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New Paradigm for Old Dogma (p. 1925, 1937, 1947, 1957, 1967)

One of the most significant energy demands that a female animal will face at any time in her life is when she is feeding her young. Unlike the intense bursts of energy that we routinely expend in daily life, lactation is a sustained demand that lasts over an extensive period of time. An important question is what limits an animal's capacity to output energy, for example in the form of milk production? Is this capacity intrinsically limited by the amount of energy that the animal can absorb across the gut lining (e.g. centrally limited), or, is it limited by the organ that is responsible for the energy output, in this case the mammary gland (peripherally limited). This debate raged for several years, and some had thought that it had been laid to rest primarily by the work of Kimberly Hammond and Jared Diamond. In the early 1990s, they described experiments that indicated that the limit appeared to be conferred by the mammary gland in Swiss Webster mice. Hammond had found that she couldn't get the mice to ingest more food, 'they'd (even) kill their young before they ate more' explains John Speakman. However, when she tested how the mice responded to the cold, she noticed that they increased their food intake. This seemed to lay the question to rest: energy intake was not limited centrally by the gut, because the mice had eaten more in cold conditions, so the mammary gland must be the culprit. Sustained energy intake must be peripherally limited, by the mammary gland.

Five years ago, Speakman and colleagues published a similar study on a different strain of *Mus musculus*, MF1, which made him suspect that these little critters weren't behaving like their Swiss Webster cousins and made him think that the issue wasn't cut and dried. So, Speakman put them to the test to see just how far they could, or would, go.

In the first of five, back-to-back publications in this issue, Speakman and his team tried to get the mice to eat more by modifying the litter size (p. 1925). The result was that even if they increased the litter size to 18, the mothers didn't increase their food intake beyond 23 g day^{-1}. But, when the litter size was decreased, they responded by reducing the amount they consumed.

In a series of follow-up experiments, they stressed the mice to see if there were any circumstances that would force them to exceed the 23 g day^{-1} asymptote. An effective way of increasing the energy demand on lactating animals is to cause a second pregnancy while the mice are still feeding the first litter (p. 1947). Even these extra demands didn't push their daily diet above 23 g day^{-1}. However these mice did exceed the 23 g limit during the second lactation. This suggested that the mice weren't limited by the amount of food that they can transport across the gut, supporting Hammond's original interpretation that the mammary gland is the dominant limiting factor.

In the next test, the mice were fed a reduced energy diet (p. 1957). Surprisingly, these mice also exceeded the 23 g day^{-1} asymptote. So it wasn't that they couldn't eat more, they can increase their intake when they choose, apparently confirming that the mammary gland is the limiting factor.

In the final test, they tried stressing the mice under cold conditions to see how that affected their energy intake, and this time they found that not only did the mice eat more, but they produced more milk (p. 1967). In this case, the mammary gland was not limiting milk production. Hammond's earlier experiments had found that cold was the only condition where the Swiss Webster mice ate more, but she hadn't explicitly looked at milk production. When Speakman's group measured the milk output, they found the increase. So, if the mammary gland is not the limiting factor, what is?

Speakman decided to test whether resting metabolic rate was somehow related to the limiting factor (p. 1937). He tested to see if variation in resting metabolic rate was correlated with the amount that the mice could eat, and therefore the possible amount of energy that they have available for lactation. If resting metabolic rate was the factor that potentiated milk production, then animals with a lower resting metabolic rate may be more limited in lactation than others with a higher rate. But, the only correlation that he found was that bigger mums, which have higher resting metabolic rates, had larger litters of bigger pups. Once the effect of body weight had been taken into account, the animal's resting metabolic rate didn't appear to be a significant factor, leaving the question wide open.

In most circumstances, the mice appeared to be limited in the amount of energy that they could intake or output. But were they really, or was this more of a choice than a hard wired response? Most of the observations were taken during the first pregnancy. How would the mice respond during later lactations? After all, the mice had worked harder and increased their intake during their second lactation. This raises the possibility that the female mice were trading off a lower yield in their first pregnancy to maximise their life-time pup production. Were they able to do this because they had 'saved themselves' by not over extending themselves during the first lactation? Whether it's a physical limit or a matter of choice, the jury is out on the question of energy balance. What guides these choices is the new question, and that will form the focus of much work in this and other systems.

Some Like it Hot (p. 1869)

Biological systems are finely tuned and optimised to function within tightly constrained temperature ranges. But take an organism out of its comfort zone and its delicate biological balance can be disturbed to the extent that life itself is threatened. The Heat-shock proteins (Hsp) are in the cell's front line of molecular defences against environmental stress. They are chaperones that protect the cell by preventing heat-damaged proteins from aggregating during a high temperature episode. Of the many chaperone proteins expressed during a heat shock response, Hsp70 is the most abundant.

Work from Martin Feder's lab in the mid 1990s showed that *Drosophila melanogaster* which had been genetically engineered to carry extra *hsp70* genes were more resistant to high temperatures than regular lab flies. These 'extra copy' flies produced more Hsp70, and survived temperatures up to 36°C that would kill weaker fly strains. The climate in sub-Saharan Africa routinely reaches such highs, and a strain of *Drosophila* that was collected in Chad in the early 1970s, has evolved to withstand the fiery climate. Feder knew he could improve thermal tolerance by boosting *hsp70* gene levels, but by what means had nature achieved this naturally in the African flies?

Using a battery of molecular techniques Feder and his Russian co-workers compared the African flies with *Drosophila* from a temperate climate to see how the flies deploy heat-shock chaperones to combat the potentially lethal temperatures. They followed the transcription of *hsp70* genes and Hsp70 protein levels at temperatures from 36–41°C. What they found was perplexing. Not

only did the African flies have little inducible thermotolerance, but Hsp70 levels were also much lower than in typical *Drosophila*!

Why would a population evolve decreased expression of heat-shock proteins? Like human fire fighters, heat-shock proteins are extremely important in preventing heat damage, but can do damage in their own right when 'putting out the fire'. These side-effects include interference with growth and development. The authors speculate that evolution has opted to reduce heat-shock expression (and inducible thermotolerance) in the African flies rather than chronically expose them to low level side-effects. So how has Mother Nature turned down heat-shock protein expression in the African flies? The heat-shock transcription factor (HSF), which regulates transcription of the heat-shock genes by binding to their promoters, itself appears normal in its behaviour although transcription is reduced. A possible explanation is that mobile genetic elements have disrupted the heat-shock promoter, reducing interaction between bound HSF and the transcriptional apparatus. Indeed, the authors report that two different mobile elements have inserted themselves into two different heat-shock gene clusters of the African flies. Although the impact of these mobile elements on heat-shock transcription awaits verification, Nature may have exploited the elements to make the flies from Chad not so hot in their heat-shock response.

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Experimental Biology 2001

Orange County Convention Center, Orlando, Florida
March 31–April 4, 2001

If you've never been to an Experimental Biology (EB) meeting, then nothing will have prepared you for the scale of the congress, or the centre that hosts it. The annually staged conference visits a different US city every year. This year, over 11,000 scientists converged on the Orange County Convention Center, Orlando, for a five-day celebration of recent developments in the biological sciences.

The American Physiological Society (APS) is one of the seven societies that together comprise the Federation of American Societies of Experimental Biology (FASEB). The APS is structured so that each section within the society contributes a selection of symposia titles to the program, which includes lectures, workshops, and poster sessions.

The Comparative Physiological Section of the APS is responsible for hosting three featured topic sessions and one symposium. This year's topics included sessions on subjects from signalling in cell stress, circadian organisation in vertebrates, evolution of the hypercapnic ventilatory response and the physiology of life history. The session chaired by Ken Storey (Session 812), working at Carleton University, Canada, presented studies on hibernation and apoptosis, and physiological responses at a molecular level. J. Woodgett from Toronto described the use of DNA microarrays to uncover the different protein expression patterns that underlie cellular responses to stress (Session 812).

More generally, the meeting covered much of the recent developments in nitric oxide and its many physiological roles, including nitric oxide regulation of hemoglobin (Session 107). The most exciting sessions looked to the future, with an emphasis on physiology in the postgenomic era and the powerful new techniques that it has ushered in. During the symposium on Functional Genomics (Session 550), M. Driscoll discussed the application of RNA interference techniques applied to mechanosensation in *C. elegans* (abstract number 710.5). The session on bioinformatics in biology and engineering (Session 616), highlighted the interface between complex mathematics and the biological world. J. Bassingthwaite, from the University of Washington, presented developments in the Physiome Project (www.physiome.org) and paved the way for a bright future in bioinformatics.

A series of symposia, supported by the United States Department of the Army, focused on the molecular basis of environmental physiology (Session 864). The second of the three sessions focused on molecular responses to hypoxia. Not surprisingly, the transcription factor Hypoxia inducible factor (Hif1) took central stage, with its regulatory effects on heme oxygenase, nitric oxide synthase and sodium transport confirming it as the key to many fundamental physiological processes.

Even as the meeting was drawing to close in Florida, the Comparative Physiology Section had already called for suggested titles for next years meeting, to be held in New Orleans.

The Scholander Prize

The APS annually awards The Scholander Prize at the FASEB Experimental Biology meeting to the young scientist who submits the most outstanding poster in the field of Comparative Physiology. The successful candidate is rewarded with a $200 bursary, and a copy of Scholander's book, 'A Life in Science' (Alaska University Press).

The prize, which is judged by the Comparative Physiological Section of the APS, is presented in memory of Per Frederik Scholander, whose career spanned five decades and covered most of the globe. Scholander entered the University of Oslo in 1924 as a medical student, but finding that medicine did not satisfy his curiosity, he neglected his medical studies in favour of his love of botany. Two years after graduating from his medical degree, his career was launched when he was awarded a PhD for his work on lichens. After graduating, he established his own laboratory in Oslo. He shifted his interests from plants to mammals, beginning a study on the physiology of diving mammals, which continued for several years in collaboration with Harald Erikson. In 1939, he was awarded a Rockefeller Fellowship to work with Larry Irving at Swarthmore. Over the following twenty years, his interests proliferated to include cold acclimation in birds animals and plants. His research took him to laboratories in Europe and the USA and included studies of acclimation in humans, which even took him to work with Aborigines in Australia. He joined the Scripps Institute of Oceanography in 1958, where he conceived the idea of a research vessel, designed to the specifications of marine research. His dream was realised in 1966 with the launch of Alpha Helix, which served the community for over 20 years and contributed to expeditions from the tropics to the poles. Throughout his career, Scholander published more than 200 research papers on subjects ranging from super cooling in fish to the contribution of vines to ocean circulation.

Thirteen posters were presented by entrants from laboratories around the world. This year's winner, Shi-Qiang Wang presented his work on calcium regulation during hypothermia in cardiac cells. He compared the behaviour of rat heart, which ceases to function at lower temperatures, with heart tissue from the hibernating ground squirrel. He found that as he lowered the temperature, intracellular calcium in the rat heart became very unstable, causing the loss of contractility, but the ground squirrel heart continued to function well, even at 4°C. Wang then showed the importance of calcium uptake by the sarcoplasmic reticulum (SR), when he disrupted the squirrel heart and made it vulnerable to hypothermia by inhibiting the SR calcium pumps. He then reasoned that if he could upregulate the pumps in the rat heart, then that would make the rats resistant to hypothermia. Miraculously, by providing the rat heart with extracellular ATP, he was able to reverse the thermal sensitivity of the rat, and keep the heart beating, even at previously catastrophic temperatures. Wang's research has significant potential for the treatment of hypothermia, and he's continuing the work, looking at the underlying signalling pathways. A beautiful, and truly comparative study that could will have far reaching beneficial consequences.

Continuing the tradition of comparative physiology, the other posters featured a wide variety of creatures with intriguing life styles. Michael Russell, this year's runner up, described his work on the sea lamprey aorta, which he's hoping to develop as a model for vasoconstriction in hypertension. Three posters discussed work on osmotic regulation in aquatic organisms, while Lynn Hartzler at U.C. Irvine explained her study of pH regulation in lizards and snakes. M. Simoyi, from Zimbabwe, gave details of his study of broiler chickens, and the possible role of uric acid as a free radical scavenger.

All of this year's contributions were presented to a very high standard with great enthusiasm. The quality of research presented was definitely a fitting tribute to a great life in science.

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