

# Chapter 2

## A History of Modern Research into Fasting, Starvation, and Inanition

Jean-Hervé Lignot and Yvon LeMaho

### 2.1 Introduction

Although detailed scientific studies on starvation physiology have been conducted since the nineteenth century, there is little uniformity in the terminology used to describe it. The term “fast” usually applies at the end of the postprandial period (basal or postabsorptive state). In this state, however, the digestive tract may still possess nutrients that can still be absorbed.

This review will briefly mention short fasting periods, underfeeding, and calorie restriction within specific nutritional conditions (low food availability, special therapeutic diets). We will also detail the physiological effects of prolonged fasting (starvation), i.e., the exclusion of all food intakes except water and thus a complete deprivation of dietary energy over extended periods. We will also focus on the history of the major scientific advances detailing starvation physiology in vertebrates (Fish, Amphibians, and “Reptiles,” but mainly Birds and Mammals). Further insights into the detailed physiology of these vertebrates can be found in previously published literature (e.g., McCue 2010) and the other chapters of this book.

Depending on the species, physiology during prolonged fasting depends on different parameters such as the preferential tissues for metabolic stores, the quantity stored, their availability, and the distinct routes of mobilization. Therefore, the capability of an animal to resist prolonged fasting is determined by its

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J.-H. Lignot (✉)

UMR 5119 ECOSYM Université de Montpellier II—CNRS—IFREMER,  
Adaptation Ecophysiologique et Ontogénie (AOE), cc 092, Place E. Bataillon,  
34095 Montpellier Cedex 05, France  
e-mail: Jehan-Herve.Lignot@univ-montp2.fr

Y. LeMaho

UMR 7178 Institut Pluridisciplinaire Hubert Curien (IPHC), Département Ecologie,  
Physiologie et Ethologie (DEPE), CNRS—Université de Strasbourg, 23, rue Becquerel,  
67087 Strasbourg Cedex 02, France

ability to store energy and to control its allocation during periods of food restriction. The accumulation of large energy stores to anticipate periods of food shortage is also highly valuable to survival. Furthermore, during prolonged fasting, carbohydrate, fat, and protein stores are successively depleted, therefore delaying protein catabolism for as long as possible. At the cellular level, intracellular ions (potassium, phosphorus, and magnesium) move to the extracellular space, inducing a cellular depletion of these electrolytes despite a normal serum balance. Eventually, organ dysfunction may occur, leading to a potentially fatal reduction in cardiac, renal, immune, and other functions.

The duration of prolonged fasting can therefore markedly differ between species and among individuals. Some maintain low resting energy expenditure (e.g., ectothermic and inactive species) but others can sustain physiological activities while fasting (e.g., reproduction, lactation, or migration). The key physiological differences and adaptations have now been revealed, allowing a better understanding of the diverse strategies to optimize the prefasting period, the fasting period itself, and the refeeding phase.

## 2.2 Early Studies

The subject of complete and partial inanition has been of interest among physiologists and clinicians for many years. Early studies investigated the physiology of fasting and starvation in humans, dogs, cats, rabbits, domestic fowls, pheasants, and pigeons. These studies mostly concerned body mass loss, urine excretion, and ketosis, i.e., the increased levels in the blood of ketone bodies formed when the liver glycogen stores are depleted (Chossat 1843; Schultz 1844; Bidder and Schmidt 1932; Falk and Scheffer 1854; Voit 1866, 1901; Schimanski 1879; Rubner 1881; Howe et al. 1912; Benedict 1915; Phillips et al. 1932; Errington 1939). The first studies on rats and mice were conducted between 1900 and 1930 (Pembrey and Spriggs 1904; Jackson 1915; Benedict et al. 1932; Benedict and Fox 1931). The first scientific studies on humans were realized between 1870 and 1890 and mostly concerned “professional fasters” (reviewed in Benedict, 1911) (see also Grant, Chap. 21). An example of this was research carried out by Luigi Luciani, professor of physiology in the University of Rome, who studied a 30-day fast undergone by Giovanni Succi, one of the professional fasters in 1889. One of his contenders, the American Henry Tanner, fasted for 40 days, while in France, Alexander Jacques fasted 50 days, drinking only an herbal mixture. Three years earlier, Steffano Merlatti had fasted for 55 days and only drank pure filtered water. Like other “hunger artists,” they were regularly accused of fraud during their “careers.” Nevertheless, the scientific supervision of some of these fasts allowed urine analyses and the recording of body weight. In 1911, Benedict also examined prolonged fasting (31 days) in a Maltese man, Mr. Levanzin, and recorded body temperature, arterial pulse rate, blood pressure and chemistry, urine, and respiratory parameters among other variables (Benedict 1915).

Most of the data collected from these early studies have been reviewed (Lusk 1909; Morgulis 1923; Phillips et al. 1932; Keys 1950; Grande 1964; Peret and Jacquot 1972), and indicate that carbohydrate stores provide a small but significant component of body fuel at the beginning of the fast. Thereafter, the unique sources of fuel are protein, contributing 15% of the necessary calories, and fat (Benedict 1915). Prolonged fasting can induce a dramatic body mass loss of up to 60% of the prefast weight, with an increased rate of body mass loss when starvation is prolonged. Lipid reserves can be almost completely depleted and a 30–50% decrease of protein content leads mammals and birds to death (Schimanski 1879; Phillips et al. 1932; Errington 1939). Therefore, one of the few tissues remaining preserved during prolonged fasting appears to be the central nervous system, while skin and muscle masses are reduced from one-third to half. The proportion of muscle and protein masses appears stable or slightly increased in comparison to body mass. The capacity to prolong fasting also improves when body mass and adiposity levels are high at the beginning of the fasting period (see Champagne et al., Chap. 19).

A number of early studies examined urinary nitrogen excretion during fasting (Lusk 1909; Howe et al. 1912; Benedict 1915; Goldblatt 1925; Martin and Robinson 1932; Phillips et al. 1932). While nitrogen excretion is lowered at the beginning of the fasting period before reaching a plateau, proteins only account for 7–17% of the energy expenditure and lipids appear to be the main source of energy. The excretion level also appeared to be directly linked to prior diet to fasting. With a low protein prefasting diet, the lowering of nitrogen excretion during fasting may be minimal or nonexistent. Finally, although nitrogen excretion is lowered for several days as seen in domestic fowls (Schimanski 1879) and dogs (e.g., a female fox terrier or “Oscar,” the adult Scotch collie (Howe and Hawk 1911; Howe et al. 1912), a “premortal rise” preceded by a slight decrease was also demonstrated in these early studies of single or repeated fasts (Voit 1866; Schimanski 1879; Howe and Hawk 1911; Howe et al. 1912). Proteins can account for up to 50% of energy expenditure (Phillips et al. 1932; Benedict and Fox 1931) during this “premortal” rise, attributed to cell degradation, autointoxication, and secondary infection (reviewed in Morgulis 1923; Keys 1950; Peret and Jacquot 1972). However, the absence of a typical premortal rise has also been reported (Benedict and Fox 1931). Therefore, both high and low protein catabolisms were observed as the loss in body weight increased from 40 to 50% in rats and dogs (Benedict and Fox 1931; Chambers et al. 1939). Interestingly, an increased starvation tolerance was observed in the low nitrogen group, suggesting that these animals had higher body fat stores. Finally, the results presented for humans in Benedict’s book “A study of prolonged fasting” (1915) and those gained from the Arrow’s study on catheterized dogs (total starvation) did not show any increase in protein catabolism and led Keys et al. in “The biology of human starvation” (1950) to refute the existence of this premortal phase.

From all the data gathered, Morgulis, nevertheless, divided the progressive changes occurring in the catabolism of body tissue during a prolonged fast into four periods, which each represented a loss of approximately one-eighth of the

original body weight (Morgulis 1923). Initially, glycogen stores decrease rapidly and the ability to oxidize carbohydrate also diminishes. In the second and third phases (intermediate phases), energy is mainly derived from stored fat and the mechanism for glucose oxidation is markedly suppressed to a minimum level. Finally, the fourth phase is usually characterized by a critical exhaustion of body fat to the point where endogenous protein is needed for fuel (a “premortar” rise in ammonia excretion and thus in protein metabolism).

### 2.3 Therapeutic Fasting in Humans

“Therapeutic fasting” in humans using either short fasting periods or prolonged underfeeding first appeared for the treatment of diabetes and was used from 1913 until the first use of insulin in 1922 (Allen 1915a, b; Heinrich 1916; Joslin 1916). It was recommended for the treatment of convulsive disorders such as seizures and epilepsy (Guelpa and Marie 1911; Geyelin 1921; Wilder 1921). Prolonged fasting was also described as a possible treatment for obesity, as early as 1915 (Folin and Denis 1915), and the metabolism of starvation was believed to have a special significance as an indicator of the lowest maintenance requirement of the body. Later, the effects of diet composition preceding fasting as initially observed by Schimanski (1879) were studied in further detail. As seen in rats, a high fat diet induces longer survival during subsequent fasting, and present better performance during exercise than individuals having eaten isocaloric high-carbohydrate or high-protein diets (Samuels et al. 1948).

The therapeutic potential of fasting as a possible treatment for obesity as initially described by Folin and Denis (1915) was later reemphasized (Bloom 1959; Drenick et al. 1964; Duncan et al. 1965). This treatment includes total starvation, intermittent fast, and semi-starvation. However, as early as 1965, Cubberly et al. reported one death that was attributed to lactic acidosis. Spencer (1968) also reported the deaths of two patients due to heart failure while they were undergoing therapeutic starvation at 3 and 8 weeks of total starvation, respectively. During the treatment of seven grossly obese patients with long-term fasting, a young woman was reported to have died on the 7th day of refeeding following a 30 week fast (Garnett et al. 1969). Autopsy revealed fragmentation of the cardiac myofibrils. These observed deaths occurred despite patients having huge fat stores at the time of their deaths. Although prolonged therapeutic starvation was still believed to be a safe and efficient procedure at the end of the 1960s (Runcie and Thomson 1970), several side effects and complications were observed during starvation. These include breakdown in electrolyte homeostasis (Runcie and Thomson 1970), cardiac arrhythmias (Duncan et al. 1965), and severe orthostatic hypotension, as well as severe normocytic, normochromic anemia, and gouty arthritis (Drenick et al. 1964).

Therapeutic starvation was finally stigmatized as an unsafe procedure exposing the patient to an undue risk of physical danger (but see Varaday, Chap. 23). As an

alternative to fasting, very low calorie diets (VLCDs) were developed to preserve lean body mass while maximizing weight loss as illustrated by the low carbohydrate and fat diet (Stillman and Baker 1967), the high fat and protein diet, and the “last chance diet” high in liquid protein with supplementary vitamins and minerals (Bistrian et al. 1976, 1977; Linn and Stuart 1976). The last chance diet, also called the “protein-sparing, modified fast diet” (PMSF), was one of the most popular diets in the 1970s and was recently remastered by Pierre Dukan (the Dukan diet). In this “last chance diet” most of the proteins were hydrolysates made from either collagen or gelatine. Here again, the diet required close supervision after a number of human deaths were attributed to the use of liquid protein products (Center for Disease Control 1977).

Experimentally, the classic study done by Benedict in 1911 on starving humans was repeated several times by Cahill and co-workers using normal, obese, and type 2 diabetic volunteers fasting for 8–60 days (Cahill et al. 1966, 1968; Owen et al. 1967, 1969; Ruderman et al. 1976). These studies showed insulin to be the primary regulator of fuel release: glucose from the liver, amino acids from muscle, and free fatty acids from adipose tissue. They also revealed that when carbohydrate stores are exhausted and glucose levels in the blood are too low during fasting (phase 1 of fasting in man); ketogenesis is subsequently initiated to make available energy that is stored as fatty acids (phase 2 of fasting in man) (Cahill 1970; Cahill et al. 1974; Saudek and Félig 1974; Balasse 1979). In the first phase of fasting, alanine and glutamine are the key amino acids involved in gluconeogenesis. The production of  $\beta$ -hydroxybutyrate and acetoacetate in the liver through fatty-acid  $\beta$ -oxidation also markedly diminish the need for muscle proteolysis to provide gluconeogenic precursors. During the second phase of fasting, the rate of gluconeogenesis is lowered due to a decreased use of glucose by the brain. Ketone bodies and thus, indirectly, lipid reserves fuel the brain for 50–60% of its energy needs (Owen et al. 1967). No data in existing literature therefore support the existence of a rise in protein utilization in fasting humans undergoing long-term therapeutic starvation, not even in those patients who died suddenly. It was demonstrated that the causes of these deaths were not due to an inability to spare overall body protein (fasting obese patients have a lower protein utilisation than nonobese persons) (Forbes and Drenick 1979; Van Itallie and Yang 1984), but could rather be attributed to a different ability in protein conservation of the various muscles (see Bauchinger and McWilliams, Chap. 12). This is seen with the myocardial mass that is not spared as illustrated in deaths occurring during the prolonged liquid protein diet, despite the improved overall nitrogen balance in this diet. More recently, a paradoxical increase in resting energy expenditure was observed in malnourished patients near death (Rigaud et al. 2000). This increase was associated with high urinary nitrogen losses, low serum fatty acid concentrations, and a very low fat mass. This profile has never been described in humans before and is similar to that described in the king penguin and other wild animals that naturally endure long fasting periods.

## 2.4 Integrating Data from Wild and Laboratory Models

It appeared from the different studies already mentioned that different metabolic phases can be reached depending on the species, age, and metabolic status of the individual before fasting and environmental cues such as temperature. These phases are related to modifications which occur during the catabolizing of tissues to provide sufficient energy to maintain physiological functions (Cahill 1970). In some species, rises in the rate of body mass loss and nitrogen excretion at the end of prolonged starvation are concomitant, whereas this phase is lacking in old and obese rats (Sprague–Dawley) and in humans (Cahill 1970; Goodman and Ruderman 1980; Goodman et al. 1980). Following the work carried out on humans and laboratory rats, studies performed on emperor and king penguins on-site from the mid 1970s onwards also added to our understanding of starvation physiology (Le Maho et al. 1976). Prolonged fasting in penguins has since been studied in great detail (Le Maho et al. 1976, 1981; Cherel and Le Maho 1985; Groscolas 1990; Cherel et al. 1995, 1988a, b; Robin et al. 1987, 1988).

Following the examination of changes in protein metabolism in fasting penguins, the three successive phases discovered in early studies on fasting (Schimanski 1879; Voit 1901) were further described (Le Maho et al. 1976, 1981; Goodman et al. 1980; Robin et al. 1987). The first phase (phase I) corresponds to a phase of transition between the fed state and starvation, during which the individual stops utilizing diet-derived energy. This transient phase is relatively short and lasts between several hours and several days, depending on the individual. It is characterized by a rapid decrease in daily protein losses, usually measured from nitrogen excretion. Throughout the following phase (phase II), daily protein losses remain approximately constant. This is the ketotic phase of fasting which is associated with protein sparing. The duration of this phase depends on the initial lipid mass and was shown to last for several days in rats to several months in obese geese, king penguin chicks, bears, and seals (Cherel and Le Maho 1985; Nelson 1987; Robin et al. 1987, 1988; Cherel et al. 1988a, b, c; Belkhou et al. 1991; Reilly 1991; Castellini and Rea 1992; Adams and Costa 1993; Atkinson and Ramsay 1995; Cherel and Groscolas 1999). As already pointed out by Voit (1901), the level of nitrogen excretion during phase II for any same body mass thus depends on the initial adiposity of the individual. Increased protein utilization is reflected by a rise in nitrogen excretion (Goodman et al. 1980; Le Maho et al. 1981) and characterizes the beginning of the terminal fasting phase (phase III).

Phase III is always a very brief phase, since the high daily protein losses quickly lead to the individual's death. During this phase glycemia and total plasma protein level start decreasing, and plasmatic concentration of uric acid increases while  $\beta$ -hydroxybutyrate values remain low and stable. Higher levels of corticosterone, the major avian glucocorticoid stimulating protein catabolism (Challet et al. 1995), are also observed during phase III (Cherel et al. 1988b; Robin et al. 1998). Therefore, wild animals that are "well-adapted" to long-term fasting achieve high levels of protein sparing during periods of fasting, with protein catabolism

contributing to only 2–10% of total energy expenditure (Nelson 1987; Robin et al. 1987, 1988; Cherel et al. 1988a, b, c; Reilly 1991; Castellini and Rea 1992; Adams and Costa 1993; Atkinson and Ramsay 1995; Cherel and Groscolas 1999), whilst these values can reach 20–40% in “non-adapted” species (Cherel et al. 1992; Lindgard et al. 1992). Furthermore, the absence of a late increase in net proteolysis in obese humans and rats (obese Zucker rats) was related to huge lipid stores which “masked” a lethal cumulative protein loss reached long before the exhaustion of fat stores (Cherel et al. 1992).

Studies conducted in the 1980 and 1990s on unexercised penguins, bears, and seals fasting spontaneously during part of their annual cycle were followed by others performed on fasting animals experiencing nutrient-demanding processes such as migration, lactation, growth, and development, for which the necessity to conserve proteins is also crucial (Costa 1991; Oftedal 1993; Piersma et al. 1993; Battley et al. 2001). An example of this is nonstop migratory birds, which have no access to supplementary water or nutrition during their multiday flight. They, therefore, have to carefully budget their body fat and protein stores to provide both fuel and life support (see Jenni-Eiermann and Jenni, Chap. 11). Some of these migratory birds can enter their third phase of fasting during the migratory season, as seen with one species of the Columbiformes order (the turtle dove) and nine other species of the Passeriformes (redstart, whinchat, whitethroat, flycatchers and warblers) (Jenni et al. 2000). The wide phenotypic flexibility of the gut and related organs can also allow migratory shorebirds and passerines to anticipate their seasonal long-distance migrations and to refuel at stopovers (Piersma et al. 1993; Klaassen and Biebach 1994; Hume and Biebach 1996; Piersma and Lindström 1997). Furthermore, high rates of fatty acid uptake by flight muscles are possible, partly due to a very high upregulation of the fatty acid translocase and fatty acid binding proteins during the migratory season (Pelters et al. 1999; Guglielmo et al. 2002; McFarlan et al. 2009, see Price and Valencak, Chap. 15).

Concomitantly, new experimental models were also investigated, in particular the Burmese python and other snake species (Secor et al. 2000; Secor and Diamond 1995; Overgaard et al. 1999; Secor et al. 2000; Starck and Beese 2001, 2002; Secor 2003; Andrade et al. 2004; Lignot et al. 2005; Starck and Wimmer 2005; Ott and Secor 2007; Secor 2008; Cox and Secor 2008; Helmstetter et al. 2009a, b). These species with high fat reserves (although leaner than some other “well-adapted” vertebrates) can withstand long and unpredictable periods of fasting and can resume prolonged fasting by ingesting and digesting large prey items. Benedict and Fox (Benedict and Fox 1931; Benedict 1932) were the first to document the large postprandial metabolic response for the Burmese python. All the other studied species present a similar coordinated response with feeding and fasting, although to a lower degree. Cellular plasticity coupled with the up and down-regulation across the different organs and tissues of the digestive and cardiac systems is a spectacular example of the phenotypic plasticity that can occur in an organism adapted to infrequent feeding (Secor and Diamond 1997; Secor 2003, 2008; Andersen et al. 2005; McCue 2007a, b) (see also Campen and Starck, Chap. 9). This allows the snake to drastically reduce its resting energy



expenditure by up to 72% (McCue 2007a). Another selective advantage of down-regulating the digestive tract with fasting is the reduction in the cost of maintaining this energetically expensive system during long periods of fasting. This energy saving absorbs the additional cost incurred with postprandial upregulation of the quiescent gut (Secor and Diamond 1997; Secor 2003).

Other recently studied species include the marine iguana (*Amblyrhynchus cristatus*), (that is able to “shrink” by as much as 20% within 2 years of low food availability resulting from El Niño events; Wikelski and Thom 2000), aestivating anurans (Cramp and Franklin 2003; Cramp et al. 2005, 2009), and several hypogean salamanders (Hervant et al. 2001; Issartel et al. 2009, 2010). These newts live in caves or karstic and porous aquifers that are generally characterized by unpredictable and severe variations in trophic resources. They are able to tolerate up to several years without food, which may make them the best adapted vertebrates to fasting conditions (see Hervant, Chap. 7). Their general adaptive strategy, as seen with the urodel *Calotriton asper*, implies the selection of fasting adaptations similar to those observed for sit-and-wait foraging snakes. A study of this species, albeit over a short period of fasting, showed that hypogean individuals rely on a lower basal metabolic rate during fasting than their epigean counterparts, with higher energy reserves, a higher capacity for metabolic depression during food deprivation, and a higher reduction in utilization rates (Issartel et al. 2010).

The physiological effects of fasting in fish have been regularly documented for many species, especially for migrating and aestivating species as well as those that are commercially harvested (see Bar and Volkoff, Chap. 6). However, some results appeared contradictory and highly dependent on environmental conditions (Inui and Ohshima 1966; Love 1970, 1980; Dave et al. 1975; Weatherly and Gill 1987; Balasse 1979; Mendez and Weiser 1993; Navarro and Gutiérrez 1995, and for recent reviews, see Wang et al. 2006; Secor and Lignot 2010). These results, nevertheless, followed those obtained in other vertebrates. For example, the energetic costs of maintaining homeostasis during food deprivation appeared to be directly related to the animal’s capacity to mobilize energy reserves such as hepatic glycogen and lipids, at least during the initial phases of fasting. As observed in examples such as carps, migratory eels, and Pacific salmon body mass loss can be drastically reduced by more than 80% (84% for male European eels after 52 months of pure fasting inducing a 13.5% decrease in body length) and up to 95% of the fat reserves can be used before catabolism of proteins starts, followed by that of carbohydrates (Pacific salmon) (French et al. 1983; Olivereau and Olivereau 1997; Shimeno et al. 1997). Prolonged fasting affects not only the digestive tract (Blier et al. 2007), but also ionic regulation, a function requiring high energy consumption (Polakof et al. 2006). There are contradictory data concerning the precise role of cortisol in regulating ion transport in fishes and the effects of cortisol during prolonged fasting remain unclear (Wendelaar Bonga 1997; Mommsen et al. 1999; Kelley et al. 2001; Peterson and Small 2004; Barcellos et al. 2010).



## 2.5 Refeeding after Prolonged Fasting

Over the last 20 years, refeeding after the late increase in nitrogen excretion characterizing prolonged fasting in mammals and birds has been repeatedly studied in the laboratory rat. These studies confirm that the third phase of fasting is reversible and is an essential part of the physiological adaptations to long-term food deprivation (Cherel and Le Maho 1991; Robin et al. 2008). The progressive decrease of water intake to almost zero in the third phase of fasting is progressively increased in the hyperphagic refeed animals. They regain muscle mass before regaining body fat, and recover a fully functional digestive tract within less than 3 days (Cherel and Le Maho 1991; Dunel-Erb et al. 2001; Robin et al. 2008, see Lignot, Chap. 14). This hyperphagia [also documented in fish (Bélanger et al. 2002)] allows compensatory growth, and overcomes transient anorexia that may be present at the beginning of the refeeding period (Hamilton 1969). Furthermore, the extent of lipid depletion at the onset of refeeding directly impacts the body reserve restoration pattern, as illustrated by the preferential restoring of body lipids via a significant contribution from endogenous lipid production in phase III refeed rats (Robin et al. 2008). Lipid use also depends on the intensity of the energy restriction (partial or total). If rats are given the ability to select their diet, refeed animals following a phase II fasting period gradually decrease their preference for fatty diets (see also Overgaard and Wang, Chap. 5). In contrast, rats refeed after a phase III fast increase fat intake first and then increase their protein intake (Thouzeau et al. 1995). Finally, and as previously seen in laboratory rats (Koubi et al. 1991), an “alarm signal” or “refeeding signal” has been described at the transition between phase II and phase III in fasting penguins (Robin et al. 1998; Groscolas et al. 2000). This can trigger behavioral changes such as egg abandonment and departure to refeed at sea (Robin et al. 1988; Le Maho et al. 1981; Groscolas 1990).

Since early scientific studies (see Benedict 1915), refeeding following prolonged fasting in humans has been proved to be difficult and a “refeeding syndrome” can occur, as observed with refeed prisoners of war, hunger strikers, severely malnourished patients with anorexia nervosa and other critically ill patients (Schnitker 1946; Schnitker et al. 1951; Gentile et al. 2010) (see also Grant, Chap. 21). This potentially fatal syndrome is due to metabolic, intestinal and cardiorespiratory dysfunctions, as well as fluid and electrolyte imbalances (hypophosphataemia) (Crook et al. 2001; Hearing 2004) and stepwise nutritional replenishment (renourishment) is necessary before tolerating a full, unrestricted diet.

## 2.6 New Challenges

It is of wide biological and medical interest to elucidate the underlying mechanisms enabling metabolic adaptations occurring during prolonged fasting and at refeeding. For example, preventing loss of weight and lean body mass in critically

ill patients and avoiding the refeeding syndrome are major therapeutic objectives (Powell-Tuck 2007). Over the last 10 years, different specific studies have been carried out in laboratory rats and wild animals not only at the tissue level (e.g., intestines) but also on the major biomolecules involved (neuropeptide Y, agouti-related peptide, circulating hormones) (Habold et al. 2004, 2005, 2006, 2007; Bertile et al. 2003, 2007, 2009; Groscolas et al. 2008; Falsone et al. 2009; Spée et al. 2010; Gerson and Guglielmo 2011).

Leptin, prolactin and corticosterone, as well as proteolytic related and orexi-genic genes have appeared as metabolic regulators during starvation (Bertile et al., 2003, 2007, 2009; Groscolas et al. 2008; Falsone et al. 2009; Spée et al. 2010; Gerson and Guglielmo 2011). For example, king and Adélie penguins starting their proteolytic third phase of fasting only abandon their egg when corticosterone levels are markedly high while prolactin levels have decreased (Cherel et al. 1994, 1995; Groscolas et al. 2008; Spée et al. 2010). Furthermore, phase II fasting penguins injected with corticosterone presented increased locomotor activity similar to that seen in phase III fasting birds (Spée et al. 2011). These data suggest that corticosterone and prolactin are two important hormones that certainly play a key role in the refeeding signal occurring in long-term fasting birds. It has also been suggested that corticosterone facilitates energy supply during endurance flight by regulating the composition of fuel types used during endurance flight, especially protein catabolism (Falsone et al. 2009).

Proteomic studies on phase II and phase III laboratory rat plasmatic fractions have also revealed differentially expressed levels of apolipoprotein A-IV, A-I, and E, haptoglobin, transthyretin, plasma retinol binding protein, and vitamin D binding protein (Bertile et al. 2009). It has been suggested that the marked reduction of apolipoprotein A-IV levels contributes to the refeeding signal, whilst other differentially expressed proteins during fasting were attributed to lipid metabolism and changes in insulin signaling. Finally, fatty acid transport in bird muscles markedly increases during migration (McFarlan et al. 2009) (see also Price and Valencak, Chap. 15). Nevertheless, the supplementary use of body protein catabolism during fasting still remains poorly understood. One hypothesis is that under dehydrating conditions, the catabolism of body protein could maintain water balance (Gerson and Guglielmo 2011). Migratory bats may also use convergent physiological processes during their flight (McGuire and Guglielmo 2009) (see also Ben Hamo et al., Chap. 16). For example, the cytosolic H-FABP is upregulated in the small brown bat *Myotis lucifugus* during hibernation, a physiological challenge which is highly dependent on fat stores, just like in migrating animals. (Eddy and Storey 1994; McGuire and Guglielmo 2009). Finally, fatty acid composition of the fat stores and the preferential use of n6PUFAs during exercise can modify metabolic rate and flight performance (Price and Guglielmo 2009; Guglielmo 2010; Price 2010).

Therefore, although still incomplete, a better understanding at the whole organism level of the integrated responses occurring during prolonged fasting is emerging. Close physiological comparisons between species are now possible (resting versus exercised fasting birds and mammals; fasting physiology in migratory birds and bats, preferential use of the different fatty acids, etc.). New and

exciting avenues for environmental research include the possibility of looking at severely disrupted populations and their growing food restrictions due to anthropization, climate change, reduced and more distant stop-over feeding sites, and so on. Optimizing the refeeding of fasting birds near death, unable to eat unaided and losing weight despite refeeding trials (e.g., oiled seabirds) is also a key challenge for applied research.

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