Adaptation to Caloric Restriction

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EVER SINCE Claude Bernard pointed out the role of the internal environment in mitigating the impact of external stresses on the cellular machinery of the body, the question as to how the body makes adjustments to difficult or new conditions has been under scrutiny. The adaptations to such diverse stresses as anemia, pregnancy, low calcium intake, and exposure to high altitude and to heat have been described in some detail. To some stresses, such as cold, the human body makes favorable adjustments, but as yet the data are inadequate to define and explain the mechanisms involved. The problem of adaptation to caloric restriction has occupied a somewhat intermediate position. On the one hand, it has been recognized that extensive adaptations occur in inhabitants of famine areas (*15*), but no data of value from the field are available. On the other hand, a mild degree of caloric restriction has been studied in the laboratory, and some of the mechanisms that help to produce the observed adaptation have been described (*2*). However, the data necessary for a more complete quantitative description of the extent of adaptation under famine conditions have been made available only recently by the results of the Minnesota Experiment on semistarvation (*8*). The general conditions of this experiment have been described, and some of the results have been reported (*4, 6, 12, 17, 19, 20*).

The subjects were 32 conscientious objectors who were resident in the Laboratory of Physiological Hygiene for a year. Following three months of control studies, they underwent six months of semistarvation and then were studied during three months of rehabilitation. During the control period the subjects ate a diet that was adequate in protein, vitamins, and minerals, but that did not provide excessive amounts of any specific nutrient. The body weight of the group was maintained on 3,492 calories per day. The activity regimen that the men followed included a set schedule of routine laboratory and housekeeping chores, 20 miles of walking each week, and participation in a special educational program.

The semistarvation diet was instituted at the end of the control period and continued for six months. It provided an average of 1,570 calories daily, or slightly less than half the control intake, and consisted of potatoes, cabbage, turnips, and cereals, with only a few grams of animal protein a week. In other words, the men ate the kind of foodstuffs used in famine in northern Europe. Analysis of the diet showed that it contained an average of 54.5 grams of protein and 27.1 grams of fat a day. The mineral and vitamin intakes of the subjects during the semistarvation period were in the general range of the National Research Council Recommended Daily Allowances (*21*), with the exception of the intakes of riboflavin and vitamin A, which were roughly one-half the recommended standards.

At the end of six months on this diet the subjects had lost 24 percent of their body weight and showed the classical signs and symptoms of famine victims, namely, edema, anemia, polyuria, bradycardia, weakness, and depression.

The weight loss curve during the semistarvation period followed the law of diminishing decrements (*3*). At the end of the period the body weight was substantially constant. During the last three weeks the average loss of weight was only 0.13 kg per week. The dimensions of the adaptation to the imposed restriction of caloric intake are defined by the fact that, in the face of a 55 percent reduction, the subjects were able, for all practical purposes, to maintain caloric balance, but at a body weight reduced to 75 percent of the original prestarvation weight.

Adjustment to Starvation

The way in which this adjustment was achieved is revealed by a detailed analysis of the energy expenditure. The essential data are presented in Table 1. The mean basal metabolism was calculated from serial determinations made on every member of the subject group. The specific dynamic action (S.D.A.) was taken as 10 percent of the total caloric intake. The cost of activity was calculated as that part of the total intake not accounted for by basal metabolism plus the

TABLE 1

ESTIMATED PARTITION OF MEAN ENERGY EXPENDITURE IN KILO CALORIES PER DAY OF 32 YOUNG MEN BEFORE AND AFTER SIX MONTHS OF SEMISTARVATION

	Before	After	Δ	Δ, as % of total Δ	Δ, as % of control
Basal metabolism	1,576	962	614	31.9	39
Specific dynamic action	349	157	192	10.0	55
Cost of activity	1,567	451	1,116	58.1	71
Total	3,492	1,570	1,922		

S.D.A. This procedure is justifiable at the balance point. The data demonstrate that a little less than two-thirds of the total saving in calories may be assigned to the cost of physical activity. We may ask, How much of this reduction was due to a decrease in activity and how much to a smaller cost of work? The subjects suffered a marked loss of strength and endurance as the starvation period progressed (*11*). The men commented that they felt as if they were rapidly growing old. They felt weak and they tired easily. They moved cautiously, climbing stairs one step at a time, and obviously reduced unnecessary movements to a minimum. All observations indicated that voluntary physical activity was markedly curtailed at the end of the starvation period.

The cost of specified work was investigated in 10 of these men, who walked on a motor-driven treadmill at 3.5 miles per hour and a 10 percent grade before, in the middle, and at the end of the semistarvation period. It was found that the oxygen consumption during work was linearly related to the body weight, regardless of whether the values were taken in the control period, or after twelve or twenty-four weeks of semistarvation (*11*). Respiratory quotient measurements in work showed no substantial change at any time; in other words, the calorie value per unit of oxygen consumption was constant. The average cost of this standard work, per kg of body weight per minute, was 0.111, 0.110, 0.111 calories for the control, and for the twelfth and twenty-fourth weeks of semistarvation, respectively. The energy cost of a given task was reduced at the end of starvation in direct proportion to the loss of body weight. Accordingly, as there was no change in efficiency, the percentage reduction in activity during the six months of starvation should be corrected for the change in body weight (minus 24 percent). In these terms, the activity level of the control period would cost 1,200 calories for the body weight at the end of semistarvation. But the actual cost of activity at that time was reduced to 499 calories. In terms of the observed total reduction in the cost of physical activity, 60 percent is due to decrease in the tasks undertaken and 40 percent to a decrease in the cost of performing these tasks.

This analysis of the way in which the cost of activity was reduced assumes that physical activity consisted in moving the body from place to place. Such an assumption is justified as a first approximation when dealing with men who are engaged in occupations like those of our subjects; it is not applicable to persons engaged in heavy physical work, where moving external objects constitutes a large part of the total work.

In a somewhat similar manner we may examine the observed reduction in basal metabolism. How much of this decrease is due to a loss of metabolizing tissue, and how much to a change in the rate of metabolism of the remaining tissue?

In the Minnesota Experiment, an effort was made to estimate the mass of the actively metabolizing tissue (*9*). To obtain this figure, measurements were made of the total body fat (specific gravity method), extracellular fluid (thiocyanate space), and blood volume (blue dye). These measurements define a large fraction of the metabolically inert portion of the body but do not include the skeleton. The x-ray density of the bones was determined from roentgen films, and it was shown that no important change took place as the result of starvation.[1] It was assumed that 4 percent of the original (prestarvation) body weight was contributed by the minerals of the bones. The metabolizing, or "active," tissue was then calculated as the body weight less the weight of the bone mineral, extracellular fluid volume (including plasma), and fat. Inasmuch as the extracellular fluid volume and fat determinations measure these items in the bones, it is felt that this calculation gives a reasonable approximation of the mass of the "active tissue." It should be noted, however, that the calculation reveals nothing about the intracellular water. In the starving rat, at least, the concentration of intracellular water in muscle and other active tissues remains constant when the serum protein concentration has not dropped below 5.5 grams per 100 ml (*14*).

The average mass of "active tissue" for the 32 men in the Minnesota Experiment was estimated, in this way, to be 39.95 kg in the control period and 29.19 kg after six months of semistarvation. The loss of 27.4 percent of "active tissue" indicates that the body weight measurement, which showed a 24 percent loss, was lower than the loss of "active tissue" by a small amount.

The metabolic rate during the six months of semistarvation decreased 31.2 percent, when the data are calculated as ml of oxygen consumption per square

[1] We are indebted to Pauline Beery Mack for these measurements.

meter of body surface (*10*). When the oxygen intake is calculated as ml per kg of body weight, the change during semistarvation amounts to 19.3 percent. Finally, when the metabolic rate is expressed as ml per kg of "active tissue," the decrease is only 15.5 percent. It appears that the conventional method of expressing basal metabolic rates in units of body surface does not properly indicate the intensity of metabolism of the cells of the body during starvation. The oxygen intake per kg of "active tissue" may be taken to give the nearest approximation to the actual metabolic rate of the cells of the body. The data indicate that the greater part of the decrease in the B.M.R. (65 percent) in starvation reflects the shrinkage of the metabolizing mass of tissue, and the smaller part (35 percent) should be ascribed to a decrease in the intensity of metabolism. From metabolic studies on severely undernourished persons in western Europe (*1*), it has been suggested that the intensity of metabolism in the "active" cells may even be undiminished in semistarvation, but the computations assume that the Minnesota findings on extracellular water and fat applied quantitatively to their subjects. In any case, these studies on "natural" famine victims are at least in rough agreement with the present conclusion that semistarvation does not produce any great change in the metabolic rate per unit mass of living cells.

We do not suggest that the rate of basal O_2 consumption of all tissues in the body was reduced by 15 percent. Kleiber (*13*) has shown that, in the rat, during starvation the decrease of the metabolic rate of various isolated organs and tissues is not constant; the present computation refers only to the sum total of basal metabolism. Finally, in considering the cause of the decrease in the metabolic rate per unit of "active tissue," it should be remembered that a small decrease in body temperature has a definite effect on the metabolic rate. In the Minnesota Experiment the body temperature decreased 0.74° C after twelve weeks of semistarvation. If we assume a temperature coefficient (Q_{10}) of 2.0, 10 percent of the 32 percent decrease in basal metabolism that had occurred at this time could be accounted for by the decline in body temperature. It is interesting to note that at the end of twenty-four weeks of semistarvation the average body temperature differed from that of the control period by only 0.126° C. This may indicate that the temperature-regulating mechanism had somehow become adjusted so as to maintain a more normal body temperature in the face of continued food restriction. It should be remarked, however, that the semistarvation began in February, so the end of this phase of the study occurred in the summer. In any case, after six months of semistarvation in the Minnesota Experiment, no appreciable part of the reduced energy expenditure could be explained on the basis of a reduced tissue temperature.

The concentration of the serum proteins is an important factor in the maintenance of a normal distribution of fluid between the plasma and the extracellular fluid. The Minnesota subjects showed a selective use of body protein during starvation that maintained the total circulating serum proteins at a substantially normal level, whereas protein was lost by the tissues and cells in large amounts (*19*). Although the concentration of the serum protein decreased slightly, this could be accounted for by a parallel increase in serum volume. The distribution of fluids between serum and extracellular fluid was well maintained in our subjects. This was shown by the fact that the absolute extracellular volume increased by only 4.3 percent, and serum volume increased by only 8 percent, as the result of six months of semistarvation (*4*). With continued starvation, of course, a point is eventually reached where the plasma proteins can no longer be safeguarded and there is development of severe hypoproteinemia, with all the attendant difficulties.

The changes in energy expenditure during semistarvation are of great importance in helping the organism to survive on a low level of food intake. But there are many other adjustments in the body of the starving man which mitigate the consequences of the negative caloric balance. A few of these may be noted.

Other Protective Changes

In spite of the adaptation in the energy expenditure, the starving body is forced to use some of its own protein for fuel. The circulating plasma proteins would seem to be most readily available for this purpose, but their preferential destruction would quickly have disastrous consequences.

Another example of a differential metabolic destruction of special tissues that is of obvious utility to the organism in survival is provided by the brain. This tissue loses a smaller fraction of its initial weight during a period of severe starvation (*5*). The brain, skeleton, and serum proteins remain almost intact, whereas fat, muscle, liver, and skin undergo large losses.

In spite of statements to the contrary by every major textbook of physiology since 1900, the heart undergoes considerable loss of muscle mass during acute and chronic starvation. Jackson (*5*) has reviewed the results of experiments on animals and autopsy material, which all indicate that the percentage loss of heart weight is 70–90 percent of the percentage loss of the body weight. In the Minnesota Experiment roentgenkymographic estimations of heart size indicated that the heart volume decreased by 17 percent (*12*). In other words, the relative reduction in the heart was not materially less than that of the body as a whole. Recent necropsy data are in agreement. But analysis of the cardiac function reveals adaptations which safeguard the heart in starvation. Measurements of pulse rate, blood pressure, stroke volume, and the time of mechanical systole before and after semistarvation made it possible to calculate the work of the heart (*12*). The work done by the heart decreases by about 50 percent as the result of starvation, or 20 percent more than would correspond to the decrease in oxygen intake. This represents a protective change that may be designated an adaptation without inquiring as to cause and effect.

Man, therefore, can achieve a not inconsiderable adaptation to the caloric restriction. The manner in which the adaptation is achieved, however, is, in part, quite different from the way in which the body adapts to such stresses as high-altitude exposure, heart disease, or an increase in the environmental temperature. It is clear that much of the adaptation is an automatic consequence of the use of the body itself as fuel for the metabolism. The life of the organism is prolonged or maintained closer to normal than would otherwise be the case by the rather desperate expedient of reducing the mass activity of the organism. This mechanism, it seems to us, is entirely passive and produces major limitations and stresses of its own. In contrast, the man who is faced with the problem of existence in an atmosphere which has a low partial pressure of oxygen and a reduced number of oxygen molecules per unit volume achieves a more positive adaptation. He reduces his demand for high rates of oxygen supply by reducing the intensity of physical work, but does not alter his oxygen use or rate of life at rest or with moderate activity. Adaptive mechanisms provide oxygen to the body in normal amounts for all except extreme exertion. The changes include an increase in red cell concentration, a higher rate of pulmonary ventilation, and a change in the acid-base balance of the blood (*7*).

The man who travels from a cool to a hot environment adapts to this stress by a more efficient elimination of heat through an improved cardiovascular performance (*16, 18*) and, apparently, through a small reduction in basal heat production. Safety in a high rate of sweating is assured by an adaptation in the composition of the sweat. Mechanisms of this kind may be classed as active or positive adaptations, and they do not in themselves impose major limitations on performance. In the semistarved individual the reduction of oxygen consumption per unit of active tissue and the lowered cardiac work load at rest appear to be examples of active adaptation to stress of caloric restriction.

The Minnesota Experiment has provided a quantitative description of a few facts concerning the adaptation of man to caloric restriction. Adaptation in general may be defined as the adjustment of the organism to its life situation. If a new or changed life situation induces changes in the organism that enable it to meet the new life situation more effectively than would otherwise be the case, then the changes are adaptive. When these changes result in full preservation of the normal "freedom" of the organism, in Claude Bernard's sense, then perfect adaptation has been achieved. The adaptations that occur in stressful, i.e., biologically difficult, situations are generally compromises. The maximal or best adaptation maintains the freedom of the organism and its prospects of survival at the highest level compatible with the situation. It is clear that the changes due to semistarvation permit man to meet the altered situation produced by caloric restriction with moderate success. The fact that these adaptive mechanisms do not result in a complete and unequivocally favorable adjustment does not detract from the advantages gained.

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