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Metabolic biochemistry and the making of a mesopelagic mammal

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Abstract. Large seals such as northern and southern elephant seals and Weddell seals are able to dive for startling duration and enormous depth. The current dive duration record is 120 minutes (recorded for the southern elephant seal); the current depth record is 1.5 km (recorded for the northern elephant seal). Equally striking is the widespread observation that these seals when at sea spend close to 90% of the time submerged and often at great depth. For practical purposes, these species can be viewed as true mesopelagic animals when they are at sea. A review of current knowledge indicates that low power output but high efficiency metabolic functions of skeletal muscles coupled with inherently low (and potentially further suppressible) metabolic rates constitute strategic biochemical components in the 'making' of a mesopelagic mammal.
Key words. Seal metabolism; metabolic efficiency; metabolic suppression; seal muscle enzymes.

The problem

The literature and international symposia on diving metabolism and physiology were unusually lively during the 1980's because of an apparent paradox: a seeming discordance between laboratory and field data on the significance of the Scholander diving response. Studies of simulated laboratory diving consistently observed powerful bradycardia coupled with peripheral vasoconstriction, serving to redistribute cardiac output with preferential perfusion of the heart and brain. In contrast, heart rate measurements of voluntary diving frequently showed little or no evidence of such patterns, which together are termed the diving response. With the development of microcomputer devices for monitoring voluntary diving in the sea[9, 10, 24, 25], this paradox has been largely resolved, and the dialogue is now far more reserved, implying relatively broad agreement between the diverse workers in this area. However, as we enter the 1990's, the diving discipline is again confronted with another equally perplexing paradox: namely, the apparent ability of large (Weddell, southern elephant, and northern elephant) seals to dive for longer times than would be required for resting metabolic rates to consume all onboard O_2 supplies. What is more, the currently available field data indicate that these large seals when diving at sea are submerged close to 90% of the time for periods of weeks to several months[6, 12, 13, 24, 25]. Hence, living in the 'slow lane' appears to be the normal metabolic state of affairs for these species. The main goals of this essay are first, to review the fundamental metabolic and physiological processes underlying these apparent low metabolic rates during diving, and secondly, to consider their ecological implications.

Background and current developments

Antecedents to the above metabolic paradox are evident in the literature as far back as the late 1930's in the work of Scholander and Irving, and based on laboratory experimentation (see Scholander[28]). We first confronted the problem in our 1982/1983 Antarctic research program studying voluntary diving in the Weddell seal. These studies[9, 11, 12, 27] showed that for some free dives, the total amount of O_2 available could only sustain low metabolic rates, lower than RMR, the resting metabolic rate of the species. The amounts of lactate formed dur-

ing, and released into blood after, such dives indicated that the energetic deficit was not being made up by anaerobic glycolysis. Thus, we concluded that the data were consistent with a relatively hypometabolic state during diving. Several subsequent reports confirmed and extended this interpretation[6, 13, 24, 25]. Studies of southern and northern elephant seals indicate that between 25% and 40% of voluntary dives at sea exceed the aerobic diving limit (ADL), which is the maximum 'aerobic' diving time possible at RMR; because, in these diving patterns, the animals spend about 90% of their time submerged with very brief time intervals at the surface, it is generally assumed that their reliance on anaerobic glycolysis must be minimal, as in the Weddell seal studies[2, 9, 20, 21]. Thus, the most plausible explanation of these data assumes a relatively hypometabolic state at least during long dives. A second type of evidence bearing on this issue arises from laboratory experiments in which northern elephant seals were allowed to dive whenever they wished for as long as they wished; metabolic rates (averaging dive plus interdive periods) were determined by O_2 uptake measurements when the animals surfaced. These data demonstrated that the longer the dive, the lower the metabolic rate (Le Beouf, pers. comm.), in agreement with analogous field measurements on Weddell seals while resting or sleeping at an ice breathing hole[2].

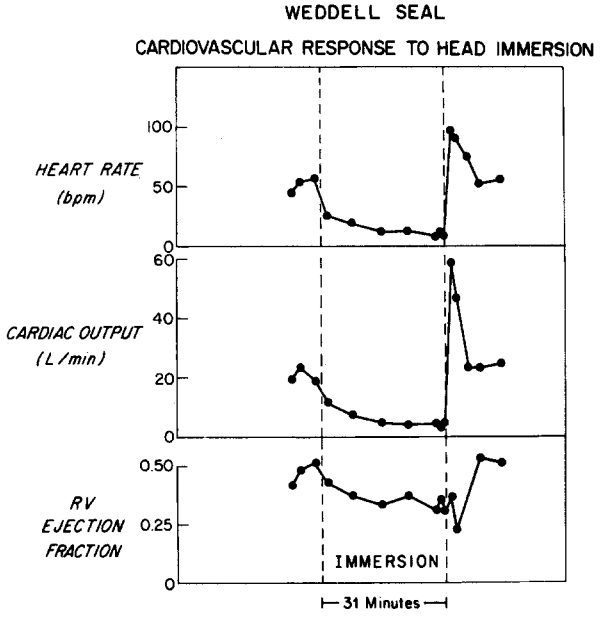
To put these observations into perspective, it is important to note that not all marine mammals necessarily show this behavior. Currently, at least two general patterns can be discerned, which appear determined by the way in which the metabolic demands of diving and swimming exercise are balanced, and gradations between them are clearly possible and probable. In high performance species (dolphins, penguins, sea lions, fur seals) the exercise metabolic demands of high swimming velocities would be expected to exceed any savings that are possible by metabolic suppression strategies of the large seals. That is why it is not surprising to find field metabolic rate estimates of such species to be substantially above RMR, rather than below RMR. These measurements utilize the doubly labelled water technique for measuring average metabolic rates usually over periods of days to weeks, and thus do not allow determination of precise relationships between dive duration and metabolic rate[4]. They are mentioned here because they illuminate boundary conditions in the marine mammal world: the energy dissipative strategies of fast swimming species vs the energy conserving strategies of the large seals. In the former active species, the demands of exercise form dominant energy sinks and the metabolic picture is presumably fairly analogous to that of exercising terrestrial mammals, including man; intuitively this is easy to understand. In the large seals, however, the situation is seemingly counter-intuitive, with swimming and foraging at sea at rather low metabolic rates, possibly suppressed well below RMR. How can this be achieved?

At two recent Biennial Marine Mammal Conferences (in 1989 and 1991 at Asilomar and Chicago, respectively) there was widespread agreement on one issue: namely, that there is no theoretical framework currently available to adequately account for this 'life in the slow lane' metabolic paradox. From studies of other organisms adapted for living at the edge of hypoxic crisis[14, 15], we know that (1) minimizing energy demands (thus reducing metabolic rates) and (2) maximizing efficiencies of various energy-producing and energy-consuming biochemical and biomechanical processes[16] are dominant survival strategies. Reviewing the evidence shows that similar strategies may be utilized by large seals.

Model for metabolic suppression

In studies of metabolic regulation during exercise in numerous terrestrial mammals, exquisite matching between perfusion (O_2 and fuel delivery) and muscle metabolic rate is typically observed. This close relationship, evident at the local tissue level (see Chinet[3] for a specific tissue example; Hochachka and Guppy[14], for overview) as well as at the global (cardiac output/$\dot{V}O_2$) level[29], characteristically begins at RMR and extends towards a $\dot{V}O_{2max}$ limit. Several data sets are consistent with the hypothesis that during voluntary diving in large seals such as the Weddell seal, this relationship also holds wherein, from RMR, metabolism moves to lower rates during diving, as is frequently reported in ischemic peripheral tissues and organs[3, 14].

Molecular mechanisms regulating this empirical relationship between metabolism and O_2 availability have been the focus of much recent research and it is now evident that there are at least two responses to changing O_2 supply: in one response (we can call this the classical pattern) as O_2 becomes limiting, the tissue activates anaerobic glycolysis to make up the energy deficit[14], while *in an alternate strategy adenosine triphosphate (ATP) demand is down-regulated to maintain energy balance*[1, 18]. In our view, many peripheral tissues during diving frequently may need to follow the second of the above cellular metabolic responses. At the level of cell energetic status (which can be monitored by following concentration changes in key intermediates in energy metabolism) the consequences of the two strategies are quite different. Very much larger perturbations in metabolite concentrations would be evident in the first than in the second of the above responses[1]. What is more, in the former response, myoglobin-bound O_2 supplies must be essentially fully exhausted, while by regulating ATP demand, changes in metabolic rate and in O_2 supply can be closely integrated. Because in this response both energy demand and O_2 supply change in step with one another[1], myoglobin need not be fully deoxygenated at the end of diving (or in the extreme case, at fatigue). ATP turnover rate and perfusion rate in this context can both be considered to be expressions of the same phe-



Cardiac output (determined using thermal dilution), heart rate, and right ventricular (RV) ejection fraction in Weddell seal during simulated diving in the Weddell seal. Experimental techniques given in ref. 30. Unpublished data of Snider, M. T., Zapol, W. M., Schneider, R. C., Qvist, J., Liggins, G. C., Creasy, R. K., and Hochachka, P. W.

nomenon (O_2 flux) under both hypo- and hyper-metabolic conditions. If correct, this model suggests that metabolism during diving in large seals is suppressed because perfusion of specific tissues and organs is suppressed; i.e. suppressed perfusion is the proximate physiological cause of suppressed metabolism of peripheral tissues and organs. We can get some idea of the magnitude of such effects from cardiac output data on simulated breath-hold diving in the Weddell seal[30]. A specific example in the figure shows that cardiac output in the resting adult Weddell seal is in the range of 25 l per min. During diving bradycardia (heart rate below 15 beats per min), cardiac output drops to about 4 l per min, while during interdive tachycardia (heart rate over 100) it can rise to 60 l per min, implying perfusion (and hence metabolic rate) changes of peripheral tissues of similar magnitude through dive-interdive intervals (fig.).

Although field data are not yet available, the catecholamines are of special interest in the control of these diving metabolic adjustments for two reasons: (1) they are known to increase drastically during forced submergence in ducks[22,23] where they are believed to enhance the sympathetically-mediated vasoconstriction of peripheral tissues for prolonged time periods, and (2) they are believed to be involved in perfusion-metabolism coupling in terrestrial mammals[29] and also in forcibly submerged aquatic mammals[10]. Taken together, such hormonal and metabolic mechanisms can go a long way towards explaining reduced metabolism during prolonged diving. However, since diving seals must swim to achieve their (foraging) goals, the question of muscle efficiency still remains.

Regulating muscle biochemical efficiencies

Traditionally, it is believed that metabolic and work efficiencies can be improved in three different ways: (1) by maximizing the yield of ATP/mole of fuel metabolized, (2) by maximizing yield of ATP/mole of O_2 consumed, or (3) by maximizing mechanical work achieved/mole of ATP utilized. In seal skeletal and cardiac muscles, we have little information on the latter two adaptive strategies, although they are clearly of major significance in mammalian adaptation to chronic hypobaric hypoxia[16]. Two lines of evidence, however, suggest that strategy (1) above – maximizing the ratio of aerobic to anaerobic support for muscle work – does appear to be utilized in large seals. The direct evidence for this mechanism, alluded to above, is that under field diving conditions in large seals lactate seldom – if ever – seems to accumulate to inordinate levels[9,21]. Even in the currently held record dive duration of 2 h by a modest sized female southern elephant seal, the surface recovery time required is only a few minutes[13]; from studies of Weddell seals, it is a fair assumption that even in such extreme cases, the lactate load is modest enough to be easily cleared either in recovery per se or in subsequent dives. As in the chronic hypoxia of high altitude man, anaerobic metabolism is deemphasized so as to increase the percentage contribution of aerobic pathways to the energy demands of working muscles.

The second line of evidence arises from studies of muscle metabolic organization implied from enzyme activity measurements[7]. Two observations are particularly instructive. Firstly, the maximum activity levels of enzymes such as citrate synthase functioning in oxidative metabolism are down-regulated to about $1/2$ the values found for skeletal muscles in terrestrial mammals[7]. Since citrate synthase activities correlate directly with mitochondrial volume densities, these data probably mean that muscles in seals are relatively poor in mitochondria[17,18]. Additionally, the glycolytic pathway displays adjustments that are seemingly designed to minimize pyruvate flux to lactate, while favoring pyruvate flux into oxidative pathways, again a set up similar to that found in muscles of altitude adaptive individuals[17]. The crucial clue to this organization arises from pyruvate kinase (PK) and lactate dehydrogenase (LDH) activities. In vertebrate fast twitch glycolytic muscle the capacity to produce pyruvate is only about $1/5$th the capacity to reduce pyruvate to lactate. In mammalian muscles with mixed fiber types the PK/LDH ratio is about 0.4–0.5, while in relatively pure red (slow twitch oxidative) mammalian muscle the ratio is about 0.8–1.0. In at least 21 skeletal muscles of seals, including the longissimus dorsi or main propulsive muscle for swimming, the PK/LDH ratio is in the range of 0.8–1.0. What is more, H-type subunits contribute to about $1/4-1/3$ of the LDH activity from these kinds of muscles[17], and this isozyme composition is also observed for Weddell seal muscles

(B. Murphy, pers. comm.) which is consistent with abundance of all three fiber types [7]. H-type LDHs are sensitive to substrate inhibition, a kinetic characteristic that is often considered a hallmark of the pyruvate branchpoint in cells whose metabolism is largely O_2 based. These characteristics are generally observed in skeletal muscles [17] where the maximization of aerobic/anaerobic contributions is an established biochemical efficiency adaptation to chronic hypoxia [16].

Considered together, these data indicate that the skeletal muscles of large seals have low capacities for both oxidative and glycolytic ATP production, with telling enzyme kinetic mechanisms for tempering potential flux of pyruvate to lactate. The only other mammalian examples displaying these characteristics are the skeletal muscles of humans adapted to chronic hypobaric hypoxia; the latter are classic examples of muscles designed for low capacity (low power output) but high efficiency [26]. That may well be the situation in skeletal muscles of large seals, since a characteristic of low capacity, high efficiency muscles is enormous (and low O_2 cost) endurance [26].

Interestingly, this relationship may not be entirely of biological origins. Gnaiger [8] points out that thermodynamics constrain the properties of muscles so that low power output may be a necessary price to pay for high efficiency. Be that as it may, it certainly is an advantageous biochemical design for simultaneously answering the demands of diving exercise and of diving hypometabolism.

From this analyis, then, we can conclude at least tentatively that minimizing metabolic rates while up-regulating biochemical efficiencies are realizable adaptational strategies in large seals for extending diving depths and durations. We consider that the biological consequences of these cell-level biochemical properties are extensive since they may be the fundamental explanation for how large seals can operate as true mesopelagic animals.

The seal as a mesopelagic mammal

Mesopelagic animals are those that spend all – or at least much – of their time below the euphotic zone and above the really deep (bathypelagic and hadal) parts of the marine water column. As already mentioned, recent field studies of both northern and southern elephant seals indicate that they spend close to 90% of the time submerged and much of the submergence time is in mesopelagic zones [6, 13, 25]. It is now also quite clear that foraging for vertically migrating prey – mainly squid in the case of the northern elephant seal [6] – is the biological or ecological reason for such deep diving. Preying upon the deep scattering layer is one reason why diving excursions follow isolumes and thus display characteristic night and day patterns [6, 12]. In principle, air breathing predators could go after this kind of food at either low or high velocities. Which is the more advantageous way to forage?

To examine this question let us consider a 30-min dive with a maximum depth of 500 m, and a total onboard O_2 pool of 1500 mmoles, conditions similar to those found in adult Weddell seals [2, 15, 20, 21]. For a 450-kg seal, this performance would require a diving metabolic rate of about 50 mmole O_2/min and an average swim speed of 33 m/min if half the time was used in descent. If the seal chose to swim 4 times faster, its metabolic costs would increase drastically (because cost rises as the third power of speed). Thus, either dive duration would have to be reduced to perhaps a few minutes or dive depth would have to be sacrificed to less than 25 or 30 m. If dive duration is enormously extended, say to 120 min and 700 m (the current duration – but not depth – record for large seals [12, 13]), the oxidative metabolic rate during diving would have to be reduced to about 12–13 mmoles O_2/min. Otherwise, there would be an energy deficit that would need to be made up by anaerobic metabolism. This is considered to be unlikely since a large lactate accumulation is inconsistent with subsequent, typically short interdive periods. (The possibility that lactate serves as a fuel for metabolism and is cleared in subsequent shorter dives cannot be fully ruled out, but is not consistent with the typically low lactate clearance and turnover rates in seals [5]).

It is interesting to compare these impressions with field measurements of metabolic rates of Weddell seals. Recent measurements averaging dive plus interdive intervals show that such averaged 'field' rates are similar to the RMR, about 90 mmoles O_2 per min for a 450-kg adult animal [2]. Let us assume a 13-min interval: a 10-min dive with a 3-min interdive interval during which the metabolic rate is 3-fold accelerated over rest. Since average metabolic rate is known, the total amount of O_2 consumed over 13 min must be 90×13 or 1170 mmoles; of this, interdive metabolism would account for 810 mmols O_2 over the 3-min interval, leaving 360 mmoles of O_2 being consumed during 10 min of diving. The estimated diving metabolic rate thus is 36 mmoles O_2 per min, representing about a 60–70% suppression of metabolism below resting levels. If dive duration is extended, the suppression may well have to be more extreme, or the energy deficit will have to be made up with anaerobic lactate production, which, as already noted, does not seem to be a common occurrence; on the other hand, many dives are far longer than the 10 min assumed for our estimates, an observation which thus drives the point home all the harder. These views are consistent with very recent microprocessor-assisted EKG studies showing very profound bradycardia associated deep, prolonged submergence (R. Andrews and D. R. Jones, pers. comm.) during voluntary (at sea) diving in northern elephant seals. Similar recent studies of grey and harbor seals, using telemetry, also show periodic and very profound bradycardia during at sea diving (M. Fedak, pers. comm.). While enough information is not available to make these kinds of calculations particularly precise, they neverthe-

less clearly illustrate the trade offs involved. What appears to be selected are metabolic rates and swim speeds that are adequate to get into the mesopelagic zone (where the squid are) with enough reserve left to allow prey capture and easy return to the surface. *Metabolic energy seemingly is used for extending submergence (or foraging) time rather than being 'wastefully' expended on swimming speedily into mesopelagic feeding zones.* Because of limited amounts of O_2 that can be stored 'onboard' (the lungs are collapsed and do not serve in gas exchange, leaving blood O_2 and myglobin bound O_2 as the two on board O_2 depots), the biological advantages of low swim speeds, biochemically efficient muscle, and a variably suppressed metabolism are readily appreciated.

Low power output, high efficiency muscle biochemical functions, and metabolic suppression capacities thus constitute strategic biochemical components in the design of a mesopelagic mammal. As far as we know, however, small seals are qualitatively similar to large ones [7], and no convolution of their biochemistry and physiology could allow these small seals to operate as mesopelagic predators; so something is still missing in our analysis. The missing (and perhaps final) element for allowing an airbreathing animal to operate in the mesopelagic zone is large body mass. While allometric effects on diving duration [6] are beyond the scope of this analysis, it should be emphasized that with increase in mass comes increased onboard O_2 pool size with a concomitant decrease in mass-specific metabolic rate; taken together, these kinds of allometric effects supply a final key component required to 'make' a successful mesopelagic mammal. In fact, armed with such arsenal, the northern elephant seal can dive to depths of at least 1.5 km [6], depths that are beyond the mesopelagic and well into the bathypelagic zone! There are probably no physiological or biochemical reasons why southern elephant and Weddell seals cannot dive as deeply, although to date [12, 13] such bathypelagic excursions by these two species have not been observed by biologists.

Finally, it may be worth emphasizing that of the above metabolic adaptations for mammalian mesopelagic life, the surprisingly low energy costs of diving make the largest quantitative impact on diving duration and diving depth. This is a particularly interesting insight, since the metabolic rates of other mesopelagic and bathypelagic organisms (invertebrates and fishes) also decline drastically as a function of depth of occurrence in the water column [15]. Although the reasons for the low metabolic rates in the two groups of organisms may be different, the symmetry of the situation is striking.

As it goes for the prey in the marine water column, so must it go for the predator?

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The biochemistry of natural fasting at its limits

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Abstract. There are several groups of animals that are adapted for extremely long duration fasting as part of their reproductive cycle. Penguins, bears and seals routinely fast without food or water for months at time. However, they do not 'starve', as the biochemical implications of starving are very different from those of successful fasting. There are distinct biochemical adaptations in lipid, carbohydrate and especially protein metabolism that allow these animals to survive. It appears, at least for penguins and seals, that the duration of the fast may be limited by changes that occur in biochemical regulation near the end of the fast. In all of these species, the biochemistry of fasting and the ecological and behavioral demands of their breeding cycles are closely interrelated.
Key words. Starvation; penguins; seals; marine mammals; bears.

There are many factors that are involved in the regulation of food intake. In healthy humans for example, food consumption on a day-to-day basis can be proximately regulated by social factors, activity levels and hormonal control of appetite, all of which are ultimately linked to providing homeostatic regulation of metabolic biochemistry[23, 49, 54, 65]. There are animals, however, that are adapted to withstanding very long periods with neither food nor water. Some of these fasting periods are related to a lack of available food while others are part of the natural history of the species. For example, the marmot *(Marmota flaviventris)* can fast for up to 3 weeks in the winter when food is lacking[22] while the northern elephant seal *(Mirounga angustirostris)* can fast for up to 90 days as part of its breeding cycle[18, 34]. In all of these cases of natural food deprivation, however, there is a critical distinction between fasting and starvation. The fasting animal is adapted to maintain a level of metabolic homeostasis so that critical organ function is maintained. Starvation, however, is a state in which homeostatic control is lost and critical organ function becomes compromised[67, 69, 74]. Thus, an animal may 'starve to death' when deprived of food but an animal that naturally fasts would not 'fast to death'. In this review we ask the question: Does extended natural fasting ultimately reach the point of starvation and if it does, what role might this metabolic switch play in the natural history and ecology of the species?

This review focuses mainly on the metabolic biochemistry of long duration fasting in normothermic mammals and its relationship to the ecology of the species. It deals with penguins, bears and seals, species in which extended fasting and reproductive behavior are closely linked. There are many species that routinely endure short periods of fasting in the order of a week or less but do not enter into long periods of food deprivation. There are excellent works available on the hormonal control of appetite and the impact of torpor and/or hibernation on fasting biology[23, 30, 41], and these issues will not be discussed here.

Non-fasting adapted species

For obvious medical reasons, a great deal of work has been carried out on the need for food in humans and fasting/starvation has been modeled extensively with laboratory animals. Some humans have been able to survive without food for over 12 months[68], but long-term fasting is not a routine part of human behavior. The basic elements of fasting and starvation have been defined in humans and animal models and are described in detail in a series of reviews[9, 10, 24, 25, 29, 31, 39, 74]. The literature in this area of human fasting/starvation is so extensive that we have summarized the field using the above general reviews with specific references only to detailed points of interest.

During the first few days of food deprivation, termed Phase I, the hepatic glycogen reserves are almost completely utilized as the body defends circulating glucose levels. Glucose is a critical fuel for the central nervous