# LIPID AND GLYCOGEN RESERVES IN HUMANS DURING PROLONGED WORK

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Running Head: Energy Reserves in Humans During Prolonged Work

ABSTRACT

Experiments were conducted in which the responses of nonesterified fatty acids (NEFA) and glucose to insulin and epinephrine were used to qualitatively assess the state of body fat and carbohydrate reserves during prolonged exercise. Intravenous insulin (0.05 units/kg) administered to normal fasting humans after 8 hr of aerobic treadmill work caused a precipitous drop in mean serum glucose and NEFA levels to 41 mg/100 ml and 0.994 meq/l, respectively. Subjects were able to continue walking despite signs and symptoms of severe hypoglycemia and glucose and NEFA returned to preinjection levels within 3 hr. Intramuscular epinephrine (0.10 mg/kg) caused a significant rise in serum glucose, but NEFA values were relatively unaffected as compared to resting controls. Indications are that at the time of injection, a) liver glycogen stores were significantly lower in the working than in the resting group, but were not depleted to the extent anticipated following a 2500 kcal energy expenditure and 21 hr of fasting, and b) NEFA were being mobilized from adipose tissue at a maximum rate. Possible mechanisms regulating the availability of energy from fat depots are briefly discussed.

INDEX TERMS

energy metabolism in humans, lipid and carbohydrate reserves, NEFA, glucose, insulin, epinephrine, prolonged work

Intensive investigative work of the past decade has led to markedly revised concepts of the role of lipids in energy metabolism. It is now recognized that the nonesterified fatty acids (NEFA), loosely bound to albumin, a) are the transport form of energy from adipose tissue, b) can be directly oxidized by a variety of tissues including myocardium (9) and skeletal muscle (15), and c) are extremely sensitive to environmental, hormonal, and drug influences. However, the conditions under which this energy is made available, the degree to which it may be used without the development of harmful ketoacidosis, and its relationships to carbohydrate utilization are not well understood.

The difficulties in investigating these problems often result from the failure to establish true steady-state experimental conditions and from the inability to evaluate the state of body energy reserves in the intact animal. Consequently, a series of experiments were initiated in which postadsorptive dogs (18) and men (19) were required to perform aerobic work on a treadmill for periods up to 40 hr and 24 hr, respectively, or until the onset of fatigue. The human studies confirmed earlier observations in dogs, a) that mean glucose values declined slowly during the first 9 hr and then remained constant for the duration of the test, b) that mean NEFA values increased fourfold during the same period and remained constant thereafter, c) that only 3-5% of the total energy expenditure was provided by protein utilization, and d) that it was possible to prevent dehydration, electrolyte imbalance, and excess lactate formation under these conditions by carefully controlling water and salt intake and the rate of energy expenditure. Hence, a set of conditions could be reproduced in which steady-state values of glucose and NEFA could be maintained for prolonged periods. In the absence of food intake and significant

protein breakdown, these constant levels are sustained by continuous influx from body lipid and carbohydrate storage depots. The ability of insulin and epinephrine to moderate glucose and NEFA release from these storage depots, and consequently blood levels, is well known and their mechanisms of action are well defined.

This paper reports the responses of serum lipids and glucose to these drugs[1] and attempts to qualitatively evaluate the extent of depletion of human glycogen and lipid reserves after approximately 8 hr of aerobic treadmill walking and 21 hr of fasting.

METHODS

Following a 3-month obligatory physical conditioning program, 20 normal male subjects between the ages of 22 and 40 years were required to participate in each of the following test situations over a 6-month period:

a) Walk on a treadmill at one-third maximum capacity for 24 hr or until the onset of fatigue.

b) Remain at rest without sleeping (basal) for 24 hr under conditions identical to (a).

c) Receive either insulin or adrenalin during the course of a 12-hr treadmill walk.

d) Receive either insulin or adrenalin as in (c) while under basal conditions.

Factors, such as room temperature, lighting, noise, and humidity, were kept constant. Water was permitted ad libitum above a minimum rate of 300 cc over 1-1/2 hr. One gram of salt was given every 4 hr. Blood samples were drawn at 1-1/2 hr intervals through an indwelling polyethylene catheter inserted into an antecubital vein. Cardiovascular status was evaluated

continuously by cardiotachometer, electrocardiogram (oscilloscope and standard readout), and blood pressure determination.

All work was aerobic and was performed by walking on a treadmill adjusted to impose a workload equivalent to one-third maximum capacity as determined prior to testing. A modified Master's Two Step Test was performed prior to working sessions. Treadmill grade and speed settings varied from 0-3 degrees inclination and from 2.6 to 2.9 mph. Subjects walked for 1-hr and 20-min periods and 10 min were allowed for rest, foot care, blood and urine sampling, and blood pressure readings.

Resting subjects remained in a semireclining position and could read, write, or watch television, but were not permitted to sleep.

Groups (a) and (b) constituted the "24-hr series" and groups (c) and (d) the "drug study." Since the same subjects performed under identical conditions in both experiments, some of the baseline information obtained in the 24-hr series was applied to the drug study. For example, determinations, such as a respiratory quotient, hematocrit, sodium, potassium, nonprotein nitrogen, urinary nitrogen, and creatinine and ketone bodies, reported in the 24-hr series experiment (19), were not repeated in the present drug study. However, serum glucose (13) (14), NEFA (3) (16), lactic acid (10), and phosphorus (6) determinations were performed.

Approximately 8 hr after the start of the test, a preinjection blood sample was drawn through the indwelling catheter and the subjects were given either 0.05 units/kg of regular insulin, intravenously (Zinc Insulin, U-40, E. R. Squibb and Sons, New York), or 0.10 mg/kg of epinephrine hydrochloride, intramuscularly (Adrenalin, 1:1000, Parke, Davis and Co., Detroit). Blood samples were then obtained 15 min, 30 min, 45 min, 1 hr, 1-1/4 hr, 1-1/2 hr and 3 hr after injection.

Fig. 1

RESULTS

1) Serum Glucose

a) Twenty-four hour series - (Fig. 1 - dotted areas). During the first 9 hr glucose levels gradually declined from mean values of 86.10 mg/100 ml (SD ±10.00) to 76.90 mg/100 ml (SD ±9.24) in the resting subjects and from 89.78 mg/100 ml (SD ±8.90) to 65.38 mg/100 ml (SD ±6.23 in the working subjects. Thereafter, mean glucose concentrations leveled off and were constant for the remainder of the work and rest periods (Scheffe's Multiple Comparison Test).

b) Epinephrine administration - (0.10 mg/kg intramuscular). Effects of epinephrine administered during the ninth hour after start of the test are shown in Figs. 1A and 1B. In the resting subjects within 45 min there was a marked increase in serum glucose levels from 77.40 (SD ±7.23) to 114.80 (SD ±21.10) with a slow return to preinjection levels after 2-3 hr. Working subjects showed a similar but less dramatic response. Levels rose from 63.90 mg/100 ml (SD ±6.58) to 87.00 mg/100 ml (SD ±15.00) 45 min after injection. The level of response of the resting subjects was significantly higher ($p < 0.005$) than that of the working subjects. The response of both groups 45-60 min after injection was significantly higher ($p < 0.001$) than preinjection levels as well as the 3-hr postinjection levels.

c) Insulin administration - (0.05 units/kg intravenous). Effects of insulin on mean serum glucose levels are shown in Figs. 1C and 1D. As expected, within 30 min there was a precipitous drop from 76.90 mg/100 ml (SD ±8.82) to 38.90 mg/100 ml (SD ±6.33) in the resting subjects and from 71.00 mg/100 ml (SD ±9.26) to 41.00 mg/100 ml (SD ±9.01) in the working

subjects. At the end of 3 hr, glucose values had returned to 100% and 92% of preinjection concentrations in rest and work subjects, respectively. The clinical manifestations of hypoglycemia appeared to be of equal severity in both groups; however, recovery was somewhat slower in the working subjects as measured by the rate of return of glucose levels (Fig. 1D) and performance on psychomotor tests (Coler, C. R., W. A. McLaurin, and D. R. Young. Effect of Adrenalin or Insulin on the Performance of Resting and Working Subjects. Presented at the Aerospace Medical Association 36th Annual Scientific Meeting, April 26-29, 1965, New York City, New York.)

2) Serum Nonesterified Fatty Acids

a) Twenty-four hour series - (Fig. 2 - dotted areas). During the first 9 hr NEFA levels rose continuously from mean values of 0.546 meq/l, to 0.940 meq/l in the resting subjects and from 0.650 meq/l to 2.244 meq/l in the working subjects. Thereafter, mean NEFA concentrations plateaued and remained constant for the remainder of the work and rest periods (Scheffe's Multiple Comparison Test).

b) Epinephrine administration - (0.10 mg/kg intramuscular). Effects of epinephrine administered during the ninth hour after the start of the test are shown in Figs. 2A and 2B. In the resting subjects NEFA levels doubled to mean values of 2.43 meq/l (SD ±0.577) 30 min after injection with slow decline to preinjection levels at the end of 3 hr. In the working subjects, however, mean values increased only from 2.50 meq/l (SD ±0.622) to 2.87 meq/l (SD ±0.612) 30 min after injection. Although statistically real ($p < 0.05$), this small change is of questionable biological significance.

c) Insulin administration - (0.05 units/kg intravenous). Effects of insulin administered during the ninth hour after the start of the test are shown in Figs. 2C and 2D. A sharp fall in NEFA levels was observed in the working subjects. Forty-five minutes after injection, levels dropped from a preinjection mean of 2.061 meq/l (SD ±0.721) to 0.994 meq/l (SD ±0.172) and then returned to 2.069 meq/l (SD ±0.350) at the end of 3 hr. The changes that occurred in the resting subjects fell within the same range as those during an equivalent time interval in the 24-hr series in which no drug was given (Fig. 2C).

3) Serum Lactate (Table 1)

a) Epinephrine administration - The lactate levels attained in both rest and work subjects within the first hour after injection did not differ statistically from each other nor did the average response differ during the postinjection period. However, the postinjection response curves were significantly different ($p < 0.001$), with lactate levels continuing to rise slightly in the workers but showing no definite pattern in the resting subjects. The observed rises within each group were significant ($p < 0.05$).

b) Insulin administration - Neither the average response nor the shapes of the response curves during the postinjection period differed significantly between the work and rest subjects. Both showed a small, but significant ($p < 0.01$), peak response at about 45 min with slow return to preinjection levels at 3 hr.

4) Serum Inorganic Phosphate (Table 2)

a) Epinephrine administration - Preinjection phosphate levels were identical in the work and rest subjects and did not change significantly in either group throughout the postinjection period.

b) Insulin administration - There was a significant ($p < 0.05$) fall in phosphate levels in both groups within 45 min after injection followed by a persistent rise. The pattern of response was the same. However, in the working subjects, the rise began somewhat earlier and by 3 hr phosphate levels were significantly higher ($p < 0.05$) than at preinjection.

## DISCUSSION

Carbohydrate Reserves. The glycemic responses observed in the resting and working subjects can be ascribed to the known abilities of epinephrine a) to stimulate liver glycogenolysis, b) to decrease the uptake of glucose by tissues, and c) to elevate blood lactate levels (lactate → liver glycogen → glucose). However, in working and resting subjects lactate levels were not significantly different during the peak glucose response following epinephrine (Table 1). Nor did phosphate levels differ significantly (Table 2), thus substantiating the observation that inhibition of uptake is extremely small at these glucose levels (2). Consequently, the greater rise in glucose concentrations attained in the resting subjects as compared to working subjects was probably due to a larger amount of liver glycogen available in the former group at the time of injection.

Although carbohydrate stores were apparently being utilized to a greater extent in the working subjects, mean blood glucose levels remained constant in both groups after the first 8 hr of testing and were only 7.2 mg/100 ml higher in the resting subjects. To maintain these conditions during work, extensive gluconeogenesis must have been taking place. In the absence of significant protein breakdown (20) and lactic acid formation, the major source of glucose is presumed to be fat. It can be estimated from the data obtained in our preliminary experiments that approximately 0.30 kg

of body fat was lost up to the time of injection, of which about one-tenth by weight, or 0.03 kg was glycerol. This amount of glycerol could conceivably sustain glycogen stores in view of its extremely rapid conversion to carbohydrate. In the fasting rat, e.g., 75-90% of endogenous glucose is derived from glycerol (12). However, the possibility that the NEFA component of fat also serves as an important precurser of carbohydrate must be considered, since a) the Krebs cycle can act as a metabolic pathway for the synthesis of glucose from NEFA in the presence of a nonacetate influx (17), b) NEFA are a major source of carbohydrate in plants and probably insects, and c) there is no direct evidence that such a conversion does not occur readily in humans. Additional studies are needed to clarify the role of NEFA as a quantitatively significant source of carbohydrate during prolonged fasting and work.

Following the administration of insulin, glucose concentrations fell to approximately the same levels in resting and working subjects (Figs. 1C, 1D) despite the differences in liver glycogen content. The failure of blood glucose levels to fall below 38.9 mg% (SD ±6.3) can be attributed, at least in part, to inhibition of glucose uptake by adrenal medullary hormones stimulated by severe hypoglycemia. Serum phosphate concentrations also fell initially to the same levels in work and rest subjects following intravenous insulin (Table 2), indicating comparable rates of carbohydrate utilization. However, within 1 hr after injection, phosphate levels in both groups began to rise. By 3 hr they exceeded preinjection values, suggesting, again, the presence of a mechanism acting at hypoglycemic levels to restore blood glucose by inhibition or depression of peripheral uptake.

Lipid Reserves. Muscle and liver biopsy techniques have contributed a great deal to the understanding of carbohydrate metabolism, despite their

many obvious limitations. Investigators of fat metabolism are deprived of even these simple tools since sampling and analysis of adipose tissue provides no information regarding the amount of energy utilized or that still available from fat. The fluctuations of blood NEFA concentrations and turnover rates under various experimental conditions represent the end result of many complex factors regulating fat utilization and have been extensively studied in recent years. However, these studies have led to many conflicting reports as, for example, those regarding the response of NEFA to exercise in the fasting state. Initially, it was shown that there was an increased turnover rate and low concentration of NEFA with short periods (approximately 15 min) of vigorous exercise followed by a sharp rise when activity was stopped (7). Subsequent observations revealed that during less severe exercise of longer duration, a brief fall in concentration occurred, followed by a gradual rise (1), and was accompanied by an increased turnover rate (8). Recently, Mager et al (11) extended periods of aerobic exercise to 7 hr and showed a continual increase in NEFA levels.

The contribution of our preliminary tests (19) to this area of intere is the demonstration that after approximately 8-9 hr of aerobic work in the fasting normal human, NEFA remained constant for periods up to 15 hr. This must mean that the rate of efflux of NEFA from the blood equaled the rate of influx during this interval. In view of the previously mentioned evidence that NEFA are a major energy source for working muscle and that their turnover rate is increased during exercise, it is presumed that the rate of flux under these conditions must be extremely rapid. Quantitative studies utilizing radioactive isotope techniques are currently in progress in our laboratory. The failure to obtain steady-state conditions probably accounts for many of the discrepancies of earlier observations.

The increase in NEFA levels following the administration of epinephrine is well known and is presumed to result from increased hydrolysis of triglycerides in adipose tissue. Such a response occurred in our resting subjects, resulting in almost a twofold increase in NEFA concentration (Fig. 2A). However, the change that occurred in the working subjects, while statistically significant ($p < 0.001$), was extremely small (Fig. 2B) and probably not of biological importance. Even if it is assumed that the total cost of energy requirements was met by fat tissue, still an insignificantly small amount of fat as compared to total body fat would have been expended and could not account for the failure of epinephrine to raise NEFA levels in the working subjects. Apparently, NEFA were being mobilized maximally at the time of injection.

One or more of the following factors could have prevented the anticipated NEFA increase: a) an inadequate supply of lipolytic enzyme to meet the new requirements, b) saturation of available binding sites on plasma albumin, c) saturation of NEFA "tissue acceptor" sites which may be located in cell membranes and organelles (5), or d) saturation of cellular metabolic pathways which are required to activate NEFA for oxidation or esterification.

The most likely possibility is that plasma albumin sites were saturated since it has been demonstrated, in vitro, that NEFA will not be released from adipose tissue even in the presence of potent lipolytic agents unless the incubation medium contains albumin (4). However, if it can be shown that insufficient lipolytic enzyme is the rate limiting step, then supplying such enzymes could, conceivably, make available large amounts of storage fat for energy metabolism.

Insulin inhibits the release of fatty acids from adipose tissue by interfering with the activation of lipase. The fall in NEFA concentrations

that occurred in the working subjects (Fig. 2D) was therefore not unexpected. However, the failure of this mechanism to act effectively in the resting subjects cannot be adequately explained in light of the present information.

It is of further interest that mean NEFA concentrations fell to approximately the same levels in the insulin-treated working and resting groups as well as in the nontreated resting controls (Figs. 2C, 2D). In no case did NEFA levels fall below 0.604 meq/l (SD ±0.155). Similarly, working and resting subjects who received epinephrine attained the same mean NEFA levels observed in the working controls who received no drug, the maximum levels being 2.87 meq/l (SD ±0.612) (Figs. 2A, 2B). Apparently, the upper and lower limits beyond which NEFA blood levels were not influenced by prolonged fasting, work, rest, or pharmacological doses of insulin and epinephrine, were approximately 2.9 meq/l and 0.6 meq/l, respectively. Similar effects were noted in the glucose experiments, the lower limits being established at about 40 mg/100 ml (Figs. 1C, 1D). Clarification of the mechanisms tending to maintain NEFA and glucose levels at these relatively rigid boundaries would contribute greatly to an understanding of the factors controlling the availability of energy from lipid and carbohydrate storage depots during prolonged work and fasting.

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FOOTNOTE

[1]The term "drug" is used in its broader sense, recognizing that insulin and epinephrine are naturally occurring hormones.

TABLE LEGENDS

Table 1.- Response of serum lactate to adrenalin or insulin*

*Adrenalin (I.M.) or insulin (I.V.) was administered to postadsorptive working and resting subjects approximately 8 hr after the start of the test. Values are mean mg/100 ml ±SD.

Table 2.- Response of serum inorganic phosphate to adrenalin or insulin*

*Adrenalin (I.M.) or insulin (I.V.) was administered to postadsorptive working and resting subjects approximately 8 hr after the start of the test. Values are mean mg/100 ml ±SD.

FIGURE LEGENDS

Fig. 1.- Serum glucose versus duration of test, hr.

Hatched areas represent the mean and standard deviation for 12 subjects who received either insulin or adrenalin 8 hr after the start of the test. Dotted areas represent the mean values expressed as standard deviation for 16 control subjects who received no drug. (A) mean response of serum glucose to adrenalin in postadsorptive resting subjects, (B) mean response of serum glucose to adrenalin in postadsorptive working subjects, (C) mean response of serum glucose to insulin in postadsorptive resting subjects, (D) mean response of serum glucose to insulin in postadsorptive working subjects.

Fig. 2.- Serum nonesterified fatty acids (NEFA) versus duration of test, hr.

Hatched areas represent the mean and standard deviation for 12 subjects who received either insulin or adrenalin 8 hr after the start of the test. Dotted areas represent the mean values expressed as standard deviation for 16 control subjects who received no drug. (A) mean response of NEFA to adrenalin in postadsorptive resting subjects, (B) mean response of NEFA to adrenalin in postadsorptive working subjects, (C) mean response of NEFA to insulin in postadsorptive resting subjects, (D) mean response of NEFA to insulin in postadsorptive working subjects.

## ADRENALIN, .10 mg/kg I.M.

SERUM LACTATE

| | 0 hr | 1 hr 30 | 3 hr | 4 hr 30 | 6 hr | 8 hr 15 | 8 hr 30 | 8 hr 45 | 9 hr | 9 hr 15 | 9 hr 30 | 9 hr 45 | 11 hr 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REST | 10.1 ± .92 | 11.3 ± 1.73 | 10.4 ± 1.31 | 10.2 ± 1.11 | 10.1 ± 1.03 | 10.8 ± 1.70 | 12.7 ± 2.32 | 13.2 ± 3.27 | 13.2 ± 2.42 | 13.3 ± 2.31 | 12.2 ± 1.70 | 11.9 ± 1.01 | 11.4 ± 1.78 |
| WORK | 10.4 ± 1.01 | 10.0 ± 1.04 | 10.2 ± 1.59 | 10.6 ± .52 | 10.4 ± .98 | 11.9 ± 1.09 | 12.4 ± 1.68 | 13.1 ± 2.06 | 13.7 ± 2.26 | 14.1 ± 1.91 | 13.8 ± 2.28 | 14.4 ± 2.03 | 14.8 ± 2.55 |

## INSULIN, .05 units/kg I.V.

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REST | 11.2 ± 1.25 | 10.9 ± 1.40 | 11.2 ± 2.20 | 10.6 ± 1.98 | 10.4 ± 1.67 | 11.5 ± 2.09 | 12.1 ± 2.52 | 13.0 ± 2.35 | 13.2 ± 2.17 | 12.4 ± 1.91 | 12.0 ± 1.90 | 11.7 ± 2.22 | 11.5 ± 1.70 |
| WORK | 10.8 ± 2.17 | 10.1 ± 1.42 | 10.2 ± 1.40 | 10.1 ± 1.03 | 10.6 ± 1.75 | 11.2 ± 1.51 | 12.0 ± 1.72 | 14.1 ± 2.89 | 14.3 ± 3.62 | 14.0 ± 3.07 | 13.4 ± 2.74 | 13.2 ± 2.90 | 12.9 ± 2.88 |

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Table 1

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## ADRENALIN, .10 mg/kg I.M.

SERUM PHOSPHATE

| | 0 hr | 1 hr 30 | 3 hr | 4 hr 30 | 6 hr | 8 hr 15 | 8 hr 30 | 8 hr 45 | 9 hr | 9 hr 15 | 9 hr 30 | 9 hr 45 | 11 hr 15 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REST | 3.6 ± .80 | 3.3 ± .62 | 3.4 ± .50 | 3.6 ± .46 | 3.6 ± .54 | 3.6 ± .50 | 3.3 ± .54 | 3.3 ± .44 | 3.4 ± .48 | 3.4 ± .43 | 3.5 ± .44 | 3.4 ± .42 | 3.5 ± .56 |
| WORK | 3.2 ± .59 | 3.1 ± .69 | 3.6 ± .41 | 3.6 ± .55 | 3.8 ± .41 | 3.6 ± .70 | 3.4 ± .75 | 3.7 ± .67 | 3.5 ± .70 | 3.8 ± .93 | 3.9 ± .87 | 3.8 ± .77 | 3.9 ± .85 |

## INSULIN, .05 units/kg I.V.

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| REST | 3.6 ± .42 | 3.2 ± .40 | 3.4 ± .34 | 3.6 ± .26 | 3.7 ± .30 | 3.7 ± .23 | 3.3 ± .28 | 2.9 ± .35 | 2.6 ± .40 | 2.9 ± .43 | 3.2 ± .33 | 3.4 ± .48 | 3.9 ± .48 |
| WORK | 3.3 ± .35 | 3.6 ± .46 | 3.7 ± .36 | 3.8 ± .33 | 3.8 ± .20 | 3.8 ± .20 | 3.4 ± .42 | 2.9 ± .41 | 3.0 ± .45 | 3.5 ± .28 | 3.9 ± .38 | 4.0 ± .40 | 4.3 ± .43 |

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Table 2

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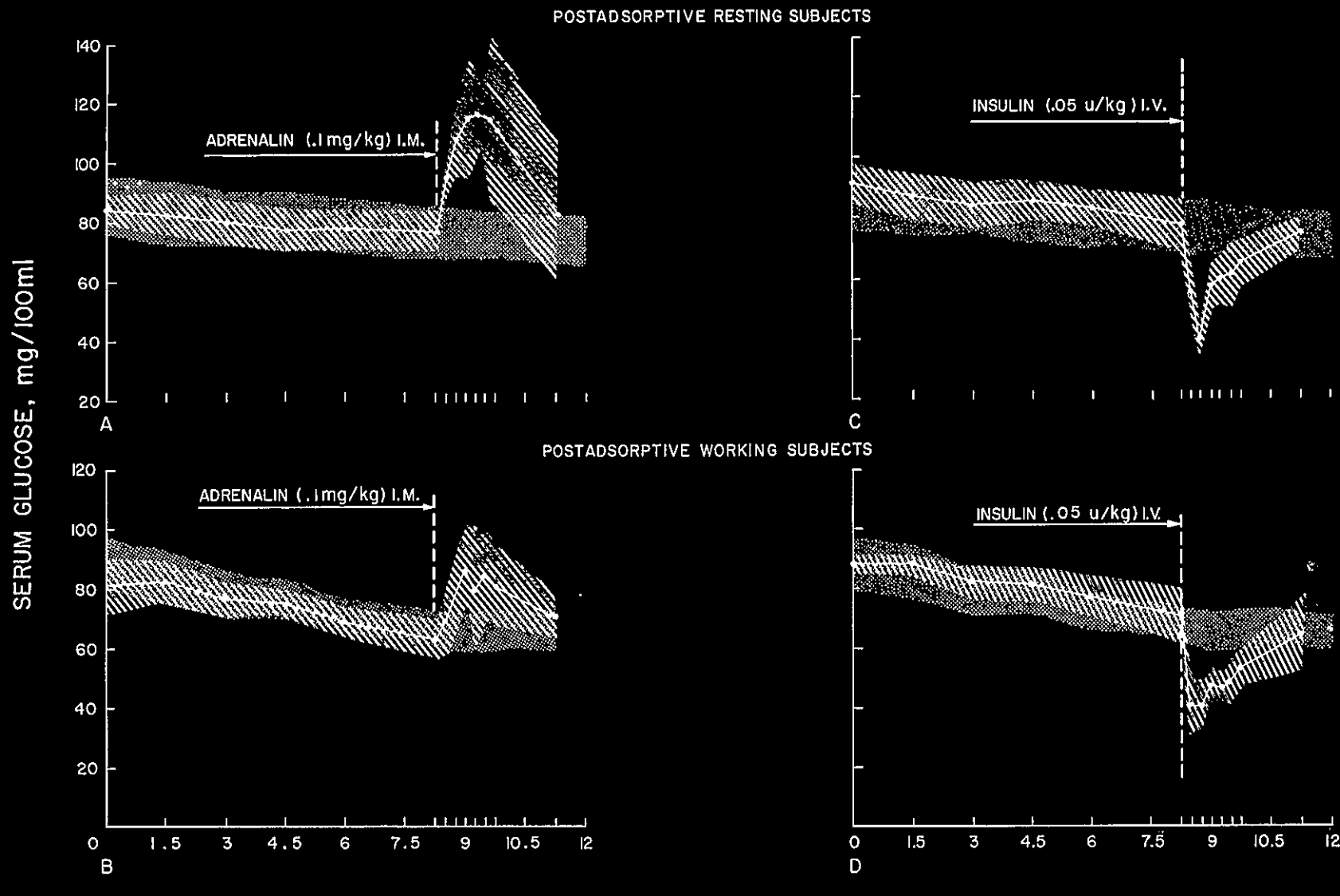


Fig. 1

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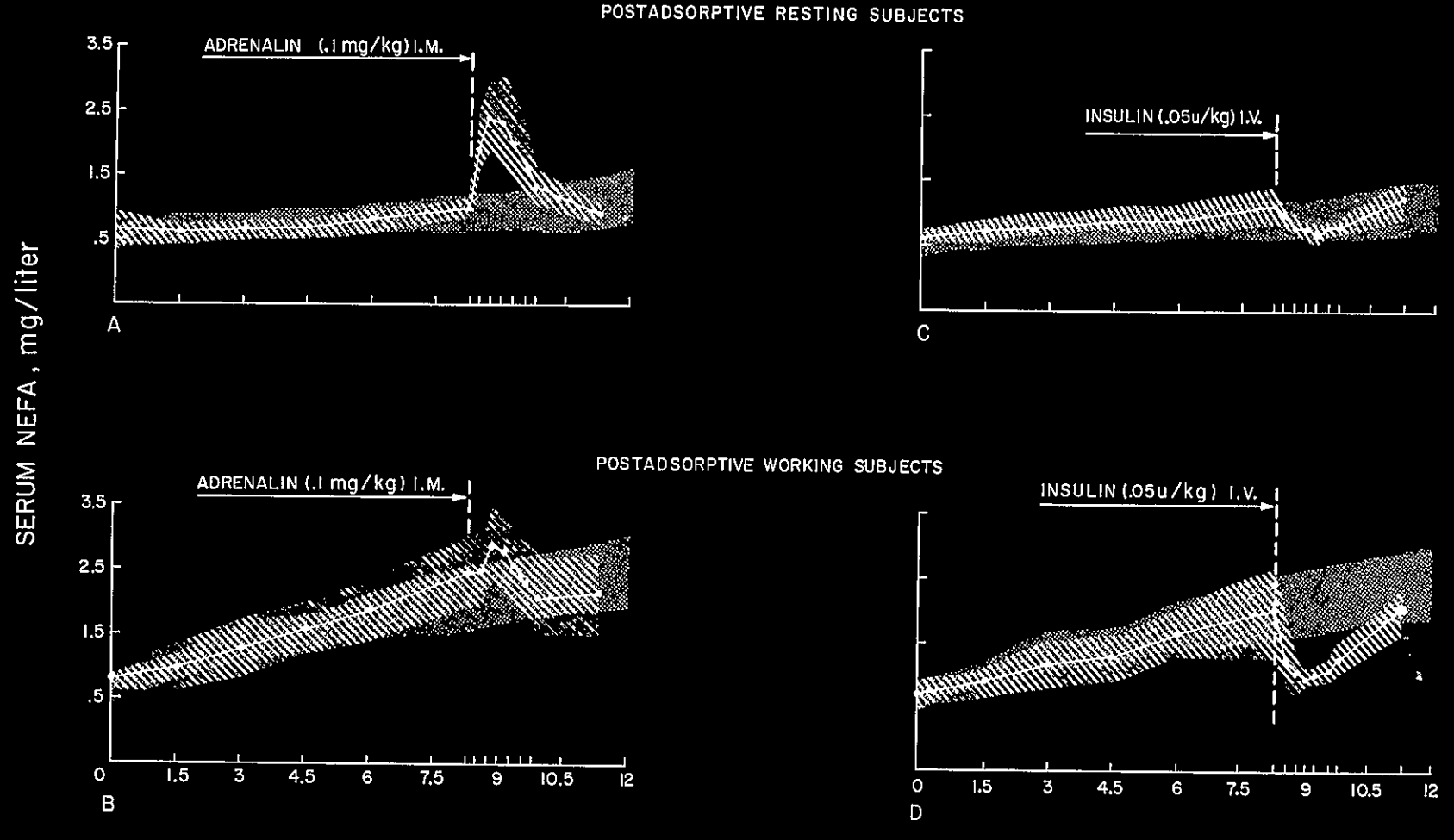


Fig. 2

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