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## Ground Walking in Chronic Complete Spinal Cord Injury

## Does Epidural Stimulation Allow “Awakening” of Corticospinal Circuits? A Wide-Ranging Epistemic Criticism

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**Key Words:** Rehabilitation, Walking, Spinal Cord Injury, Epidural Stimulation, Research Designs, Logic

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## THE AIM OF THE ARTICLE

This article aims to foster methodological reflections on previous researches making causal inferences between biological interventions and behavioral outcomes. In a thorough study, electrical lumbar epidural stimulation added to an intense and prolonged exercise program seemed to be effective in allowing independent standing and assisted overground gait in two of four chronic complete spinal cord injury subjects. The conclusions from this research are debatable and therefore potentially misleading as the message that some chronic complete paraplegic persons can return to walk strongly appeals to patients and professionals. A warning is provided against overconfidence in deterministic, bottom-up modeling of treatment effects across the many functional levels linking the body's biology to a person's behavior.

## OUTCOME MAY NOT BE THE EFFECT OF THE HYPOTHESIZED CAUSE

## Gait Training and Recovery of Patients With Chronic Motor Complete Spinal Cord Injury

A recent article in *New England Journal of Medicine*<sup>1</sup> reported a case series of four chronic spinal cord injury patients (aged 22–32 yrs; 2.5–3.3 yrs after trauma). Two patients (participants P1 and P2, gender unspecified) were motor and sensory complete (grade A, ASIA Impairment Scale-AIS, 2011 Version<sup>2</sup>), both at the T4 level. Two other participants (P3 and P4), a man and a woman, as observed in the supplementary

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videos,<sup>1</sup> were motor complete and sensory incomplete (AIS B), at level C5 and T1, respectively. An intense training program was initiated, consistent with the patients' progress and focused on three types of training sessions: stepping on a treadmill, overground standing, and overground walking. “Core” exercises (ie, exercises targeting force and coordination of trunk and lower limb muscles) were also associated. Stepping on a treadmill was performed “with bodyweight support and manual facilitation of stepping.” Bodyweight was supported on the treadmill through the use of a custom-built apparatus. Trainers moved the patients' “legs through the step cycle if needed, during which the participant made voluntary attempts to perform elements of the step cycle” (Appendix<sup>1</sup>). Training also included assistance to overground standing” and to overground walking, which occurred only if the former skill was attained. The subjects were allowed to use their arms to aid in posture and balance. Manual assistance for the knees and hips was supplied as needed. During overground walking, patients were allowed to use walkers, and parallel bars were held by two therapists.

The exercise program was applied daily, in one or two 1-hr sessions. All four participants failed to attain independent standing and walking either on the treadmill or overground after the initial training period that lasted for 2 hrs per day, 5 days a week, for 8–9 wks. Subsequently, an epidural stimulator was implanted in all subjects. A 16-electrode array was placed over spinal segments L2 to S1-S2. Details can be found in the original article (main text and supplements). Thus, the selected anode-cathode pairs and stimulation parameters presumably induced the “rhythmic activation of ensembles of leg muscles that simulated walking movements” and the “combinations were selected that enhanced standing and stepping movements while participants focused on each of these tasks.”<sup>1</sup>(p1247) The participants resumed an intensive training program (one to two 1-hr session per day, 5 days a week) during which the epidural stimulation was continuously provided. “Both standing and stepping stimulation configurations were modified every 2–4 wks to determine whether adjustments resulted in better standing and stepping, on the basis of observation and electromyographic (EMG) activity” (Appendix<sup>1</sup>). The number of training sessions with epidural stimulation and the treatment duration were as follows: 375 sessions and 52 wks for P1 (with a 1-yr gap because of a spontaneous hip fracture while stepping on the treadmill in week 2); 290 sessions and 41 wks for P2; 278 sessions and 85 wks for P3; and 81 sessions and 15 wks for P4.

## Outcomes

The outcome looked favorable for P3 and P4 (C5 and T1 level, both AIS B; see supplementary videos<sup>1</sup>). P3 was able to

walk continuously for up to 90.5 m at  $0.19 \text{ m s}^{-1}$  “while using horizontal poles for balance or when holding hands with two persons (one on each side).” P3 was also able to stand with a walker and sit independently for 5 mins. P4 was able to walk with a walker (unspecified distance) and stand while holding on elastic bands for 50 min and fully autonomously for 7–10 secs at a time. All of these results could only be possible in trials where the stimulator was on, and the subject provided volitional efforts. Participants P1 and P2 (both AIS A, T4 level) were able to achieve some components of independent stepping on the treadmill with body support but not for overground walking. The authors concluded that the recovery of walking, standing, and trunk mobility can occur under special circumstances with intensive training and electrical stimulation even with years after a spinal cord injury that caused complete leg paralysis. Spared sensation may characterize more suitable candidates.

### The Theoretical Underlying Context: The Spinal “Central Pattern Generators” of Walking

The study is well grounded within a sound theoretical model (see refs. 11–26 in<sup>1</sup>). This model dates back to Sten Grillner’s team experiments in the 1970s on paraplegic kittens.<sup>3</sup> The animals were shown to be able to walk on a treadmill (with the pelvis supported), to adapt to treadmill velocity changes, and to provide corrective reactions after stumbling on obstacles. The kitten could also adapt to split-belt walking (parallel treadmill belts rotating at different velocities). In adult cats, the “awakening” of the central pattern generators (CPGs) became dependent on intravenous injection of drugs (eg, Levo-Dihydroxyphenylalanine, L-DOPA) or on supraspinal facilitation, eg, mesencephalic electric stimulation in incomplete cases. Consequently, evidence grew that in all legged vertebrates, including man, the lumbar spinal cord contains “CPGs” that allow the rhythmic activation of flexor-extensor muscles of the hind limbs during walking in response to sensory stimulation (eg, the extension of the hips “dragged” by the treadmill belts or, of particular interest here, epidural stimulation).<sup>4</sup> The spinal CPG model supports the hypothesis that the pattern of recruitment of the lower limbs in walking is essentially a supraspinally or peripherally triggered spinal activity (although a very complex and flexible one). Walking in man would simply require triggering and modulating the CPGs from sensory stimuli and volitional drive combined. This model inspired various rehabilitation methods such as robot-assisted gait training.<sup>5</sup> Moreover, the model could be reasonably advocated for explaining human’s effortless adaptation to split-belt training<sup>6</sup> and, consequently, for motivating therapeutic attempts with “split walking” in asymmetric pathologic gaits.<sup>7,8</sup> The same model was referred to in a subsequent article by the same research group authoring the article under examination here and included an exhaustive reference list.<sup>9</sup>

### FROM CAUSE TO EFFECT: AN INSIDIOUS LEAP

#### The Observed Results Do Not Necessarily Stem From the “Awakening” of the Brain-Spinal CPGs Interplay

There is strong evidence that epidural stimulation can facilitate the emergence of voluntary movements after chronic complete spinal cord paralysis in humans.<sup>10</sup> Other forms of

sensory stimulation (more precisely, proprioceptive stimulation) may also “facilitate” the voluntary movement, such as in the case of muscle vibration.<sup>11</sup>

The article (and a subsequent study based on a sophisticated analysis of EMG signals from the lower limb muscles<sup>9</sup>) showed that the same principle may hold for the voluntary activation of spinal CPGs of walking in paraplegia cases. Let us consider a more mechanical explanation. Participants P3 and P4 may have learned to overload the upper limbs and the trunk in a way that induced the lower limb movements, suitable to trigger the CPGs activity in a reflexive manner. The same kind of objection was raised to a separate article<sup>12</sup> that reported that motor complete/sensory incomplete spinal cord injured rats could achieve bipedal walking on the rear limbs only upon receiving systemically applied drugs, a food reward, and epidural stimulation. The authors suggested that rats could achieve “supraspinal control over the electrochemically enabled lumbosacral circuits.” It was objected that because of the imposed bipedal posture on rear limbs, “the animals developed a new strategy to facilitate postural adjustments required to initiate locomotion, rather than establishing new connections with the lumbosacral locomotor centers.”<sup>13</sup>

Human bipedal standing and walking can be achieved in many adaptive ways. In these participants, lateral stability was provided by the upper limbs.

This fits with the CPG model: in cats and rats, autonomous lateral stability could never be achieved, so that the question whether the spinal CPGs only control flexion-extension EMG patterns remain unanswered. Support on the lower limbs could reflect ligamentous stability due to the knee and hip hyperextension and ankle full dorsal flexion, mediated by spine hyperlordosis. Classic kinesiology shows that this posture allows the resulting ground reaction force to cause an extensor moment (dorsal-flexor at the ankle), allowing to passively lock all of these joints. The propulsive power could be provided by the upper limbs, as in paraplegic subjects walking with reciprocating gait orthoses.<sup>14,15</sup> The advancement of the swinging lower limb, in the absence of power from hip flexors (iliopsoas and rectus femoris), could be achieved by the inward rotation of the supporting hip. This could be driven by rotating the thorax toward the supporting hip, entraining the pelvis passively. This mechanism could be achieved by recruiting a muscle chain around the scapular-humeral joint on the supporting side involving the subscapularis, the pectoralis major, and the latissimus dorsi muscles, sharing a C6 innervation. This mechanism was conceivable in P4 (AIS B, T1). As for P3 (AIS B, C5), a strong contraction of the brachioradialis muscle (C6) is evident on both sides. The supplementary material assigns motor grade 2/5 to his elbow extensors (C7; no baseline data are provided). The article does not provide a recording of the “zones of partial preservation” below the lesion level. This analysis was not mandatory for sensory incomplete patients by the 2011 AIS classification; however, it should have been recorded in the most recent one.<sup>16</sup> The same classification recommends that “the presence of nonkey muscle activity can be documented in the comment box on the worksheet. While these muscle functions are not used in determining motor levels or scores, at this time the International Standards allows nonkey muscles to determine motor incomplete status; AIS B versus C.”<sup>16(p93)</sup> Furthermore, doubt is raised by the observation that P1 and P2, unable to achieve overground walking, could

achieve independent sitting and standing nonetheless; these two performances were hardly attributable to the rhythmic CPGs of locomotion.

### Refutable Explanatory Arguments

At least four considerations may support the authors' claim for the pivotal role of epidural stimulation in activating the spinal CPGs. However, their arguments are refutable:

1. Participants found no benefit from a previous training without stimulation. Notably, the previous program was of much shorter duration compared with the following one.
2. The improvement of standing and walking performances could only be observed in patients with residual sensation, which is a requirement for the transmission of the facilitating information conveyed by the stimulation to the brain. Alternatively, the enhanced sensation could provide better feedback helping the patients steer the motor output from the upper limbs.
3. Improvements in standing and walking could only be achieved with the epidural stimulation switched on. However, the experiment was open; thus, a placebo/motivational effect (both on patients and trainers) could not be excluded, fostering the learning and execution of complex adaptive behaviors relying on upper limb mechanics.
4. "Standing and voluntary movements occurred only with the intention to move." This observation may reflect the efficacy of a volitional corticospinal drive, although it does not rule out the possibility that the supraspinal mechanical activity entrained mechanically the muscular activity below the lesion as well.

### UNRESOLVED QUESTIONS (WHICH POSSIBLY CAN BE RESOLVED)

The more adaptive and mechanical upper limb explanation proposed here can be ruled out with a different design. The authors' study design only hypothesizes that their treatment generates a unidirectional cause-effect chain, from changes in spinal cord biology to whole-person walking behavior. This leaves their results open to conflicting interpretations.

### The Biological Substrate of Changed Behavior: Changed Spinal Cord Physiology

The damage of the spinal cord lesion was not described, preventing an investigation of the link to the AIS classifications. The degree of disconnection (anatomical and neurophysiological) between the spinal cord segments above and below the lesion, before and after training, remains unclear. Nowadays, magnetic resonance imaging allows detecting remaining tissue bridges across the lesion.<sup>17</sup> "Tractography" through diffusion tensor magnetic resonance imaging allows detecting after even single neural fascicles.<sup>18</sup> As for neurophysiology, in the two sensory-incomplete cases, the authors found rhythmic activation of the lower limb muscles (as seen from the EMG signals) "not entrained to the frequency of stimulation."<sup>1(p125)</sup> The authors claim that in P3 "muscle activation during walking was timed appropriately to the step cycle."<sup>1(p1248)</sup> This pattern, however, was far from the well-known pattern observed in healthy adults.<sup>19(p524)</sup> Looking at Figures S2<sup>1</sup> and S3<sup>1</sup>

(participants P3 and P4, respectively), it seems that the plantar flexors were recruited at mid-stance, synchronous (not alternating) with knee extensors: a pattern that might stem from enhanced spasticity. A "spastic crutch" may be helpful in fostering some form of functional stepping and may even foster the enhancement of the supraspinal drive.<sup>20</sup> However, enhanced muscle stretching (hence, enhanced spasticity) could have been made possible by the new standing and walking performances. Let us accept that the emerging muscle activation was the effect of the stimulation; however, the suggestion that "... suprasegmental excitation of spinal networks is entrained for walking after cord injury by the technique we describe"<sup>1(p1250)</sup> still remains unsubstantiated.

With the data at hand, there is no way to disentangle the "peripheral stimulation first" versus the "volitional drive first" interpretation. Neither tendon reflexes nor the H-reflex,<sup>20</sup> nor measures of corticospinal drive (eg, motor evoked potentials), and the central muscle activation through the interpolated twitch technique<sup>21</sup> were provided in the article. A more substantial investigation on neurophysiology and the spinal cord anatomy would have been beneficial.

### Behavioral Changes as a Cause, Not Only an Effect, of Biological Changes

The EMG pattern associated with the epidural stimulation could either be the originating egg or the reflex (spastic) chicken, with respect to the whole-body posture and locomotory motion. Stepping might have been facilitated by increased motivation and volitional drive mostly directed toward the upper limbs (by the way, reinforced by intensive training). Once a higher volitional effort was elicited, the cortical modulation of sublesional spinal reflexes might have been increased, allowing neural circuitries to be established or revitalized below the lesion. Loading and stretching of the lower limb muscles might have fostered the previously mentioned "spastic crutch." Studies of the H-reflex during paraplegic gait suggest that multiple inhibitory mechanisms are depressed.<sup>22</sup> Beyond muscular and spinal stimulation, training itself can enhance the capacity of the brain to modulate the spinal reflexes. For instance, in subacute and incomplete patients, the facilitation of the H-reflex induced by TMS has been found to increase after gait training.<sup>22</sup> Last, a high-order adaptation might have been fostered by the intense and prolonged training. Participants might have optimized the dynamics of normal, weakened, and paralyzed body segments to obtain the best possible stepping pattern.

### TAKE-HOME MESSAGES

#### Do Not Split Neurophysiology From Biomechanics

One should never forget that "most of the processing in the nervous system is dedicated to producing movements. The final expression of most cognitive and emotional processes includes motor actions."<sup>24</sup> This statement, inspired by the fundamental historical work of Sir Charles Sherrington,<sup>23</sup> highlights that the neural control of movement cannot be explained without a parallel investigation of the mechanical output. This advice holds by greater force for walking, where the many degrees of freedom of many joints allow a wide variety of

adaptive motions in case of impairments. Why is a given solution privileged? As a rule, the answer is very difficult and may require interpreting segmental motions in the light of their effect on motion of the body system as a whole, represented by its center of mass. Contemporary gait analysis allows a thorough examination of most mechanical and neurophysiological parameters of walking in most various impairments.<sup>24</sup>

Hence, an alternative, “more adaptive and more mechanic,” upper limb-based interpretation of the results could not be disputed. The main reason was that no comprehensive quantitative mechanic analysis (either kinematic or dynamic) of the participants’ standing and walking was provided. This prevents deciding whether the activation of lower limb muscles follows passive movements induced by active supraspinal muscles (eg, through lower limb stretch reflexes), rather than genuine and valid corticospinal activation below the lesion (possibly mediated by CPGs awakened by the epidural stimulation). If the latter explanation is preferred, it remains to be determined whether cortical activation reflected rather than generated any rearrangement of spinal circuits. These two “explanations” are not mutually exclusive, of course. The point is that the authors ascribed the outcome (some form of stepping) to the observed emerging patterns of recruitment of flexor-extensor muscles of the lower limbs. In so doing, the authors did not clarify whether this pattern was cause or effect of the whole-body locomotory mechanism.

### Causal Inference Within Single Subjects Needs Linking Levels of Increasing Complexity

Rehabilitation medicine spreads from biology to behavior; thus, looking for intermediate “causes” is essential in its well-designed paradigms.

Given the limited sample at hand, it is true that a simple treatment-outcome association is not sufficient for a causal inference, as per the historical Bradford Hill’s lesson.<sup>25</sup> However, how could the association in one or a few cases become “significant” without statistical modeling, thus representing sound support of the causal hypothesis?

A human being is a complex organism in which hierarchical levels<sup>26</sup> of organization must be acknowledged: from molecules, to cells, to organs, up to the conscious person. Biological functions (far from a simple concept itself<sup>27</sup>) permit behavioral functions; hence, the concept that biological causes must be looked for behind diseases, illnesses,<sup>28</sup> and disability.<sup>29</sup> However, the reverse may also be true. There may be a reciprocal causal interaction between levels (see the debate on the illness-disease dichotomy).<sup>30</sup> For instance, in this case, neural and muscular cellular events disclosed by the EMG patterns perhaps ultimately permit standing and walking, yet the person’s adaptive choices may determine the optimal EMG pattern. One should consider the possibility of both *upward* and *downward* causation, the latter<sup>31</sup> implying a critical rethinking of the blamed concept of teleological explanation.<sup>32</sup>

### Test the Intermediate Rings of the Cause-Effect Chain

From the article discussed here, the real usefulness of epidural stimulation for standing and gait recovery in AIS B persons remains doubtful. Hence, the explanation through the

underlying theory of “awakening” of supraspinal control of CPGs remains doubtful, too. A hard bet has been made on epidural stimulation (a focal biological treatment) as the critical cause of recovery of high-level behaviors. The overall functional outcome is limited, and—as the previous paragraphs strived to demonstrate—difficult to explain. The same authors are now renewing their efforts in the direction of finding the parameters of epidural stimulation providing optimal EMG patterns (also in terms of the signal spectrum), thus raising the stakes on the biological-behavioral shortcut.<sup>9</sup> An ultimate message can be proposed here to researchers in psychiatry: look for *explanations along* the causal chain, not only for the association between its extreme rings. Explanation implies nesting the observation within a theory, generally resting on established knowledge, thus allowing predictions and generalization.<sup>31</sup> Often, thorough checks are possible of the strength of each ring and hence of their links.

### FINAL AND GENERAL REMARKS

When a biological/focal intervention is a crucial ingredient of the treatment of disability, and a complex whole-person behavior is a primary end point, one should strive to demonstrate the consistency between observations reflecting increasing levels of complexity (eg, anatomy and physiology of the spinal cord, the reflex or voluntary nature of muscle contractions, the strength of the corticospinal drive, the torques acting on key joints, etc.). Consistency means the demonstration of fit between theory-expected and observed phenomena, along intermediate rings of an *explanatory chain*, as simply associating treatment and outcome may be hazardous to the least. Association is not necessarily causality. In addition, one should always consider the possibility for downward causation between levels of complexity, consistent with a spiraliform rather than unidirectional process of knowledge advancement.<sup>30</sup> Mental and behavioral levels may influence biological levels, not less than the other way around. “[This influence] could take the form of changed biological parameters. For instance, ‘stress’ . . . could cause detectable changes in blood steroid concentration and immunity markers.”<sup>31,33</sup> Analogously, motor learning and motivation may lead to a more skillful triggering of below-lesion spinal circuitries and the musculoskeletal machinery. The trial design should be conceived accordingly, in an effort to highlight the prevalent direction of the causal flow.

### REFERENCES

1. Angeli CA, Boakye M, Morton RA, et al: Recovery of over-ground walking after chronic motor complete spinal cord injury. *N Engl J Med* 2018;379:1244–50
2. Committee Membership, Burns S, Biering-Sørensen F, Donovan W, et al: International Standards for Neurological Classification of Spinal Cord Injury, revised 2011. *Top Spinal Cord Inj Rehabil* 2012;18:85–99
3. Forssberg H, Grillner S, Halbertsma J: The locomotion of the low spinal cat. I. Coordination within a hindlimb. *Acta Physiol Scand* 1980;108:269–81
4. Grillner S, El Manira A: Current principles of motor control, with special reference to vertebrate locomotion. *Physiol Rev* 2020;100:271–320
5. Nam KY, Kim HJ, Kwon BS, et al: Robot-assisted gait training (Lokomat) improves walking function and activity in people with spinal cord injury: a systematic review. *J Neuroeng Rehabil* 2017;14:24
6. Prokop T, Berger W, Zijlstra W, et al: Adaptational and learning processes during human split-belt locomotion: interaction between central mechanisms and afferent input. *Exp Brain Res* 1995;106:449–56
7. Helm EE, Reisman DS: The split-belt walking paradigm: exploring motor learning and spatiotemporal asymmetry poststroke. *Phys Med Rehabil Clin N Am* 2015;26:703–13

8. Tesio L, Malloggi C, Malfitano C, et al: Limping on split-belt treadmills implies opposite kinematic and dynamic lower limb asymmetries. *Int J Rehabil Res* 2018;41:304–15
9. Mesbah S, Gonnelli F, Angeli CA, et al: Neurophysiological markers predicting recovery of standing in humans with chronic motor complete spinal cord injury. *Sci Rep* 2019;9:14474
10. Angeli CA, Edgerton VR, Gerasimenko YP, et al: Altering spinal cord excitability enables voluntary movements after chronic complete paralysis in humans. *Brain* 2014;137:1394–409
11. Ribot-Ciscar E, Butler JE, Thomas CK: Facilitation of triceps brachii muscle contraction by tendon vibration after chronic cervical spinal cord injury. *J Appl Physiol* 2003;94:2358–67
12. Van Den Brand R, Heutschi J, Barraud Q, et al: Restoring voluntary control of locomotion after paralyzing spinal cord injury. *Science* 2012;336:1182–5
13. Sławińska U, Rossignol S, Bennett DJ, et al: Comment on “restoring voluntary control of locomotion after paralyzing spinal cord injury”. *Science* 2012;338:328
14. Johnson WB, Fatone S, Gard SA: Walking mechanics of persons who use reciprocating gait orthoses. *J Rehabil Res Dev* 2009;46:435–46
15. Lotta S, Fiocchi A, Giovannini R, et al: Restoration of gait with orthoses in thoracic paraplegia: a multicentric investigation. *Paraplegia* 1994;32:608–15
16. Betz R, Biering-Sørensen F, Burns SP, et al: The 2019 revision of the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI)—what’s new? *Spinal Cord* 2019;57:815–7
17. O’Dell DR, Weber KA, Berliner JC, et al: Midsagittal tissue bridges are associated with walking ability in incomplete spinal cord injury: a magnetic resonance imaging case series. *J Spinal Cord Med* 2020;43:268–71
18. Ducreux D, Fillard P, Facon D, et al: Diffusion tensor magnetic resonance imaging and fiber tracking in spinal cord lesions: current and future indications. *Neuroimaging Clin N Am* 2007;17:137–47
19. Tesio L, Rota V: Gait analysis on split-belt force treadmills: validation of an instrument. *Am J Phys Med Rehabil* 2008;87:515–26
20. Thompson AK, Mrachacz-Kersting N, Sinkjær T, et al: Modulation of soleus stretch reflexes during walking in people with chronic incomplete spinal cord injury. *Exp Brain Res* 2019;237:2461–79
21. Dongés SC, Boswell-Ruys CL, Butler JE, et al: The effect of paired corticospinal-motoneuronal stimulation on maximal voluntary elbow flexion in cervical spinal cord injury: an experimental study. *Spinal Cord* 2019;57:796–804
22. Benito Penalva J, Opisso E, Medina J, et al: H reflex modulation by transcranial magnetic stimulation in spinal cord injury subjects after gait training with electromechanical systems. *Spinal Cord* 2010;48:400–6
23. Sherrington CS: *The Integrative Action of the Nervous System*. New Haven, Yale University Press, 1911
24. Tesio L, Rota V: The motion of body center of mass during walking: a review oriented to clinical applications. *Front Neurol* 2019;10:999
25. Wakeford R: Association and causation in epidemiology - half a century since the publication of Bradford Hill’s interpretational guidance. *J R Soc Med* 2015;108:4–6
26. Craver C: Role functions, mechanisms, and hierarchy. *Philos Sci* 2011;68:53–74
27. Garson J: *A Critical Overview of Biological Functions*. Switzerland, Springer Int Publisher AG, 2016:113
28. Wilshire C, Ward T: Conceptualising illness and disease: reflections on Sharpe and Greco (2019). *Med Humanit* 2020;46:532–6
29. Granger CV, Linn RT: Biologic patterns of disability. *J Outcome Meas* 2000;4:595–615
30. Tesio C, Buzzoni M: The illness-disease dichotomy and the biological-clinical splitting of medicine. *Med Humanit* 2020. doi: 10.1136/medhum-2020-011873
31. Bertolaso M, Buzzoni M: Causality and levels of explanation in biology, in: Paolini Paoletti M, Orilia F (eds): *Philosophical and Scientific Perspectives on Downward Causation*. New York, NY, Routledge, 2017:164–79
32. Allen C, Neal J: Teleological Notions in Biology, in: *Stanford Encyclopedia of Philosophy* [Internet]. Spring 2019. Available at: <https://plato.stanford.edu/archives/spr2019/entries/teleology-biology/>. Accessed December 28, 2019
33. Yarıbeygi H, Panahi Y, Sahraei H, et al: The impact of stress on body function: a review. *EXCLI J* 2017;16:1057–72