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## A PERSONAL VIEW

# Superhero physiology: the case for Captain America

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Submitted 8 July 2016; accepted in final form 20 December 2016

**Brown SP, Smith JW, McAllister M, Joe L.** Superhero physiology: the case for Captain America. *Adv Physiol Educ* 41: 16–24, 2017; doi:10.1152/advan.00106.2016.—Using pop icons in the science classroom represents a creative way to engage often-distracted students in a relevant and, perhaps more importantly, fun way. When the pop icon is as universally known as Captain America, the pedagogical stage is set. However, when the movies can also be employed to link dramatic references to the science concepts at hand, we may have a very powerful tool by which linkages between fiction and science can be forged. In this regard, Captain America's performances in several movies to date can be used to explain actual science. Granted, script writers and movie directors may or may not be interested in whether the physical performances they depict can be explained, but that is irrelevant. The point is to make a connection using science to explain how the superhero can run faster, jump higher, or lift more than is humanly possible. If a teachable moment has occurred and an important concept has been communicated, the educator has accomplished his or her job well.

popular culture; messaging; science; education; superheroes

THE IDEA OF THE FANTASTIC has a long literary history, going back to ancient times when writers of myth and legend “recorded” the feats of their gods and demigods. In a similar fashion, fantasy novelists of the 19th and 20th centuries have had their own influence on the larger culture. It can be argued that the works of Mary Shelley, Jules Verne, George MacDonald, and Edgar Rice Burroughs, among others, laid the foundation for the Golden Age of comics (1930s to the early 1950s), introducing iconic characters whose stories continue to be retold in the cinema today.

Inherent in these stories is the idea of the hero becoming more than what he is. For example, in *Tarzan of the Apes*, Burroughs (5) creates a protagonist who has to overcome impossible odds to survive the nurturing of a female anthropoid. The boy adapts in body and mind to become perhaps the most enduring character of the 20th century. Sufficiently stressed by his feral existence, Tarzan is a perfect example of the innate adaptability of normal human biology, acquiring what we would consider superhuman abilities, yet of a purely natural origin.

Genre novelists often employ strange or supranormal physical/physiological capabilities gained through mysterious means as major plot devices. For example, in Mary Shelley's classic work *Frankenstein* the antagonist uses arcane science to create his monster. Ironically, the monster ends up being more human than his creator and, it can be argued, has achieved

superhero status (30). In fantastic literature, superheroes generally gain their abilities in many and varied ways, usually as an accidental encounter with chemicals, radiation, or some agent of otherworldly origin.

In his cinematic origin story, Captain America was also given his abilities through mysterious experimentation. As portrayed in the 2011 movie *Captain America: The First Avenger* (Marvel Studios), Steve Rogers is injected with the super soldier serum and exposed to Vita-Rays. The result is a transformation from weakling to superhero. One example of his new capabilities around which this article is based came in the 2014 film *Captain America: The Winter Soldier* (Marvel Studios). Cap is shown performing what for him is an easy training run of 13 miles in half an hour. This example and statements made in various other Marvel Studio productions are used as a backdrop as we seek to give a scientific explanation for the abilities displayed on film.

But why should the thoughtful inquirer of science think about these fictional characters? Surely, the answer must be, what better way to engage the imagination of today's oft-distracted student than by considering how superhuman feats can be, at least partially, illumined via actual science (36)? A body of literature has developed in the field of science pedagogy using such cultural markers to illustrate important scientific principles. If science education is attracting fewer students to graduate level study, constituent members of the American Physiological Society should search for ways to popularize physiology. Perhaps exploring superhero physiology is a way to reach people with the real thing. This is especially important now given the inordinate amount of time students spend consumed by popular culture (12). There is an opportunity here for science educators to connect with their students and turn pop icons to their advantage by linking course content to a properly scientific exploration into the fantastic.

Building on the work of Zehr (36) and others (13), this paper presents the physiology of physical performance by channeling the creations of those whose imaginations gave us all of the great heroes of our youth. Our premise is that by connecting science to pop culture, students will learn to value the principles of human physiology, taking their knowledge into places they would least expect to need it, for example, a superhero movie. As Zehr (36) puts it, “Superheroes can make great foils for exploring the limits of human biology and the impact of technology on training and performance.”

Recently, we challenged our graduate exercise physiology students with this very principle via pointed questions posed using such pop icons. Superhero physiology can help students grasp the normal adaptations biological systems undergo when repeatedly stressed. Our purpose in writing this article is

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twofold: 1) to explore the physiological basis of Captain America's physical capabilities as shown on film and 2) to show how educators can use the pop icon in their lectures to help students better understand normal performance physiology.

### *Super Soldier Serum: Mechanisms of Action*

The 1940s story of a young man who did not meet physical screening criteria for entry into the US Army is inspiring to many, including professionals in the field of exercise physiology. The Vita-Rays and intramuscular injection of the super soldier serum provided extensive physical and physiological changes, all of which are unachievable even with years of intense exercise training. It is most plausible that the super soldier serum precipitated genetic mutations and significant alterations in gene expression, affecting multiple protein pathways involved in the promotion of skeletal muscle hypertrophy and improvements in structural and metabolic mechanisms of exercise endurance capacity and body composition. This paper considers some of the physiological changes that may have occurred in Steve Rogers, a.k.a. Captain America, to permit such extraordinary performances while limiting fatigue and overheating. These changes are displayed graphically in Fig. 1.

One likely action of the super soldier serum was deactivation of the muscle-specific nuclear receptor corepressor 1 (NCoR1) (34). To illustrate, trials utilizing knockout mice to examine the physiological effects of the suppression of this gene reported tremendous physiological enhancements, including increased muscle mass and endurance, improved lipid oxidation, and skeletal muscle oxidative capacity (22, 34). These adaptations are extremely difficult to achieve through a single mode of training, especially since endurance training has been shown to deactivate the mammalian target of the rapamycin (mTOR)

pathway of protein synthesis, which is important to facilitate skeletal muscle hypertrophy and increased strength (2).

The complexity of the transcriptional factors affected by suppression of NCoR1 is significant since this intramuscular injection could modulate several proteinaceous molecules involved in muscular strength and endurance capacity adaptations. To demonstrate the breadth of proteins involved in such adaptations, endurance training is typically associated with various transcription factors and coactivators such as the peroxisome proliferator-activated receptor (PPAR) and receptor  $\gamma$  coactivator 1 $\alpha$  (PGC-1 $\alpha$ ), the estrogen-related receptor (ERR), cAMP response element binding protein (CREB), and the NAD<sup>+</sup>-dependent deacetylase sirtuin-1 (SIRT1) (6). These signaling molecules are known to work to increase PGC-1 $\alpha$  activity and allow for mitochondrial biogenesis, thus facilitating aerobic adaptations to exercise training. However, some reports demonstrated that the activation of these proteins may downregulate mTOR, which may have an adverse effect on skeletal muscle hypertrophy. This may occur via phosphorylation of the mTOR inhibitor tuberlin (tuberous sclerosis complex 2) via AMP-activated protein kinase (AMPK) (2). Previous studies demonstrated that the suppression of NCoR1 may facilitate increases in both aerobic capacity and muscular strength/hypertrophy (22, 34). Therefore, it is possible that the super soldier serum acted upon these pathways, especially since these physiological adaptations are difficult to achieve concurrently.

Among Cap's numerous likely genetic alterations are those affecting the *MTSN* and *ACTN3* genes. The *MTSN* gene codes for myostatin [part of the transforming growth factor- $\beta$  (TGF- $\beta$ ) superfamily], a group of proteins that regulates skeletal muscle growth and differentiation (21). Disruption of *MTSN* leads to myostatin-related muscle hypertrophy in sev-

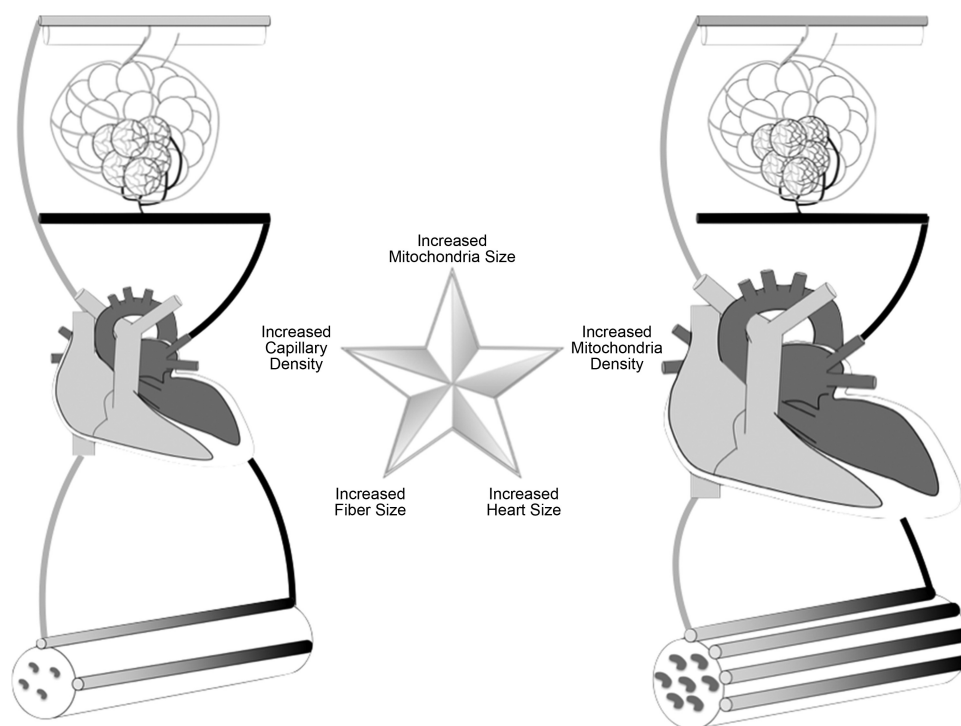


Fig. 1. Summary of the likely physiological changes Steve Rogers endured to become a superhero. The iconographic star is a well-known symbol of Captain America.

eral species, most notably the Belgian Blue and Piedmontese cattle breeds and the Whippet dog breed (14). This has also been demonstrated via a case study in humans (29). Problematic are reports of reductions in myostatin, leading to increased fatigability and reduced aerobic capacity (21). However, there is evidence to suggest that these decrements are not observed when knockout occurs postdevelopmentally (32). Additionally, it is likely that other genetic changes in Captain America, such as the suppression of NCoR1 described above, prevent these adverse consequences.

Our second example is the *ACTN3* mechanism of adaptation. The *ACTN3* gene codes for the  $\alpha$ -actinin-3 protein, which is an actin-binding protein found on the Z-line that not only functions in cross-linking the actin filaments but also plays a regulatory role in muscle contraction (35). Whereas several forms of  $\alpha$ -actinin exist, the *ACTN3* isoform has been found in nearly all anaerobic athletes tested and has been termed the “sprinter gene” due to its extremely high prevalence in elite anaerobic athletes (35). It is likely that Steve Rogers possessed *ACTN3*, as the *ACTN3*-deficient genotype is exhibited in only 18% of Europeans (35). Thus, we can see how these and other changes in gene expression profoundly influence physical performance via increased force production potential and improved metabolic efficiency.

### Metabolic Efficiency

Referencing the scene mentioned earlier, Cap is shown to perform a 13-mile training run in 30 min. Calculations using the American College of Sports Medicine (ACSM) equation to estimate  $\dot{V}O_2$  during running (1a) yield a value of  $142 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . Estimating that his level of intensity during the run was 80% of  $\dot{V}O_{2\text{max}}$ , his  $\dot{V}O_{2\text{max}}$  is predicted to be  $177 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . This value far exceeds human capability, as only a small number of elite male endurance athletes have recorded maximal values in the range of  $94$  to  $96 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (16). An increased metabolic efficiency could translate to improved endurance capacity, decreased susceptibility to muscular fatigue, and improved muscle force generation. Below, we delve more directly into the role played by the cardiovascular system in giving Captain America such a heightened aerobic power.

Captain America is rarely seen ingesting food. This is significant since energy substrate utilization depends on caloric consumption. This is also directly relevant to statements made in the movies that Captain America has a resting metabolic rate four times above the normal human, making him resistant to the effects of alcohol (shown in *Captain America: The First Avenger*). The normal resting rate of oxygen consumption is  $3.5 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  (15). Four times this value places Captain America's resting metabolic rate at  $14 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . With a body mass of 109 kg and an estimated body fat percentage of 10%, this means that his resting caloric expenditure is 7.63 kcal/min, contrasted to a normal human of the same body mass who expends roughly 1.9 kcal/min at rest. Hence, the elevated resting metabolic rate tremendously increases Cap's caloric demand to maintain body weight. However, that Captain America is not shown constantly eating to meet this elevated resting caloric demand indicates that he does not need to ingest four times the amount of calories as would a normal 109-kg adult male with a greatly exaggerated resting metabolic rate.

The scientific explanation for this lies with metabolic efficiency. The normal adult male or female is very inefficient, as roughly 75–80% of the energy liberated in the body during metabolic processes is lost as heat (31). Thus, roughly 20–25% of ingested calories are utilized for energy production. A case could be made that Captain America's dietary demands are not different due to an improved metabolic efficiency. This is supported by the fact that constant eating is not a part of his character as displayed in the movies. Nor do we see him sweating to dissipate the heat load associated with normal physiological inefficiency. We propose three main adaptations to explain this: 1) a major improvement in digestive efficiency mediated through both greatly increased absorptive capacity and reduced dietary-induced thermogenesis (this aspect will not be discussed further in this paper), 2) a greatly reduced metabolic energy expenditure in processes such as the  $\text{Na}^+/\text{K}^+$  pump (discussed briefly below), and 3) tremendously enhanced cellular substrate utilization (discussed in greater detail since many physiological changes occur in response to chronic exercise training to allow for this effect).

Captain America has a heightened metabolic efficiency through genetic mutations altering the ATPase family of proteins. These include those of the  $\text{Na}^+/\text{K}^+$  pump, sarcoplasmic reticulum  $\text{Ca}^{2+}$  transporter (SERCA pump), and others. Energy expenditure through the  $\text{Na}^+/\text{K}^+$  pump is responsible for a significant portion of the energy demands of the resting body. It is conceivable that genetic mutations generated a  $\text{Na}^+/\text{K}^+$  pump that has superior ion transport capacity per ATP utilized, thereby greatly diminishing energy expenditure for the body and affording improved regulation of the membrane potential. Greatly attenuated energy expenditure in these and other areas would substantially reduce heat production, thereby allowing more of Cap's energy production to directly fuel muscle contraction.

### Body Mass and Energy Storage

The body mass of Captain America is normal for a well-muscled adult male of equal stature. Therefore, in terms of immediately available stored energy, it could be theorized that Captain America has roughly 8 kcal of energy stored in the form of ATP and 29 kcal of available energy stored as phosphocreatine (PCr). These phosphates contribute to events that demand an immediate or rapid source of energy (31). For a person of his mass, Captain America likely stores roughly 2,900 kcal as carbohydrates, with the overwhelming majority (~2,200 kcal) stored in lean tissue (i.e., skeletal muscle). The remaining 670 kcal is found in the liver (560 kcal stored as glycogen) and serum (112 kcal as circulating glucose) (19).

His muscle characteristics (mainly improved mitochondrial capacity and greater aerobic enzyme concentrations) allow for considerably enhanced capacity for aerobic oxidation of this substrate. Aerobic oxidation of carbohydrate is paramount since the breakdown of glucose or glycogen via substrate level phosphorylation in glycolysis allows for the generation of 2 or 3 ATP, which is not sufficient to allow Captain America to achieve superhuman performance. Aerobic oxidation of these substrates allows for the generation of 32 or 33 ATP (~233 kcal/mol of glucose), which is in high demand to support the rate of energy demand by his skeletal muscles.



Furthermore, enzyme activity is enhanced, allowing for extremely rapid ATP generation via aerobic oxidation. One of the greatest benefits of anaerobic oxidation of carbohydrates is the rapidity by which ATP can be generated. However, it is likely that Captain America's enzyme activity is enhanced by specific changes allowing for extremely rapid progression of the oxidative pathways. Thus, ATP is generated at a much more rapid rate.

Although it may not be apparent, Captain America does have a significant amount of energy stored as fat (roughly 100,000 kcal) that can potentially be used for energy. Ninety-three percent of this energy is found in adipose tissue, with 2% found in muscle and the remaining found in plasma as triglycerides or free fatty acids (19). We estimate between 30,000 and 50,000 kcal of energy is available in the form of protein. However, he probably has a reduced reliance on the utilization of amino acids for energy since he is much more efficient at utilizing fats and carbohydrates.

In terms of the energy available in glucose, roughly 453 kcal/mol remain unliberated through oxidative metabolism. In addition to a greatly increased oxidative capacity, we propose that Captain America also possesses novel pathways through which he can unleash most of the chemical bond energy in carbohydrates and fats unavailable in normal humans. We theorize this adaptation because Captain America needs much larger energy availability to perform his superhuman feats. He is apparently able to do so without consuming greater quantities of food.

To allow for Captain America's improved ability to oxidize carbohydrates and lipids, mitochondrial changes are imperative. Suppression of NCoR1 allows for significant aerobic adaptations (22, 34), which are facilitated mainly by various protein complexes. These complexes include CREB and SIRT1, which facilitate the activation of PGC-1 $\alpha$  (6). This pathway is normally activated by the changes in cellular AMP/ATP ratios seen during intense energy deficit or a high cellular demand for ATP (i.e., high intensity exercise). The removal of NCoR1 activity results in significant activation of PGC-1 $\alpha$ , which is independent of physical conditioning and can account for increases in aerobic capacity via mitochondrial biogenesis (22). However, this is likely only one mechanism of action of the super soldier serum, since the cellular changes that occurred in him are likely unachievable with only suppression of NCoR1.

### Skeletal Muscle

Captain America's muscle cells likely contain a much higher mitochondrial density in contrast to normal humans. Given the extremely high oxidative capacity of his skeletal muscles, it is likely that he has either a very high or nonexistent lactate threshold (LT). Chronic exercise training leads to an increase in LT, which is attributed largely to an improvement in the oxidative capacity of muscle fibers. Hence, Cap has a very high ability to directly and indirectly oxidize lactate via lactate shuttling (4) and stimulate the production of glucose from lactate via the hepatic Cori cycle.

The other major changes noted with Captain America are increases in muscle endurance, muscle strength, and muscle power. Cap is able to exert a tremendous amount of muscular force, demonstrated by his ability to strike another individual

(either a punch or kick) and send them airborne. Superhuman muscle capabilities are displayed throughout these movies. In *Captain America: The First Avenger*, Steve Rogers is in basic training and unable to keep up with other recruits while running. He lacks the strength to pull himself up a cargo net and is unable to do a proper pushup. In the super soldier experiment, he instantaneously gains >100 lbs. and grows >1 ft. in stature. In the ensuing action sequence, he easily leaps a fence that is  $\geq 7$  ft. tall. This type of superhuman power generation is shown repeatedly, demonstrating that the changes to his physiology are not solely metabolic.

Captain America exhibits a power-producing potential much greater than Olympic level track and field athletes. Skeletal muscle ratios vary across all track and field events, with endurance athletes having a greater percentage of type I fibers and sprint athletes and jumpers generally possessing greater percentages of type IIx fibers. To allow the power outputs we see Captain America demonstrate, it is fair to speculate that his fibers possess the characteristics of fast twitch (type IIx) fibers, yet his resistance to fatigue suggests that his muscle fibers also possess the characteristics of slow twitch (type I) fibers.

Some of the special fiber characteristics that could account for the high-force generation capacity found in type IIx fibers are the myosin heavy chain (MHC) type and ATPase activity. Muscle fiber characteristics are further elucidated in Table 1. However, it is not always possible to make such a clear distinction in terms of muscle fiber type. The majority of his skeletal muscle fibers are likely a hybrid between type IIa and IIx fibers, hence his ability to sustain high-force production while being highly resistant to fatigue. These fibers have mixed concentrations of MHC isoforms that allow for the performance effects noted in Table 1.

The combination of these characteristics is not dissimilar to what is noted in type IIa fibers. Type IIa fibers have contraction velocities similar to those seen in type IIx fibers but also much of the fatigue resistance of type I fibers. It could be hypothesized that much of his musculature is functionally similar to normal type IIa fibers. However, this cannot be his sole muscle fiber type. Captain America needs muscle characteristics not only to facilitate muscle action during fights and superhuman feats but also during the execution of activities of daily living. Activities of daily living rarely require large-force production or rapid movements similar to what we would expect from type IIa and type IIx fibers. Thus, at least a small percentage of his muscle fiber type must still consist of type I fibers.

Table 1. *Characteristics of representative muscle types*

| Characteristic                           | Type I       | Type 2A       | Type 2X |
|--|--------------|---------------|---------|
| Performance effect                       |              |               |         |
| Force production potential               | Low          | Moderate-high | High    |
| Fatigue resistance (endurance potential) | High         | Moderate      | Low     |
| Contractile speed                        | Low          | Fast          | High    |
| Cellular characteristic (mechanism)      |              |               |         |
| Glycolytic enzyme activity               | Low-moderate | Moderate-high | High    |
| ATPase activity                          | Low          | Moderate      | High    |
| Myoglobin concentration                  | High         | Moderate-high | Low     |
| Mitochondrial enzyme activity            | High         | Highest       | Low     |
| Capillary density                        | High         | Moderate      | Low     |

## Fatigue

A common utterance by Steve Rogers throughout his appearances in Marvel movies is “I can do this all day.” Fatigue is often described as the inability to maintain desired force or power output during repeated muscle contractions, and its causes have been the subject of much study and debate. Potentially, any decrement in any one part of the chain of events that occurs from muscle stimulation to movement execution may be a source of fatigue. Thus, the causes of fatigue are multifactorial. Fatigue theories revolve around central and peripheral sources, with central fatigue referring to causes originating in the central nervous system (CNS), whereas peripheral fatigue originates outside the CNS.

Ironically, the first instance of the phrase “I can do this all day” occurs in *Captain America: The First Avenger* as Steve Rogers is being pummeled in an alleyway while still the quintessential 90-lb. weakling. When motivational and arousal factors are changed, fatigue can be altered. During fatiguing contractions, decreased activity of spinal motor neurons is observed and thought to be caused by both decreased neural drive from higher brain centers and peripheral feedback (27). Apparently, Steve Rogers possesses a high level of psychological drive from higher brain centers to “will” himself to endure through painful circumstances. However, in this first instance of the phrase, if not for the intervention of Steve’s best friend, Bucky Barnes, the mousy Steve Rogers would have succumbed eventually due to physical/physiological limitations.

A central fatigue factor that has received much attention recently is the ratio of serotonin to dopamine. A rise in this ratio contributes to tiredness and fatigue, whereas a reduced ratio appears to cause arousal and improve performance (20). Neurochemical changes may have imparted to Cap an optimum ratio, allowing for a mechanism that would help stave off central fatigue.

Central fatigue factors are thought to be minor contributors to fatigue when compared with peripheral factors (10). There are many potential sites to consider when examining peripheral fatigue. These include events originating in the excitation-contraction coupling process, at the cross-bridge, and/or in the metabolic pathways (10). The type of exercise dictates the nature of the peripheral fatiguing factor. These may include dehydration, hyperthermia, glycogen depletion, declining blood glucose levels, posttranslational changes in proteins, and the accumulation of metabolic products. Metabolites suggested to have varying roles in fatigue include ADP, PCr,  $Mg^{2+}$ ,  $H^+$ ,  $K^+$ , lactate, inorganic phosphate ( $P_i$ ), and reactive oxygen and nitrogen species (1). Although Captain America likely displayed better control of most, if not all, of the preceding factors listed, for illustrative purposes this discussion is limited largely to two key factors paramount to Captain America’s great endurance: better regulation of acid-base balance and lack of a significant rise in  $P_i$ .

## Regulation of Acid-Base Balance

Acid-base balance must be tightly controlled. Historically, acidosis occurring during exercise was implicated as a major cause of fatigue, although recent evidence calls this into question (33). The mechanisms of action by which the accumulation of  $H^+$  (low pH) is thought to cause fatigue include the following: 1) reduced activity of enzymes of aerobic and

anaerobic energy production (27), 2)  $H^+$  being a competitive inhibitor of the  $Ca^{2+}$ -binding site on troponin C, thereby reducing available active sites on actin (11, 27), 3) reduction in  $Ca^{2+}$  release from the sarcoplasmic reticulum (SR), possibly by reducing the opening of the ryanodine receptors on the SR that release  $Ca^{2+}$  (33), and 4) promoting the reverse rate constant between the weakly and strongly bound states of the actomyosin complex in the cross-bridge cycle (11).

How does Cap control his acid-base balance? He may experience little rise in  $H^+$  because most of what is produced is taken up by the mitochondria for use in the electron transport chain (ETC). Cap likely possesses a greater chemical buffering potential similar to that derived from training. He may also have improved lung capacity and mechanics for improving his ventilatory buffering capabilities.

## Accumulation of $P_i$

Accumulation of  $P_i$  in muscle is increasingly implicated as a cause of fatigue, whereas the importance of accumulated  $H^+$  has been increasingly challenged (33). Intracellular  $[P_i]$  normally rises from a resting value of 5 to ~30 mmol in heavy fatigue (1). Captain America’s experiences a negligible rise in  $[P_i]$  during most types of exercise because of his huge aerobic capacity ( $P_i$  will be taken up by the mitochondria for use in oxidative phosphorylation). Only in extremely intense events would Captain America exceed his aerobic capacity to the point that significant amounts of  $P_i$  would accumulate. Additionally, he would recover more quickly than the normal individual during these short bursts of very intense activities because his high aerobic capacity would quickly replenish his PCr stores and clear the  $P_i$ . The following briefly describes and provides support for a couple of the mechanisms through which accumulation of  $P_i$  is thought to contribute to the power decline in fatiguing exercise. Several other mechanisms exist beyond those detailed below.

$P_i$  interferes with force production through multiple means, including direct interference with the cross-bridge and decreasing  $Ca^{2+}$  release from the SR.  $P_i$  is theorized to enter the SR through a phosphate-permeable channel discovered by Laver et al. (17), where it forms a  $Ca^{2+}P_i$  precipitate. The  $Ca^{2+}P_i$  precipitate causes a decline in  $Ca^{2+}$  release from the SR, reducing the number of available actin active sites capable of forming cross-bridges due to steric blocking of actin active sites by tropomyosin, when  $Ca^{2+}$  is not bound to troponin C. This mechanism is supported in the literature (7, 8, 26).

Both  $H^+$  and  $P_i$  are thought to directly interfere with the cross-bridge through a reduction in the number of cross-bridges and/or the amount of force produced per cross-bridge. Upon initial actomyosin complex formation, a weak bond state is formed, which then transitions to more strongly bound high-force states. It seems that both of these metabolites favor the reverse rate constant between the weakly and strongly bound cross-bridge states. This certainly would make sense for  $P_i$ , as it is normally released from the actomyosin complex in the transition from the weakly to strongly bound state. Therefore, an increase in  $P_i$  would tend to drive the reaction toward the weakly bound state. Likely,  $H^+$  accumulation more greatly stimulates the reverse reaction by changing reaction kinetics. Support for  $P_i$  and  $H^+$  acting through separate mechanisms

within the cross-bridge is given through research showing their effects to be additive (11).

### Cardiovascular System

As previously noted, Captain America has a predicted  $\dot{V}O_{2\max}$  of  $177 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$  ( $19,293 \text{ ml/min}$  for a  $109\text{-kg}$  person). This doubles the typical  $\dot{V}O_{2\max}$  (usually in the 80s) of Boston Marathon winners who achieve this level through rigorous physical training as an outgrowth of great genetic propensity. High values for this key metabolic variable correlate quite well with endurance performance but usually do not perfectly explain performance differences. In Captain America's case, his aerobic power is similar to what the thoroughbred horse and the racing greyhound can produce, with both of these athletes often exceeding  $200 \text{ ml}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ . But how is this possible for a human athlete?

This paper is limited to cardiovascular changes only given that the upper range of normal pulmonary ventilation is not a limiting factor in Cap's elevated aerobic power. Thus, we believe the super soldier experiment did not result in substantial alterations to normal ventilatory dynamics. This section, therefore, explores only a small portion of the cardiovascular possibilities for such a high aerobic power, with the determinants of  $\dot{V}O_{2\max}$  discussed via the Fick equation [ $\dot{V}O_{2\max} = \dot{Q}_{\max} (\text{CaO}_2 - \text{CvO}_2)_{\max}$ ]. The Fick equation can be rewritten as follows:  $\dot{V}O_{2\max} = \text{HR} (\text{EDV} - \text{ESV}) \times (1.34 \times [\text{Hb}] \times \text{SaO}_2) - (1.34 \times [\text{Hb}] \times \text{SvO}_2)$ , where EDV is the end-diastolic volume and ESV is the end-systolic volume. Inherent in Fick's formulation is a central delivery component: the volume of blood sent to the working muscles [ $\text{HR} (\text{EDV} - \text{ESV})$ ], representing the maximal outflow from the heart ( $\dot{Q}_{\max}$ ). The peripheral component,  $(1.34 \times [\text{Hb}] \times \text{SaO}_2) - (1.34 \times [\text{Hb}] \times \text{SvO}_2)$ , represents the maximum amount of oxygen extracted by the working muscles.

The value of each of the variables in the equation can be manipulated in such a way as to arrive at Cap's high  $\dot{V}O_{2\max}$ . Reading the equation from left to right, the first step is to consider the heart. A high cardiac output is aided by a high ratio of heart weight to body weight (g/kg). For elite normal humans, this ratio approaches 1% ( $\sim 0.8\%$ ), with untrained humans mostly falling in the 0.4% range. However, the relative weight of thoroughbred horse hearts averages  $\sim 1.5\%$  (25). We can hypothesize that with gains in overall body size during the super soldier experiment, Captain America's heart grew at a disproportional rate, placing his ratio closer to that of species with far greater aerobic power than the best human athletes can achieve. The increased heart mass comes with a commensurate increase in left ventricular chamber diameter, the ultimate effect being much greater EDV, stroke volume (SV), and resultant cardiac output.

Assuming that his blood volume changed proportionally to his body mass, he has  $\sim 6.6$  liters of blood, the predicted value for a  $240\text{-lb.}$  man. For Captain America, this value may be higher given that one goal of the super soldier experiment was to endow the subject with a large aerobic power. Cardiac performance is governed by three mechanisms: preload, afterload, and inotropic (contractile) state. A greater blood volume accommodated by a larger heart would lead to a much larger maximal SV ( $\text{SV} = \text{EDV} - \text{ESV}$ ) due to enhanced Frank-Starling (preload, i.e., increases in EDV) and contractility

(lower than usual ESV at maximal exercise) mechanisms. These factors working alone or in combination would maximize SV at a much higher level than normal human physiology allows.

An enhanced sympathetic drive during maximal exercise would also aid Cap's cardiac performance by producing a higher maximal HR and an even lower ESV, the latter by a greatly enhanced myocardial contractility. Myocardial contractility can be viewed as the rate of change of the ventricular pressure with respect to time ( $dP/dt$ ). Captain America is able to achieve a much higher than normal inotropic state, affecting cardiac performance independent of preload and afterload. Potential mechanisms for this would be anything that enhances  $\text{Ca}^{2+}$  channel activity in myocardial cells. Also, similar to normal human endurance exercise adaptation, Cap could have an enhanced ability to reduce his cardiac afterload via a larger than normal decrease in peripheral vascular resistance, which plays a permissive role in increasing cardiac SV.

Maximal  $\dot{Q}$  is also greatly influenced by maximal HR. If Captain America is 30 yr old (he actually is nearly 100 yr old, but that's a different story for another paper), his hypothesized maximal HR would be 190 beats/min ( $220 - \text{age}$ ). However, the relationship between age and maximal achievable HR is no longer valid for him. So then, to achieve superhuman values for  $\dot{Q}$  and in keeping with the thoroughbred comparison, we can say that Cap's maximum rate of cardiac depolarizations is closer to 250 beats/min. This is the approximate upper limit for thoroughbred race horses (24).

At this point, we can speculate on Cap's maximal  $\dot{Q}$  as a function of HR and SV:  $\dot{Q} = \text{HR} \times \text{SV}$  ( $\dot{Q} = 250 \text{ beats/min} \times 300 \text{ ml/beat} = 75,000 \text{ ml/min}$  or  $75 \text{ l/min}$ ). The prediction of a SV of  $300 \text{ ml/beat}$  is made on the basis of Cap's hypothesized relative heart mass of 1.5% of his body mass ( $109 \text{ kg}$ ), putting his heart mass at  $1.6 \text{ kg}$ . The  $300 \text{ ml/beat}$  value is proportional to that of a thoroughbred horse (i.e.,  $1,400 \text{ ml/beat}$  at a heart mass of  $7.5 \text{ kg}$ ) as we continue the interspecies comparison representative of how Cap's heart structure and function changed during the experiment (25). This heart size is much larger than normally functioning human hearts and is even larger than hearts subjected to years of pathological load stresses, i.e., chronic volume or pressure overloaded conditions. Like the well-trained human athlete, however, Cap's cardiac hypertrophy is not accompanied by decrements in myocardial performance. Thus, in combination with a larger than normal blood volume, heart mass, ventricular chamber diameter, and probable greater contractile state at maximal exercise, Captain America produces a much larger than normal maximal SV.

Elite male distance runners have been shown to generate maximal SVs in the range of  $187 \text{ ml/beat}$  (37). The size of Cap's maximal SV is 60% greater than what normal elite distance runners typically produce. Together with Cap's elevated maximal HR, the large SV accounts for his (maximal)  $\dot{Q}$  being 114% larger than normal for the athlete with a maximal  $\dot{Q}$  approaching  $\sim 35 \text{ l/min}$  (37). The  $\dot{Q}$  value now determined, we can derive the peripheral factor ( $\text{CaO}_2 - \text{CvO}_2$ ) given in the Fick equation:

$$19,293 \text{ ml } O_2/\text{min} = 75,000 \text{ ml } \text{bl}/\text{min} (\text{CaO}_2 - \text{CvO}_2)$$



Solving the equation yields a value for  $\text{CaO}_2 - \text{C}\bar{\text{v}}\text{O}_2$  of 0.257 ml  $\text{O}_2$ /ml bl (~26 vol%), ~63% larger than the maximum value (~16 vol%) reached by top human athletes (37).

The variables of Fick's equation can be manipulated in several ways to yield Cap's predicted  $\dot{V}\text{O}_{2\text{max}}$  of 177 ml·kg<sup>-1</sup>·min<sup>-1</sup> (19,293 ml  $\text{O}_2$ /min). One way to derive such a high aerobic power is to alter the equation's parameters so that such a drastic increase in heart size is not necessary. To accomplish this, consider more closely the peripheral extraction portion of the equation.

In some species, the spleen acts as a reservoir for erythrocytes, which can be tapped into when the animal is under duress, as in exercise (9). Blood cells stored in the spleen can be mobilized into the circulation when there is an increased demand. When the plasma volume remains essentially unchanged or when there is a reduced plasma volume, the result will be an increase in hematocrit of ~30% in the thoroughbred, with a concomitant increase in blood viscosity (25). Interestingly, the increase in viscous resistance is not enough to impede  $\dot{Q}$ .

Therefore, we can hypothesize a similar mechanism for Captain America thanks to the super soldier serum and the use of genetic manipulation, giving Cap this same splenic reserve. During exercise, then, Cap calls on his erythrocyte reserve, which would allow him to increase Hb concentration from 15 (at rest) to 24 g/dl (roughly the same as a thoroughbred would produce during exercise). This increased amount of Hb elevates the amount of  $\text{O}_2$  that can be delivered to the tissues (18).

How does this play out in the Fick equation? Provided Cap's Hb molecule remained normal after the experiment, 1 g of Hb still binds ~1.34 ml  $\text{O}_2$ . If during exercise his Hb concentration reaches 24 g/dl, this would give him an oxygen carrying capacity ( $\text{CaO}_2$ ) of 31.2 ml  $\text{O}_2$ /dl [(24 × 1.34 × 0.97) + 0.03], a 48% increase at 97% saturation using a reference value of 21.1 ml  $\text{O}_2$ /dl. The 0.03 in the previous workup represents the amount of oxygen dissolved in physical solution. Therefore, based on a value of 31 ml  $\text{O}_2$ /dl for  $\text{CaO}_2$  and ~24 ml  $\text{O}_2$ /dl for the arteriovenous oxygen difference, the  $\text{C}\bar{\text{v}}\text{O}_2$  would be 7 ml  $\text{O}_2$ /dl. If Cap's  $\text{C}\bar{\text{v}}\text{O}_2$  was even lower, his maximal arteriovenous oxygen difference would be even higher, thus reducing the need for the central circulation [ $\dot{Q} = \text{HR} (\text{EDV} - \text{ESV})$ ] to play such a large role in his maximal aerobic power.

Also, it is known that  $\text{O}_2$  transport capacity is correlated directly with aerobic performance, as can be seen from an increase in performance after infusion of red blood cells (3). There is also a strong correlation between total Hb and  $\dot{V}\text{O}_{2\text{max}}$  in athletes (28). Given that Captain America can deliver much more  $\text{O}_2$  than normal to the working muscles due to central cardiac and hematological changes, it also makes sense that he would have the ability to extract more  $\text{O}_2$ . Extra extraction would be dependent on the microvasculature in the working muscle and an increased mitochondrial density with the commensurate aerobic enzymatic machinery necessary to facilitate such a high aerobic power and eventual ATP production.

### Pedagogical Applications

We have explored some of the physiological changes that could have occurred in Captain America to explain the feats he performs in Marvel movies. We now turn our attention to ways this

information can be used in the classroom. The key here is to use the pop icon as a fun way to encourage critical thinking and spark in-class discussions. The Socratic Method is perfect for leading students in the analysis of key concepts and ideas to help them question assumptions being made and to explore the implications and consequences of those assumptions.

In-class discussions regarding superhero physiology are encouraged, as is the use of essay questions during testing. Additionally, questions involving calculations related to metabolism and aerobic capacity could be posed as a group assignment, an individual assignment, or part of a test. As long as the student is given the necessary parameters to use and a set of suppositions to make, they can derive concrete answers similar to that which is presented in the bioenergetics and cardiovascular portions of this paper. Multiple approaches can be employed in teaching physiology using a superhuman specimen like Captain America. Applications may be made repeatedly throughout the term with each new topic addressed. Or, at the end of the term, the instructor could dedicate one or more class periods to the pop icon in question. Another possibility is to design a class project (either individually or in groups) centered on the icon. Other superheroes could also be used, comparing one superhero with the next and discussing the physiological reasons why one hero would beat another if they were to fight. Ultimately, we believe the use of superhero physiology in the classroom is limited only by one's imagination as a teacher.

Proposed questions are as follows:

1. Discuss the modulations in protein pathways that likely occurred to allow Cap to perform his superhuman feats.
2. Discuss genetic mutations that likely occurred in Cap.
3. Physiologically, how is Cap able to have a metabolic rate four times that of a normal human that does not necessitate increased food consumption?
4. Propose a likely muscle fiber type profile for Cap and defend your hypothesis.
5. Considering the physiological changes induced by the super soldier serum, explain how these factors can allow for reductions in exercise-induced acidosis and/or fatigue.
6. Regarding Cap's physiological/metabolic alterations, discuss which of these (if any) are realistic in terms of potential occurrence in humans, and if so, to what extent.
7. Using Cap's training run on The Mall in Washington, DC (shown in *Winter Soldier*), discuss estimations of the expected  $\dot{V}\text{O}_{2\text{max}}$  of Captain America.
8. Discuss the physiological adaptations necessary for Cap to run 13 miles in 30 min.
9. Considering the changes brought about in Cap's cardiovascular system via the super soldier experiment, address the following: 1) find alternate ways in which Cap could achieve a maximum aerobic power of 177 ml·kg<sup>-1</sup>·min<sup>-1</sup> and 2) compare and contrast exercise performance capabilities between different species and superheroes like Captain America.

### Conclusion

To treat our hypothesis adequately, this article has necessarily dealt exclusively with Captain America. We also chose to focus this discussion on his movie exploits, which compel-



lingly demonstrate enhanced cardiovascular and metabolic functioning. Each section of this paper summarizes the changes that give Cap his enhanced abilities. However, we recognized that there is a pantheon of superheroes available for use as pop icons. Some of these have very different physical/physiological capabilities that could be explored to bolster our hypothesis. An easy example is the superhero Daredevil, also of Marvel Comics/Studios. His powers are quite subtle, and a subsequent article would have to focus on areas of motor control and sensory perception to cover his superhero gifts/antics. Left blinded by a radiological agent, his “sight” now is a kind of radar perception of the sounds of the world around him, which is so keen that he can hear individual heartbeats and “see” with radar-like acuity. His gifts also extend to an extreme level of kinesthetic awareness far greater than that achieved by the most advanced Olympic gymnasts.

In short, there are many other superheroes whose iconic personas could serve as foils for exploring the limits of human biology and by their inclusion make science lectures far more interesting. Science education can and should be fun if teachers make the necessary effort. The speculative science presented in this paper may seem frivolous, but think of the student who may be otherwise hard to reach. The numbers and concepts of the science being taught may potentially have a far greater impact when pop icons such as Captain America are used in the classroom. Suddenly, the concepts are not so dry, and the numbers can be rather compelling and entertaining. The use of the icon in this way may lead to a teachable moment rather than an effort that seems as hard as pulling teeth. Eyes may sparkle and grow wider, and there may even be some in-class snickering at the use of such examples. Having thus gained the attention of the class, the good teacher will seize the moment, and perhaps actual learning will ensue.

The truth is that pop icons engender thoughts of greater possibilities, taking us out of ourselves and opening our minds. Are we ascribing too much to this brand of science pedagogy? Maybe, but such is the power of pop icon messaging. It begs to be used this way, to be explored, maybe even to win over the next great imaginative genius who otherwise would not have given science, any science, a second thought.

## ACKNOWLEDGMENTS

We acknowledge and thank Katherine E. Wood (an undergraduate kinesiology student at Mississippi State University) for her artistic contributions in the creation of the images in this paper.

## DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

## AUTHOR CONTRIBUTIONS

S.P.B. prepared figures; S.P.B., J.S., M.M., and L.J. drafted manuscript; S.P.B., J.S., M.M., and L.J. edited and revised manuscript; S.P.B. approved final version of manuscript.

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