© 2021. Published by The Company of Biologists Ltd | Journal of Experimental Biology (2021) 224, jeb243324. doi:10.1242/jeb.243324

COMMENTARY

Safety factors as a 'design' principle of animal form and function: an historical perspective

James W. Hicks[1,]* and Tobias Wang[2]

ABSTRACT

For well over 150 years, factors of safety (also known as safety factors) have been a fundamental engineering concept that expresses how much stronger a system is compared with the intended load. The pioneering work of Robert McNeill Alexander in the early 1980s applied this engineering concept to biomechanics. Over the next decade, evidence from comparative biomechanics supported the idea that safety factors are a fundamental principle of animal form and function. In terms of physiology, Jared Diamond related the maximal capacity of a physiological process to normal functional demands and incorporated evolutionary thinking into the concept of safety factors. It was proposed that evolutionary reasoning is required to understand the magnitudes of biological reserve capacities, an idea called 'quantitative evolutionary design'. However, the general idea of safety factors as related to organismal form and function is much older. In 1906, Samuel James Meltzer, a physiologist and physician, presented the 5th Harvey Lecture to the New York Academy of Medicine; a lecture entitled 'The Factors of Safety in Animal Structure and Animal Economy', which was later published in Science in 1907. The 1907 paper is rarely cited and has never been cited within comparative biomechanics or comparative physiology. The purpose of this Commentary is to highlight Meltzer's historical contribution to the concept of safety factors as a general principle of organismal 'design'.

KEY WORDS: Biomechanics, Comparative physiology, History, Safety factors

Introduction

As the industrial revolution unfolded in the 19th century, engineers building bridges, sky-scrapers and other structures had a detailed understanding of the 'factor of safety', also known as the 'safety factor', of their various building materials, such as steel, iron and wood. The safety factor reflects how much stronger a given structure needs to be compared with the intended load to be placed upon it (see Box 1). A frequently used textbook example is an elevator, where cable strength must exceed the weight of the fully-loaded car by 12 times, whereas the requirement for the safety factor of elevators that merely lift food are considerably lower (Roark, 1965; Shigley, 1972). Although anthropocentric, this popular example also emphasizes that the safety factor varies with the importance of the structure or function. Robert McNeill Alexander (Alexander, 1981, 1984; Alexander et al., 1984) is credited with pioneering the application of the safety factor concept to biomechanical systems, and numerous studies on the biomechanical forces during locomotion, primarily in mammals, revealed the concept of safety factor as an essential 'design' feature of locomotor elements (bone, tendon, muscle) (Biewener, 1982, 1983, 1989). Throughout this Commentary, the term 'design' is shorthand for the evolution of phenotypic traits that arise primarily through the process of natural selection.

In 1991, Jared Diamond applied the concept of safety factors to physiological systems. Diamond focused on the functional capacity in relation to natural loads for intestinal nutrient transport (Diamond, 1991; Lam et al., 2002; O'Connor and Diamond, 1999; Weiss et al., 1998), and extended the concept to symmorphosis (Diamond, 2002). Symmorphosis hypothesizes that a complex system, such as the oxygen transport system, is 'built reasonably' and 'economically' (Taylor and Weibel, 1981). Consequently, for each step of the oxygen transport system, 'no more structure is formed and maintained than is required to satisfy functional needs' (Taylor and Weibel, 1981). Diamond and Hammond (1992) applied the concept of safety factors to processes that limit metabolic output in animals with high sustained energy demands, e.g. lactation or physical activity. The notion of safety factors has also been included in discussions of biochemical and metabolic control systems (Suarez et al., 1996, 1997; Cornish-Bowden and Cardenas, 1990).

As a central theme in the application of safety factors to living systems, Diamond and colleagues highlighted the apparent contradiction in form and function. Animals, at times, must rely on excess capacity to survive brief periods of high functional demands. In contrast, maintaining capacities that are much larger than average functional demand is energetically 'wasteful'. To resolve this issue, Diamond argued that evolutionary reasoning is required to understand the magnitudes of biological reserve capacities, and that safety factors provide a natural interface for evolutionary biology and physiology. He termed this approach 'quantitative evolutionary design' (Diamond, 2002).

In comparative physiology and biomechanics, the concept of safety factors as a general 'design' principle of animal form and function appears to have been firmly entrenched over the past 40 years. Yet, the application of the safety factor concept to biological systems is much older. As recently argued, history matters in scientific endeavors and is needed to understand the development of scientific concepts (Petersen, 2021). In this spirit, the purpose of this Commentary is to highlight the historical contribution of Samuel James Meltzer (1851–1920; Fig. 1), a physiologist and physician, to the concept of safety factors in relation to animal form and function.

Samuel James Meltzer

Samuel Meltzer was born on 22 March 1851, in a small Jewish settlement near Panevezys, a region that today is in Lithuania (Meltzer, 1990). Details of his youth are scarce, but he was noted to be a voracious reader, and he possessed an exceptional memory and

[1]Department of Ecology and Evolutionary Biology, UC Irvine, CA 92697-2525, USA. [2]Zoophysiology Section, Bioscience, Aarhus University, 8000C Aarhus, Denmark.

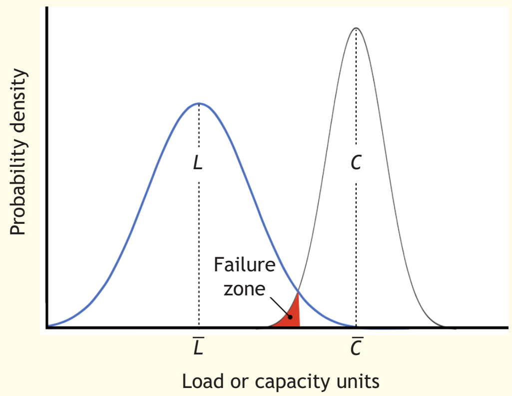
*Author for correspondence (jhicks@uci.edu)

J.W.H., 0000-0001-7465-8962

Journal of Experimental Biology (2021) 224, jeb243324. doi:10.1242/jeb.243324

Box 1. Definition of the safety factor

In engineering or biomechanics, the safety factor is the ratio between the load that would cause a given to structure to fail (i.e. the load that would cause a bone or a tendon to break) and the maximal load that the same structure is required to withstand (Alexander, 1981). Similarly, in physiology, the safety factor is the maximal attainable rate of a process – for example, the maximal capacity of a transport protein in the intestine – relative to the normal rate of this process, i.e. the typical rate at which this nutrient is absorbed across the intestine (Diamond, 2002). Formally, the safety factor (SF) can therefore be written as the capacity (C) relative to the normal load (L): SF=C/L.



The safety factor is obviously akin to what biologists sometimes refer to as the 'reserve capacity' (RC), which is the difference between maximal capacity and normal load: RC=C–L.

As most biological systems are characterized by a certain degree of variation within structures and function, both Alexander and Diamond reasoned that both normal load and capacity could be portrayed as two normal distributions (see figure), where the overlap between the distributions was termed the 'failure zone'. Figure redrawn based on Alexander (1981) and Diamond (2002).

Fig. 1. Samuel James Meltzer (1851–1920). Source: The National Library of Medicine (https://collections.nlm.nih.gov/catalog/nlm:nlmuid-101423443-img).

a passionate desire for learning (Howell, 1921). At 20 years of age, he married and relocated to Konigsberg (today known as Kaliningrad, Russia), where the young Meltzer set out to become a manufacturer of soaps (Howell, 1923). That business venture eventually failed, but during this period, Meltzer entered a gymnasium (i.e. high school) to receive a more formal education and to learn German (Meltzer, 1990). His academic interests focused on philosophy, and he matriculated to the University of Berlin in 1876 to pursue this topic (Howell, 1923). Early in his studies, he was mentored by German philosopher Heymann Steinthal, who apparently advised Meltzer that medicine provided a more reliable material existence and encouraged him to abandon philosophy (Meltzer, 1990). Meltzer took the advice and graduated in 1882 with a medical degree. Interestingly, at the University of Berlin, Samuel Meltzer's academic lineage was closely associated with that of some important figures in comparative physiology. Meltzer was mentored by Karl Hugo Kronecker, director of The Physiological Institute. Kronecker was a pupil of the German physiologist, Carl Ludwig who also trained Christian Bohr. One of Bohr's students was August Krogh, who subsequently mentored Knut Schmidt-Nielsen.

After his graduation, Meltzer was offered positions in Germany, but decided to emigrate to the USA. Following a brief employment as a ship's doctor, he arrived in New York City, and set up a practice in Harlem (Meltzer, 1990). In addition to practicing medicine, Meltzer paid for the privilege of using facilities at Columbia Medical School, Bellevue Hospital and Harlem Hospital to conduct physiological research (Meltzer, 1990). As his practice grew, his enthusiasm for connecting laboratory science to medical practice led to his frequent engagement with other scientists and scientific societies, resulting in his growing reputation in physiology (Howell, 1921; Meltzer, 1990).

At the age of 53, Meltzer was invited to join the Rockefeller Institute for Medical Research. He subsequently became Chair of the Department of Physiology, remaining at the Institute until his death in 1920. During his scientific career, Meltzer published over 240 articles on a variety of topics including shock, cardiac arrhythmias, thyroid therapy, hemolysis and edema (Howell, 1921), with much of his work appearing in the American Journal of Physiology, Journal of the American Medical Association and the Journal of Experimental Medicine. During his career, he became a leader among the growing numbers of prominent American physiologists and professional societies (Howell, 1921). He was a co-founder and first President of the Federation of the American Society for Experimental Biology (FASEB) (Weissmann, 2012), was elected the 5th President of the American Physiological Society (1911–1913) and in 1912 was elected to the National Academy of Sciences.

Meltzer's introduction of safety factors in biology

In 1906, Meltzer was invited to present a Harvey Lecture. This annual series of lectures, sponsored by the Harvey Society, continues to this day (https://harveysociety.org/). Meltzer's presentation, delivered at the New York Academy of Medicine, was entitled 'The Factors of Safety in Animal Structure and Animal Economy'. Meltzer's lecture was published both in the Journal of the American Medical Association (Meltzer, 1907a), and Science (Meltzer, 1907b), and later in Scientific American in 1908. In addition, the lecture was republished by Lippincott in 1908 as part of a collection of the 1906–1907 Harvey Lectures. The Harvey Lecture and subsequent publications provided a surprisingly contemporary analysis of safety factors in animal form and function.

Journal of Experimental Biology (2021) 224, jeb243324. doi:10.1242/jeb.243324

Meltzer began his lecture with the opening statement:

"The living animal body is like a machine in action. Like a machine its structures are subject to a variety of stresses, and like a machine the work is accomplished by an expenditure of energy derived from a supply of fuel. I intend to discuss in this lecture, whether, as in the human-made machines, the structures and functions of the animal mechanism are provided with factors of safety… As far as I know, that question has never yet been clearly raised, and certainly was never made the subject of a direct investigation."

Today, the above introductory remarks seem rather benign, but several of Meltzer's contemporaries believed that excess capacity could not exist in living systems, because 'nature is economical and wastes neither material nor energy' (Meltzer, 1907a,b).

Meltzer's lecture and the later publications were organized around a series of 'well-established facts' that supported the notion that factors of safety are a fundamental 'design' feature of living systems. He provided examples from the musculoskeletal system, the cardiovascular system, the pulmonary system, the gastrointestinal system and the reproductive system, as well as describing redundancy in regulatory control and mentioning the importance of evolution. Meltzer's examples and observations foreshadowed the more comprehensive theoretical and quantitative work by Alexander, Diamond and others. However, several of his examples are remarkably similar to those published some 75 years later (see Boxes 2–4).

Meltzer's biomechanical examples (Box 3) are relatively simple and lacked the deeper quantitative insights that would later be advanced by Alexander and colleagues. However, to be fair, the field of biomechanics was still in its infancy, and comparative biomechanics would not begin to emerge as a field until the work of James Gray (Alexander's mentor) in the 1930's (Vogel, 2007). Yet, Meltzer was on the right track, recognizing the low safety factors of tendons and other elastic components and that the anatomical aspects of the musculoskeletal system were important in determining functional safety factors.

It is not surprising that, as a physiologist and physician, Meltzer was more comfortable with providing several examples of safety factors from organs and organ systems than from biomechanics, and the majority of his lecture focused on such systems (Boxes 2 and 4). Although, he did suggest that natural selection played a role as a driver of capacities and loads (Box 2).

Despite his apparent interest in this subject, Meltzer did not experimentally pursue the concept of safety factors in animal form and function, and focused the remainder of his career investigating topics relevant to medicine. Following Meltzer's death in 1920, William Howell, the prominent American physiologist, physician and philosopher, wrote:

"but probably the most original and helpful of his general papers is his well-known Harvey Lecture…. He applied this engineering term [factor of safety] in a convincing way to describe the reserve powers possessed by many of the mechanism of the body. Doubtless the general conception involved had occurred to many others, but no one before him, so far as I know, had developed the idea so comprehensively and made of this provision a leading factor in the adaptation of the economy to its environment." (Howell, 1921)

Box 2. On matching capacities and loads: the role of evolution

Physiological capacities and loads

Meltzer (1907a,b): 'The subject of this lecture will be an investigation of this question, an investigation whether the structures and functions of the animal organism are constructed with a special consideration for the greatest economy or for the greatest safety…perhaps put it more correctly by saying that it will be essentially an investigation into the ratios of the supply of material in many organs of the body to the amount of work they are expected to perform. I believe that the investigation may lead to some instructive general conclusions of a theoretical and practical character.'

Diamond (2002): 'What are the costs that penalize excess capacities? Many capacities vary among individuals of a wild animal population within only narrow limits, with inter-individual coefficients of variation of 20% or less. This implies strong natural selection against individuals with capacities either much above or much below the mean value. The penalty for too low a capacity is, obviously, performance failure; for example, an animal whose bones are too small and weak is prone to break its bones and be caught by a predator. But what penalty eliminates animals with much higher than average capacities?'

Meltzer (1907a,b): 'Furthermore, the potential energies with which some organs, like the heart, diaphragm, etc., are endowed, are very abundant, and exceed by far the needs for the activities of normal life. The mechanisms of many functions are doubled and trebled to insure the prompt working of the function.'

Diamond (2002): 'Many biological elements have more than one function. Such an element might possess excess capacity for one function, mandated by the need to have a sufficient quantity of the element present to provide enough capacity for a second function.'

The role of evolution in matching biological capacities and loads

Meltzer (1907a,b): 'It seems to me that the factors of safety have an important place in the process of natural selection. Those species which are provided with an abundance of useful structure and energy and are prepared to meet many emergencies are best fitted to survive in the struggle for existence.'

Toloza et al. (1991): 'Recall that animals evolve by natural selection so as to tend to match their capacities to the loads they encounter under natural conditions.'

Diamond (1993): 'Natural selection in effect plays the same role in matching biological capacities to their natural loads.'

Box 3. On the musculo-skeletal system

Meltzer (1907a,b): 'Triepel [referring to Hermann Triepel, German embryologist and anatomist] investigated the elasticity and resistance of several tissues, like muscle, tendon, elastic tissue, bone, cartilage, etc. For us, the following statements are of special interest. For muscle, tendon and elastic tissue, Triepel found that the maximum stretching which may occur in the animal body is not far below that degree which can cause tearing of these tissues.'

Alexander (1981): 'Tendons which store elastic strain energy are, therefore, working within narrow safety margins…Some of the factors of safety for tendons…are remarkably low…tendons which store elastic strain energy in running seem to have lower factors of safety than bone.'

Meltzer (1907a,b): 'Tendon and elastic tissues have no factors of safety in the structures themselves; but they are provided, nevertheless, with some such factors by their connections with other tissues.'

Alexander (1981): 'The loads on tendons and apodemes are limited by the strengths of their muscle…Development of a large force involves considerable stretching of the tendon or apodeme, so the joint is likely to reach the end of its travel before the force becomes dangerous.'

Box 4. On organ systems

The pancreas

Meltzer (1907a,b): 'We shall mention here first the pancreas with respect to its internal secretion. It is now common knowledge that the complete removal of the pancreas leads to glyceamia and glycosuria. But here we note the fact that if a small part of the gland, say not more than one tenth, is left in the body, no ill effects follow such an extirpation. One tenth of that gland is capable of completely protecting the animal against glycosuria; but the body is, nevertheless, provided with ten times as much.'

Diamond and Hammond (1992): 'Patients with a damaged pancreas do not suffer malabsorption until pancreatic enzyme output drops below 10% of normal levels. Conversely, patients with no functioning pancreas escape malabsorption only if pancreatic enzymes are supplied exogenously at at least 10% of their normal secretion rate. These observations suggest that the pancreas's enzyme secretory capacity exceeds natural loads by about a factor of 10.'

The kidneys

Meltzer (1907a,b): 'We shall begin with the bilateral mechanisms. Here are, in the first place, the kidneys. Every medical man knows now that one kidney can be removed with entire impunity, if the other kidney is normal. The amount and the composition of the urinary secretion remains practically unaltered and this even soon after the removal of the kidney. That can only mean that normally the kidney has an abundance of tissue which can do at a moment's notice at least twice the normal amount of work.'

Diamond and Hammond (1992): 'Do actual capacities tend to be 1.1, 10, or 100 times their natural loads? This quantitative question pervades all of biology. Some indications of answers can be gleaned from clinical experience and the experimental literature. For example, healthy people can safely donate one kidney to a sibling or child with no functional kidney. If the donated kidney is not rejected, both the host and the donor can live relatively normal lives with just one kidney each. This suggests that our natural quota of two kidneys provides us with at least twice the capacity that we actually need.'

Meltzer's Harvey lecture and its subsequent publications were praised by influential physiologists at the time (Lee, 1908; Howell, 1921). However, the concept of the safety factor as a general design principle of animal form and function appears to have been mostly unappreciated by much of the biomedical community. From 1907 to 1946, Meltzer's observations were rarely cited. In 1946, the Journal of the American Medical Association published an editorial entitled 'Factors of Safety in the Human Body' (doi:10.1001/jama.1946.02870180035012). The editorial cites Meltzer as 'introducing the term into the medical [physiological] literature'. In 1953, physiologist Robert S. Alexander and cardiologist, Carl Wiggers, published an editorial, in Circulation Research, entitled 'Cardiac Factors of Safety'. This short paper opens with an acknowledgement that 'Meltzer introduced the term "factors of safety" into physiologic thinking'. Since 1953, Meltzer's ideas regarding safety factors in biology have been cited only 14 times, and as far as we know, have never been cited by those working in comparative biomechanics or comparative physiology.

Conclusion

R. McNeill Alexander and Jared Diamond rediscovered the application of safety factors as a design principle in the anatomy and physiology of living systems. The pioneering insight into biomechanics (Alexander, 1981, 1984; Alexander et al., 1984) advanced the concept of safety factors well beyond Meltzer's introduction in 1906, expanding the concept of safety factors both theoretically and quantitatively in comparative biomechanics. Subsequent work, notably by Biewener (1982, 1983, 1989), further advanced the concept by quantifying safety factors during locomotion and revealing general design principles within birds and mammals. The application of safety factors to physiological systems (Diamond, 1991, 1993, 2002; Diamond and Hammond, 1992; Hammond and Diamond, 1992, 1994) advanced the importance of evolutionary thinking to understanding ultimate causation in determining biological reserve capacities.

It is nevertheless quite clear that Samuel J. Meltzer foreshadowed many of these structural and functional connections, even relating safety factors to evolution. Samuel Meltzer was clearly ahead of his time. Given that safety factors within biological systems would be independently rediscovered and gain resonance amongst comparative biologists some 70 years later, Meltzer's Harvey Lecture should be acknowledged, and we hope that this Commentary goes some way towards raising awareness of Meltzer's contributions in this area.

Competing interests

The authors declare no competing or financial interests.

References

Alexander, R. M. (1981). Factors of safety in the structure of animals. *Sci. Prog.* **67**, 109-130.

Alexander, R. M. N. (1984). Optimum strengths for bones liable to fatigue and accidental fracture. *J. Theor. Biol.* **109**, 621-636. doi:10.1016/S0022-5193(84)80162-9

Alexander, R. M. N., Brandwood, A., Currey, J. D. and Jayes, A. S. (1984). Symmetry and precision of control of strength in limb bones of birds. *J. Zool.* **203**, 135-143. doi:10.1111/j.1469-7998.1984.tb06050.x

Biewener, A. A. (1982). Bone strength in small mammals and bipedal birds: do safety factors change with body size? *J. Exp. Biol.* **98**, 289-301. doi:10.1242/jeb.98.1.289

Biewener, A. A. (1983). Allometry of quadrupedal locomotion: the scaling of duty factor, bone curvature and limb orientation to body size. *J. Exp. Biol.* **105**, 147-171. doi:10.1242/jeb.105.1.147

Biewener, A. A. (1989). Scaling body support in mammals: limb posture and muscle mechanics. *Science* **245**, 45-48. doi:10.1126/science.2740914

Cornish-Bowden, A. and Cardenas, M. L. (1990). *Control of Metabolic Processes*. New York: Plenum Press.

Diamond, J. (1991). Evolutionary design of intestinal nutrient absorption: enough but not too much. *Physiology* **6**, 92-96. doi:10.1152/physiologyonline.1991.6.2.92

Diamond, J. M. (1993). Quantitative design of life. *Nature* **366**, 405-406. doi:10.1038/366405a0

Diamond, J. (2002). Quantitative evolutionary design. *J. Physiol.* **542**, 337-345. doi:10.1113/jphysiol.2002.018366

Diamond, J. and Hammond, K. (1992). The matches, achieved by natural selection, between biological capacities and their natural loads. *Experientia* **48**, 551-557. doi:10.1007/BF01920238

Hammond, K. A. and Diamond, J. (1992). An experimental test for a ceiling on sustained metabolic rate in lactating mice. *Physiol. Zool.* **65**, 952-977. doi:10.1086/physzool.65.5.30158552

Hammond, K. and Diamond, J. (1994). Limits to dietary nutrient intake and intestinal nutrient uptake in lactating mice. *Physiol. Zool.* **67**, 282-303. doi:10.1086/physzool.67.1.30163847

Howell, W. H. (1921). Samuel James Meltzer. *Science* **53**, 99-106. doi:10.1126/science.53.1362.99

Howell, W. H. (1923). Biographical Memoir: S. J. Meltzer. In 1923 Annual Meeting, National Academy of Sciences, pp. 1-23.

Lam, M., O'Connor, T. P. and Diamond, J. M. (2002). Loads, capacities, and safety factors of maltase and the glucose transporter SGLT1 in mouse intestinal brush border. *J. Physiol.* **542**, 493-500.

Lee, F. (1908). The Harvey Lectures. Delivered under the Auspices of The Harvey Society of New York, 1906-4, by Professors A. E. Wright, C. A. Herter, W. T. Porter, J. G. Adami, F. G. Benedict, E. B. Wilson, George S. Huntington, W. T. Councilman, Friedrioh Muller and Dr. S. J. Meltzer. Pp. 1414 Philadelphia and London, J. B. Lippincott Company. 1908. *Science* **28**, 566-567. doi:10.1126/science.28.721.566

Meltzer, S. J. (1907a). The factors of safety in animal structure and animal economy. *JAMA* **XLVIII**, 655-664. doi:10.1001/jama.1907.25220340001001

Meltzer, S. J. (1907b). The factors of safety in animal structure and animal economy. *Science* **25**, 481-498. doi:10.1126/science.25.639.481

Meltzer, A. (1990). Dr. Samuel James Meltzer: physiologist of the Rockefeller institute. *Am. Jew. Arch.* **42**, 49-56.

O'Conner, T. and Diamond, J. M. (1999). Ontogeny of intestinal safety factors: lactase capacities and lactose loads. *Am. J. Physiol.* **276**, R753-765.

Petersen, O. H. (2021). When a discovery is a rediscovery: do we know the history of our own subject? *Function* **2**, zqab030. doi:10.1093/function/zqab030

Roark, R. J. (1965). *Formulas for Stress and Strain.* Tokyo: McGraw-Hill.

Journal of Experimental Biology (2021) 224, jeb243324. doi:10.1242/jeb.243324

Shigley, J. E. (1972). *Mechanical Engineering Design*. New York: McGraw-Hill.

Suarez, R. K., Lighton, J. R., Joos, B., Roberts, S. P. and Harrison, J. F. (1996). Energy metabolism, enzymatic flux capacities, and metabolic flux rates in flying honeybees. *Proc. Natl. Acad. Sci. USA* **93**, 12616-12620. doi:10.1073/pnas.93.22.12616

Suarez, R. K., Staples, J. F., Lighton, J. R. B. and West, T. G. (1997). Relationships between enzymatic flux capacities and metabolic flux rates: Nonequilibrium reactions in muscle glycolysis. *Proc. Natl. Acad. Sci. USA* **94**, 7065-7069. doi:10.1073/pnas.94.13.7065

Taylor, C. R. and Weibel, E. R. (1981). Design of the mammalian respiratory system. I. Problem and strategy. *Respir. Physiol.* **44**, 1-10. doi:10.1016/0034-5687(81)90073-6

Toloza, E. M., Lam, M. and Diamond, J. M. (1991). Nutrient extraction by cold-exposed mice: a test of digestive safety margins. *Am. J. Physiol.* **261**, G608-620.

Vogel, S. (2007). The emergence of comparative biomechanics. *Integr. Comp. Biol.* **47**, 13-15. doi:10.1093/icb/icm004

Weiss, S. L., Lee, E. A. and Diamond, J. (1998). Evolutionary matches of enzyme and transporter capacities to dietary substrate loads in the intestinal brush border. *Proc. Natl. Acad. Sci. USA* **95**, 2117-2121. doi:10.1073/pnas.95.5.2117

Weissmann, G. (2012). Bully for science! The FASEB centennial (1912–2012). *The FASEB J Biology*. **26**, 1-4.