A 35-year-old woman demonstrated severe hypermetabolism (BMR + 200 percent) since the age of seven, profuse perspiration, polydipsia without polyuria, thinness despite polyphagia, severe asthenia, and pronounced muscular wasting and weakness. Thyroid tests were normal, and no known extrathyroidal causes of hypermetabolism could be demonstrated. Electron microscopy revealed in the perinuclear area of striated muscle cells an increased amount of mitochondria of extremely variable size and shape. The hypermetabolic state of the patient was probably caused by a defect in mitochondrial enzyme organization resulting in severely lowered capacity for respiratory control. This represented the first clinical instance of an endogenous defect at this level of biological organization.

The disease started at the age of seven and had aggravated successively. The cause of the increased oxygen consumption has not been disclosed by detailed studies extending over several months. Thyroid tests were normal, and no known extrathyroidal causes of hypermetabolism could be demonstrated. Electron microscopy revealed in the perinuclear area of striated muscle cells an increased amount of mitochondria of extremely variable size and shape. The hypermetabolic state of the patient was probably caused by a defect in mitochondrial enzyme organization resulting in severely lowered capacity for respiratory control. This represented the first clinical instance of an endogenous defect at this level of biological organization.

The high respiration of the mitochondria even in the absence of phosphate and phosphate acceptor (ADP) explains why the patient was unable to adapt oxygen consumption to the actual need for energy. The hypermetabolism (high BMR) explains (1) the increased perspiration to relieve the body of excess heat, (2) the thirst to compensate for the loss of fluid, (3) the polyphagia to compensate for the increased combustion of food, and (4) the thinness as a sign that the enormous caloric intake still was only sufficient to sustain her low body weight.

We thought the mitochondria of the cells might be involved; these cellular constituents are the site of cell respiration and respiratory control. It was proposed that the increased basal metabolic rate could be a manifestation of a defect in the maintenance of respiratory control in her mitochondria.

Human mitochondria had never been studied before, and techniques were developed for isolation of mitochondria from the only tissue available in sufficient amounts at biopsy—skeletal muscle. Biochemical studies revealed a virtually complete lack of control of respiration by ADP or inorganic phosphate while the capacity for phosphorylation was only slightly impaired—characteristic of "loose-coupling" of the oxidative phosphorylation system. Later complementary analyses showed a marked increase in the protein content of the mitochondria, in cytochrome oxidase activity, and in RNA content of the muscle cells. Electron microscopy revealed a greatly increased number of mitochondria in the perinuclear areas of the muscle fibers. The mitochondria were extremely variable in size, shape, and structure, and contained a vast amount of densely packed cristae. The cell nucleus was large and very dense.

This 35-year-old woman presented a hitherto undescribed clinical picture: an enormous perspiration. She had to change clothes 10 times a day; she drank about three liters of fluid a day while the urine volumes remained small; and she had a tremendous appetite with an intake of more than 3,000 cal per day for a body weight of 39 kg (height 159 cm). The dominant laboratory finding was an enormous oxygen consumption, with a BMR around +200 percent—perhaps twice as high as had the oxygen consumption been calculated per unit lean body mass. The disease started at the age of seven and had aggravated successively. The cause of the increased oxygen consumption could not be disclosed by detailed studies extending over several months. Thyroid tests were normal, and no known extrathyroidal causes of hypermetabolism could be demonstrated. Electron microscopy revealed in the perinuclear area of striated muscle cells an increased amount of mitochondria of extremely variable size and shape. The hypermetabolic state of the patient was probably caused by a defect in mitochondrial enzyme organization resulting in severely lowered capacity for respiratory control. This represented the first clinical instance of an endogenous defect at this level of biological organization.