V difference/glucose A-V difference). Since production of 2 moles of lactate implies dissimulation of 1 mole of glucose, this ratio yields the percentage of glucose uptake accounted for by lactate production. Mean value for L/G is calculated from the mean lactate A-DV difference and the mean glucose A-DV difference, and its SEM is calculated from variance of A-V lactate and A-V glucose differences.

‡ G - L/O<sub>2</sub> = 100 (glucose A-V difference -  $\frac{1}{2}$  lactate A-V difference)/ $\frac{1}{2}$  oxygen A-V difference. Since that fraction of glucose, unaccounted for by lactate production, is available for complete oxidation and since 6 moles of oxygen are required for complete oxidation of 1 mole of glucose, this ratio yields the fraction of oxygen accounted for if all the glucose abstracted from blood were completely oxidized. Mean value for G - L/O<sub>2</sub> is calculated from the mean glucose A-V difference, mean lactate A-V difference, and mean O<sub>2</sub> A-V difference.

TABLE III  
*Arterio-superficial venous differences in obese subjects and in controls\**

	Controls		Obese subjects	p
Potassium, $\mu\text{mole/ml}$	$-0.03 \pm 0.021$	[33]	$+0.01 \pm 0.026$	NS
Glucose, $\mu\text{mole/ml}$	$+0.19 \pm 0.027$	[26]	$+0.23 \pm 0.047$	NS
Lactate, $\mu\text{mole/ml}$	$-0.18 \pm 0.015$	[33]	$-0.14 \pm 0.020$	NS
L/G, %	$47.3 \pm 7.6$	[33]	$31.6 \pm 8.3$	<0.05
Oxygen, $\mu\text{mole/ml}$	$1.93 \pm 0.273$ †	[5]	$1.55 \pm 0.24$	NS
CO <sub>2</sub> , $\mu\text{mole/ml}$	$-1.56 \pm 0.285$ †	[5]	$-1.45 \pm 0.178$	NS
FFA, $\mu\text{mole/ml}$	$-0.13 \pm 0.028$	[34]	$-0.07 \pm 0.020$	<0.05

\* Abbreviations as in Tables I and II. Values are means  $\pm$  SE of means. Number of control subjects shown in brackets.

† Means  $\pm$  SE of means from a previously unreported study of five young subjects of normal body weight.

ues (8). Although mean A-SV concentration differences for potassium, glucose, and lactate were changed in a direction similar to changes in A-DV, *t* tests of these changes suggested ( $p > 0.05$ ) that they occurred by chance. Mean A-SV difference for FFA was, however, significantly less negative than in controls.

#### *Evidence for endogenous hyperinsulinism*

In control subjects, A-DV concentration differences reflect chiefly metabolism of muscle and A-SV, chiefly metabolism of skin and subcutaneous adipose tissue. A-SV glucose differences are greater (more positive) and A-SV O<sub>2</sub> differences are smaller (less positive) than the respective A-DV differences. Lactate and FFA SV-A differences are greater (more negative), whereas potassium SV-A differences are smaller (less negative) than the respective DV-A differences (8).

It is conceivable but unlikely that differences between control and obese subjects with respect to A-DV concentrations and values for  $\dot{Q}$  represent nothing more than the increased contribution to DV effluent of blood draining the larger mass of adipose tissue in the obese forearm. If this effect were responsible for the increase in  $\dot{Q}$  of glucose and absence of negative  $\dot{Q}$  of potassium in obese subjects, then A-DV differences of all metabolites in obesity ought to show the same tendency to resemble A-SV differences of controls. Our studies do not, however, support this interpretation: A-DV O<sub>2</sub>, CO<sub>2</sub>, and lactate differences in obese subjects did not differ from A-DV concentrations of control subjects, but clearly differed from their A-SV concentrations (Tables I and II).

These findings also negate the possibility that our observations merely represent redistribution

of blood between deep and superficial forearm drainage beds. This would uniformly obscure or eliminate the differences normally found in A-V concentration differences of metabolites from the two drainage beds. A-DV O<sub>2</sub>, CO<sub>2</sub>, and FFA differences clearly differ from A-SV differences in obese subjects. (Compare Tables I and II with Table III.)

It is probable, therefore, that deviations from normal forearm metabolism in obese subjects cannot be attributed solely either to alterations in forearm blood flow or to the undoubtedly greater mass of adipose tissue in the obese forearm.

Previous studies from this laboratory (7) have demonstrated that insulin infused into the brachial artery of control subjects reverses the net potassium efflux and increases glucose uptake by forearm muscle. Only a minor fraction of the glucose is accounted for by lactate production and none is oxidized to CO<sub>2</sub>. The RQ of forearm muscle does not rise. The effect of insulin on the superficial drainage bed of the forearm is to increase A-SV glucose concentration difference, with a fall in the L/G ratio, and to convert basal negative A-SV FFA differences to a net positive A-SV difference (11). Metabolic events in the forearm of obese subjects in the absence of exogenous insulin resemble those in the normal forearm exposed to insulin and suggest that in obesity there is hyperinsulinism that is presumably adaptive to unusual quantities of substrate. This hypothesis was advanced by Brobeck, Tepperman, and Long (12) some years ago and gains support from the demonstration of islet cell hyperplasia in the early or "active" phase of obesity by Ogilvie in man (13) and by Mayer (14) in rats.

We are very grateful to Drs. S. A. Berson and R. S. Yalow for determining for us by their im-

immunoassay technique (15) plasma insulin concentrations in our six obese subjects and in four normal subjects of the same age group. Results appear in Table IV. Plasma insulin concentration was higher in obese subjects than in those of normal body weight ( $p < 0.01$ ), although insulin concentration in our normal group may be slightly less than in the over-all experience of Yalow and Berson (15).

#### Effect of insulin on forearm muscle metabolism

Results appear in Table V.

**Insulin concentration in forearm plasma.** This is established by determining the ratio of the known rate of injection of insulin, 100  $\mu\text{U}$  per kg per minute, to forearm plasma flow measured by Evans blue dye. Values varied from 200 to 450  $\mu\text{U}$  per ml, levels comparable to those achieved in an earlier study on control subjects (7).

**Plasma flow.** It has been pointed out repeatedly that both blood flow and arterial concentration must remain constant for proper employment of the Fick principle (16). Plasma flow before and during the period of insulin infusion remained acceptably constant; that is, it did not vary by more than 20 per cent about the mean in any of the subjects studied. In one subject, P, a marked increase in plasma flow occurred in the period after the insulin infusion.

**Arterial concentrations.** Mean changes of less than 4 per cent were recorded in arterial glucose, lactate, and potassium concentrations during and after insulin administration. Arterial concentration of FFA tended to be more unstable than other

TABLE IV  
Arterial plasma insulin concentrations  
in control and obese subjects\*

Controls†		Obese subjects	
$\mu\text{U/ml}$		$\mu\text{U/ml}$	
5		W	15.5
9		Z	19.0
10.5		G	36.0
11.5		F	29.0
		P	46.0
		L	42.0
Mean	9.0		31.3
SEM	1.43		4.96
		$p < 0.01$	

\* Plasma insulin concentrations were determined by Drs. S. A. Berson and R. S. Yalow by their immunoassay technique (15). All values are the means of two independent assays;  $p$  is probability that difference between mean in control and in obese group might occur by chance, estimated by  $t$  test.

† Controls were four normal nonobese young men from whom blood samples were obtained in the basal state after a fast of 15 hours.

metabolites, as is consistent with the much greater lability of this plasma lipid fraction.

**Glucose.** Glucose uptake in obese subjects after insulin administration was distinctly less than in controls (Figure 1). In only one of the six obese subjects did the A-DV concentration difference exceed 1  $\mu\text{mole}$  per ml, and the maximal uptake achieved was always less than 5  $\mu\text{moles}$  per minute per 100 ml forearm, which was the lowest peak effect recorded in any of the control subjects (7).

**Lactate.** There was a small but definite increase in lactate production during and after insulin administration. Since glucose uptake increased to

TABLE V  
Mean effect of insulin on forearm metabolism in obesity\*

Time after insulin started	Plasma flow		A-DV FFA		A-DV lactate	
	Obese†	Control ‡	Obese†	Control §	Obese†	Control ‡
<i>min</i>	<i>ml/min/100 ml arm</i>		<i><math>\mu\text{moles/ml}</math></i>		<i><math>\mu\text{moles/ml}</math></i>	
0	2.6 $\pm$ 0.62	2.1 $\pm$ 0.14	+0.02 $\pm$ 0.021	+0.02 $\pm$ 0.038	-0.10 $\pm$ 0.015	-0.14 $\pm$ 0.026
12	2.5 $\pm$ 0.42	2.7 $\pm$ 0.32	+0.04 $\pm$ 0.024	+0.02 $\pm$ 0.022	-0.12 $\pm$ 0.071	-0.16 $\pm$ 0.035
18	2.9 $\pm$ 0.84	2.6 $\pm$ 0.26	+0.05 $\pm$ 0.027	+0.06 $\pm$ 0.021	-0.08 $\pm$ 0.022	-0.16 $\pm$ 0.026
26	2.7 $\pm$ 0.55	3.1 $\pm$ 0.28	+0.09 $\pm$ 0.020	+0.08 $\pm$ 0.014	-0.12 $\pm$ 0.024	-0.22 $\pm$ 0.034
40	2.6 $\pm$ 0.10	2.7 $\pm$ 0.24	+0.09 $\pm$ 0.020	+0.09 $\pm$ 0.033	-0.13 $\pm$ 0.038	-0.24 $\pm$ 0.042
60	3.9 $\pm$ 1.70	2.6 $\pm$ 0.32	+0.09 $\pm$ 0.020	+0.02 $\pm$ 0.041	-0.15 $\pm$ 0.027	-0.24 $\pm$ 0.034

\* Abbreviation as in Table I. All values are means  $\pm$  SE of means. Insulin administered intra-arterially for 26 minutes beginning at time zero.

† Group of six subjects.

‡ Group of ten young subjects of normal body weight (7).

§ Group from a previously unreported study of five young subjects of normal body weight. Reported control plasma flows therefore cannot be employed to calculate  $\dot{Q}_{\text{FFA}}$  for control subjects.

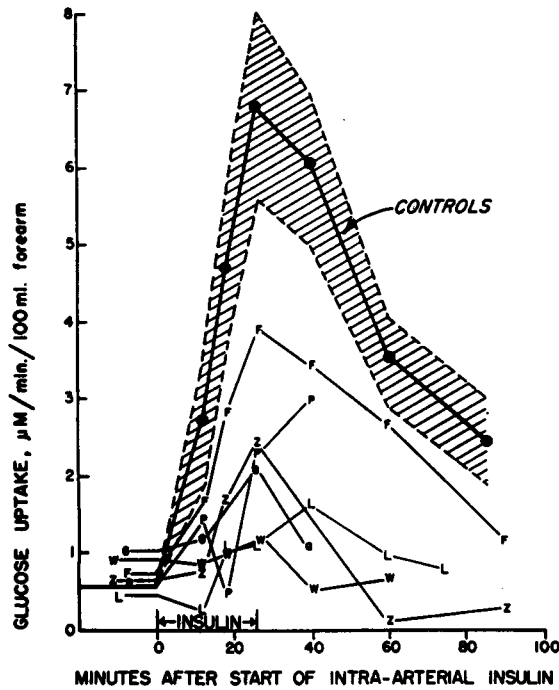


FIG. 1. EFFECT OF INSULIN ON FOREARM GLUCOSE UPTAKE IN OBESE SUBJECTS. Shaded area represents mean  $\pm$  SE of mean among 10 control subjects (7). Individual lines indicate glucose uptake in obese subjects, identified by initials.

a greater extent than lactate production, the L/G ratio dropped from a control value of 0.24 to less than 0.10.

$\dot{Q}_{O_2}$ ,  $\dot{Q}_{CO_2}$ , and RQ. Observations on  $O_2$  consumption,  $CO_2$  production, and RQ were fragmentary only, being confined to the 26 minute sample, taken just before the conclusion of the insulin infusion, and the 60 minute sample. Such measurements as were made showed no change in either  $\dot{Q}_{O_2}$ ,  $\dot{Q}_{CO_2}$ , or RQ which corresponds with our experience in control subjects.

*Potassium.* In the basal state, the net movement of potassium out of forearm muscle into venous blood is absent in obese subjects. Administration of insulin resulted in mean potassium A-DV differences becoming more positive. Total movement of potassium achieved under the influence of exogenous insulin was significantly less in obese subjects than the comparable change in control subjects (Figure 2).

*FFA.* A-DV concentration difference of FFA increased from a mean basal value not significantly

different from zero to  $0.1 \mu Eq$  per ml after insulin administration. This effect is probably achieved through inhibition of FFA release from adipose tissue interspersed between muscle fibers. Uptake of FFA by forearm muscle unmasked by insulin administration is sufficient to account for about 50 per cent of its  $O_2$  consumption.

#### *Effect of insulin on forearm skin and subcutaneous adipose tissue metabolism*

Values for A-SV concentration differences of glucose, lactate, and FFA after insulin administration, determined in five obese subjects, are shown in Table VI. In the sixth subject, L, the SV catheter was accidentally dislodged.

*Glucose.* Glucose A-SV differences increased after insulin administration, but significantly less so than in controls.

*Lactate.* There was a small but significant increase in lactate SV-A differences. The L/G ratio dropped from 0.31 to 0.22.

*FFA.* Insulin effectively inhibited release of FFA from forearm adipose tissue in obese subjects. Insulin-induced change in A-SV FFA concentration difference was significantly less in obese subjects than in controls (Figure 3).

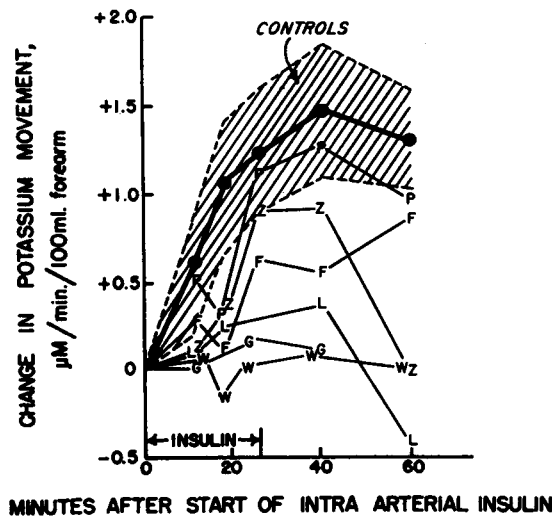


FIG. 2. EFFECT OF INSULIN ON FOREARM POTASSIUM UPTAKE IN OBESE SUBJECTS, EXPRESSED AS THE INCREASE IN NET INWARD MOVEMENT OF POTASSIUM COMPARED TO POTASSIUM MOVEMENT AT TIME ZERO. Shaded area represents mean  $\pm$  SE of mean among 10 control subjects (7). Individual lines indicate change in potassium movement in obese subjects, identified by initials.

TABLE VI  
 Mean effect of insulin on arterio-superficial venous concentrations of glucose, lactate, and FFA in obesity\*

Time after insulin started min	A-SV glucose		A-SV lactate		A-SV FFA	
	Obese†	Control ‡	Obese†	Control ‡	Obese†	Control ‡
	$\mu\text{mole/ml}$		$\mu\text{mole/ml}$		$\mu\text{mole/ml}$	
0	0.23 $\pm$ 0.047	0.17 $\pm$ 0.013	-0.14 $\pm$ 0.020	-0.15 $\pm$ 0.015	-0.07 $\pm$ 0.020	-0.16 $\pm$ 0.033
12	0.21 $\pm$ 0.044	0.43 $\pm$ 0.048	-0.17 $\pm$ 0.009	-0.12 $\pm$ 0.011	-0.06 $\pm$ 0.010	+0.02 $\pm$ 0.054
18	0.27 $\pm$ 0.054	0.65 $\pm$ 0.060	-0.13 $\pm$ 0.014	-0.17 $\pm$ 0.029	+0.01 $\pm$ 0.036	+0.06 $\pm$ 0.016
26	0.36 $\pm$ 0.078	0.83 $\pm$ 0.038	-0.17 $\pm$ 0.031	-0.23 $\pm$ 0.030	+0.02 $\pm$ 0.032	+0.06 $\pm$ 0.020
40	0.30 $\pm$ 0.084	0.80 $\pm$ 0.032	-0.13 $\pm$ 0.044	-0.21 $\pm$ 0.035	+0.02 $\pm$ 0.014	+0.09 $\pm$ 0.023
60	0.35 $\pm$ 0.039	0.50 $\pm$ 0.044	-0.16 $\pm$ 0.012	-0.24 $\pm$ 0.037	+0.03 $\pm$ 0.020	-0.03 $\pm$ 0.013

\* Insulin administered intra-arterially for 26 minutes beginning at time zero. Values are means  $\pm$  SE of means.

† Group of five subjects.

‡ Group from a previously unreported study of five young subjects of normal body weight.

*The apparent paradox of endogenous hyperinsulinism and insulin resistance in obesity*

In early obesity there is increased circulating insulin in the basal state, and the obese subjects, judged by the observations of forearm metabolism,

do respond to this increased endogenous insulin. Yet they resist, i.e., respond less than normals to administered insulin. This apparent paradox can be resolved only if it can be shown either that they are not really resistant to exogenous insu-

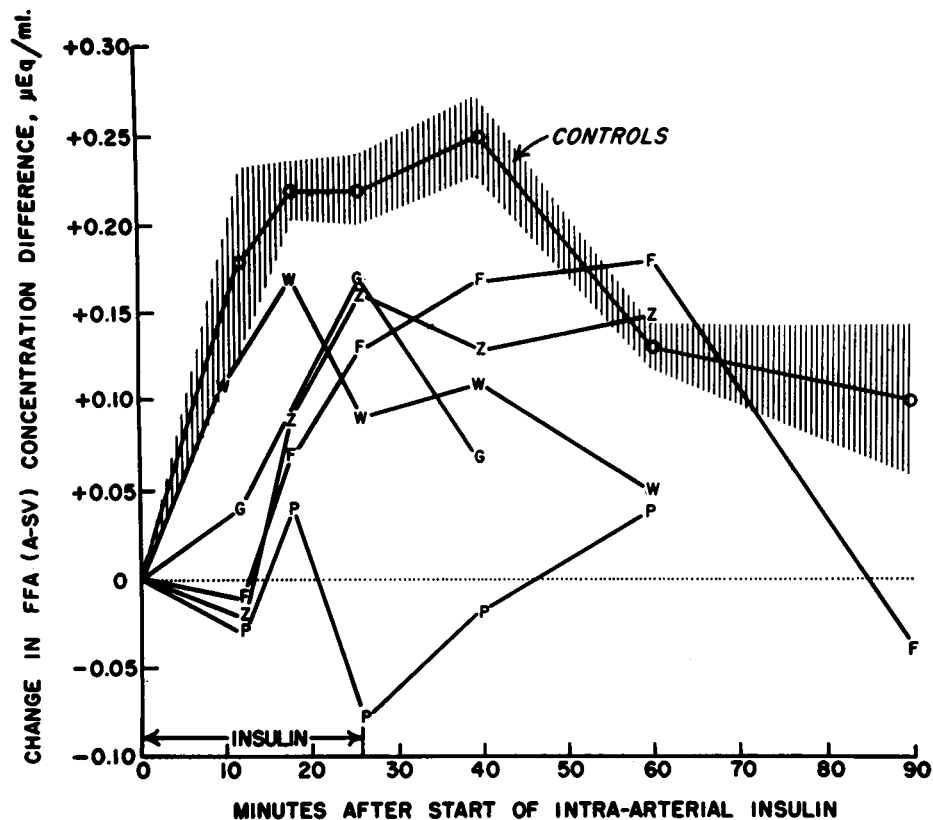


FIG. 3. EFFECT OF INSULIN ON FFA ARTERIO-SUPERFICIAL VENOUS (A-SV) CONCENTRATION DIFFERENCES IN OBESE SUBJECTS, EXPRESSED AS THE CHANGE IN FFA A-SV CONCENTRATION DIFFERENCE COMPARED TO A-SV DIFFERENCE AT TIME ZERO. Shaded area represents mean  $\pm$  SE of mean among 5 previously unreported control subjects of normal body weight. Individual lines indicate change in A-SV differences in obese subjects, identified by initials.

lin or that they are in fact also resistant to their own insulin.

For the first solution, we have considered only the possibility that they might appear superficially to resist exogenous insulin if the quantity administered were superimposed on such a large pool that the relative increase in concentration is small compared to that after administration of the same amount to normal subjects. The obese subject, moving up the dose-response curve only slightly, would then display only a small metabolic response to insulin, appropriate to the normal dose-response curve, and would not be truly insulin-resistant. This hypothesis, however, is untenable in that the quantity of insulin administered to obese subjects was sufficient to raise forearm arterial insulin concentration by about 15 times, so that if they were not truly insulin-resistant, as we have defined the phrase, they ought to have responded quantitatively like normal subjects.

The second solution to the paradox is more likely, i.e., obese subjects may be resistant to their own insulin. We have no data on the insulin dose-response curve describing forearm metabolism, so we cannot say that normal subjects, in whom insulin concentration was as high as that found endogenously in obese subjects, would respond to a greater extent, but we suspect that this is the case. This suspicion is not weakened by the report by Karam, Grodsky, and Forsham (17) that in obesity an apparently normal response to glucose tolerance tests occurs only at the expense of an abnormally large increase in circulating insulin. This is reminiscent of the pattern described by Yalow and Berson (15) in maturity onset stable diabetes.

*Relationship between simple obesity and maturity onset stable diabetes*

About 80 per cent of patients with maturity onset stable diabetes are obese (18). It is apparent that some of the features associated with this condition are shared by subjects with simple obesity, for example, elevation of plasma insulin concentration (15), resistance to exogenous insulin with respect to glucose movement into forearm muscle (19), and a greatly exaggerated plasma insulin response to a glucose load (17). The following sequence is suggested: chronic substrate excess

in obesity causes adaptive hyperinsulinism, leading ultimately to "high output failure" of the pancreatic islets. In line with this, Ogilvie (20) found that whereas glucose tolerance was usually normal in the early phases of obesity, it was abnormal in all subjects in whom obesity had been present for longer than 18 years. In John's series (21), evidence of glucose intolerance was present in over half the adult obese subjects he examined, but this was not the case in obese children. The factors that determine whether the obese subject adapts successfully or not to chronic substrate excess remain to be established. One important link is probably provided by the recent demonstration by Vallance-Owen and Lilley (22) of an antagonist to insulin in the plasma of obese prediabetics.

*Possible factors producing insulin resistance in simple obesity*

There remains the question of why insulin resistance occurs in obesity. Eckert, Green, and Migeon (23) found cortisol production increased in simple obesity. Although this suggests that insulin resistance in obesity may result from cortisol antagonism, it is unlikely that this is the case. In disturbances of the hypophyseal-adrenocortical axis, including Cushing's syndrome (24), the metabolic pattern of insulin resistance differs from that in obesity. In obesity, there is resistance to all the metabolic effects of insulin we have studied, but in disease of the hypophyseal-adrenocortical axis, expressions of insulin resistance are limited to less responsiveness with respect to glucose and potassium uptake by the forearm tissues, and insulin-induced inhibition of FFA release from forearm adipose tissue is at least normal.

We are left with no really completely satisfying explanation of insulin resistance in obesity. It is possible that resistance in this case is simply a manifestation of tolerance to chronic (endogenous) administration of insulin.

Whatever the explanation, insulin resistance appears to be a consequence of obesity and not a primary defect. It was reversed after shedding of excess adipose tissue in one subject (unpublished observations by Andres, Baltzan, and Zierler), and Newburgh and Conn (24) found that, even in later stages of obesity, abnormal responses to glucose tolerance tests disappeared after weight loss.



## SUMMARY

1. Forearm metabolism (glucose and potassium uptake and lactate production by muscle, and release of free fatty acids from adipose tissue) in obese subjects not receiving insulin resembles that of normal subjects in whom insulin is infused intra-arterially. From this effect, confirmed by assay of plasma insulin concentration, it is likely that hyperinsulinism accompanies early obesity.

2. The respiratory quotient of forearm muscle in obese subjects is 0.7, as in normal muscle, which is compatible with oxidation of lipid.

3. Intra-arterial administration of insulin produces significantly less glucose and potassium uptake by forearm muscle and significantly less glucose uptake and movement of free fatty acids in forearm adipose tissue in obese subjects than in controls.

4. These studies may provide a link in the chain of evidence incriminating simple obesity as a precursor of maturity onset stable diabetes.

## ACKNOWLEDGMENT

We are indebted to those who volunteered for these experiments, and to Misses Ellen Rogus and Sara Ann Verplanck and Mrs. James Cullen for technical assistance.

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