

Available online at [www.sciencedirect.com](http://www.sciencedirect.com)

ScienceDirect

Biomedical Journal

journal homepage: [www.elsevier.com/locate/bj](http://www.elsevier.com/locate/bj)

## Highlights

# About gladiators and a sacred disease

Aila Akosua Kattner\*

Freelance Journalist, Berlin, Germany

### ARTICLE INFO

#### Article history:

Available online 23 March 2022

#### Keywords:

Leishmania  
Natriuretic peptide  
Extracellular vesicles  
Fecal microbiota transplant  
Ketogenic diet  
COVID-19

### ABSTRACT

In this special edition of the *Biomedical Journal* the reader gains an insight into drug-resistant epilepsy and according treatment approaches involving deep brain stimulation, the ketogenic diet and fecal microbiota transplant. Another emphasis is put on personalized medicine strategies, and covered in articles about the use of natriuretic peptides against cancer, along with an article about companion diagnostics involving extracellular vesicles. Recurrent infection with *Clostridium difficile*, associated risk factors and therapeutic options are discussed. We learn about a mechanism that helps *Leishmania* evade a host control mechanism, receive an update about human adenovirus and are presented with characteristic magnetic resonance neuroimaging in COVID-19 pediatric patients. An advanced assessment in pediatric septic shock and an improved model for a pediatric early warning system are proposed. Some of the genetic causes of renal hypomagnesemia are explored, the impact of air pollution on children is examined, and an antisiphon device is described for surgical treatment of hydrocephalus. The relation between energy metabolism, circadian rhythm and its influence on the ATPase in the SCN are investigated, and among others some of the genetics influencing smoking duration and lung cancer. Finally it is discussed how embryo quality can be improved in *in vitro* fertilization, and what impact high estradiol has on blastocyst implantation. The outcome of surgery to correct mandibular deficiency is assessed, and in two letters the inclusion of observational studies in the evaluation of clinical trials related to COVID-19 is elaborated.

## Spotlight

Pythia, the most influential women in Ancient Greece, were highly sought after in their role as priestesses in the temple of Apollo and Oracle of Delphi. The Pythia would be consulted in matters ranging from trivial to not so trivial, and their insight

was valued for receiving guidance in personal questions and beyond that in questions of major public importance. Modern scholars have put forward various theories in order to explain how Pythia would enter into trance to then express her visions and prophecies. Early hypotheses suggested that volcanic vapors in the temple and the consumption of specific herbs by the priestess would lead to a state and symptoms that could

\* Corresponding author. Freelance Journalist, Berlin, Germany.

E-mail address: [aila.kattner@gmail.com](mailto:aila.kattner@gmail.com).

Peer review under responsibility of Chang Gung University.

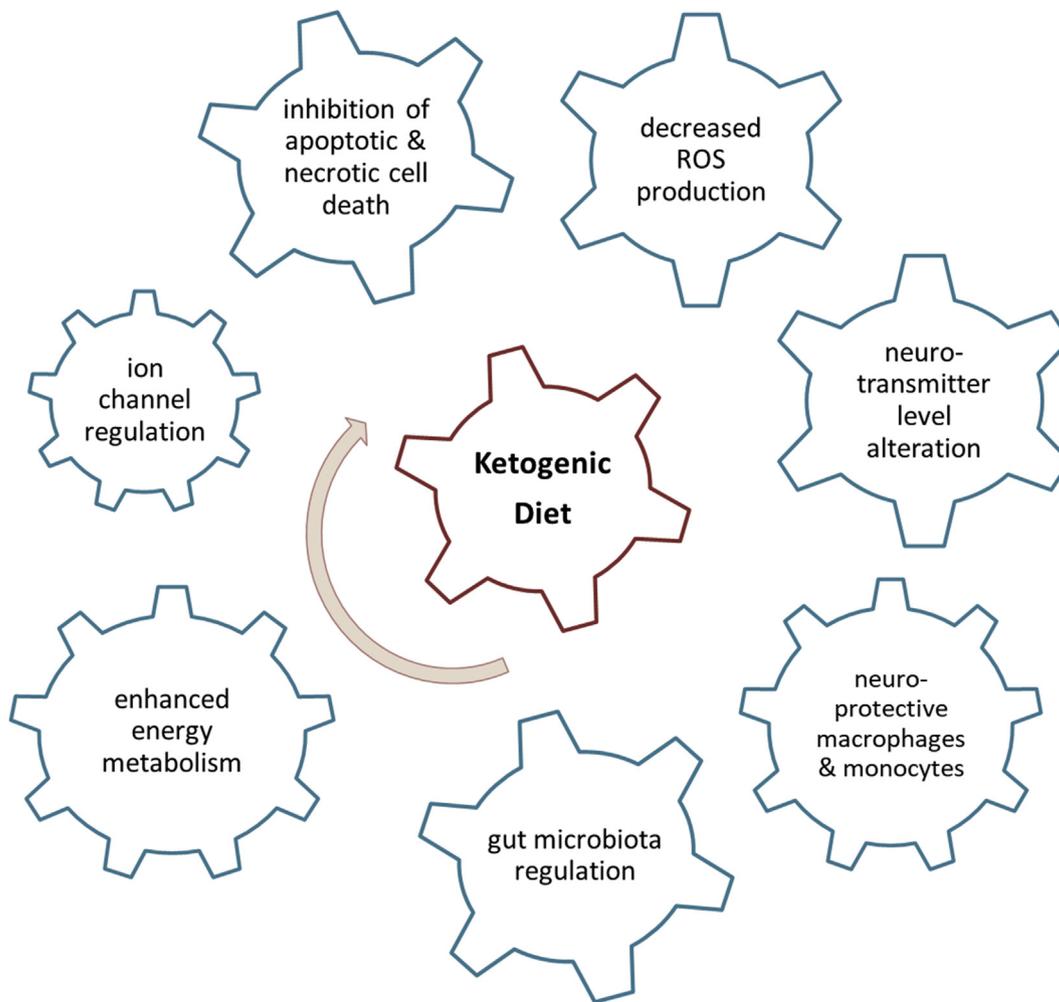


Fig. 1 Mechanisms of action of the ketogenic diet (KD) following proposition by Ko et al. The ketogenic diet acts as a cogwheel leading to complex interconnection of multiple mechanisms. The KD is thus contributing to the anti-seizure effect and exerting neuroprotective effects in patients with epilepsy [6].

be described as epilepsy. In Homeric times the common people thought that epilepsy was induced by the gods and termed it Sacred Disease [1].<sup>1,2,3,4</sup>

Drug-resistant epilepsy (DRE) affects a third of people with epilepsy and potentially poses a life-threatening condition. Treatment strategies include resective surgery or neuro-modulation through devices [2].

Foutz et al. dive into the open questions surrounding Responsive Neural Stimulation and Deep Brain Stimulation as alternative therapeutic options for DRE epilepsy. In their article, the team discusses the clinical use, mechanisms

of action as well as choice of device for both kind of stimulation [3].

#### *Thicc like a gladiator*

It has been shown that DRE patients display an altered gut microbiome composition in comparison to drug-sensitive epilepsy patients and healthy controls. Fecal Microbiota Transplant (FMT) is one way to influence a recipient's gut microbiota, as presented in the article highlight following this highlight section.

Also low-carbohydrate diets change the taxonomic and functional composition of the gut microbiome. They might therefore promote select microbial interactions as well as variance in brain neurotransmitter levels influencing seizures [4].

The latest desire for improved athletic performance and physique is closely associated with trends in diet and nutrition. Traditional fueling strategies have been emphasizing high carbohydrate utilization, especially in endurance sports. Gladiators for instance seem to have been primarily vegetarian and loading on carbs like grains and beans. They were

<sup>1</sup> <https://medium.com/swlh/the-oracle-at-delphi-was-the-most-important-woman-of-the-ancient-world-who-was-she-7016f0a38cb5>, last access 02/25/2022.

<sup>2</sup> <https://theconversation.com/hidden-women-of-history-the-priestess-pythia-at-the-delphic-oracle-who-spoke-truth-to-power-108401>, last access 02/25/2022.

<sup>3</sup> <https://oxford.universitypressscholarship.com/view/10.1093/oso/9780198844549.001.0001/oso-9780198844549-chapter-10>, last access 02/25/2022.

<sup>4</sup> <https://www.tandfonline.com/doi/full/10.1080/15563650701477803>, last access 02/25/2022.

thus able to build a solid cushion of subcutaneous fat as protection against cut wounds, at the same time shielding nerves and blood vessels in a fight. Being ripped, as idolized in modern pop culture, would have been of disadvantage for a gladiator.<sup>5,6</sup>

On the other hand low-carb diets have been flourishing since the 1960s under names like the Drinking Man's Diet, the Martinis and Whipped Cream Diet, the Atkins Diet, South Beach Diet, or Paleo Diet. Most low-carb diets focus on protein, whereas a ketogenic diet is low-carb and supplies 90% of daily calories through fat.<sup>7,8</sup> In the 1920s, a ketogenic diet (KD) proved to be as efficient as fasting in the treatment of patients with epilepsy and has since been widely used in that regard [5].

Ko et al. review the current knowledge on the KD and its mechanisms of action. The team concludes that the KD is a good treatment option for patients with drug-resistant epilepsy. The anti-seizure effect is proposed to be caused by the KD altering neurotransmitter levels. On top of that it enhances mitochondrial function and reduces oxidative stress, thus exerting further neuroprotective effects [Fig. 1]. Ko et al. propose the exploration of KDs for potential use in other, neurologic disorders [6].

### Designer Shit

The documentary “Designer Shit” explores the therapeutic use of Fecal Microbiota Transplant (FMT) for various disorders and explains possible applications in an accessible way for a mainstream audience.<sup>9</sup>

FMT can be used to directly change a recipient's gut microbiota, thus allowing the patient to potentially gain a therapeutic benefit. FMT is considered a promising candidate for the development of personalized therapeutics in the future [7].

FMT is currently approved in several countries for treatment of recurring *Clostridium difficile*. According to a newspaper article from 2015, donating feces – provided that a person qualifies as extensively healthy and hence suitable for the project – to the nonprofit organization OpenBiome would be compensated with up to 13,000 USD per year.<sup>10</sup> OpenBiome is an initiative committed to providing safe, convenient and affordable access to FMT by supplying physicians with ready-to-use fecal microbiota preparations.<sup>11</sup>

However, FMT might have further applications for instance for patients with neurological disorders. Although conclusive research data is still sparse, it has been suggested that FMT

might be a successful treatment option for autism spectrum disorder, multiple sclerosis, Parkinson's disease, epilepsy, Tourette syndrome, diabetic neuropathy, stroke, Alzheimer's disease and Guillain-Barré syndrome [8].

*C. difficile* is a nosocomial pathogen and leading cause of hospital-acquired, antibiotic-associated diarrhea in Europe and North America. Its name reflects the difficulty with its culture and isolation [9]. *C. difficile* infection (CDI) is characterized by a decline in gut microbial diversity and an overgrowth of *C. difficile* with an increased risk of recurrent infection [10].

As CDI currently is the only approved indication in Taiwan for FMT, Chen et al. are reviewing previous research data of FMT application in pediatric patients to contribute to the discussion about further development and use of FMT. The team confirms FMT as safe and effective therapy for recurrent CDI and inflammatory bowel disease in children. They expect further application options in the future and beyond that a shift from applying FMT via colonoscopy to oral, laboratory-designed microbial products [10].

---

## Also in this issue

### Editorial

For this issue of *Biomedical Journal*, guest editor Wang warmly invites experts to share their updates on important issues in pediatric care, highlighting the importance of pediatricians in view of the currently falling birthrates on a global level. He prepares the floor for the review about applying fecal microbiota transplantation in various disorders, as well as for another article proving the growing attention the ketogenic diet receives as treatment option in neurological disorders. Wang further announces an article offering insight into different brain stimulation techniques and advances in their application.

Wang then introduces the review about human adenovirus in children, and the presentation of characteristic neuroimaging features in pediatric COVID-19 patients.

He finally prepares the reader for an article about the need for advanced hemodynamic assessment in pediatric septic shock, genetic contributing factors to renal hypomagnesemia, the risks of air pollution for infants and children, and anti-siphon devices used to counteract overdraining of cerebrospinal fluid by ventriculoperitoneal shunt [11].

### Reviews

#### Unlucky numbers

Throughout different cultures and centuries, specific numbers were or are associated with various beliefs. In China, Korea, Japan, Taiwan, Vietnam, Singapore and Malaysia for instance the number four is often avoided in elevators, apartment buildings and hospitals as it is considered an unlucky number.<sup>12,13</sup> The reason is that the pronunciation of four in the

<sup>5</sup> <https://www.acc.org/latest-in-cardiology/articles/2020/01/02/10/33/expert-opinion-crazy-for-ketones>, last access 02/23/2022.

<sup>6</sup> <https://archive.archaeology.org/0811/abstracts/gladiator.html>, last access 02/23/2022.

<sup>7</sup> <https://timeline.com/drinking-mans-diet-carbs-82a38400bfff>, last access 02/23/2022.

<sup>8</sup> <https://www.health.harvard.edu/staying-healthy/should-you-try-the-keto-diet>, last access 02/23/2022.

<sup>9</sup> <https://designershitdocumentary.com/>, last access 02/26/2022.

<sup>10</sup> <https://www.washingtonpost.com/news/speaking-of-science/wp/2015/01/29/you-can-earn-13000-a-year-selling-your-poop/>, last access 02/26/2022.

<sup>11</sup> <https://www.openbiome.org/about>, last access 02/26/2022.

<sup>12</sup> <https://people.howstuffworks.com/number-4-unlucky.htm>, last access 03/08/2022.

<sup>13</sup> [https://www.jidanni.org/geo/house\\_numbering/four.html](https://www.jidanni.org/geo/house_numbering/four.html), last access 02/28/2022.

respective languages is close or identical to the word for death.<sup>14</sup>

Triskaidekaphobia, the fear of the number 13, could be considered as analogue in Western countries. The origins however are not entirely clear. It is suggested that the negative perception of the number 13 is associated with the Last Supper, the final meal Jesus is said to have shared with his 12 apostles before his crucifixion.<sup>15,16</sup> The myth surrounding 13 as an unlucky number has been picked up later in other stories. In the original version of “Sleeping Beauty” by the Brothers Grimm, the king invites only 12 and not all 13 fairies of the kingdom to the celebration party for the newborn princess. As the 13th fairy unexpectedly shows up, tragedy entails with her cursing the princess to fall asleep for 100 years later on in her life.<sup>17</sup>

Neglected tropical diseases (NTDs) are found across several African, Asian and Latin American countries and are especially common in tropical areas where access to clean water and organized disposal of human waste is limited or not given.<sup>18</sup> Feasey categorizes 13 core NTDs that have been neglected, initially due to general disregard of the developing world and more recently due to the focus on other diseases like HIV/AIDS, tuberculosis and malaria. One of the 13 core NTDs is Leishmaniasis [12].

Chaves et al. present a review on extracellular signaling mediated by purine nucleotides and nucleosides that aids in the survival of *Leishmania*. In summary, the team highlights understanding the purinergic signaling in *Leishmania* infection as crucial in order to tackle the pathogen's resistance to control pathways of the host [13].

#### *Modified endocrine hormones against cancer*

Peptide therapy receives increased attention in pharmaceutical research and development. In general, peptides have a pharmacologically attractive profile due to their high selectivity, efficacy, and lower production complexity than protein-based pharmaceuticals. At the same time they can be applied safely and are well-tolerated. However, the low-hanging fruits of obvious peptide targets have been picked and research has moved to explore new routes beyond traditional peptide design. Also, intrinsic weaknesses like poor chemical and physical stability of peptides and furthermore short circulating plasma half-life need to be addressed [14].

In 2018, the global peptide therapeutics market was valued at 25 billion USD and is expected to expand further. Key drivers include the surge in prevalence and incidence of chronic diseases caused by a sedentary lifestyle and unhealthy diet, an increasingly geriatric population prone to cardiovascular diseases, and most importantly the global rise in prevalence of cancer. The peptide therapeutics market is

highly competitive, and progressively more complex syntheses are a major challenge.<sup>19</sup>

In targeted cancer therapy the most common drug conjugates are antibody–drug conjugates. However, as they have limitations due to their size and complexity especially in solid tumors, peptide–drug conjugates offer a number of benefits with peptides functioning as tumor targeting carriers [15].

Xu et al. review the members of the natriuretic peptide (NP) family, their anti-cancer mechanisms and corresponding receptors. The team summarizes *in vivo* and *in vitro* results about the therapeutic application of NPs in cancer respectively cancerous cells, and the undertaken effort to improve peptide stability for therapy through fusion with a backbone protein [16].

#### *Allies in personalized cancer medicine*

Companion diagnostics (CDx) describe the co-development of a drug with a diagnostic in order to create a personalized therapeutic approach. However, the process presents its own challenges for product developers, regulators, payers and clinicians. The three key factors providing an economic value for CDx developers are the therapeutic effect, predictive biomarker prevalence and the clinical performance of the CDx [17]. At the same time setting standards on an international level is essential to ensure reproducibility and sensitivity of specific analytical assays and *in vitro* CDx device technologies [18].

Braig criticizes the lack of CDx in personalized cancer therapy. He sees an increase in understanding molecular targets but a slack in the concurrent drug development. According to Braig, the procedures necessary for timely and accurate diagnostics as well as monitoring of treatment responses are either flawed or challenging to perform. He hence proposes the use of liquid biopsy of circulating tumor cells, cell-free DNA or extracellular vesicles (EV). Braig especially advocates use of the latter as cutting edge since the cargo of EVs is highly specific and enables access to multidimensional data. Furthermore, diagnostic uses of EVs are far reaching and applicable to any cancer subtypes. With the information received from EVs, it might even be possible to predict the individual therapeutic response to various chemotherapies. Standard protocols however would need to be established [19].

#### **Original articles**

##### *An update on human adenovirus infections*

Human adenovirus (HAdV) infections can cause many symptoms and illnesses related to the respiratory tract, gastrointestinal tract, bladder, eye, and nervous system. It can affect anyone, and is especially common in those with a weakened immune system as well as babies and young children.<sup>20,21</sup> Shieh reviews the basic virology and epidemiology of HAdVs

<sup>14</sup> <https://www.acclaro.com/blog/tetraphobia-and-doing-business-in-asia/>, last access 02/28/2022.

<sup>15</sup> <https://www.straightdope.com/21341845/why-is-the-number-13-considered-unlucky>, last access 02/28/2022.

<sup>16</sup> <https://www.daytranslations.com/blog/meaning-numbers-world/>, last access 02/28/2022.

<sup>17</sup> <https://www.waltdisney.org/blog/grimm-sleeping-beauty>, last access 03/01/2022.

<sup>18</sup> <https://www.cdc.gov/globalhealth/ntd/diseases/index.html>, last access 03/01/2022.

<sup>19</sup> <https://www.transparencymarketresearch.com/peptide-therapeutics-market.html>, last access 02/27/2022.

<sup>20</sup> <https://www.hopkinsallchildrens.org/Patients-Families/Health-Library/HealthDocNew/A-to-Z-Adenovirus>, last access 03/04/2022.

<sup>21</sup> <https://www.cdc.gov/adenovirus/about/symptoms.html>, last access 03/04/2022.

with a focus on the clinic–pathologic correlation in pediatric population [20].

#### Neuroimaging in COVID-19

In 2013, scientists of the Erwin Hahn Institute for Magnetic Resonance Imaging performed a study to explore recent trends in robotic assisted living. The team acquired MRI images from participants that were being shown different videos. One video set displayed an either friendly or torturing interaction between a human and his robotic pet dinosaur. Another video set exhibited a friendly gesture or interaction of torture between two humans. Participants' brain activation showed no difference when comparing the response to human–human and human–robot interaction videos, suggesting that participants were showing empathy towards the lifeless animatron [21].<sup>22</sup>

Children with COVID-19 are mostly asymptomatic or mildly symptomatic. They are hence less frequently tested. However, cases of severe post-infectious multisystem inflammatory syndrome have been described in children as well as rarely neurologic complications [22]. Neurologic manifestations of SARS-CoV-2 infection include encephalopathy, encephalitis, meningitis, ischemic and hemorrhagic stroke [23].

Wong and colleagues provide a description of the characteristic magnetic resonance neuroimaging features of these neurological diseases in children and their differentiations from other imaging mimics [24].

#### Advanced hemodynamics in septic shock

Sepsis and septic shock are considered to be leading causes of in-hospital mortality in children and adults alike. As every hour of delayed treatment increases mortality, using risk models for early prediction of sepsis facilitates a better outcome [25]. On account of key differences on the whole-organism level, organ-system level, distribution of body fluids as well as differences in cardiovascular and respiratory function, pediatric sepsis can be considered as a related but separate entity from adult sepsis [26].

Early goal-directed therapy (EGDT) used for severe sepsis and septic shock had been introduced in 2001 as an alternative to standard therapy. EGDT involves adjustments of cardiac preload, afterload and contractility to balance oxygen delivery with oxygen demand [27].

From Lee and team's point of view, EGDT has lost its advantage. For better therapeutic guidance in pediatric septic shock the researchers deem it necessary to include advanced hemodynamics such as cardiac output and systemic vascular resistance into the assessment. They hence propose a modified EGTD algorithm in their paper [28].

#### Devil of a fellow

The German anatomist and pathologist Friedrich Henle was considered an extraordinarily progressive and charismatic man. His discoveries in the 19th century led to a number of anatomical structures to be named after him. He established microbial anatomy into the curriculum of medical students, inspired his student Robert Koch to provide proof for Henle's

belief in microbes, and Henle's explanation of metastasis in cancer became a forerunner of Virchow's cellular pathology. Henle published several works, drastically advancing the contemporary knowledge on the structure of the human body. He was known for witty conversations, a sociable lifestyle and his musical talent. Against conventions of the time, Henle married a former maid, which gave rise to various authors writing books and plays about the relationship without the couple's consent. In 2004, letters between the couple have been published under the title “My dear, nasty darling”, portraying an unparalleled love story against all odds.<sup>23,24</sup>

The cause of hypomagnesemia may lie in the kidneys when filtration is increased and reabsorption is impaired in the loop of Henle. Hypomagnesemia may also have an extra-renal source. Magnesium ( $Mg^{2+}$ ) acts as a major player in numerous processes maintaining cell function and a lack thereof affects multiple organs. A multitude of genes have been identified to be involved in  $Mg^{2+}$  transport in renal tubules. Tseng et al. examined the role of genetic defects in renal hypomagnesemia in order to predict clinical outcome and to uncover underlying mechanisms [29].

#### Every breath you take

According to a WHO study in 2018, around 93% of children worldwide breathe heavily polluted air. Children absorb more pollutants than adults due to their respiratory rate, are closer to the ground where some pollutants reach peak concentrations and are at a period in their lives, where their brains are still in development. Poisoning through air pollution hence potentially impacts neurodevelopment and cognitive ability, triggers asthma or childhood cancer and might in the long run contribute to cardiovascular disease manifesting later in life.<sup>25</sup> It was found that outdoor and indoor air pollution led to a loss of the forced vital capacity in children. Furthermore, it is estimated that this young generation with compromised lung health before adulthood may experience an additional burden in terms of individual health. Additional load might be put on national social security as those children have an increased predisposition for pulmonary and extrapulmonary diseases at a later age [30].

Wu et al. performed a review of the currently major air pollutants in Taiwan and the impact on pediatric respiratory health. The team's goal thereby is to support policy makers in developing public health guidelines to control and prevent pollution [31].

#### To drain but not to overdrain

The symptomatic accumulation of cerebrospinal fluid (CSF) may be due to obstruction in the normal flow of CSF, excessive production of the fluid or decreased absorption into the venous system. Surgical treatment of hydrocephalus with a ventricular shunt placement is the first treatment option [32].

<sup>23</sup> <https://www.ub.uni-heidelberg.de/Englisch/helios/digi/anatomie/henle.html>, last access 02/22/2022.

<sup>24</sup> <http://www.mrcophth.com/ophthalmologyhalloffame/henle.html>, last access 02/22/2022.

<sup>25</sup> <https://www.who.int/news/item/29-10-2018-more-than-90-of-the-worlds-children-breathe-toxic-air-every-day>, last access 02/27/2022.

<sup>22</sup> [https://hahn-institute.de/uploads/images/annrep/hahn\\_institute\\_annual\\_report\\_2012\\_web.pdf](https://hahn-institute.de/uploads/images/annrep/hahn_institute_annual_report_2012_web.pdf), last access 02/23/2022.

A ventriculoperitoneal shunt drains excess CSF into the peritoneal cavity through a catheter. The differences between shunts depend on the type of valve used and whether the valve is programmable or not [33]. The surgery is associated with a number of potential complications like malfunctioning of the catheter due to obstruction [34]. Shunt overdrainage is another well-known complication and the pathophysiology is progressively multifactorial, requiring shunt optimization [35].

In their article Huang et al. describe the basics of siphoning which leads to overdrainage of CSF and discuss the clinical efficacy of three kinds of antisiphon devices and according patient outcome [36].

#### *Energy needs and rhythmic patterns*

Biological systems tend to be intrinsically rhythmic rather than in a steady state. The time scale observed in biological processes ranges from milliseconds to months, for instance when it comes to neuronal firing, heartbeat, breathing, reproduction etc. Circadian rhythms with a period of approximately 24 h are crucial for normal energy metabolism in most living animals [37]. Energetic cycles are optimized with light–dark cycles and molecular clocks organize the daily switch between periods of feeding and fasting, energy storage and utilization [38]. A circadian rhythm manifests at different levels in an organism and is controlled by the central circadian clock in the suprachiasmatic nucleus (SCN) [37]. Feeding/fasting cycles are the main cues (Zeitgeber) for synchronization of peripheral clocks [39]. External disruption of the circadian clock network influences metabolism. At the same time, altered feeding behavior and metabolism affect the clock [38].

Lin et al. set out to investigate the relationship between  $\text{Na}^+/\text{K}^+$  ATPase (NKA) and energy metabolism in the SCN, as  $\text{Na}^+$  pumping by NKA is considered the most important energy consumer. By using microelectrodes to measure the extracellular pH in hypothalamic slices, the team found that the glycolytic metabolism and activation of the glycolysis-fueled NKA pumping activity adds to the standing acidification in the SCN. Furthermore, results show that the mitochondria-associated oxidative glycolytic pathways are sensitive to glucose shortage, and play a role in metabolic regulation of the circadian clock. In contrast, the non-oxidative glycolytic pathways are relatively insensitive to glucose shortage, maintaining  $\text{Na}^+$  pumping activity [40].

#### *Deep learning in pediatric intensive care*

Park et al. developed a deep-learning-based pediatric early warning system (pDEWS) using five vital sign parameters. The team tested the system in a retrospective study, using pDEWS for early prediction of cardiopulmonary arrest and unexpected transfers to pediatric intensive care 24 h before an event. The model of Park et al. proved to be superior in performance in comparison to existing methods [41].

#### *Thank You For Smoking*

In “Thank You For Smoking”, a satirical black comedy from 2005, the plot follows a lobbyist of the tobacco industry who denies any link between tobacco consumption and lung disease. Meeting regularly with his friends, a firearm lobbyist and

an alcohol lobbyist, they jokingly call themselves the “Merchants of Death”. The movie does not lack in grotesque scenes that are outdoing each other: In a TV show the spokesman does not shy away from using a teenager that is bald from chemotherapy for his own purposes. The lobbyist makes the observation that the tobacco industry is more interested in keeping the boy alive and smoking instead of killing him. The lobbyist then further bribes the former famous icon of the tobacco industry, the now retired and cancer-struck Marlboro Man, to not campaign against cigarettes. Finally, the spokesmen coldly dismisses a little girl whose mother told her that cigarettes kill, by declaring her mother as incompetent as she is not a doctor [42].<sup>26</sup>

Albeit a complex and polygenic disease, smoking is known as the most important risk factor for lung cancer. Yin et al. set out to study the role of five haplotype-tagging single nucleotide polymorphisms (htSNPs) of the tumor suppressor protein TP53 in lung cancer [43]. TP53 has been characterized as a frequently mutated gene in human cancers [44]. The research team furthermore looked at the association between smoking-duration and haplotypes, and found a potentially genetic predisposing factor for long-term smoking [43].

#### *Fertile grounds*

Fertility tourism as a form of medical tourism describes the phenomenon of patients seeking reproductive treatment in another country as to circumvent laws, access restriction, or waiting lists in their home country [45]. Procedure cost followed by anonymity and procedure success were main drivers in the choice of assisted reproductive technology, although priorities vary depending on the age group.<sup>27</sup> Sought after procedures include *in vitro* fertilization (IVF), artificial insemination by a donor and surrogacy. The outcome however varies strongly by region [46].

Necessary steps during IVF might have adverse effects on the outcome of the procedure. Elevated estradiol (E2) concentrations are a consequence of controlled ovarian stimulation in IVF. Studies suggest that high E2 might indirectly impact blastocysts during implantation or directly affects the endometrium in an unfavorable way. Chang et al. performed a study to clarify the influence of high E2 levels on blastocysts *in vitro* and on embryo implantation in mice. In both set-ups exposure to high E2 concentrations proved to be harmful for blastocyst implantation and implantation development [47].

#### *Embryo quality*

Extended *in vitro* culture of human embryos until day 5/6 instead of until day 3 has been shown to increase the degree of embryo selection, thus optimizing the choice of best quality embryos for transfer. This potentially reduces the need to transfer a greater numbers of embryos for increased pregnancy rates and additionally reduces the risk for multiple implantation. However, blastocyst formation itself does not fully reflect the viability of the embryo and not all blastocysts are of equal quality [48].

<sup>26</sup> <https://blogs.longwood.edu/politicsandfilm/satirical/thank-you-for-smoking/>, last access 02/23/2022.

<sup>27</sup> <https://www.fertilityclinicsabroad.com/ivf-clinics-abroad/fts-2020/>, last access 02/27/2022.

In autologous IVF, the presence of only morphologically poor embryos (MPEs) on day 3 is common in patients who are poor responders or of advanced maternal age. Lin et al. performed a retrospective study to investigate whether extended culture of MPEs on day 3 in fresh transfer cycles would increase the live birth rate (LBR), as treatment strategies for that patient group are limited. This was not the case. However, as confirmed in previous studies, extended culture followed by frozen embryo transfer led to significantly higher LBR, thus potentially improving outcome in patients with poor embryo quality [49].

#### French gangsters and antibiotics

Following the article by Chen et al., a second article in this journal issue provides an insight into *C. difficile* infection (CDI).

In a retrospective study, Tijerina-Rodríguez and her team assessed the risk factors connected to the development of severe-complicated and recurrent outcomes in CDI patients in a Mexican hospital. The team confirms age to be a factor that increases vulnerability to severe CDI. Furthermore, Tijerina-Rodríguez et al. report rifampin and colistin as independent risk factors for recurrent CDI [50].

Anecdotally, the research group that discovered rifamycins – later marketed in the form of a more stable product labeled rifampicin – named the compounds after the beloved French film noir “Rififi”, a crime story from 1955 involving a jewel heist [51].

#### A beautiful smile

Class II malocclusion has a significant incidence in the population and may compromise esthetics and smile as well as masticatory and respiratory functions [52]. It is often characterized by a deficient mandible and both environmental and genetic factors interacting have been associated with this type of malocclusion [53]. As mandibular deficiency is more common among Caucasians than Africans or Asians, it is suggested that a hereditary component is a predominant part of the etiology.<sup>28</sup>

Ruslin et al. present their evaluation of the stability on dental and skeletal aspect after surgery for the correction of mandibular deficiency with high mandibular plane angle. Clinical and radiological data were recorded and cephalometric changes were compared. The results of counterclockwise surgical advancement of the mandible to correct mandibular deficiency proved an overall acceptable stability during the one-year follow-up of the study [54].

#### Letter

##### Interventional and observational studies in COVID-19

Castillo-Aleman et al. raise concerns about a review by Verma et al. [55], in which data from 60 clinical trials related to COVID-19 had been extracted. In their letter, Castillo-Aleman and team question the inclusion of observational studies, since those are not deemed to belong to the category of clinical

trials according to the WHO. The researchers additionally suggest that a larger number of databases should have been included in the review [56].

In a follow-up letter in this issue of Biomedical Journal, Verma et al. reply, and state that upon writing the review they did not yet have a clear idea about the drug target for treatment of COVID-19. They hence included both – interventional and observational – studies in their review to acquire a greater insight. Verma et al. moreover mention that the database results they chose were picked from three clinical trial platforms they consider most extensive [57].

#### Conflicts of interest

The author declares no conflicts of interest.

#### REFERENCES

- [1] Baloyannis SJ. Epilepsy: a way from herodotus to hippocrates. *Epilepsy Behav* 2013;28:303–32.
- [2] Yoo JY, Panov F. Identification and treatment of drug-resistant epilepsy. *Continuum (Minneapolis Minn)* 2019;25:362–80.
- [3] Foutz T, Wong M. Brain stimulation treatments in epilepsy: basic mechanisms and clinical advances. *Biomed J* 2022;45:27–37.
- [4] Holmes M, Flaminio Z, Vardhan M, Xu F, Li X, Devinsky O, et al. Cross talk between drug-resistant epilepsy and the gut microbiome. *Epilepsia* 2020;61:2619–28.
- [5] Wheless JW. History of the ketogenic diet. *Epilepsia* 2008;49 Suppl 8:3–5.
- [6] Ko A, Kwon HE, Kim HD. Updates on the ketogenic diet therapy for pediatric epilepsy. *Biomed J* 2022;45:19–26.
- [7] Wang JW, Kuo CH, Kuo FC, Wang YK, Hsu WH, Yu FJ, et al. Fecal microbiota transplantation: review and update. *J Formos Med Assoc* 2019;118 Suppl 1:S23–31.
- [8] Vendrik KEW, Ooijselaar RE, de Jong PRC, Laman JD, van Oosten BW, van Hilten JJ, et al. Fecal microbiota transplantation in neurological disorders. *Front Cell Infect Microbiol* 2020;10:98.
- [9] Heinlen L, Ballard JD. Clostridium difficile infection. *Am J Med Sci* 2010;340:247–52.
- [10] Chen CC, Chiu CH. Current and future applications of fecal microbiota transplantation for children. *Biomed J* 2022;45:11–8.
- [11] Wang HS. Updates in Pediatrics. *Biomed J* 2022;45:9–10.
- [12] Feasey N, Wansbrough-Jones M, Mabey DC, Solomon AW. Neglected tropical diseases. *Br Med Bull* 2010;93:179–200.
- [13] Chaves M, Savio LE, Coutinho-Silva R. Purinergic signaling: a new front-line determinant of resistance and susceptibility in leishmaniasis. *Biomed J* 2022;45:109–17.
- [14] Fosgerau K, Hoffmann T. Peptide therapeutics: current status and future directions. *Drug Discov Today* 2015;20:122–8.
- [15] Lindberg J, Nilvebrant J, Nygren PÅ, Lehmann F. Progress and future directions with peptide-drug conjugates for targeted cancer therapy. *Molecules* 2021;26:6042.
- [16] Xu M, Liu X, Li P, Yang Y, Zhang W, Zhao S, et al. Modified natriuretic peptides and their potential role in cancer treatment. *Biomed J* 2022;45:118–31.
- [17] Trusheim MR, Burgess B, Hu SX, Long T, Averbuch SD, Flynn AA, et al. Quantifying factors for the success of stratified medicine. *Nat Rev Drug Discov* 2011;10:817–33.
- [18] Valla V, Alzabin S, Koukoura A, Lewis A, Nielsen AA, Vassiliadis E. Companion diagnostics: state of the art and

<sup>28</sup> <https://pocketdentistry.com/19-primary-mandibular-deficiency-growth-patterns-with-or-without-maxillary-arch-constriction/>, last access 03/05/2022.

- new regulations. *Biomark Insights* 2021;16:11772719211047763.
- [19] Braig Z. Personalized medicine: from diagnostic to adaptive. *Biomed J* 2022;45:132–42.
- [20] Shieh WJ. Human adenovirus infections in pediatric population - an update on clinico-pathologic correlation. *Biomed J* 2022;45:38–49.
- [21] Rosenthal-von der Pütten AM, Krämer NC, Hoffmann L, Sobieraj S, Eimler SC. An experimental study on emotional reactions towards a robot. *Int J Soc Robot* 2013;5:17–34.
- [22] Nikolopoulou GB, Maltezou HC. COVID-19 in children: where do we stand? *Arch Med Res* 2022;53:1–8.
- [23] Korálnik IJ, Tyler KL. COVID-19: a global threat to the nervous system. *Ann Neurol* 2020;88:1–11.
- [24] Wong AM, Toh CH. Spectrum of neuroimaging mimics in children with COVID-19 infection. *Biomed J* 2022;45:50–62.
- [25] Liu R, Greenstein JL, Fackler JC, Bergmann J, Bembea MM, Winslow RL. Prediction of impending septic shock in children with sepsis. *Crit Care Explor* 2021;3:e0442.
- [26] Sawyer JR. Children are not small adults. *Am J Orthop* 2014;43:19–20.
- [27] Rivers E, Nguyen B, Havstad S, Ressler J, Muzzin A, Knoblich B, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med* 2001;345:1368–77.
- [28] Lee EP, Wu HP, Chan OW, Lin JJ, Hsia SH. Hemodynamic monitoring and management of pediatric septic shock. *Biomed J* 2022;45:63–73.
- [29] Tseng MH, Konrad M, Ding JJ, Lin SH. Clinical and genetic approach to renal hypomagnesemia. *Biomed J* 2022;45:74–87.
- [30] Wang T, Wang H, Chen J, Wang J, Ren D, Hu W, et al. Association between air pollution and lung development in schoolchildren in China. *J Epidemiol Community Health* 2020;74:792–8.
- [31] Wu IP, Liao SL, Lai SH, Wong KS. The respiratory impacts of air pollution in children: global and domestic (Taiwan) situation. *Biomed J* 2022;45:88–94.
- [32] Yousaf J, Parlato SR, Mallucci CL. Hydrocephalus. In: *Losty P, Flake A, Rintala R, Hutson J, Iwai N, editors. Rickhams Neonatal Surg*. London: Springer; 2018. p. 931–56.
- [33] Hauk L. Ventriculoperitoneal shunt. *AORN J* 2018;107:P10–2.
- [34] Pillai S. Techniques and nuances in ventriculoperitoneal shunt surgery. *Neurol India* 2021;69:S457–61.
- [35] Ros B, Iglesias S, Linares J, Cerro L, Casado J, Arráez MA. Shunt overdrainage: reappraisal of the syndrome and proposal for an integrative model. *J Clin Med* 2021;10:3620.
- [36] Huang AP, Kuo LT, Lai DM, Yang SH, Kuo MF. Antisiphon device: a review of existing mechanisms and clinical applications to prevent overdrainage in shunted hydrocephalic patients. *Biomed J* 2022;45:95–108.
- [37] Ding G, Gong Y, Eckel-Mahan KL, Sun Z. Central circadian clock regulates energy metabolism. *Adv Exp Med Biol* 2018;1090:79–103.
- [38] Peek CB, Ramsey KM, Marcheva B, Bass J. Nutrient sensing and the circadian clock. *Trends Endocrinol Metab* 2012;23:312–8.
- [39] Kalsbeek A, La Fleur S, Fliers E. Circadian control of glucose metabolism. *Mol Metab* 2014;3:372–83.
- [40] Lin HY, Huang RC. Glycolytic metabolism and activation of Na<sup>+</sup> pumping contribute to extracellular acidification in the central clock of the suprachiasmatic nucleus: differential glucose sensitivity and utilization between oxidative and non-oxidative glycolytic pathways. *Biomed J* 2022;45:143–54.
- [41] Park SJ, Cho KJ, Kwon O, Park H, Lee Y, Shim WH, et al. Development and validation of a deep-learning-based pediatric early warning system: a single-center study. *Biomed J* 2022;45:155–68.
- [42] Yamey G. Tobacco industry satire fails to ignite. *BMJ* 2006;332:920.
- [43] Yin J, Hou W, Vogel U, Li X, Ma Y, Wang C, et al. TP53 common variants and interaction with PPP1R13L and CD3EAP SNPs and lung cancer risk and smoking behavior in a Chinese population. *Biomed J* 2022;45:169–78.
- [44] Donehower LA, Soussi T, Korkut A, Liu Y, Schultz A, Cardenas M, et al. Integrated analysis of TP53 gene and pathway alterations in the cancer genome atlas. *Cell Rep* 2019;28:1370–84. e5. Erratum in: *Cell Rep* 2019;28:3010.
- [45] Bergmann S. Fertility tourism: circumventive routes that enable access to reproductive technologies and substances. *Signs (Chic)* 2011;36:280–8.
- [46] Kushnir VA, Barad DH, Albertini DF, Darmon SK, Gleicher N. Systematic review of worldwide trends in assisted reproductive technology 2004-2013. *Reprod Biol Endocrinol* 2017;15:6.
- [47] Chang KT, Su YT, Tsai YR, Lan KC, Hsuuw YD, Kang HY, et al. High levels estradiol affect blastocyst implantation and post-implantation development directly in mice. *Biomed J* 2022;45:179–89.
- [48] Graham J, Han T, Porter R, Levy M, Stillman R, Tucker MJ. Day 3 morphology is a poor predictor of blastocyst quality in extended culture. *Fertil Steril* 2000;74:495–7.
- [49] Lin PY, Lin CY, Tsai NC, Huang FJ, Chiang HJ, Lin YJ, et al. Disposition of embryos from women who only produced morphologically poor embryos on day three. *Biomed J* 2022;45:190–9.
- [50] Tijerina-Rodríguez L, Garza-González E, Martínez-Meléndez A, Morfín-Otero R, Camacho-Ortiz A, Gonzalez-Diaz E, et al. Clinical characteristics associated with the severity of *Clostridium [Clostridioides] difficile* infection in a tertiary teaching hospital from Mexico. *Biomed J* 2022;45:200–5.
- [51] Aronson J. That's show business. *BMJ* 1999;319:972.
- [52] Rédua RB. Different approaches to the treatment of skeletal class II malocclusion during growth: bionator versus extraoral appliance. *Dental Press J Orthod* 2020;25:69–85.
- [53] Moreno Uribe LM, Howe SC, Kummet C, Vela KC, Dawson DV, Southard TE. Phenotypic diversity in white adults with moderate to severe class II malocclusion. *Am J Orthod Dentofac Orthop* 2014;145:305–16.
- [54] Ruslin M, Hajrah Yusuf AS, Forouzanfar T, Greebe RB, Tuinzing DB, Thamrin SA, et al. One-year stability of the mandibular advancement and counterclockwise rotation for correction of the skeletal class II malocclusion and high mandibular plane angle: dental and skeletal aspect. *Biomed J* 2022;45:206–14.
- [55] Verma HK, Merchant N, Verma MK, Kuru Ci, Singh AN, Ulucan F, et al. Current updates on the European and WHO registered clinical trials of coronavirus disease 2019 (COVID-19). *Biomed J* 2020;43:424–33.
- [56] Castillo-Aleman YM, Ventura-Carmenate Y, Rivero-Jimenez RA. Clinical studies on coronavirus disease 2019 (COVID-19) in the WHO registry network. *Biomed J* 2022;45:215–6.
- [57] Verma HK, Merchant N, Bhaskar LVKS. Reply to the comments on letter to the editor on review article “current updates and treatment strategy of the European and WHO registered clinical trials of coronavirus disease 2019. *Biomed J* 2022;45:217–8.