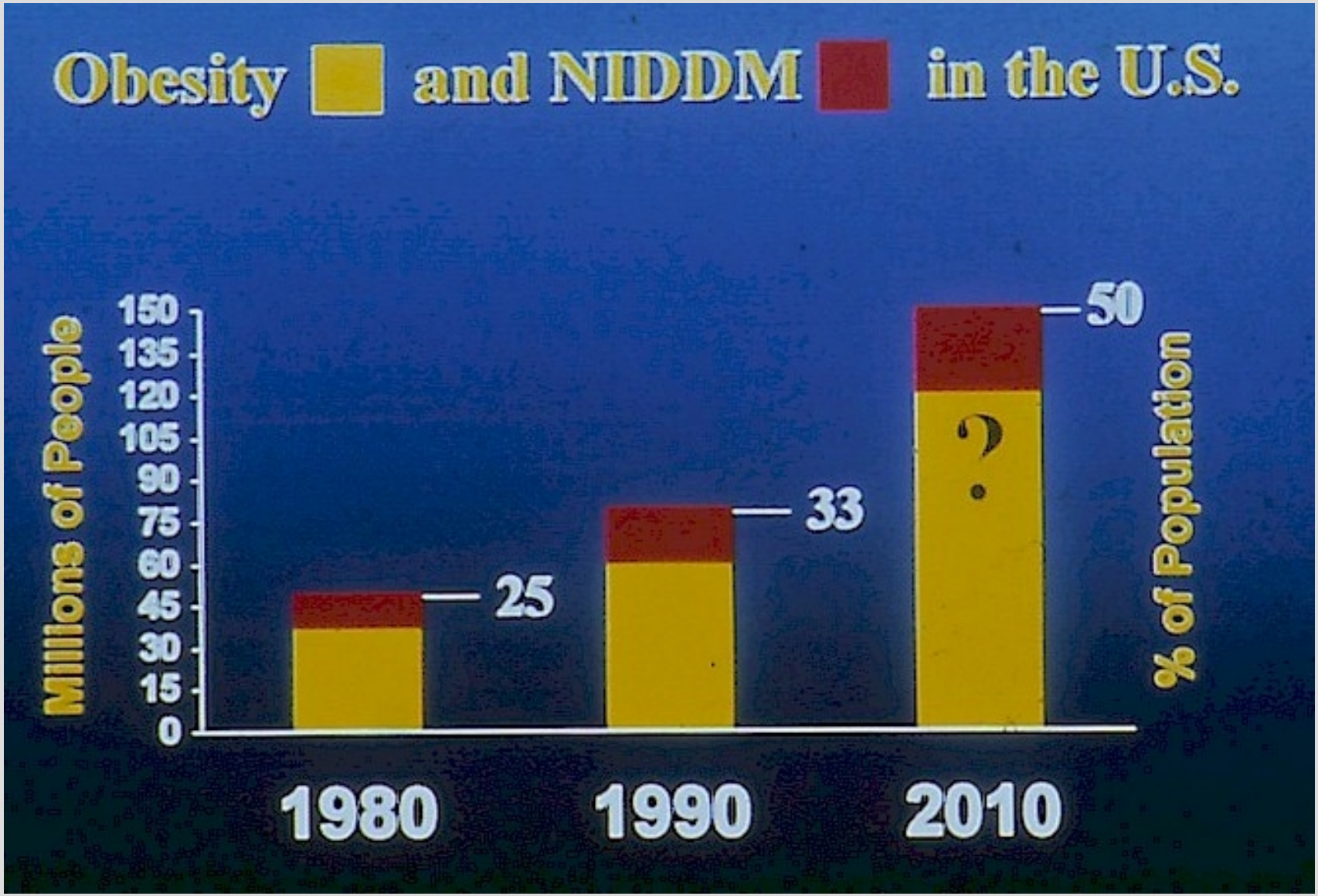

Obesity and NIDDM in the U.S.
Millions of People
150
135
120
105
90
75
60
45
30
15
0
25
33
50
?
% of Population
1980
1990
2010

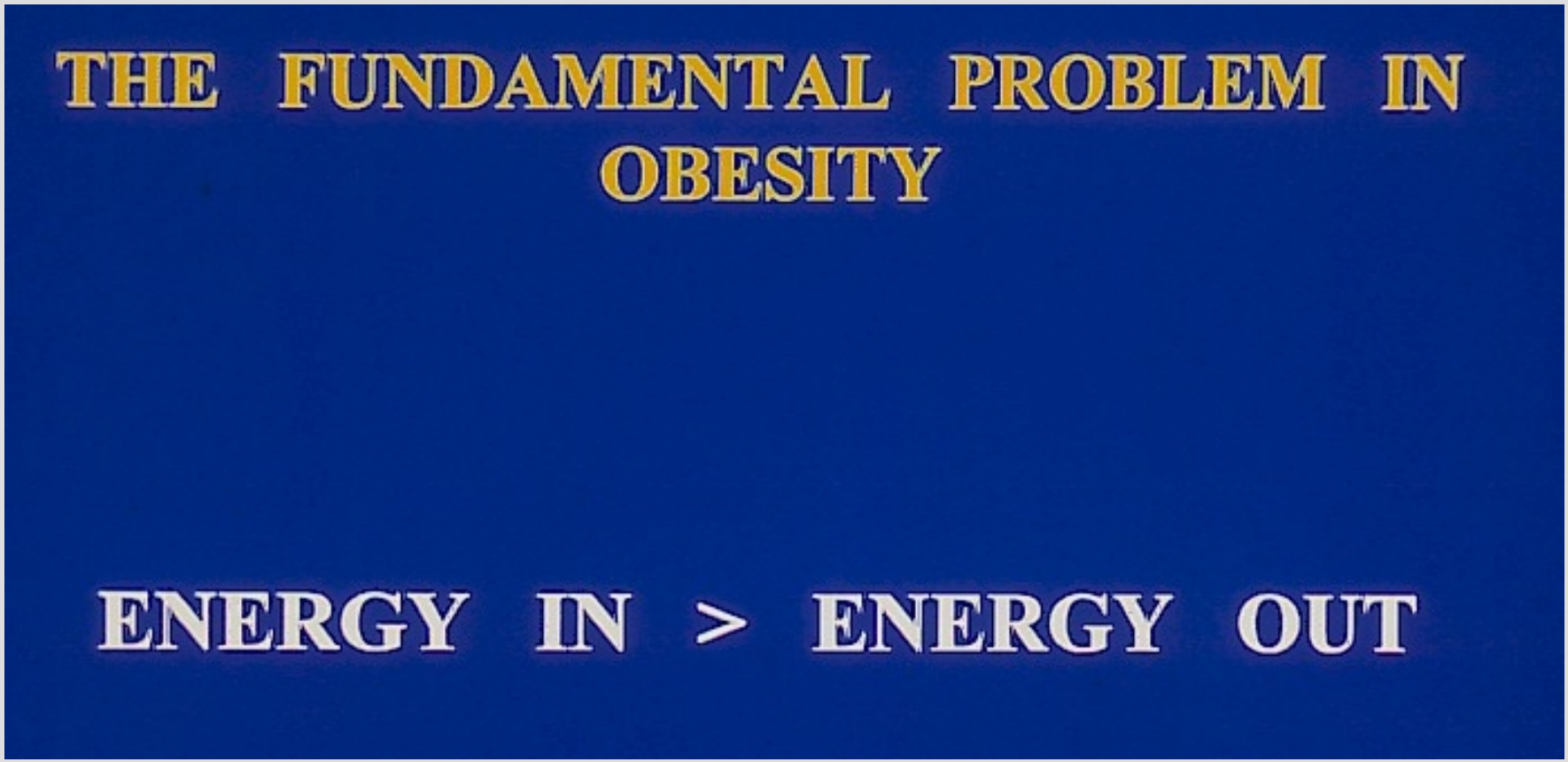

THE FUNDAMENTAL PROBLEM IN OBESITY
ENERGY IN > ENERGY OUT

Table 1. Protocol for Long-Term Overfeeding of Monozygotic Twins

A. Twelve pairs of young adult male identical twins were sequestered.

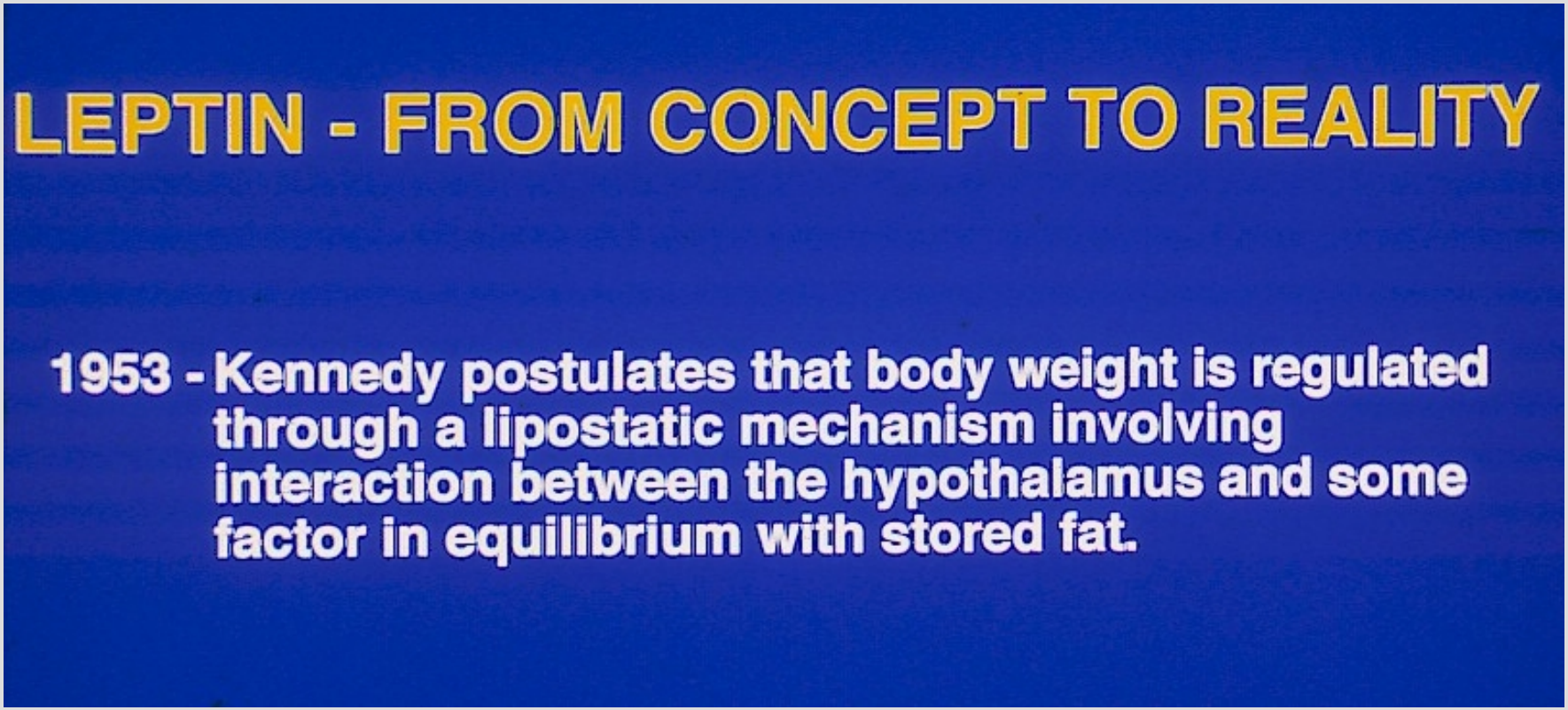
B. Baseline daily caloric intake at a stable body weight was established during a 14 day observation period.

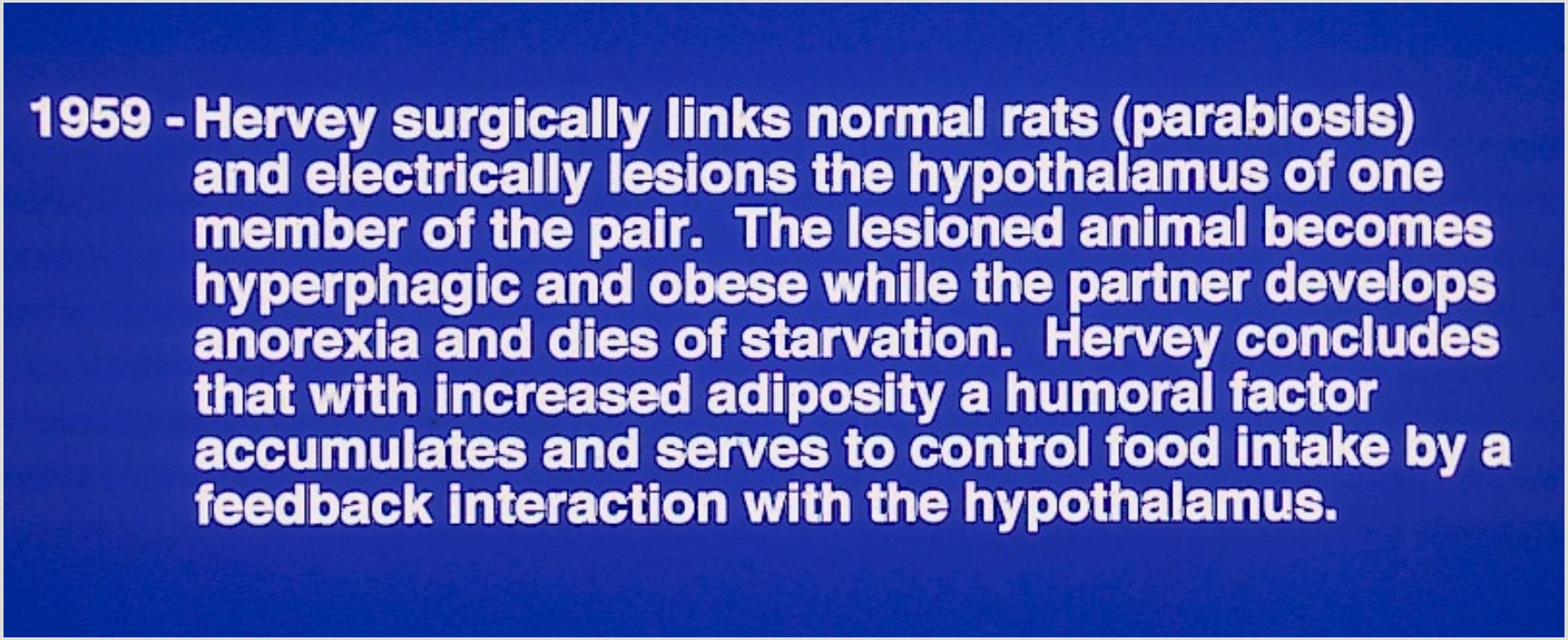
C. During the next 100 days each subject consumed 1,000 kcal more than his baseline intake for 6 days a week.

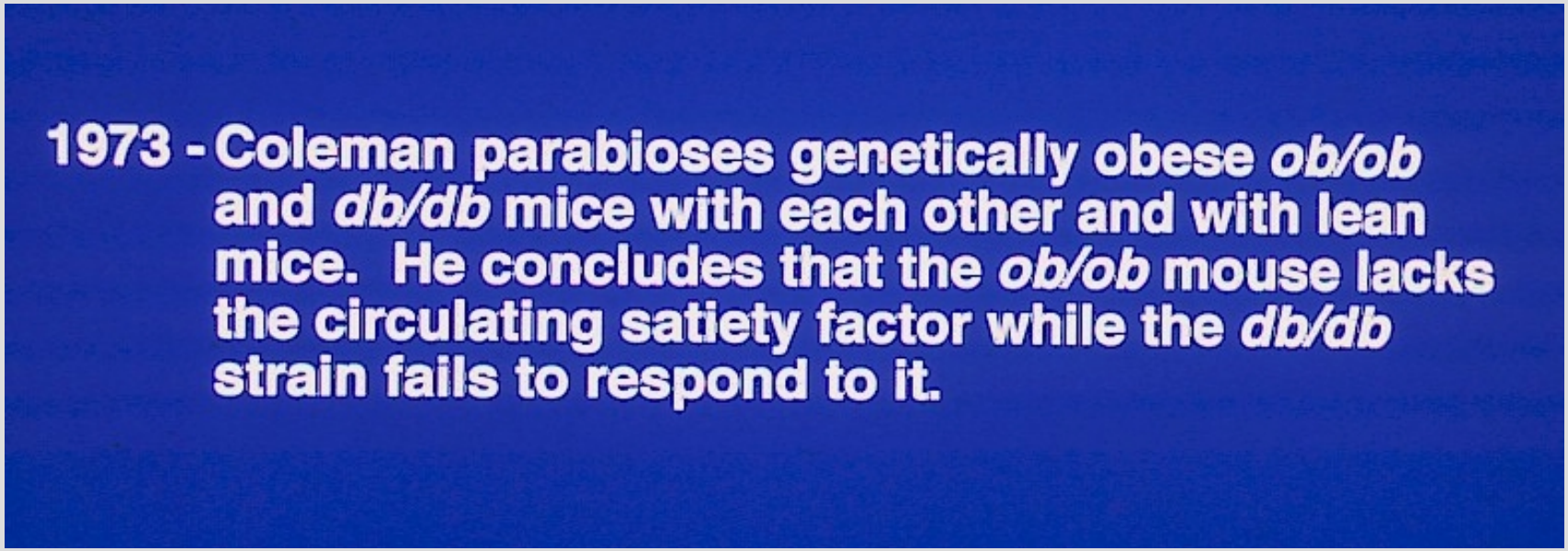
D. The total excess amount each subject consumed was 84,000 kcal.

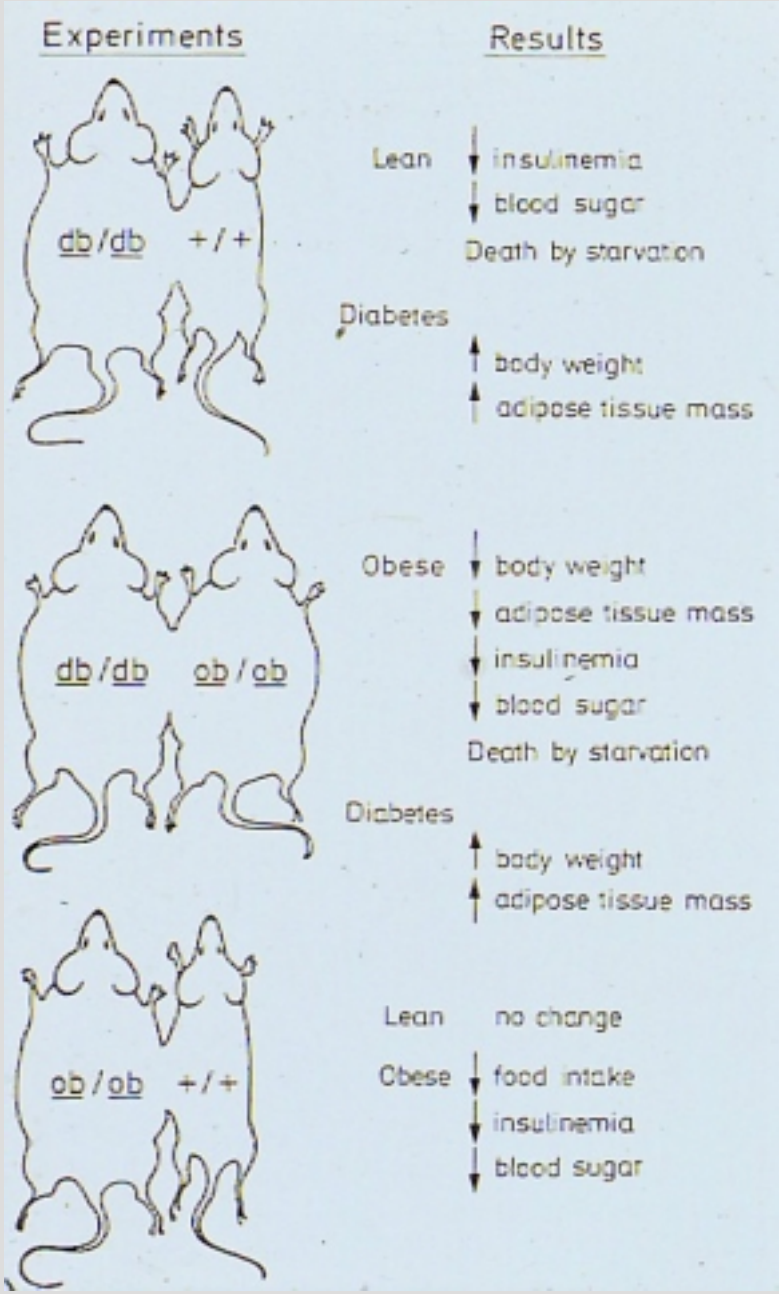
Table 2. Effect of 100 Days of Overfeeding in 12 Pairs of Male Monozygotic Twins

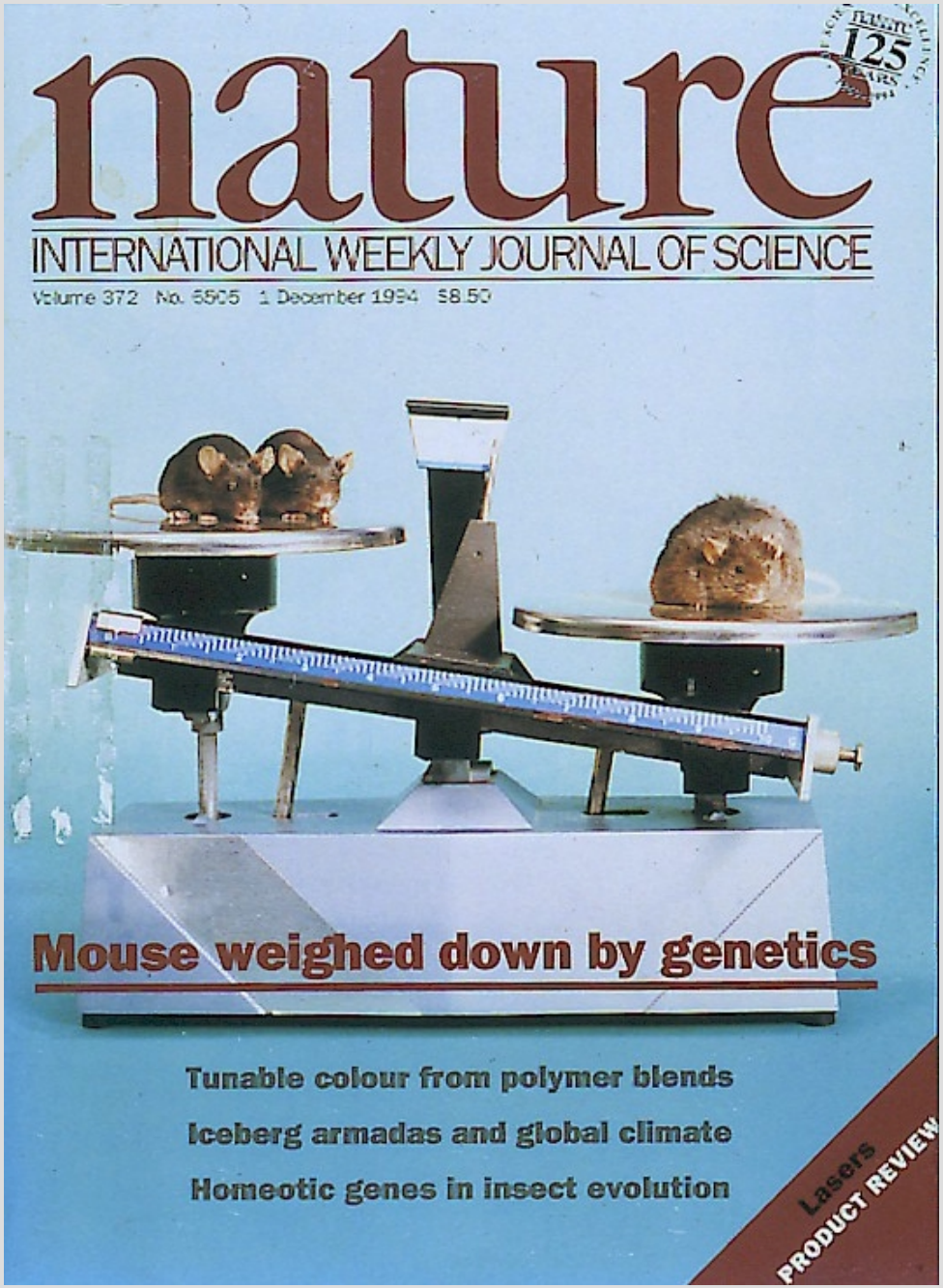
	Averages*
Gain in body weight	8.1 ± 2.4 kg (SD)
Range	4.3 to 13.3 kg
Ratio of fat mass to fat free mass	0.13 increased to 0.22
Estimated change in subcutaneous fat	76 increased to 129 mm
*Statistical significance $P < 0.001$ for all above values	
Gain in fat mass	5.4 kg or 52, 220 kcal
Gain in fat free mass	2.7 kg or 2,754 kcal
Calculated energy dissipated	29,000 kcal


LEPTIN - FROM CONCEPT TO REALITY
1953 - Kennedy postulates that body weight is regulated through a lipostatic mechanism involving interaction between the hypothalamus and some factor in equilibrium with stored fat.

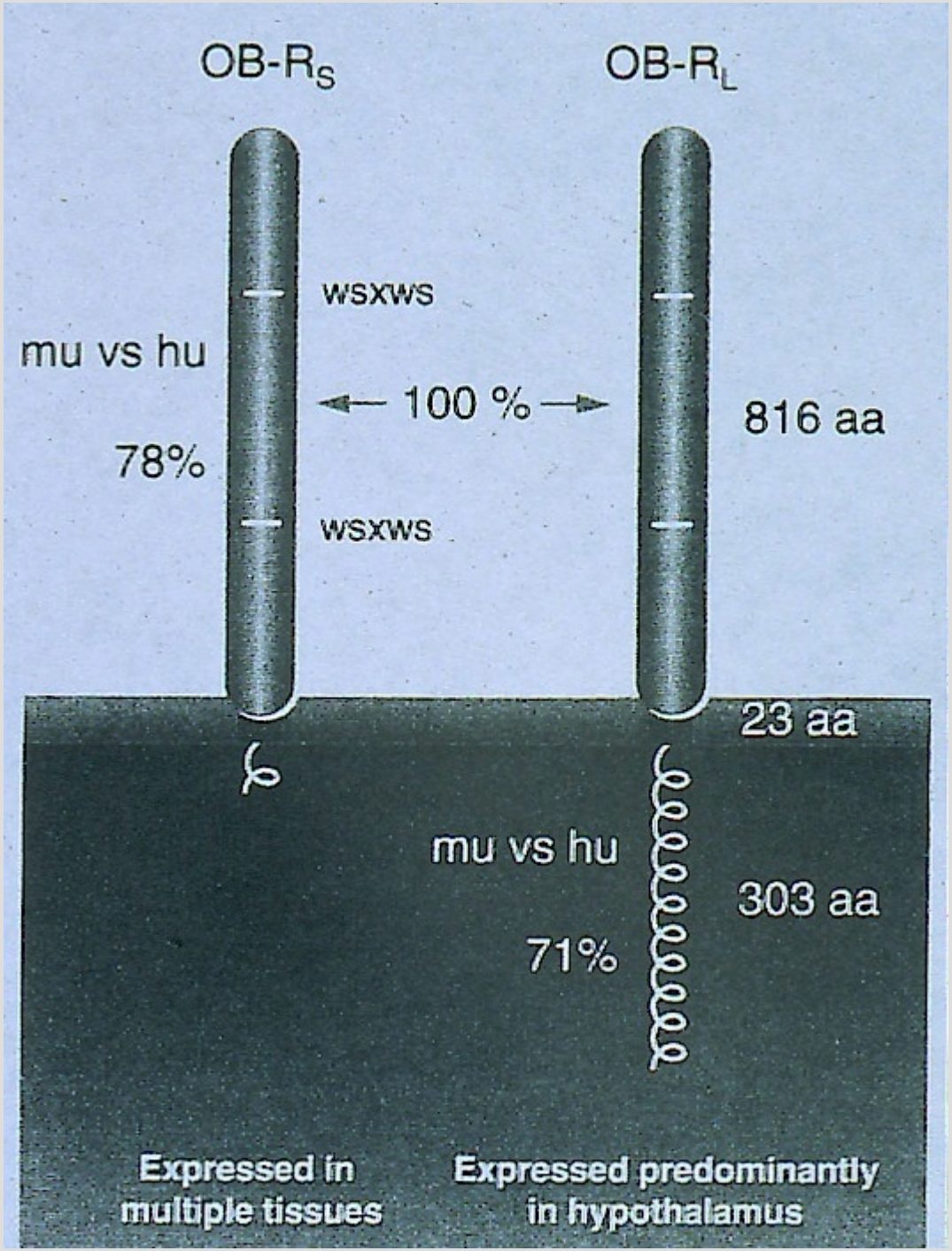

1959 - Hervey surgically links normal rats (parabiosis) and electrically lesions the hypothalamus of one member of the pair. The lesioned animal becomes hyperphagic and obese while the partner develops anorexia and dies of starvation. Hervey concludes that with increased adiposity a humoral factor accumulates and serves to control food intake by a feedback interaction with the hypothalamus.

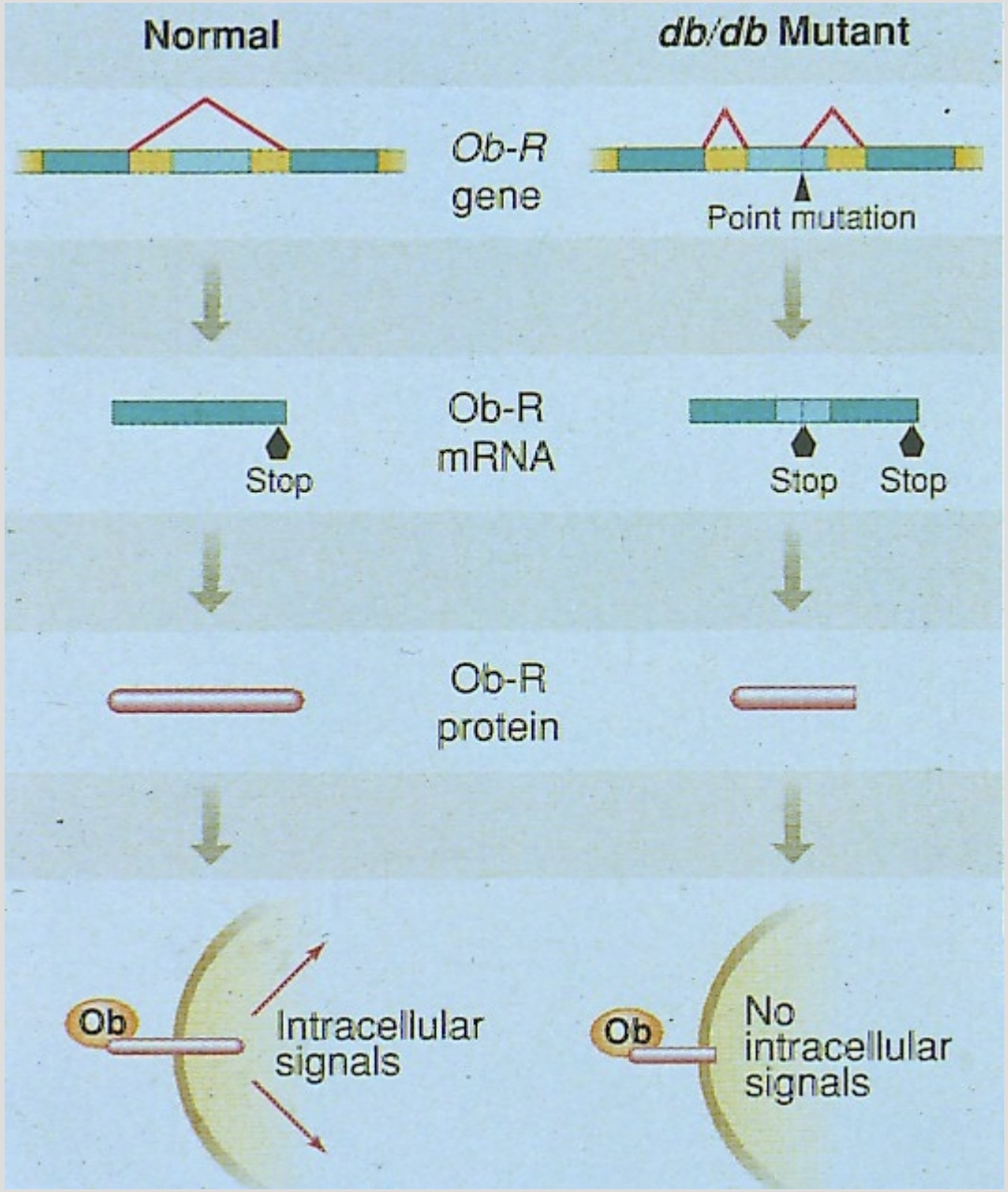

1973 - Coleman parabioses genetically obese *ob/ob* and *db/db* mice with each other and with lean mice. He concludes that the *ob/ob* mouse lacks the circulating satiety factor while the *db/db* strain fails to respond to it.


Experiments
Results
db/db +/+
Lean
insulinemia
blood sugar
Death by starvation
Diabetes
body weight
adipose tissue mass
db/db ob/ob
Obese
body weight
adipose tissue mass
insulinemia
blood sugar
Death by starvation
Diabetes
body weight
adipose tissue mass
ob/ob +/+
Lean
no change
Obese
food intake
insulinemia
blood sugar

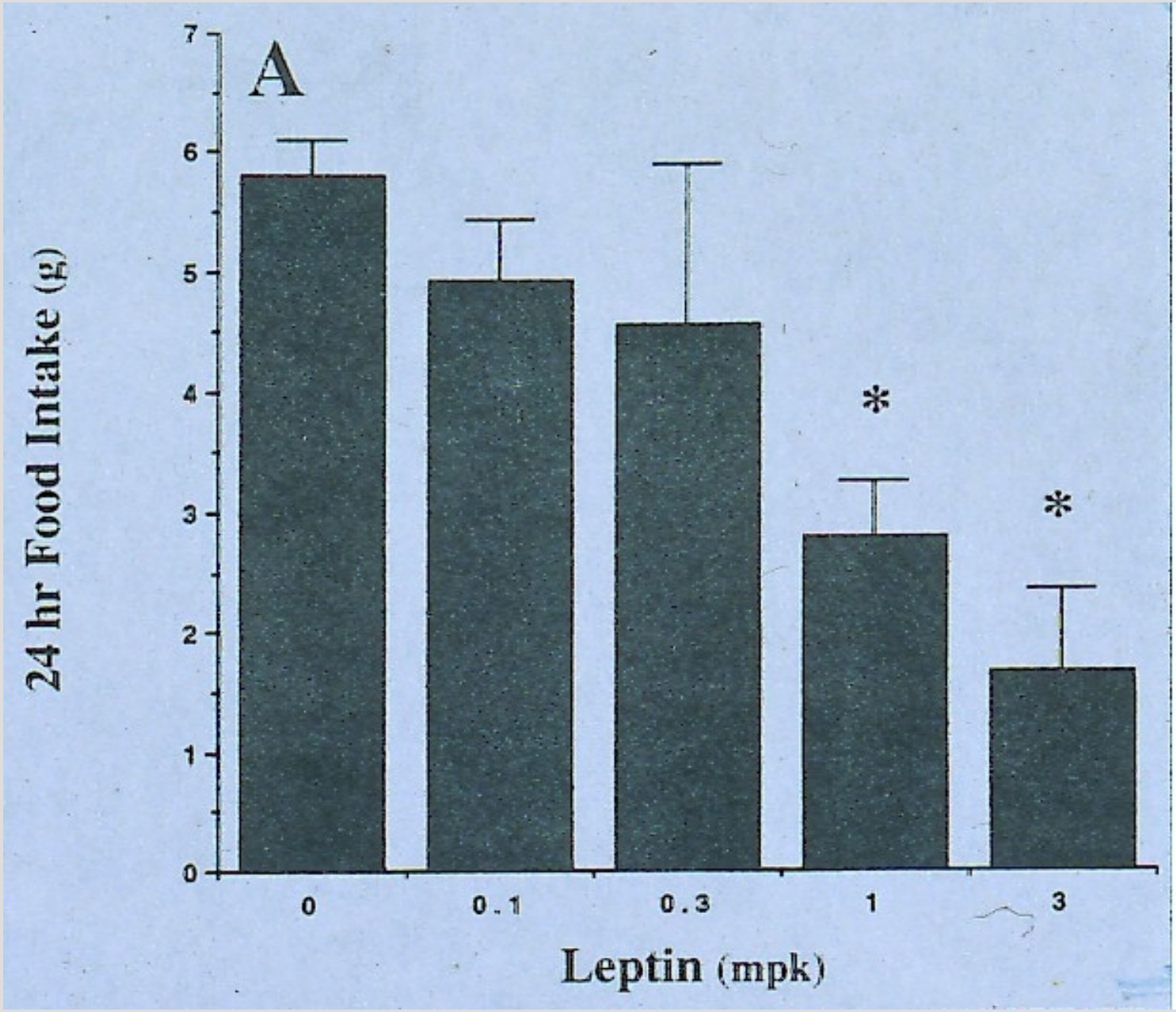

nature
INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
Volume 372 No. 6505 1 December 1994 $8.50
Mouse weighed down by genetics
Tunable colour from polymer blends
Iceberg armadas and global climate
Homeotic genes in insect evolution
Lasers
PRODUCT REVIEW

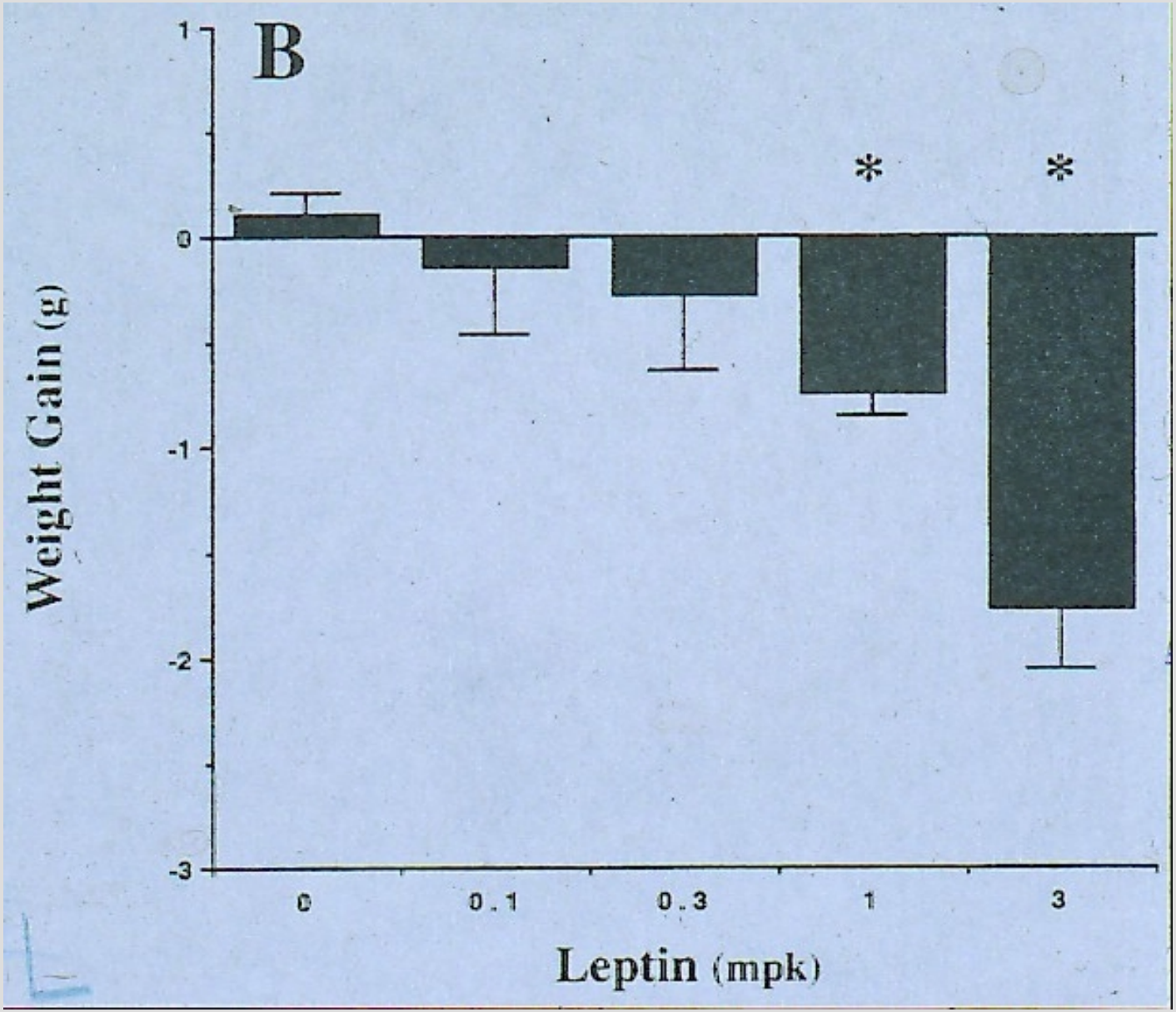
1994 - Friedman and colleagues clone the murine and human *ob* genes and define the mutations in two strains of *ob/ob* mice. The gene is expressed only in fat tissue. The predicted size of the nascent OB protein is ~18 kDa. The presence of a 2 kDa leader sequence suggests that the mature 16 kDa protein is secreted from fat depots.

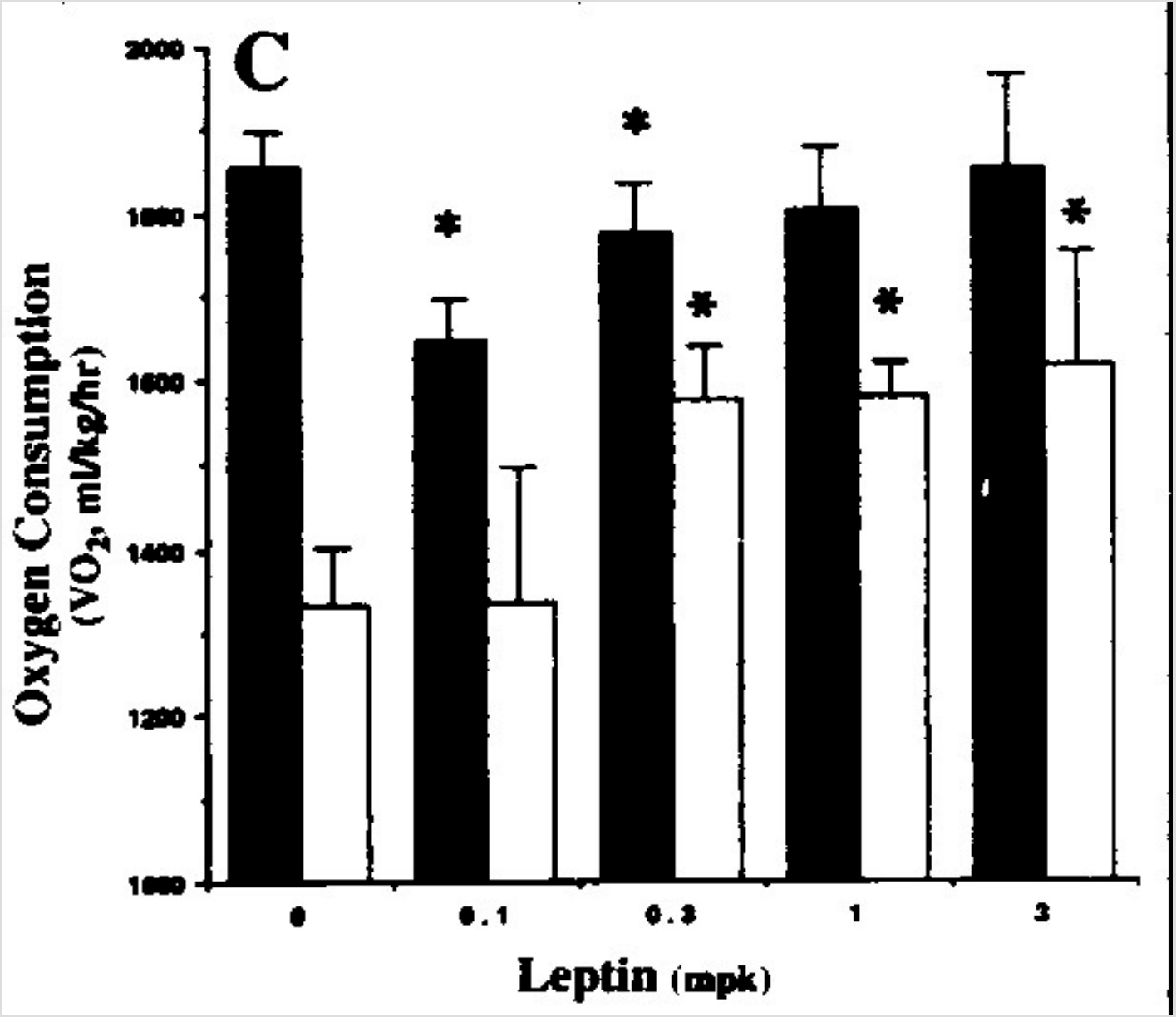

OB-R$_S$
OB-R$_L$
WSXWS
mu vs hu
100 %
816 aa
78%
WSXWS
23 aa
mu vs hu
303 aa
71%
Expressed in multiple tissues
Expressed predominantly in hypothalamus

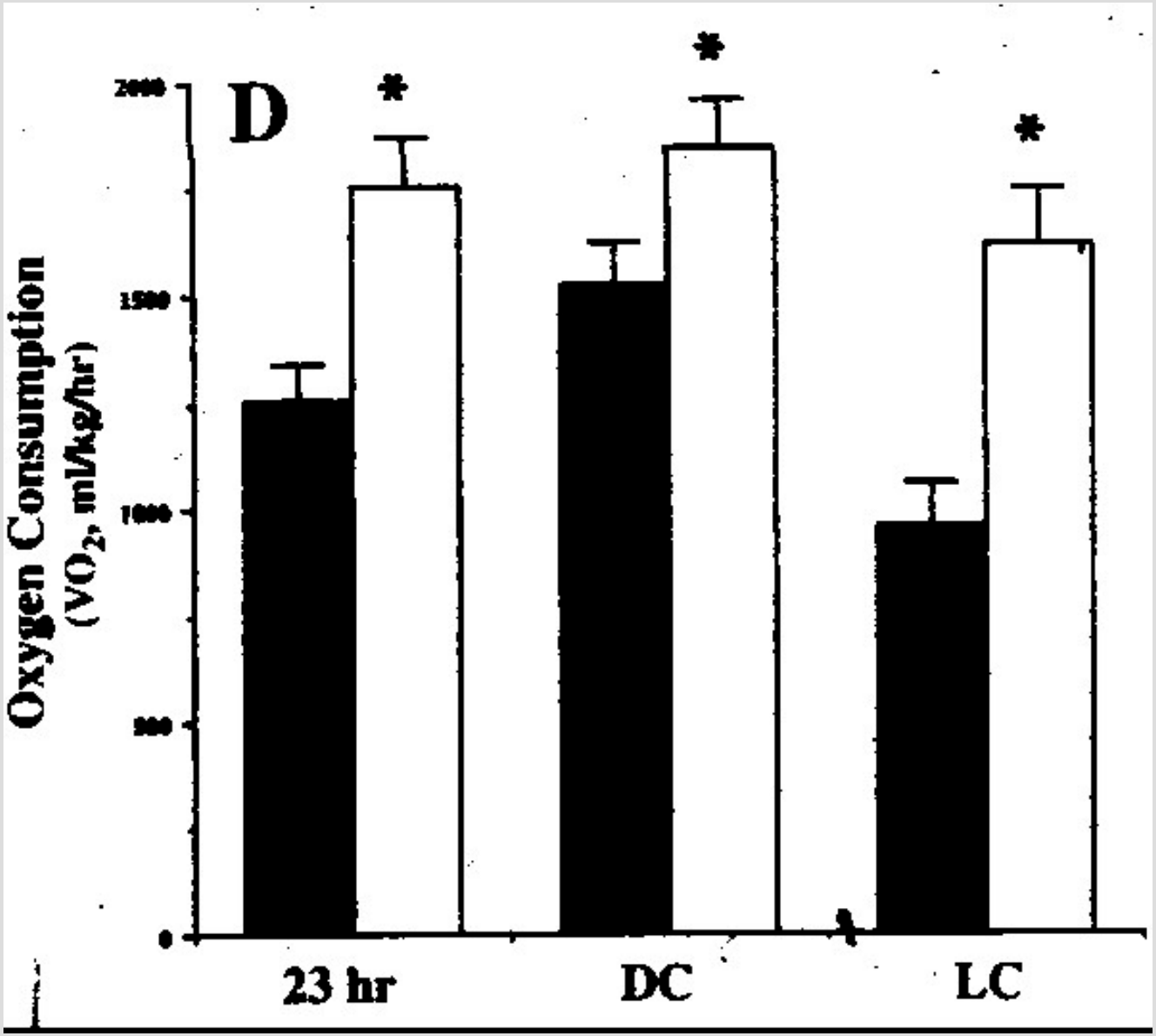

Normal
db/db Mutant
Ob-R gene
Point mutation
Ob-R mRNA
Stop
Stop
Stop
Ob-R protein
Ob
Intracellular signals
Ob
No intracellular signals

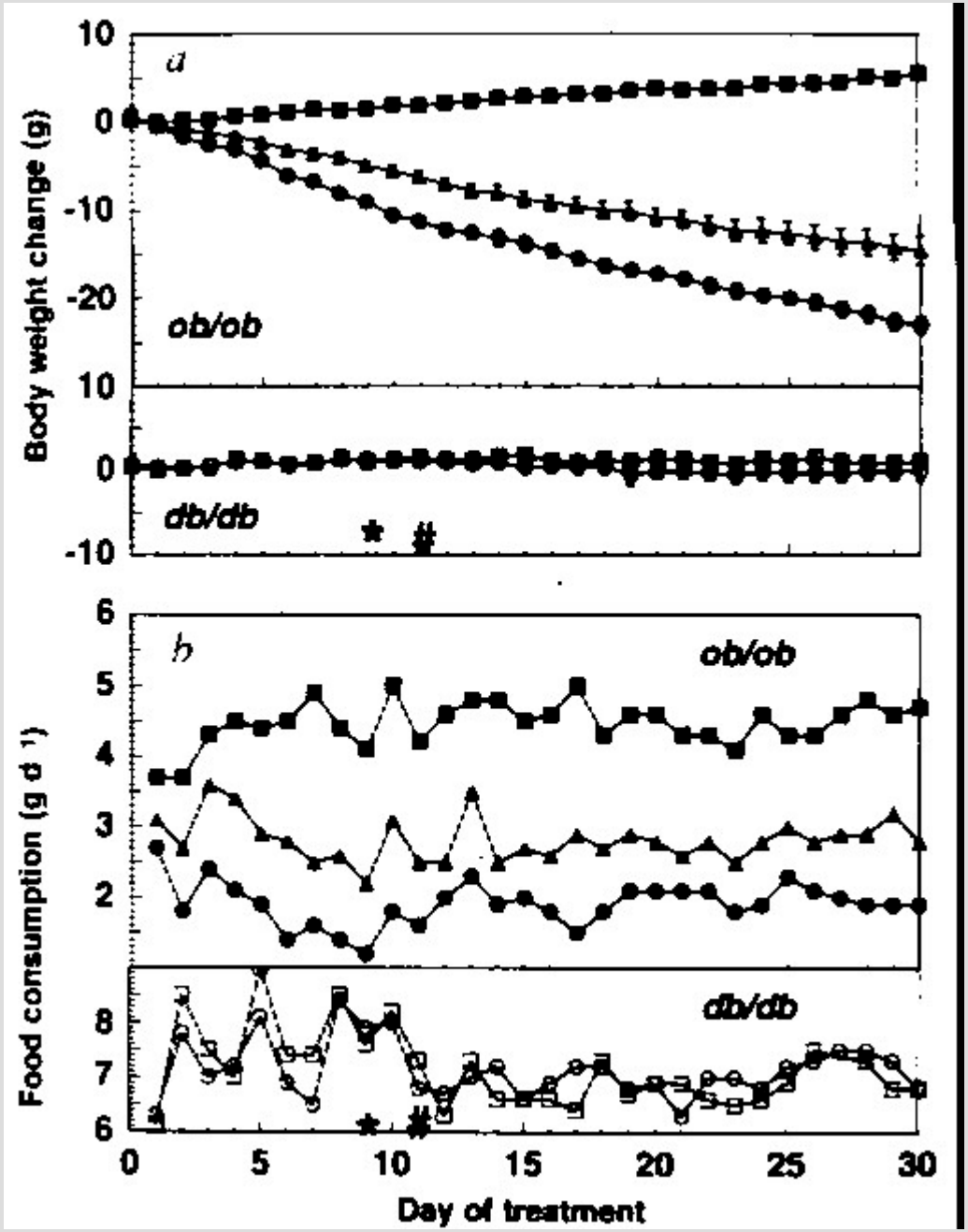
1995 - Pellymounter *et al.* (Amgen), Halaas *et al.* (Rockefeller) and Campfield *et al.* (Hoffman-La Roche) find that treatment of *ob/ob* mice with recombinant OB protein (leptin) corrects their hyperphagia and obesity. Similar results obtained in mice with dietary-induced obesity. No effect of leptin in *db/db* mice. No leptin in plasma of *ob/ob* mice - high levels in *db/db* animals.

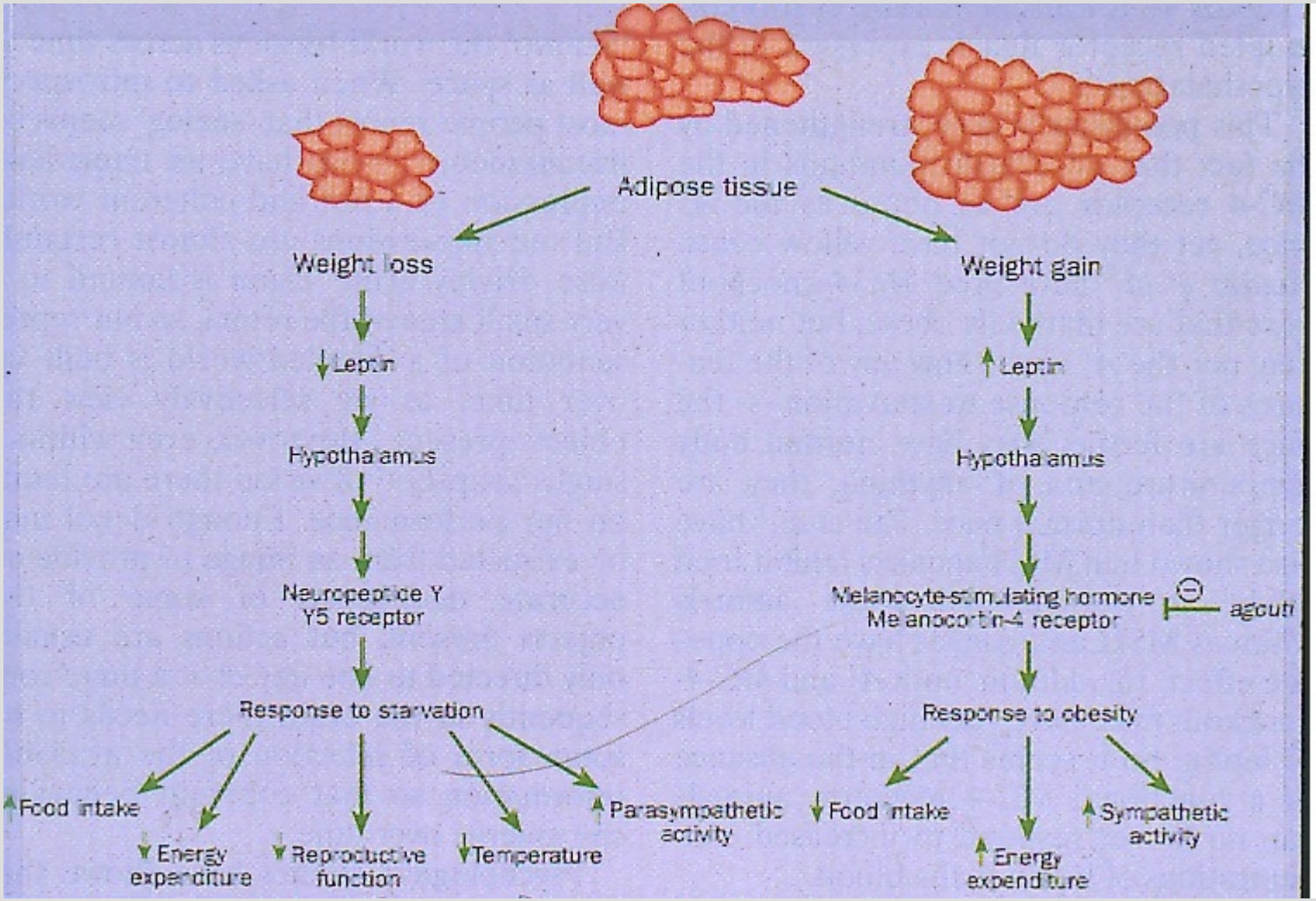

A
24 hr Food Intake (g)
0
1
2
3
4
5
6
7
*
*
0
0.1
0.3
1
3
Leptin (mpk)


B
Weight Gain (g)
1
0
-1
-2
-3
*
*
0
0.1
0.3
1
3
Leptin (mpk)


C
2000
1800
1600
1400
1200
1000
Oxygen Consumption
(VO_2, ml/kg/hr)
*
*
*
*
*
0
0.1
0.3
1
3
Leptin (mpk)


D
*
*
*
Oxygen Consumption
(VO_2, ml/kg/hr)
2000
1500
1000
500
0
23 hr
DC
LC


a
Body weight change (g)
10
0
-10
-20
ob/ob
10
0
-10
db/db
* #
b
Food consumption (g d⁻¹)
ob/ob
6
5
4
3
2
db/db
8
7
6
* #
0
5
10
15
20
25
30
Day of treatment


Adipose tissue
Weight loss
Weight gain
Leptin
Leptin
Hypothalamus
Hypothalamus
Neuropeptide Y
Y5 receptor
Melanocyte-stimulating hormone
Melanocortin-4 receptor
agouti
Response to starvation
Response to obesity
Food intake
Energy expenditure
Reproductive function
Temperature
Parasympathetic activity
Food intake
Energy expenditure
Sympathetic activity

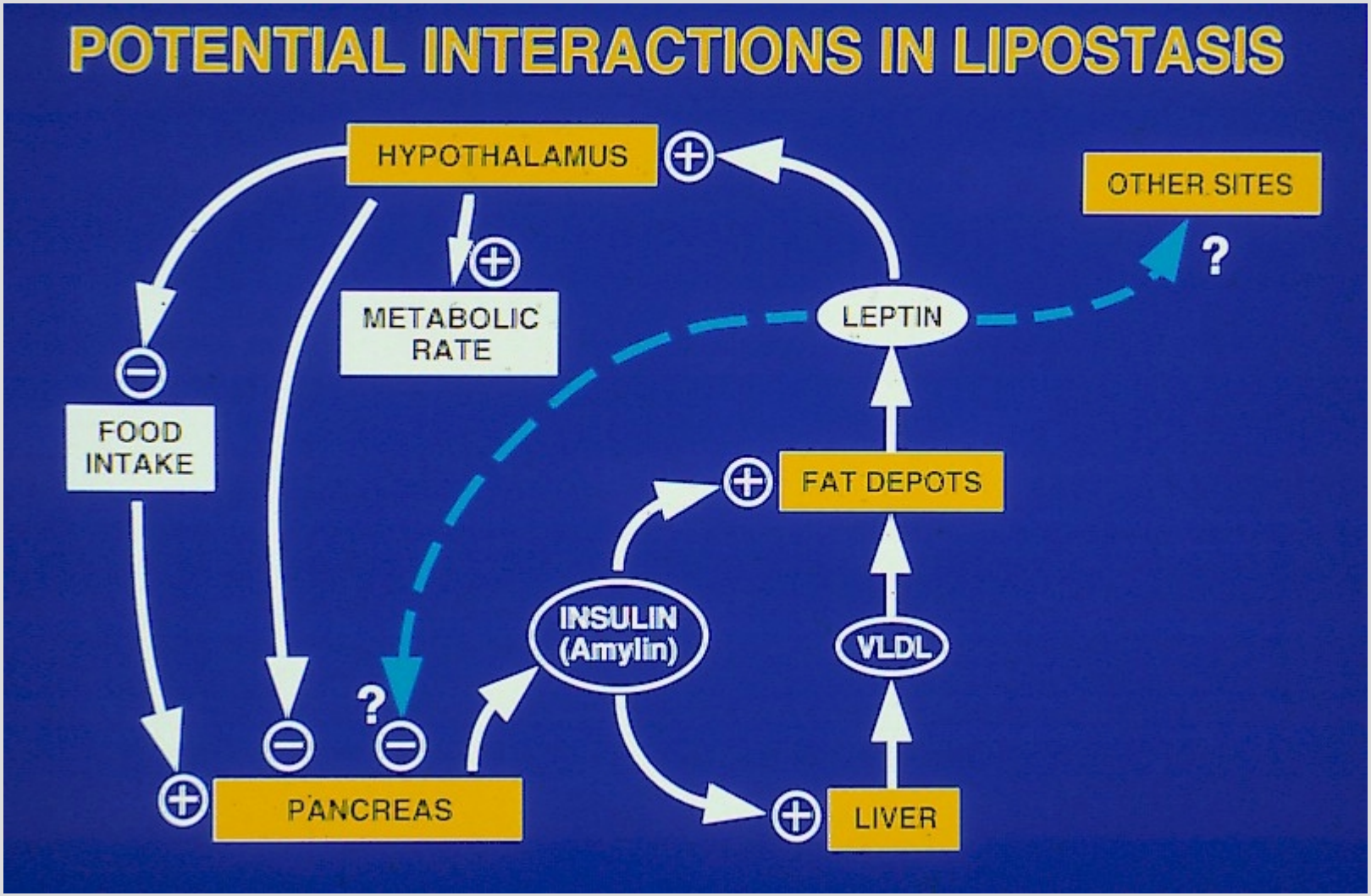

POTENTIAL INTERACTIONS IN LIPOSTASIS
HYPOTHALAMUS
OTHER SITES
METABOLIC RATE
LEPTIN
?
FOOD INTAKE
FAT DEPOTS
INSULIN (Amylin)
VLDL
?
PANCREAS
LIVER

Table 3. Possible derangements in human obesity.

1. Defect in leptin's accessibility to its hypothalamic receptor.
2. Failure of leptin to suppress hypothalamic neuropeptide Y (NPY) synthesis.
3. Abnormalities in the melanocyte stimulating hormone (MSH) - melanacortin 4 (MC-4) receptor system in the hypothalamus.
4. Mutations in the β_3-adrenergic receptor on fat cells and possibly other tissues.
5. Defects at the level of uncoupling proteins (UCP1, 2, 3…).