TWENTIETH EDITION - SEPTEMBER 2021

RAMS

Radboud Annals of Medical Students

BRIEF MESSAGE EDITION

- Psychosis in criminal law
- "The cat is out of the bag: unravelling imposter syndrome"
- The power of plants: a cure for COVID-19
- More than a quirk of the human mind – the fascinating concept of synesthesia

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FROM THE EDITORIAL BOARD

Dear reader,

Whether you have just started your studies or have been studying in Nijmegen for quite some years, the start of the academic year brings a lot of excitement and change. Therefore, thank you for taking the time to read the newest edition of RAMS during this busy part of the year!

RAMS is not spared of change either. By now, the new board members have started their board year. Edition 20 is the last edition that we (the seventh board) have handled together with the new board members. We spent a tremendous amount of energy and effort on RAMS throughout the past year, making it difficult for us to leave RAMS. However, we are confident that RAMS is left in capable hands and that the new board will improve RAMS even further.

We –once again– have a unique edition, containing, amongst others, the brief messages. These are short articles written by our editors, highlighting a topic of their choice. Each brief message is accompanied by an exam question, which you can use to test your knowledge! In addition, we have a submitted article regarding a suspect's juridical accountability during a (supposed) psychosis. This submission marks the first article in RAMS highlighting the crucial interface between law and medicine. The variety of topics will offer a piece of interest for anyone!

I want to thank everyone involved with RAMS for their time and effort during the last year. The editors have delivered articles of high quality, and, as editorial editor-in-chief, it has pleased me to see their steep improvement in writing, reaching the pinnacle with this edition. I could not be prouder; this edition provides the brief messages and the submitted article with the attention they deserve!

Now, it is time to give the floor to the board members of the eighth board. Good luck, and remember to enjoy your time as board members! Before you know it, the board year has ended.

Kind regards,
On behalf of the editorial board 2020/2021,

Yfke Prins
Editorial Editor-in-Chief

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FROM SEPSIS TO A PARALYSED IMMUNE SYSTEM

Kavita Lips[1]

[1]Master's student Medical Biology, Radboud university, Nijmegen, the Netherlands

Brief message

Hi everyone! I am Kavita, and I am currently pursuing my master's in Medical Biology. The past academic year, I got the pleasure to be part of RAMS as the chair of the editorial board. Working with an enthusiastic and motivated team of editors, with different interests, was truly amazing. During my bachelor's, I followed several courses regarding the immune system and cancer. Whereas my main topic of interest is mostly cancer, I thought of exploring another part of immunology when writing this brief message. This is when I decided to write about another fascinating topic, namely sepsis and its role in immunoparalysis.

According to the World Health Organization, 49 million people are affected by sepsis yearly, leading to 11 million deaths each year [1]. In short, sepsis can be described as a life-threatening organ dysfunction due to a dysregulation in the host immune response caused by an infection [2]. This dysfunction is characterised by the presence of a pro- and anti-inflammatory cytokine storm [2]. Nowadays, due to the advances in medical healthcare, a major part of septic patients can survive this disease. Remarkably, the cytokine storm, which can be seen as an over-activation of the immune system, can also result in a long-term immune dysfunction called immunoparalysis [2,5,9]. These immunoparalysed patients have an increased susceptibility to secondary infections and viral reactivation, resulting in an attenuated five-year survival compared to individuals who never had sepsis [3,4]. But how does immunoparalysis occur, and what is its long-term effect on sepsis treatment?

During the septic stage, an unstable shift in specific immune cell subsets' representation and function occurs, contributing to the ongoing septic response and the later immunodeficiency [5]. The proposed mechanism of immunoparalysis is the apoptosis of B-lymphocytes, CD4 T-lymphocytes, and follicular dendritic cells in septic patients, resulting in decreased numbers of circulating lymphocytes and dendritic cells [5]. Furthermore, the presence of apoptotic lymphocytes increases the production of anti-inflammatory cytokines and impairs the release of pro-inflammatory cytokines [5,6]. Lastly, these apoptotic cells can also increase the tolerance of lymphocytes to pathogens [5]. Overall, the combination of these pathways lead to the induction of paralysis of the immune system.

Now we know how immunoparalysis occurs, it is also essential to look at the implications of these findings for long-term treatment of sepsis. New insights have led to the emergence and possible implementation of a new, promising treatment option for sepsis, known as personalised healthcare. In order to make this treatment possible, patients are endotyped, which means that you divide the patient into various subgroups based on specific differences such as gender, age, genetics, and environment [7].

Personalised approaches can be applied when a patient is admitted to the hospital. During this treatment stage, they can be subjected to supportive therapies and samples are taken for laboratory analyses [8]. With some of these relatively simple methods like clinical scales, mediator concentrations, or the activation of immune cells, you can stratify the patient in a specific category [8]. Hereafter, a threshold is

applied to decide if a patient is a suitable candidate for a particular therapy. This approach is already used in some clinical trials and for some measurable biological characteristics, known as biomarkers, feasible at the bedside [7,8]. For sepsis, some biomarkers are already established, including measuring the number of cytokines produced by leukocytes [7].

Application of suitable biomarkers for patients will aid in a personalised treatment, as the biomarker gives you a better understanding of the patient's immune status. Although sepsis is now easier to treat than before with the medical advances, it concerns critically ill patients, and the mortality remains high. Therefore, the application of a personalised treatment approach is a promising option to decrease the vast number of deaths related to sepsis and its later consequences, including immunoparalysis.

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EXAM QUESTION

Question 1

Practise your knowledge regarding the topic of this brief message. Do you know the answer?

What could be a treatment strategy for patients with a decreased function of the immune system during sepsis?

A. Blocking TNF-alpha
B. Vaccination with BCG
C. Block PD1-PD1L interaction
D. Stem Cell Transplantation

The answer to this question can be found on page 33 in this journal.

HAPPY VALENTINE'S DAY OR A BROKEN HEART?

Anne Valk[1]

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Brief message

One year ago, I finished my bachelor's Biomedical Sciences, after which I took a gap year. The main goal of this gap year was to investigate what I really enjoy doing, and this included scientific writing. During my bachelor's, I mainly focussed on topics related to cancer and the immune system. As a scientific editor at RAMS, I wanted to broaden my view, and I decided to write about a variety of topics. I started writing my brief message just before Valentine's Day. To be honest, Valentine's day has never been a really important celebration day for me. While making jokes with friends about how sad it is to be single on Valentine's day, I realised that for people with a broken heart this might actually really be a bit of a painful day. Out of curiosity I started googling, and the idea for my brief message was born: the broken heart syndrome.

The 14th of February. The restaurants are fully booked for romantic candle light dinners, loving couples give each other sweet presents, and some daredevils even send roses to someone they have a secret crush on. Valentine's day: a day to celebrate love and romance. At least, for some of us. For others it is the perfect day to stay inside under a blanket with a big tub of Ben & Jerry's ice cream. Maybe those people just do not like Valentine's day, they do not have a partner to celebrate it with, or worse… they have a broken heart.

The broken heart syndrome, or Takotsubo syndrome, is an acute and reversible cardiomyopathy that was first described by Hikaru Sato in 1990 [1]. In the past decades, it has been increasingly reported, and interest in this syndrome has gained among cardiologists [2]. The broken heart syndrome is characterised by left ventricular dysfunction, and the most common symptoms are chest pain, dyspnoea, and/or dizziness [3]. As the syndrome was discovered quite recently, various diagnostic criteria have been suggested, of which the Heart Failure Association diagnostic criteria are the most commonly used [2,3]. Those criteria include transient abnormal movement of the ventricle's wall and newly emerged electrocardiogram abnormalities, but absence of or only minor coronary artery disease [2].

You might already have noticed that the broken heart syndrome shows quite some overlap with acute myocarditis, such as its clinical presentation with chest pain and dyspnoea. However, the broken heart syndrome should be recognised as a unique type of heart failure. First of all, there are differences in cardiac biomarkers such as troponin, C-reactive protein, and serum natriuretic peptide [2]. The troponin peak, for example, is generally higher in acute myocarditis than in the broken heart syndrome [2]. In addition, electrocardiography, echocardiography, and magnetic resonance imaging show differences between both syndromes [2].

A difference that might be even more striking is that the broken heart syndrome is more common in women (90%), and that it is generally preceded by a stressful event [4]. In a cohort of 1750 patients, it was shown that the broken heart syndrome followed an emotional or physical trigger in 71.5% of the cases [4]. Examples of emotional triggers, observed in 27.7% of the cases, included violence, serious financial problems, but also… losing a loved one [3,4].

Luckily, there is also some good news. In case you were heartbroken this Valentine's day, do not lose hope for next year. A broken heart, just as a broken heart syndrome, is reversible and has a relatively good prognosis [5].

Do you want to know more about the differences between broken heart syndrome and myocardial infarction? Have a look at the Zebras of Medicine from the 11th edition of RAMS (2018).

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EXAM QUESTION

Question 2

Do you want to test your cardiology knowledge? Then, try to answer the exam question!

In rehabilitation programs, *e.g.* cardiac rehabilitation for patients who have had a myocardial infarction, promoting a healthy lifestyle is an essential element. These programs are an example of...

A. primary prevention
B. secondary prevention
C. tertiary prevention

The answer to this question can be found on page 33 in this journal.

ARE TROPICAL MOSQUITOES BREEDING IN YOUR BACKYARD?

Efi Tsouri[1]

[1]MSc Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, The Netherlands

Brief message

Hi everyone! My name is Efi Tsouri, and I have just graduated from the Molecular Mechanisms of Disease Master's program at Radboud University. I joined RAMS in October 2020 as an editorial editor, and I have truly enjoyed being part of this diverse team. Through RAMS, I got to develop my writing skills and learn about many interesting topics. One of the topics that captured my attention was arboviral diseases, *i.e.* diseases that are transmitted through infected insects. Living during the Corona pandemic, we can all appreciate the devastating effects of infectious diseases, so I wanted to draw attention into these viruses as well. In my article, I focus on arboviral transmission through mosquitoes, which have found their way to the Netherlands.

In October of 2020, the first Dutch patient was infected with the West Nile virus (WNV) in Utrecht [1]. Subsequently, five additional cases of WNV infection were reported in the Netherlands [1]. What did these patients have in common? They were all previously stung by WNV-carrying tropical mosquitoes. Such mosquitoes are not commonly found in the Netherlands, raising concerns about the spread of tropical diseases in Europe.

WNV belongs to the arboviruses (arbo: arthropod-borne), a group of RNA-viruses that can infect vertebrate hosts [2]. But what is so special about them? As their name indicates, arboviruses are transmitted through blood-sucking arthropods; the most important of them all: mosquitoes (Figure 1) [2]. Not all mosquito species can be infected with and transmit arboviruses; three species, *Anopheles, Aedes,* and *Culex,* are responsible for the transmission of most arboviruses [2]. These so-called tropical mosquitoes originate from tropical regions in Asia, Africa, and America [3]. However, due to different factors, such mosquito species have spread to Europe as well. In general, viral genetic variability, natural adaptation to various mosquito species, and climate change are the most important driving forces behind the emergence of arboviruses in Europe [3].

Arthropod-human and human-human transmission are vital in the spread of arboviral diseases (Figure 1). It is estimated that 17% of the infectious diseases caused worldwide are a consequence of arboviruses, causing almost 700,000 deaths globally per year [5]. Arboviral infections are associated with different symptoms, ranging from mild to life-threatening. For example, WNV is characterised by flu-like symptoms such as fever, headache, and back pain [6]. However, more severe symptoms can develop too after infection with the virus, including rashes, myocarditis, hepatitis, and even encephalitis. Therefore, the severity and global spread of such viruses underline the need for more effective strategies to limit arboviral infections.

Several methods to control arboviruses already exist. Similar to most infectious diseases, researchers have focused on developing vaccines and antiviral drugs [6]. However, a controversial but theoretically more effective method to limit the spread of such diseases is vector control [7]. Vector control, instead of focusing on the virus itself, targets the vectors, i.e. the mosquitoes. In this way, the transmission of arboviruses to humans can be prevented. An example of this

strategy is gene drive, which can be used to introduce new genetic traits in mosquitoes [7]. Mosquito fertility genes can be silenced using the CRISPR-Cas9 system, whereby female mosquito populations can be suppressed. Alternatively, gene constructs providing resistance to arboviral infections or transmission can be introduced to mosquitoes' genome. Over time, these modified mosquitoes can replace the pathogenic mosquito populations and ultimately control arboviral spread. Yet, the feasibility and ecological impact of such methods remain to be evaluated. New strategies, similar to the ones described, are continuously being developed.

In conclusion, arboviral infections represent an emerging public health problem worldwide that should be addressed urgently in the

Figure 1: Schematic representation of arboviral transmission cycle.

following years. So next time you take a stroll through your backyard, and you spot a mosquito, you will know to duck for cover.

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EXAM QUESTION

Question 3

Do you want to practise your knowledge of this brief message's topic? Then, let's see if you can answer the following exam question.

How is the transmission of diseases from bats, monkeys, and antelopes to humans called?

A. Vector-borne transmission
B. Vertical transmission
C. Zoonotic transmission

The answer to this question can be found on page 33 in this journal.

"THE CAT IS OUT OF THE BAG: UNRAVELLING IMPOSTOR SYNDROME"

Harshitha Ramu[1]

[1]Master's student Molecular Mechanisms of Disease, Radboud university medical center, Nijmegen, The Netherlands

Brief message

I am Harshitha, a Master's student at Radboud University studying Molecular Mechanisms of Disease. I wrote about imposter syndrome because I suffer from it, and I wanted to make other people who were possibly feeling the same way feel recognised and not alone. I truly believe that everyone deserves a chance to celebrate both their mistakes and successes that occur during the pursuit of their professional goals without feeling doubtful or fearful of their earned merit!

Have you ever felt like the perfect score you got on your recent test was because you had sheer good luck? Or that sometimes you find yourself wallowing in misery because your experiments did not work, and you feel like you are not meant to be a scientist?

Although you may seldomly feel fully confident and feel like you truly belong in your professional landscape, psychologists have described what you feel as a common experience amongst many people [1]. They call it the "Impostor Syndrome", a roller-coaster of an internal experience, often characterised by a fear of being perceived as incompetent, with bouts of self-doubt [2]. It was first described in 1978 when Pauline Rose Charles and Suzanne Imes discovered that numerous high-achieving women in academia were convinced they had fooled everybody who thought of them as intelligent, despite possessing legitimate degrees, promotions, and awards [3].

"Impostors" often attribute their warranted successes to intangible factors, such as luck and good timing [3]. The debilitating syndrome also drives its sufferers to deny praise for their achievements and overwork in order to cope with their constant fear of being exposed as frauds, further fuelling the development of low self-esteem, low self-confidence, and feelings of inadequacy [4]. Long term effects of feeling insecure and incompetent can include aversion to participation in professional settings and a lower drive to achieve set aspirations and goals. A distinct implication of impostor syndrome is the fear of failure [3]. This fear is augmented when "impostors" are faced with challenging tasks that involve evaluation of their performance on completion. The fear of failure causes sufferers to resort to dysfunctional practices, such as procrastination and perfectionism. Sufferers who strive for perfection tend to overwork themselves, which can sometimes cause burnout. They further credit their successes to the amount of work they put in, although it may have been disproportionate to the amount of impact it had on the calibre of the task itself [4]. People who indulge in procrastination and intensely work at the last-minute associate their successes with luck. Unfortunately, sufferers of impostor syndrome are usually unable to break their cycle of maladaptive habits due to the fear that breaking them may increase their chances of failing [4]. Ironically, some people also experience a fear of succeeding, as this increases visibility and responsibility, therefore increasing the likelihood of being "found out"[1].

Although breaking free from the shackles of impostor syndrome may seem daunting, it is not impossible. As the fear of being discovered as fraudulent forms the cornerstone of feeling like an impostor, most people suffer in silence and seldom seek help [4]. The first step towards navigating through impostor syndrome is to recognise negative, overly self-critical thoughts and acknowledge them for what they are. This strategy not only makes these thoughts less intimidating but also opens up a dialogue between people who experience the same thoughts and feelings [4]. Another remedy would be to consciously try internalising one's accomplishments to counter repeated thoughts of self-doubt. Breaking out of the vicious circle of impostor-like thinking is imperative to triumph over impostor syndrome [4]. Two cognitive interventions, namely thought stopping and shipping, can be practised to break toxic cycles of impostor-like thinking. Thought stopping involves identifying negative thoughts and replacing them with positive thoughts rooted in self-compassion

and affection [4]. This will aid in evolving impostors into people capable of constructive self-criticism of their abilities while fostering compassion instead of striving for impossible perfectionism. Thought shipping promotes the concept of pitching an idea to others without waiting for it to be perfect [4]. This forces sufferers to venture out of their comfort zone, boosting personal growth and creativity through learning from mistakes. Finally, seeking professional counselling and therapy can prove extremely beneficial in overcoming impostor syndrome [4].

If you feel overwhelmed at any moment in the future, remember that you are not alone and that probably many people around you feel the same. Dare to pursue your goals and prove impostor syndrome wrong!

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EXAM QUESTION

Question 4

Do you want to practise your knowledge regarding the topic of this brief message? Then, let us see if you can answer the following exam question.

Primary and secondary appraisal of a stressor is both included in the stress-coping model. Lack of social support and a social network affects...

A. primary appraisal
B. secondary appraisal

The answer to this question can be found on page 33 in this journal.

TO SEE OR NOT TO SEE

ABOUT ANTON-BABINSKI SYNDROME AND BLINDSIGHT

Lessa Schippers[1]

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Brief message

My name is Lessa Schippers, and I am a second year master's student Cognitive Neurosciences in the Plasticity and Memory track. I became an editorial editor at RAMS in October 2020, because I like writing and wanted to improve. I chose the topic for my brief message, because it was introduced to me during a neurophilosophy lecture on consciousness. The lecturer used the described disorders as an example that consciousness as a concept is not always as straightforward as we think it is. With my biomedical background, however, I was interested in the mechanisms. In this brief message, I tried to explore those mechanisms.

Would you rather be blind and be under the impression that you can see, or think you are blind, while you can actually see? The former is called Anton syndrome, and the latter blindsight. This brief message will discuss both of these rare conditions involving vision and vision loss.

Anton-Babinski syndrome is named after the neurologist Gabriel Anton, who defined the disease at the end of the 19th century; however, the syndrome was already described in 63 AD. by Seneca [1,2]. Patients with Anton syndrome suffer from cortical blindness due to damage in the occipital lobe. This syndrome is often caused by stroke but other causes can include head trauma or hypertensive encephalopathy [1]. Interestingly, these patients are unable to recognise the fact that they are visually impaired. In general, a condition related to the inability of recognising an impairment is called anosognosia, a term coined by François Babinski in 1914 [3]. In the case of Anton-Babinski syndrome, other brain areas besides the occipital lobe, such as speech-language areas, construct made-up images due to a disconnection between brain areas [3]. This construction of images is called confabulation [3]. Due to these images, the patient believes they are still able to see. For example, if you ask a patient with Anton-Babinski syndrome to comment on your outfit, and you wear a dress, they might respond, 'I really like your pants'. Confabulation can also occur in the case of deafness or amputations. Treatment consists of treating the origin of the occipital damage to the extent possible [1].

On the other hand, blindsight is a condition where patients think that they cannot see, although these patients should be able to see. Interestingly enough, unconsciously they do see. For instance, if you ask them to describe an object you are presenting to them, *e.g.*, a red mug, they will tell you that they are blind and cannot see the object. If you ask them to guess the object, they will most likely, unconsciously, guess right. Blindsight is caused by damage in the V1 area, the primary visual cortex, in the brain [4]. Patients with blindsight can still see because the V1 area is not the only area in the brain receiving input from the visual tract [4]. Some other areas receiving input from the visual tract are extrastriate visual areas, the inferotemporal cortex, and the amygdala [4]. In this way, patients unconsciously receive visual information, but they lack coordination by the V1-area to put the pieces together, creating the final image we consciously see. Treatment can consist of either interventions that try to recover vision or learning to use aids for people who are blind [5].

We presented two different syndromes here that can be seen as polar opposites regarding their symptomatology. Despite this remarkable disparity, the pathophysiology is curiously similar. It is only the location of the brain damage that decides which syndrome a patient will develop. This delicateness of the brain fascinates and drives neuroscientists every day.

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EXAM QUESTION

Question 5

Do you want to test your knowledge regarding this topic? Then, try to answer the exam question below.

Several distinct forms of blindness have a neurological origin. Which of the conditions described below is caused by compression of the optic chiasm by a pituitary gland tumour?

A. Complete loss of eyesight in the left OR right eye
B. Heteronymous bitemporal hemianopsia
C. Left OR right homonymous hemianopsia
D. Total loss of vision in BOTH eyes

The answer to this question can be found on page 33 in this journal.

PHARMACOGENETICS

Aster Witvliet [1]

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Brief message

I have always loved genetics. The way that DNA can so utterly and completely shape an organism amazes me. Specifically the field of pharmacogenetics appeals to me because it has such a strong link to the medical field by improving patient care. By writing this brief message, I wanted to share how our increasing understanding of our genetics and the variation found in it gives us the opportunity to start personalising treatment and reduce side effects. So many people rely on their medications for various needs, and the field of pharmacogenetics helps to find ways to improve their quality of life.

Have you ever taken medication that had a nasty side effect? Or have you taken medication that appeared to do absolutely nothing to alleviate your health complaint? Not all people respond the same to taking a specific drug; for some people it might work well, while it might not work at all for others or come with troubling side effects. Your genes might be to blame for the side effects and reduced effectiveness of your medication, as your genes can influence your body's response to a drug [1]. The field of pharmacogenetics studies this relationship between people's genes and their response to medications [1]. Research in this field can help personalise treatment, as looking at someone's genetics can help a physician choose a medication that is likely to be effective and avoid medication that is likely to be ineffective or cause major side effects [1].

One case where looking at the relationship between genetics and medication has already proven beneficial is treatment with the immunosuppressant drug azathioprine. Azathioprine reduces the immune system's activity, which can be useful in treating patients with an autoimmune disorder where the immune system has started attacking the body [2, 3]. The enzyme thiopurine methyltransferase (TPMT) is involved in the metabolism of azathioprine [2]. Some people have a mutation in their *TPMT* genes that causes their TPMT enzymes to be less functional, or sometimes even not work at all [2]. Patients with lower or no TPMT enzyme activity have a severely increased risk of bone marrow suppression, a life-threatening side effect of azathioprine [3]. A patient that is found to have deficient TPMT enzymes upon genetic testing can then be prescribed a lower dose of azathioprine or receive an alternative medication to prevent life-threatening side effects [2, 3].

The case of azathioprine and the TPMT enzyme shows the potential power of personalising treatment based on a patients' genetics. Currently, pharmacogenetics is starting to become a part of clinical practice. In the Netherlands, a general practitioner or specialist can have patients genetically tested for the generation of a so-called DNA-passport by the Erasmus Medical Center [4]. For this DNA-passport, the activities of over 20 enzymes are investigated, and the results can have implications for dozens of medication types. However, concerns about the evidence base and healthcare workers' lack of knowledge on pharmacogenetics remain important roadblocks to wide implementation [5]. In the future, as evidence base for pharmacogenetics strengthens and physicians become more familiar with its potential, you might be saved from serious side effects if your doctor takes a quick glance at your genetics.

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EXAM QUESTION

Question 6

Do you want to test your knowledge regarding this topic? Then, try to answer the exam question below.

Medication is not always suitable for every patient. An important part in respect to choice of treatment is individualising the therapy based upon specific, patient-bound factors (personalised medicine). A representative example of personalised medicine is...

A. the choice of a particular antibiotic based upon the disease-causing bacterium in a patient.
B. the adjustment the dosage of a beta-blocker based upon the patient's kidney function.
C. the adjustment of the pain medication according to the source of the pain.

The answer to this question can be found on page 33 in this journal.

THE USE OF LONG-ACTING ANTIVIRALS IN HIV TREATMENT

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Brief message

Hi! I am Thomas Nieuwenstein, a second-year Master's student Biomedical Sciences. I am really interested in the mechanisms of action of medication and the opportunities that novel compounds or novel regimens offer. I discovered the topic of my brief message during my internship at the Pharmacy department at the Radboud Institute of Health Science. The use of long-acting antivirals is a big topic in the department, and while my internship was not connected to this subject, the possibilities of this treatment option intrigued me and sparked my interest to write the brief message about the long-acting antiviral treatment against HIV.

Human Immunodeficiency Virus (HIV) treatment has come a long way since the introduction of the first anti-HIV treatment –azidothymidine, or better known as zidovudine, a nucleoside reverse transcriptase inhibitor– in 1987 [1]. While the drug proved to be effective at reducing opportunistic infections and AIDS-related deaths, it caused severe adverse effects in the patient population [1]. Since then, new drugs have been developed which have turned HIV into a chronic affliction rather than a death sentence [1]. Depending on which regimen is followed, the current treatment consists of one or more pills per day. Adherence to the dosing regimen is key in HIV treatment, as the virus may develop resistance to the medication in non-virologically suppressed individuals [1]. Long-acting antiretroviral drugs may offer a solution by eliminating the need for daily oral therapy [1,2].

In January 2021, the European Medicines Agency approved the first combination of sustained-release injections of non-nucleoside reverse transcriptase inhibitor (NNRTI) rilpivirine and integrase inhibitor (INI) cabotegravir for marketing [3]. Rilpivirine inhibits the HIV's reverse transcriptase enzyme, preventing the HIV RNA from being converted into DNA. Cabotegravir inhibits the integrase enzyme, preventing HIV DNA from being integrated into the human DNA. So far, this treatment can only be used in patients who are already virologically suppressed (<50 copies of HIV-1 RNA per mL blood) and have not developed any resistance against NNRTIs or INIs. After a four-week oral lead-in period, the injections must be given intramuscularly into the gluteus muscle once every four weeks or once every other month, depending on the dosing schedule. If a dose cannot be administered at the designated interval, the extra time can still be bridged with oral therapy. Long-acting injectable therapy of rilpivirine and cabotegravir is indicated as non-inferior to daily oral therapy of the same drugs [4]. The use of the long-acting injectables greatly reduces the medicinal burden compared to the usual daily oral therapy.

Sadly, non-adherence or dropping out of a long-acting injectable regimen is a much larger problem than in oral therapy. As the injections have a sustained release mechanism, concentrations of cabotegravir and rilpivirine can still be measured in the blood up to a year later. As these concentrations are too low to provide virological suppression, there is a high chance that the virus will develop resistance to cabotegravir or rilpivirine if viral suppression is not achieved through other means, such as oral therapy. This means

that the patients will not be able to use these long-acting injectables anymore. This may extend to other drugs in the NNRTI or INI drug class. Patients who cannot or will not continue the long-acting injectable treatment schedule should start on other (oral) treatment as soon as possible to minimise the risk of developing resistance.

The long-acting injectables have another downside, as the injectables also have more side effects, such as pain at the injection site due to the thick needle or other local reactions, on top of the drug-related side effects shared with their oral counterparts [4].

Apart from the clinical treatment of HIV, long-acting injectables have

shown to be beneficial as pre-exposure prophylaxis (PrEP) for at-risk populations, such as healthcare workers, men who have sex with men, or sex workers, to prevent infection with HIV in the first place [5]. Oral PrEP is already available but is not used often by those who could benefit most from it due to the burden of daily oral treatment. The use of monthly, or once every two months injections may be more acceptable to the populations that may benefit from PrEP and lead to a higher efficacy of PrEP treatments [5].

Overall, the long-acting injectables offer advantages over daily oral therapy but are only approved for a limited population thus far. The population for whom these long-acting injectables are currently approved are already the least vulnerable HIV-infected population (must be virologically suppressed and have good adherence to oral therapy). Exploring the options long-acting injectables could offer in more vulnerable populations, such as those that frequently forget their oral therapy, could have an even larger impact. Possible new solutions also cover other combinations of HIV drugs or non- or less invasive methods of drug delivery, such as skin patches. Research concerning expanding the population and expanding the arsenal of injectable agents is the next step in HIV treatment.

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EXAM QUESTION

Question 7

Do you want to test your knowledge regarding immunology? Then, have a look at the exam question below.

The human immunodeficiency virus (HIV) is an example of an acquired immunodeficiency. The HIV virus infects CD4+ T-cells, leading to...

A. a reduced activation of macrophages.
B. a decreased production of anti-HIV antibodies.
C. both a reduced activation of macrophages and a decreased production of anti-HIV antibodies.

The answer to this question can be found on page 33 in this journal.

GET RID OF THAT LATE-NIGHT SNACK!

THE RELATION BETWEEN THE TIMING OF FOOD INTAKE AND WEIGHT GAIN

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Brief message

Welcome to my brief message. I am Quentin Marsman, 21 years old, and currently in my fourth year of the study Medicine. I joined RAMS because of my interest in science and writing and to develop my scientific skills. I have written articles for RAMS for almost three years now. Unfortunately, this brief message was my last. About the topic, I have been interested in food and lifestyle for quite some time now as it is an important part of one's health. Then I came across the topic of late-night eating. I became interested and decided to make a brief message about it. I hope you enjoy reading this brief message!

Late-night eating is an activity we all participate in once in a while. We all enjoy that snack right before bed after an evening with intense exercise or a hamburger after going to the bar. Nevertheless, these snacks could be more detrimental to our health than we might think. Studies show that the timing of food intake has a relation to weight gain [1]. Experimental studies in animals show that unusual feeding times lead to obesity, even in the absence of changes in total energy intake [1]. These results are in line with studies performed in humans that found that consuming many calories in the evening is associated with higher risks of being overweight or obese [1,2].

Some proposed mechanisms for this association are lower diet-induced thermogenesis, which is related to nocturnal insulin resistance and reduced-fat oxidation [1]. Nevertheless, disruption of the circadian rhythm due to abnormal feeding times is hypothesised as the main mechanism. The internal clocks that regulate this rhythm are sensitive to feeding times, even more when the eating occurs during times usually reserved for sleeping or resting [3]. As a result, daily lipolytic activity and the lipolytic response to fasting is decreased [3].

A special case is when people make a habit out of eating late. For this instance, a new clinical syndrome was defined. If a person eats twice or more per week at night or eats at least twenty-five per cent of their caloric intake after the evening meal, this person suffers from the night eating syndrome (NES) [4]. These people often also cope with morning anorexia and sleep disturbances. People with NES consume more calories per day than people without it, with the difference caused by night-time eating [5]. Patients with NES also gain more weight than people without the syndrome [5]. The circadian rhythm, whose disruption can lead to weight gain, is also thought to play a role in the weight gain of these people [4,5].

More research is necessary to assess the details of the relation between late-night eating and weight gain and obesity. However, based on the current knowledge, the timing of eating seems to be an alternative strategy in the reduction of obesity and the prevention of being overweight [1,2,5]. Therefore, getting rid of that midnight snack might not be a bad idea.

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EXAM QUESTION

Question 8

Do you want to test your knowledge regarding our metabolism? Have a look at the exam question below.

The body starts to produce its own glucose in case of a glucose shortage (gluconeogenesis). Which molecules are the sources of this gluconeogenesis?

A. Amino acids
B. Proteins
C. Fatty acids

The answer to this question can be found on page 33 in this journal.

THE POWER OF PLANTS: A CURE FOR COVID-19?

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Brief message

Hi everyone! My name is Minke Holwerda, and I am a master's student Biomedical Sciences with a specialisation in epidemiology. In light of the COVID-19 pandemic, I thought it would be interesting to take a look at what research for a cure is currently out there. Plant-based medicine is one of the approaches to this problem that we do not hear as much about. I was definitely surprised by how many different plants are being researched as they might have medicinal properties that can fight COVID-19 as well as other diseases.

Unless you have been living under a rock, it has probably not escaped you that we are currently in the midst of a worldwide pandemic, caused by severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2). While vaccines are being developed, produced, and injected in a (more or less) high tempo, a cure for coronavirus disease 2019 (COVID-19) has not yet been found.

In the race for the COVID-19 cure, some countries have turned to exploring the potential of plant-based medicine [1]. Plant-based medicine is an ancient practice that plays a role in traditional medicine as well as modern drug development [2,3]. Plants produce secondary metabolites, which assist in the survival of the plant, such as alkaloids, flavonoids, phenolic acids, and terpenoids [2,4]. These compounds have, among others, anti-inflammatory, antioxidant, anticancerous, and –most importantly– antiviral properties [4]. Well-known examples of plant-based medicines are acetylsalicylic acid (aspirin), which is isolated from willow tree bark, and artemisinin, which is extracted from the plant *Artemisia annua* and used as treatment for malaria [2,5].

A wide range of plants is currently being reviewed for their potential to treat COVID-19, including those that can be found in the average Dutch kitchen cabinet or garden. For example, research is being done into *Anthemis hyaline*, better known as chamomile. In one study, virus load decreased after adding extracts of *Anthemis hyaline* to CoV infected cells [6].

Curcuma Longa contains curcumin, which is a polyphenol that has previously been shown to have anti-viral activity against SARS coronavirus [7]. This name might sound familiar to you since curcuma, a spice currently very popular due to its superfood-status, is also made from this plant. A recent molecular docking study reported that curcumin binds and inhibits SARS-CoV-2 target receptors, supporting the use of this plant as prophylaxis against SARS-CoV-2 [8].

Another promising contender is a compound called diammonium glycyrrhizinate found in *Glycyrrhiza glabra*; the plant from which liquorice is made. In traditional medicine, liquorice is used against colds, coughs, and to calm disturbed digestion, and diammonium glycyrrhizinate can be used to treat liver damage caused by hepatitis B due to its anti-inflammatory properties [9]. Recently, clinicals trials have been approved researching diammonium glycyrrhizinate in combination with vitamin C as a therapy for COVID-19 [10].

The use of plant-based medicine has many advantages. In countries with a rich tradition of herbal medicine, plant-based medicines have been used in a clinical setting for a long time, repeatedly proving their efficacy and safety. Theoretically, herbal medicines with known antiviral properties and established safety could immediately be used to treat COVID-19 patients [9]. Even more so because they are often widely available, in contrast to other medicines such as the recently approved remdesivir [11,12]. In particular in low- and middle-income countries, where up to four billion people already depend on plant-based medicine as their primary source of healthcare, this is an attractive prospect [13] .

However, a lot has to happen before any traditional medicine is turned into a modern drug. Because plants contain multiple phytochemicals, the exact mechanism of action is often unclear, and it takes a long time to develop high-quality plant-based medicine

with sufficient data on long-term safety and pharmacokinetics. In addition, developing reference standards is also more challenging for plant-based medicine than for synthetic drugs [1].

So, unfortunately, plant-based medicine is no quick fix for our COVID-19 cure conundrum. You might enjoy a calming cup of chamomile tea, curcuma in your food, and some liquorice to snack on, but this is no replacement for the vaccine or test needed to hit the clubs again!

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EXAM QUESTION

Question 9

Do you want to practise your knowledge concerning the topic of this brief message? Then have a look if you know the answer to the following question.

After someone has recovered from a viral infection, a re-infection often occurs asymptomatically. One of the explanations is the rapid neutralisation of the virus after it has entered the body. Which component of the immune system is responsible for the neutralisation?

A. Antibodies
B. Cytotoxic T-cells
C. NK-cells

The answer to this question can be found on page 34 in this journal.

A NEW SIBLING FOR CRISPR-CAS9: CAS13

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Brief message

Hi everyone! My name is Femke van Hout, and I am a master's student from the Molecular Mechanisms of Disease program. I have been an editorial editor for RAMS since March 2020 but I will unfortunately 'retire' this summer after my graduation. I have greatly enjoyed being part of RAMS, and I have learned a lot about a diverse range of topics. Thanks to writing for RAMS, I can now tell you everything about our microbiome and (non-existing) sex pheromones! For this brief message, I chose the hot topic of CRISPR/Cas systems, but instead of the well-known CRISPR/Cas9 I wrote about CRISPR/Cas13. Even though the molecular mechanisms may seem a bit daunting at first, I hope that this brief message can inspire you about the beauty of CRISPR/Cas systems!

The last decade marks the exciting revolution of CRISPR/Cas9 genome editing. While the revolution still continues with further development and refinement of the Cas9 systems, the first patients are already receiving Cas9-based treatments. The Cas9 enzyme is a so-called 'RNA-guided DNA nuclease', which means that Cas9 is directed by RNA, the guide RNA, to find and cut the complementary target DNA. As this cutting mechanism is very precise and programmable, Cas9 can in theory be used to change any DNA sequence. Many diseases could potentially be cured, including sickle cell disease, Duchenne muscular dystrophy, and Huntington's disease [1]. However, changing someone's DNA could have severe implications regarding safety and ethics.

Luckily, it turns out that Cas9 has many siblings. Among them is the recently discovered Cas13 that cuts RNA instead of DNA, making Cas13 an 'RNA-guided RNA nuclease' (Figure 1) [2]. This means that Cas13 can be used to cut RNA encoding for disease-causing proteins. In this way, the production of the disease-causing protein is prevented without modifying the genome!

The first successes with Cas13 in human cell lines and mice have recently been published [3]. In one important example, the mRNA encoding for the KRAS protein, which is often found to carry mutations in pancreatic cancer, was targeted [3]. However, no drugs exist to target the KRAS protein. Cutting KRAS mRNA would therefore be an effective strategy to prevent the production of the mutant protein. With guide RNAs that recognise the KRAS mRNA, Cas13 reduced the mRNA level by 94%. This resulted in the apoptosis of cancer cells *in vitro* and tumour shrinkage in the mice model.

The fact that Cas13 can prevent the production of disease-causing proteins without changing the DNA is a very important advantage of Cas13 over Cas9. Moreover, Cas13 can be used to cure diseases for which there is no DNA to target. The vast majority of the viruses that cause human disease have an RNA genome. Apart from the retroviruses, these RNA viruses do not have any DNA intermediate in their replication cycle. Therefore, Cas9 cannot be used to target these viruses, while Cas13 can. With guide RNAs targeting influenza virus A and SARS-CoV-2, Cas13 has already been shown to effectively degrade the viral RNA, mitigating the viral infection in human cell lines [4]. All in all, the Cas13 enzyme has great potential for the treatment of various human genetic diseases, cancers, and virus infections.

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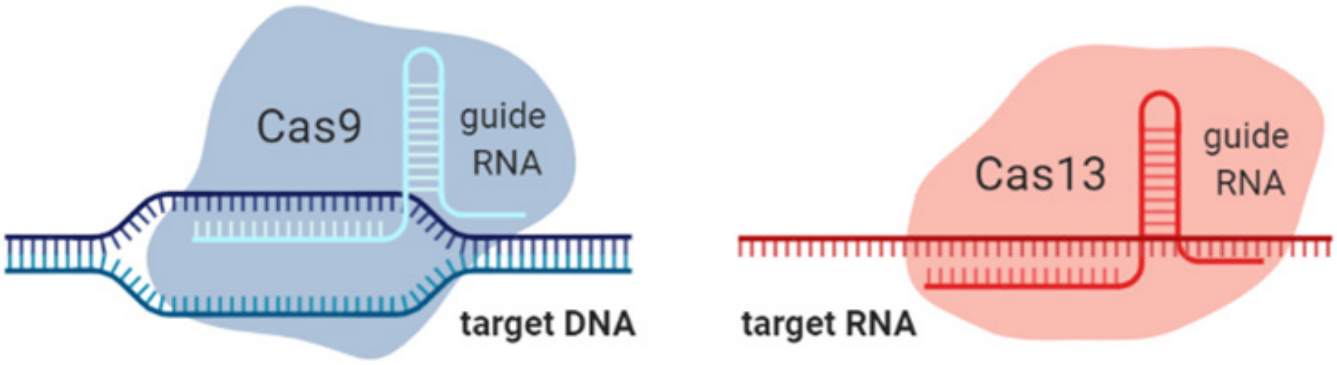

Figure 1: *Schematic representation of the Cas9 and Cas13 enzymes with guide RNA and target DNA/RNA, created with Biorender.com.*

EXAM QUESTION

Question 10

Do you want to test your knowledge about genetics? Then, try to answer the following question.

DNA and RNA, both amino acids, are very similar. Yet, there are a few differences. One typical difference is that RNA...

A. contains deoxyribose as a sugar.
B. is not capable of forming a double helix.
C. contains uracil as a base.

The answer to this question can be found on page 34 in this journal.

MORE THAN A QUIRK OF THE HUMAN MIND – THE FASCINATING CONCEPT OF SYNESTHESIA

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Brief message

My name is Natalie, and I joined RAMS in May 2020 as a scientific editor. Since then, I have enjoyed writing several articles, as well as the brief message about colour synesthesia. How we individually perceive what is commonly referred to as "reality" has fascinated me for the longest time, especially when we consider that it is slightly different for every single person we meet. Nobody perceives the world just like you. Colour synesthesia is just another form of how these individual differences can come to light, and to me, it is truly a breathtaking phenomenon. Sue me, but the brain is fascinating! I hope you enjoy reading the brief message just as much as I did writing it. And maybe it even gets you to marvel at your very own reality for a little while. I know; it definitely did it for me. Have a fabulous day, and take a step back to admire life whenever you can.

Let us perform an experiment. What do you perceive when I say the following numbers: five, eight, and twenty-three? You might think that sounds silly and be inclined to put this piece away to do something more fun. You might, however, also be one of the lucky few to experience a phenomenon called 'synesthesia'.

Synesthesia describes a condition where one sensory stimulation elicits another unstimulated sensory output, in addition to the output corresponding to the primarily stimulated sense. In easier words, so-called "synesthetes" (people who experience synesthesia) will connect two unrelated outputs. For example, synesthetes can associate visual information (like seeing a particular letter or number) with specific smells or colours [1]. Interestingly, they do so in a reproducible way, so the same letter will always be associated with the same colour. Additionally, the association seems to be unidirectional, so a letter will be connected to a colour, but not the other way around. The field of synesthesia is vast, and there are numerous subforms, ranging from experiencing colours from sounds, specific letters or numbers, to perceiving tastes from phonetic sounds [2-5].

The ability can be either congenital, acquired via neurological conditions, like migraine or thalamic strokes, or it can result from drug ingestion [6-9]. Synesthesia has, furthermore, been described in the case of sensory deprivation, such as blindness [6]. About 4.4 per cent of the population is thought to have congenital synesthesia, although the prevalence differs between the different subforms [10]. Of note, though, the prevalence of this condition in the general population is probably underestimated due to stigmas surrounding the idea that an individual perceives inputs that the majority would not [6]. Strikingly, synesthesia seems to be quite common among people in art-related fields. One study, in particular, determined the prevalence of synesthesia among fine arts students using a questionnaire and found it to be as high as 23 per cent [11]. This is supported by anecdotal evidence of synesthesia in several well-known and impactful artists, like Vincent van Gogh and Wassily Kandinsky [6].

But what are the mechanisms behind synesthesia? While we do not know the pathophysiology exactly, it is most likely due to either direct crosstalk between two brain regions or indirect feedback via a third brain region [12]. Which regions are involved depends on the form of synesthesia an individual has. In the case of grapheme,

referring to letters or numbers, and colour synesthesia, for example, synesthetes show specific brain activity patterns compared to non-synesthetes [13]. Upon hearing audio recordings of graphemes, they display a significantly increased number of connections between six regions associated with colour perception and three so-called 'grapheme regions' ($p<0.024$) [13]. Nonetheless, the anatomical basis of synesthesia remains elusive. Further research will be essential to fully understand the underlying mechanisms, as well as to determine the prevalence of the different subtypes of synesthesia in the general populations.

So maybe, next time when you see colours and shapes appearing in front of your eyes while you are listening to music, you will appreciate your super ability a bit more. Remember, you are not going crazy; you are just special.

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EXAM QUESTION

Question 11

Do you want to test your knowledge regarding neurology? Then, have a look at the exam question below.

The somatosensory cortex is organised in a specific pattern, often depicted as the sensory homunculus. The sensory homunculus is a map that identifies several cortical areas based upon a particular factor. Which factor is this?

A. Frequency
B. Place
C. Proprioception
D. Tonotopy

The answer to this question can be found on page 34 in this journal.

THE TREACHEROUS EFFECT OF THE LYMPH: HOW ITS FLUID CAN ADVANCE CANCER CELLS

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Brief message

Hi, my name is Mèlanie Reijnaers, master's student Biomedical Sciences and former scientific editor-in-chief of RAMS. During my bachelor's, I followed the cancer mechanisms and immunology course, which I found truly fascinating. Even though cancer is a devastating disease that has an impact on almost everyone's life, I believe the way metastasis occur is mesmerising. It reminds me of how quick species, and also our body, can evolve, which then again reminds me of all there is in the world. It makes me realise again that things might look straightforward but actually can be very complicated; it strengthens my curiosity. For this and more, I decided to write about the interesting phenomenon that is helping cancerous cells become more aggressive: the fatty lymphatic system. I hope you enjoy the read and that it makes you curious about how this phenomenon could be used for beneficial purposes.

Cancer, being the second leading cause of death worldwide, is a major public health problem [1]. Every day, thousands of researchers are trying to make a difference, to help patients fight the devastating effects the disease brings. This research is not only focussed on trying to create new treatments but also on figuring out the behaviour of the disease. Recently, in August 2020, Ubellacker *et al.* revealed the advantage that melanoma cells have when they migrate through the lymphatic system instead of the blood system [2]. This phenomenon is believed to have a pivotal role in the prognosis of cancer. For this reason, the intriguing mechanism behind this advantage will be discussed in this brief message, highlighting the importance of further research on this topic.

The migration of cancer cells from one tissue to another, leading to the formation of secondary tumours, is known as metastasis. Metastasis can occur through multiple routes of which the primary ways are transcoelomic spread (via the abdominal cavity), hematogenous spread (via the blood), lymphatic spread, and a combination of the latter two. Even though metastasis is common in cancer patients, the process is known to be inefficient as not many cells survive in the blood [3, 4]. The main reason for this inefficiency is the presence of oxidative stress in the blood [5]. As you might have already learnt during your studies, oxidative stress can induce cell death in multiple ways. Ubellacker *et al.* observed in *in vivo* assays that the melanoma cells are killed in the blood via a process called ferroptosis, which is induced by oxidative stress [2].

Ferroptosis is an iron-dependent form of cell death and causes lipid peroxidation. Polyunsaturated fatty acids (PUFAs) are in particular sensitive to the oxidative mechanism [6]. The rule goes as follows: the more unsaturated a phospholipid is, the more prone it is to undergo ferroptosis [7]. The oxidation of these PUFAs is the main reason why cells that transit through the lymphatic system have an advantage in spreading compared to cells that travel via the blood. To understand why this is the case, it is essential to know that the cell membrane usually contains many PUFAs. However, what is the reason for the advantage for cells that have been in the lymphatic system? Why does this milky-white, lymphocyte rich, fatty fluid lead to a beneficial effect for metastasis?

Well, that the lymphatic fluid is rich in triglycerides, alias fatty, is mostly the reason. Ubellacker *et al.* observed that malignant cells that entered the lymphatic system were significantly more enriched with oleic acid, which is a monounsaturated fatty acid (8.7 ± 0.9 (mean ± standard deviation)) [2]. This oleic acid, as well as other monounsaturated acids, acts as an inhibitor for ferroptosis by replacing and thereby reducing the density of PUFAs in the cell membrane. The reduced density of PUFAs leads to fewer available sites that can undergo ferroptosis. Therefore, when malignant cells enter the blood after they have been in the lymph nodes/vessels, the process of ferroptosis is avoided [2]. Subsequently, these cells have a higher chance to survive in the bloodstream leading to an increased risk of metastasis and a worse prognosis of the disease [Figure 1].

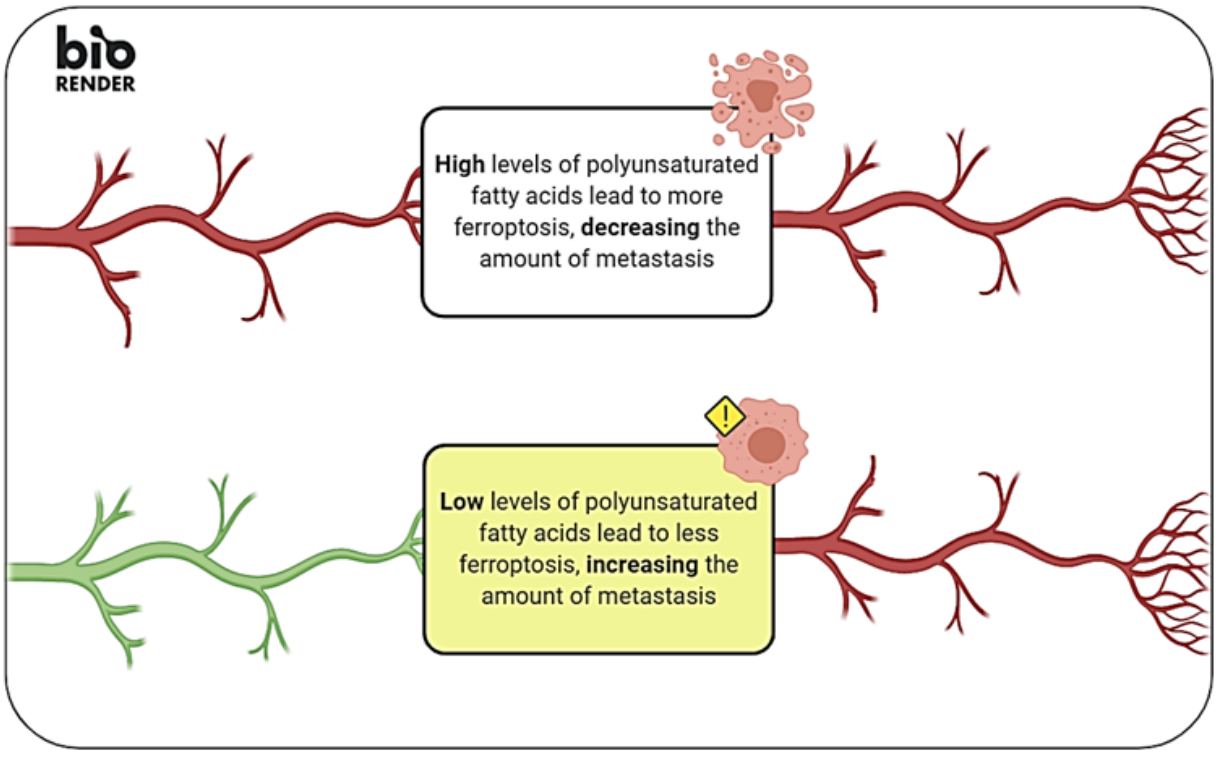

Figure 1: *How migration through the lymph can advance metastasis (created with biorender.com).*

This result was supported by additional results showing that melanoma cells in the presence of ferroptosis-inhibitor molecules led to the same amount of metastasis as the malignant cells that entered the lymphatic system without the inhibitor, suggesting that such cells did not undergo ferroptosis [2]. Moreover, the study of Ubellacker *et al.* measured a higher concentration of malignant cells in the lymphatic system compared to the blood system, which indicates as well that the fatty environment of the lymph contributes to an anti-cell-death mechanism [2]. These findings, and many more results from the study of Ubellacker and colleagues, provide a deeper understanding of the behaviour of malignant cells and lay the groundwork for future research into the protective environment of the lymph.

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EXAM QUESTION

Question 12

Do you want to test your knowledge? Try to answer the exam question below.

One of the biggest hurdles in cancer treatment is the occurrence of resistance to therapy in tumour cells. Which of the tumours mentioned below will respond to chemotherapy the fastest? Tumours with a...

A. large growth fraction
B. low growth fraction

The answer to this question can be found on page 34 in this journal.

AN ACT OF KINDNESS A DAY KEEPS THE DOCTOR AWAY?

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Brief message

Hi everyone! My name is Yfke, and I am currently studying for my master's in Medicine. During the past year, I have been the editorial editor-in-chief at RAMS. It has been a great pleasure to read all of the articles written by our editors and to see all of the editors becoming (even) better writers. Unfortunately, all good things must come to an end, and I will pass the baton to the next editorial editor-in-chief. When I had to write this brief message, I wanted to write a piece related to Christmas, considering it was supposed to be published in December. And after all, what speaks most to the mind when discussing Christmas? Kindness!

As you are all well aware by now, it is almost Christmas. The time of the year where it is allowed, even encouraged, to watch Christmas movies while wearing atrocious-but-yet-funny Christmas sweaters. It is the time of warm socks, blankets, and cheerful Christmas decorations. However, above all, it is a time of compassion and kindness towards one another. Speaking of kindness – have you ever noticed that an act of kindness made you feel happy? I certainly have, and that made me wonder what the neurobiological basis of kindness is. How do we, from a neuroendocrinological perspective, display kindness?

Humans exhibit high amounts of prosocial behaviour, including empathy, cooperation, care, and altruism [1]. Out of an evolutionary perspective, this behaviour is essential to sustain us, and mammals as a species in general, as the offspring of mammals are born relatively early and vulnerable in comparison to other classes of animals [1]. Therefore, proper care and nursing of the offspring are needed to ensure their longevity, promoting the survival of the species [1]. Several hormonal circuits in the brain have been implicated in this care-centred behaviour, including oxytocin [2].

You might have already heard of oxytocin, which is also referred to as the 'cuddle hormone' [2]. Oxytocin is secreted by the hypothalamus, after which it is secreted systemically through the posterior pituitary gland [3]. The secretion of oxytocin, and the expression of the oxytocin receptor, is altered during pregnancy, which is vital for care-based behaviour of the mother; hence its nickname as the cuddle hormone [4]. In accordance with this line of thought, the intranasal administration of oxytocin has also been shown to increase prosocial behaviour [5]. Although the predominant effect of oxytocin is an increase in prosocial behaviour, in rare cases, the intranasal administration of oxytocin can result in increased antisocial behaviour, including jealousy and aggression [5]. This variability in the results suggests that there are interpersonal variables affecting one's response to oxytocin [5].

Considering oxytocin's effect on prosocial behaviour, it is not surprising that this hormone has also been associated with several health benefits [7]. For example, oxytocin is capable of inhibiting adrenocorticotropic hormone, which together with its effector hormone cortisol forms the hormonal 'stress-axis' [7]. Inhibition of this axis results in a decreased secretion of cortisol and, therefore, also in reduced levels of stress [7].

Overall, we can conclude that oxytocin is a central player in prosocial behaviour. Perhaps, an act of kindness does keep the doctor away (partially)! Let that serve as a reminder during this Christmas time to keep an eye out for others; call your grandparent(s), call your friends, or write a Christmas card to the elderly at a nursing home. They will appreciate it, and it will not harm you either –give your brain an oxytocin boost! Lastly, I want to wish you, on behalf of the board of Radboud Annals of Medical Students, a merry Christmas and a fantastic 2021, a year in which we hope to see many of you at our (online) activities!

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EXAM QUESTION

Question 13

Do you want to test your knowledge regarding the topic of this brief message? Try to answer the exam question below.

The aim of organising personal meetings in the neighbourhoods serves the purpose of reducing loneliness amongst frail elders. This activity is targeted at...

A. increasing social cohesion
B. improving socialisation
C. decreasing social injustice
D. decreasing social stratification

The answer to this question can be found on page 34 in this journal.

PSYCHOSIS IN CRIMINAL LAW

CAN PSYCHOSIS MAKE YOU NOT CRIMINALLY RESPONSIBLE?

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Critical appraisal

On May 5th 2019, a body was found. Two days later, two more bodies were found [1]. All victims were killed by stabbing while walking their dogs [1]. Thijs H. was swiftly arrested as the suspect of the three murders [1]. The prosecution requested to examine Thijs H.'s criminal responsibility for these crimes in the Pieter Baan Centre (PBC) [1]. The PBC advised the judge to not charge Thijs H. as criminally responsible for his actions and consequently give him 'terbeschikkingstelling' (TBS) with compulsory mental treatment [1]. However, contrary to this advice, the court considered him diminished criminally responsible [2]. This contradiction is remarkable, since the PBC exists to advise the court on the interpretation of a mental disorder and what it entails in relation to the offence. The court does not possess expertise in this field. In any case, the judgment is important because the court did not follow the advice of the PBC to declare Thijs H. not guilty by reason of insanity and has provided direction for the concrete interpretation of the spectrum of criminal responsibility. In which way is criminal responsibility assessed, given that the criteria are not defined in concrete terms? Is the current interpretation of criminal responsibility favourable for the suspect without losing sight of protecting society?

KEYWORDS: Psychosis, criminal law, criminal responsibility, diminished criminal responsibility, insanity

Thijs H. was arrested on May 8, 2019 as a suspect of three murders. Subsequently, the criminal responsibility of Thijs H. was investigated due to a possible psychotic condition. For this, it is crucial to know whether the mental disorder already existed at the time the crime was committed and if the disorder could have influenced the suspect's behaviour. Then, taking into account the presence of the disorder and the causal relation of the disorder with the crime, in combination with all the circumstances of the case, an assessment is made of what judgment should be pronounced regarding criminal responsibility. If the behaviour stems from a mental disorder, someone cannot be held fully criminally responsible for their behaviour [3]. The behaviour therefore remains unacceptable, but instead of a penalty a measure called terbeschikkingstelling (TBS) is imposed. On account of the case of Thijs H., the criminal significance of a psychosis and criminal responsibility of a suspect has come up for discussion. In this article, we aim to explain the legal and psychiatric factors of the case against Thijs H. Consecutively, we explain shortly when TBS is imposed, what criminal responsibility means, what psychosis is, what the case against Thijs H. was, and conclude with a contemplative conclusion.

TBS and when it is imposed

TBS is a security measure applied by the court in the Netherlands when a criminal offence is committed that warrants more than four years of imprisonment, the general safety of the public is compromised, and when the suspect was diminished criminally responsible or not guilty by reason of insanity during the commitment of the crime [4]. Insanity defence is described as follows: "Not punishable is he who commits a crime that because of his poor development or morbid mental disorder cannot be imputed" [3]. In other words: when the behaviour arises from a mental disorder, the suspect cannot be penalised for his behaviour. This defence is in accordance with the principle of 'no punishment without guilt'. This principle does not mean that there was not any intent; someone in a psychosis can completely act knowingly. The behaviour remains criminal, but a so-called measure will be applied instead of a penalty.

Exactly how insanity should be formulated is left open under Dutch law. So, the court retains discretion [5]. As a judge does not have the expertise to determine whether somebody has a mental disorder, advice from behavioural experts is usually needed before the court comes to a judgement. Usually, the judge follows the advice of the experts. The behavioural experts can use international criteria, such as judgement of the unlawfulness of behaviour of a suspect and the ability to direct that behaviour to assess criminal responsibility of a suspect, although in essence, the concept of criminal responsibility remains an open concept (Table 1)[4].

Table 1: An overview of the international criteria to determine accountability as used by behavioural experts at the Pieter Baan Centre.

1. Judgement	a. the lack of awareness of the unlawfulness of their behaviour by the suspect; b. and/or the lack of awareness of what they are doing;
2. Ability to direct behaviour	c. and/or the inability to be consistent with that realisation (a/b) to determine their behaviour.

The behavioural experts investigate whether the mental disorder was already present at the time of the criminal offence [4]. This is also called the simultaneity context [4]. Secondly, there will be an investigation on whether the present mental disorder has caused the criminal behaviour, or if there exists a meaningful connection between the disorder and the criminal behaviour, and what these connections imply for the subject's criminal responsibility [4].

Far-reaching consequences

The aim of TBS is to remove the danger that has led to the criminal offence and for a safe return of the suspect to society [4]. The measure can have far-reaching consequences, as infinite extension of TBS under conditional termination is possible. This extension is only possible in case of a criminal offence against the inviolability of the body [6]. Secondly, conditional TBS can be converted into TBS with compulsory treatment when the conditions (*e.g.* going to therapy) are not followed [6]. The judge must at all times verify whether imposing TBS is proportional; it must be the last possible measure to guarantee the safety of society. When (in case of diminished criminal responsibility) imprisonment as well as TBS is imposed; the imprisonment will be executed before TBS [4]. This can be counterproductive because the mental state of a person can deteriorate in prison [4]. However, TBS before imprisonment is also not ideal: prison may diminish the efficacy that TBS had on the criminals [4]. Additionally, TBS is mainly aimed at resocialisation, whereas imprisonment is not [4].

From psychosis to PBC

Now that we have defined the law behind criminal responsibility, it is important to look at criminal responsibility during psychosis from a medical perspective. Psychosis is a condition of the mind in which someone does not sufficiently test their own observations and beliefs against reality [7]. Psychosis often presents with delusions, hallucinations, and/or disorganisation of behaviour or thoughts [4,7,8]. Delusions include certain ideas or beliefs that are inconsistent with generally accepted beliefs [4]. The person experiencing the delusion cannot change their mind when evidence is presented that proves their views are incorrect [4]. In addition, a person can hallucinate during a psychosis. Hallucinations are observations that are not caused by an external stimulus [4]. In case of Thijs H., he said he heard voices that gave him further orders to commit a murder. Disorganisation is the inability to bring order to thoughts, behaviour, or emotions [4]. As a result, someone can no longer perform actions that they previously were able to perform, like performing administrative tasks, or making statements that are difficult to follow [8]. However, being able to perform these actions does not indicate that someone cannot be psychotic.

A short-term psychotic disorder can last from one day to a month, with a full recovery of functioning [8]. A psychotic disorder increases the risk of aggression and violence [9]. This increased risk is mainly caused by concomitant use of alcohol and/or drugs [10]. Violent behaviour is more likely to occur in the presence of imperative hallucinations, which order the person that experiences the hallucinations to do something violent to another person [4]. When under the influence of alcohol or drugs, the hallucinated commands are more likely to be obeyed [4].

If the criminal responsibility of a defendant of a serious (violent) crime is questioned due to mental health, the defendant can be send to the PBC. An example of a condition that can lead to questioning whether a criminal is responsible for the crime or not is a suspicion for psychosis, such as in the case of Thijs H. The psychiatrists of the PBC work within a multidisciplinary research team consisting of a psychologist, social-environment researcher, jurist, and a social worker [11]. The PBC advises the judge to which extent the suspect can be held criminally responsible for the crime [11]. In addition, the PBC advises on treatment and the risk of recidivism [4,12]. However, it is up to the judge to decide whether there is reason to impose TBS [4].

A suspect may have an interest in a certain outcome of the investigation at the PBC, which means that suspects sometimes feign a mental disorder [11]. The investigation of the subject in the PBC lasts six weeks and may be extended [11]. The length of the observation significantly reduces the possibility of feigning a psychiatric disorder, as it is difficult to keep up an act under supervision for weeks [11]. In addition, a suspect is given a psychological assessment in which investigators test whether what a suspect says is consistent with the results of the test psychological assessment [11].

Trial and judgement of the case Thijs H.

At the hearing, Thijs H. stated that he suffered from delusions and fears and used drugs [1]. Experts from the PBC concluded that Thijs H. had serious reality testing problems at the time the crimes were committed and that he was, therefore, unable to reflect properly [1]. Furthermore, they concluded that he was not properly helped by mental health care in the months prior to the disintegration [1]. As the focus of his treatment was on treating his other mental disorders (attention deficit hyperactivity disorder and an autism spectrum disorder), the psychotic disorder was overlooked. Besides, during the treatment of attention deficit hyperactivity disorder, the antipsychotic medication was stopped and other medication was started that could have caused or worsened his psychosis [1]. Due to these circumstances, the PBC advised the judge to not let Thijs H. be criminally responsible for his crimes and, consequently, give him TBS with compulsory treatment [1].

However, during the trial it becomes clear that Thijs H. has had paramount influence on the onset of his own psychiatric disorder by using both prescribed and non-prescribed medication and drugs [4]. In addition, Thijs H. regularly searched the internet for the signs of psychosis and how this can be induced by the (combined) use of certain drugs. This suggests that he knowingly caused his own psychosis and that he had the freedom of choice in doing so [1].

The court concludes that at the time of the offense there is a decompensated psychotic picture of the situation [1]. The causal relationship between the disorder and the offences is sufficiently plausible, leaning towards the insanity plea. The judge also ruled that Thijs H. had enough time to consider the murders and that, within the commands, he was given a choice of how these should be completed in terms of victim, place, and time [1]. The combination of these two considerations, led to the court's ruling to consider Thijs H., contrary to the advice of the PBC, diminished criminally responsible [2].

The judge's ruling of diminished criminal responsibility is based upon the impression that Thijs H. was still in control of his own behaviour to a certain extent. Firstly, the court questions whether the way Thijs H. presented himself is a call for help or an exaggerated way of obtaining a certain desired sentence [1]. This is based upon the finding that Thijs H. searched for information about psychosis and the effect of substance use on the development of psychoses and aggressive behaviour before the alleged crimes were committed.

Furthermore, a practitioner of the penitentiary institution of Vught described his story as little lived through, as if it were not his own story [2]. It is noted that Thijs H. takes the moment of the emergence of the delusions further and further back in time, and he can tell only few details about the content of the messages [2]. Secondly, the court reiterates the importance of freedom of choice in the execution of his assignment. The court also mentions that he made the conscious choice well before the offence to not share correct information about his psychological state [13]. As a result, his disruption could not be properly noticed [13]. The court also ruled that he made a conscious choice to take narcotics and (non-)prescription medication, despite advice not to do so [14].

In view of this choice, his searches on the internet, and his intellect, he could be expected not to use the narcotics and non-prescription drugs [2]. In addition, during the entire period of disruption, there were also times when Thijs H. did not use drugs, which makes substance dependence less plausible. By abusing drugs, Thijs H. contributed to the increase in the seriousness of his psychological state and chose the dangers himself [14].

Corresponding to their ruling that Thijs H. is deemed diminished criminally responsible, the court imposes an 18 year prison sentence on Thijs H. and, because of the safety of others and the high risk of recidivism, TBS with compulsory treatment [2]. The compulsory nursing is considered necessary because there is no confidence that Thijs H. will adhere to the treatment given his behaviour in previous treatments [2]. Thijs H. has appealed the decision [15].

Contemplative conclusion

In conclusion, the court agreed with the psychotic disorder that was found in the PBC. In Thijs H.'s case it seems abundantly clear to us that he was suffering from a mental disorder at the time of the offence. We would, like the PBC, in first instance plead for complete insanity. After all, to what extent did he truly have freedom of choice? However, the court also has to look at other aspects such as substance use, his search queries, his intellect, and freedom of choice in his behaviour. Looking at these circumstances, it seems as if he has been able to oversee and foresee the situation of disruption. The court thus arrived at a judgment deviating from the advice of the PBC. We also think it is right for the court to declare him "only" diminished criminally responsible, so that in addition to treatment, retribution can also take place.

This case seems to clarify what psychosis means in criminal law. Being fully criminally responsible in a psychotic state is possible, but is not applicable when judgment and direction were lacking. However, two gradations are left on this spectrum in the Netherlands: diminished criminal responsibility and not guilty by reason of insanity. In this judgment, the court has made it clear that having freedom of choice in a psychotic state can mean that a suspect is not considered 'not guilty by reason of insanity', but diminished criminally responsible. The tipping point therefore lies on both the assessment and control capacity and the degree to which a person has had freedom of choice. This provides a broad spectrum of criminal responsibility and seems to us to be a "favourable" interpretation for both the suspect and society. On the one hand, a disorder that a suspect may have acknowledged and treated by means of the imposition of a measure. On the other hand, there is room for retribution by imposing a punishment. The judgment is in any case important, for the court has not followed the advice of the PBC and has given direction in the concrete interpretation of the spectrum of criminal responsibility. How this will pan out on appeal or perhaps even before the Supreme Court afterwards remains to be answered. Perhaps the assessment of the concept of criminal responsibility will proceed differently after the appeal. To be continued…

Affiliations

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ANSWERS TO THE EXAM QUESTIONS

Question 1

Answer: C. Block PD1-PD1L interaction

The binding of PD1 to PD1L has an immunosuppressive effect, as the binding leads to the suppression of PD1. Thus, by blocking PD-1PD1L binding, the inhibition of the immune system is inhibited, leading to an increased activation system.

For further reading: Parham, P. Chapter 17: Cancer and Its Interactions With the Immune System in The Immune System, 4th edition (Garland Science, New York, 2015).

Question 2

Answer: C. tertiary prevention.

Primary prevention refers to strategies to avoid diseases from occurring at all. Secondary prevention describes an early intervention to prevent complications. However, tertiary prevention aims to improve general health and prevent long-term complications after the disease (*e.g.* atherosclerosis) and/or complication (*e.g.* myocardial infarction) has already occurred. Therefore, cardiac rehabilitation programs are a form of tertiary prevention.

Question 3

Answer: C. Zoonotic transmission

Zoonotic transmission describes the transmission of an infection from animals to humans. Vertical transmission describes a disease that is transmitted from mother to child. In contrast, vector-borne transmission has been described in the brief message: vectors, such as mosquitos, carry the pathogen from animals to humans.

For further reading: Parham, P. Chapter 13: Failures of the Body's defences, in The Immune System, 4th edition (Garland Sciences, New York, 2015).

Question 4

Answer: B. secondary appraisal

Primary appraisal is your response to the stressor, e.g. is this a positive or a negative stressor for you? What does this mean for you? After this initial reaction, you reflect upon whether you have enough capabilities and support to handle a stressor. Social support and social network affects your possibilities of dealing with a stressor and is, therefore, a part of the secondary appraisal.

For further reading: Kaptain, A., Prins, J., Colette, E., Hulsman, R. Chapter 11: Stress, in Medical Psychology, 2nd edition. (Bohn Stafleu van Loghum, Houten, 2010).

Question 5

Answer: B. Heteronymous bitemporal hemianopsia

A pituitary gland tumour that presses on the optic chiasm will disrupt the nerve fibres that cross over in the centre of the optic chiasm. These are responsible for the temporal vision of both eyes, leading to heteronymous bitemporal hemianopsia. Complete loss of eyesight in one eye would be caused by retinal damage or damage to the nervus opticus. On the other hand, homonymous hemianopsia is caused by damage to the optic tract or damage to the optical lobe.

Further reading: Siegel A., Sapru, H. Chapter 15: Visual Systems, in Essential Neuroscience, 4th edition (Wolters Kluwer, 2019).

Question 6

Answer: B. the adjustment of the dosage of a beta-blocker based upon the patient's kidney function.

In the case of personalised medicine, the medication should be adjusted based upon patient-bound factors. A kidney function differs per person and is, therefore, an example of a patient-bound factor. The source of pain or the type of pathogen is more associated with the disease than the patient.

For further reading: Jerome, P., John, B.m Richard, I. Chapter 7: Therapeutic Decision Making, in Learning Clinical Reasoning, 2nd edition (Lippincott Williams & Wilkins, Baltimore, 2010).

Question 7

Answer: C. both a decreased activation of macrophages and a decreased production of anti-HIV antibodies.

HIV can infect both macrophages –leading to a decreased activation– and the CD4+ T cells, leading to a decreased production of anti-HIV antibodies. Furthermore, the CD4+ T-cells are involved in activating macrophages, contributing further to the decreased activation of macrophages.

For further reading: Parham, P. Chapter 13: Failure of the Body's Defenses, in The Immune System, 4th edition (Garland Science, New York, 2015).

Question 8

Answer: B. Proteins

In case of a lack of glucose, the human body will start a chemical reaction which converts proteins into glucose.

For further reading: Baynes, J., Dominiczak, M. Chapter 31: Glucose Homeostasis and Fuel Metabolism: Diabetes Mellitus, in Medical Biochemistry, 5th edition (Elsevier, 2019).

ANSWERS TO THE EXAM QUESTIONS

Question 9
Answer: A. Antibodies

Antibodies are amongst the final products of the immune response. After generation, these pathogen-specific antibodies circulate throughout the body. This allows for a quick, neutralising response if a re-infection occurs.

For further reading: Parham, P. Chapter 4: Antibody Structure and the Generation of B-Cell Diversity, in The Immune System, 4th edition. (Garland Science, New York, 2015).

Question 10
Answer: C. contains uracil as a base.

Both DNA and RNA consist of nucleotides, which contain a sugar molecule, a nitrogenous base, and a phosphate molecule. DNA contains the bases cytosine (C), guanine (G), thymine (T), and adenine (A). RNA uses similar bases; however, RNA contains uracil (U) instead of thymine. Although RNA is usually single-stranded, it can –under certain circumstances– form a double helix. The sugar groups also differ per nucleic acid; whereas DNA contains deoxyribose, RNA contains ribose.

For further reading: Turnpenny, P. Chapter 2: The Cellular and Molecular Basis of Inheritance, in Emery's Elements of Medical Genetics, 15th edition (Elsevier, 2017).

Question 11
Answer: B. Place

The sensory homunculus is divided into several regions based upon the location of the sensory input, *e.g.* the sensory input from the upper extremities is processed in a specific region. In contrast, the sensory input from the low extremities will have its own space on the sensory map.

For further reading: Siegel, A., Sapru, H. Chapter 25: The Thalamus and Cerebral Cortex, in Essential Neuroscience, 4th edition (Wolters Kluwer, 2019)

Question 12
Correct answer: A. large growth fraction

Chemotherapy interferes with the cell cycle and will, therefore, have the most significant effect on fast-dividing cells. The growth fraction defines the proliferative part of the tumour. Accordingly, tumours with a large growth fraction will have a large percentage of dividing cells, meaning that the chemotherapy will be more effective.

For further reading: Nais, J. Chapter 6: Infection, Immunity, and Pathology, in Medical Sciences, 3rd edition (Elsevier, 2019).

Question 13
Correct answer: B. improving socialisation

Socialisation describes the phenomenon of learning the morals and norms of others, whereas social cohesion describes the preparedness of people to connect with one another, *i.e.* the solidarity and connectedness between different groups in society. Therefore, improving socialisation is the most fitting answer.

For further reading: Gazzaniga, M. Chapter 12: Social Psychology, in Psychological Science, 6th edition (W. W. Norton & Company, Canada, 2018).

A Word from the Board of RAMS

Dear reader,

Thank you for reading this special 20th RAMS edition! Releasing the 20th edition of our journal is something to celebrate and to be proud of. We want to thank everyone who has contributed to this latest release, and we appreciate every person who has supported RAMS along the way. We believe this collection of brief messages, especially selected by our own editors, shows us the great variety of scientific topics that can be undertaken, and we hope it inspires you to expand your scientific knowledge.

Despite the COVID restrictions, the seventh board worked very hard to make this year a success, and I as chair could not be prouder. I am delighted that we published four editions packed with different articles and that a record number of students attended our activities. It has been a wonderful year for RAMS, and we are grateful for all the support we received. Now that the 20th has been published, it is not only goodbye for us as the seventh board and for me as chair, but it is also the end of my Bachelor of Medicine. During my time at RAMS, I was able to marvel over all the different facets of medical science and research. This has shown me that besides becoming a medical doctor, I also enjoy research. Thus, I can already see myself working in an academic hospital in the future.

Now, all good things come to an end, but every ending indicates a new beginning. The seventh board will be replaced by the eight board, who are eager to start their year as they plan to make RAMS grow even further as an organisation. I have full confidence in my successor, and I am sure the eight board will keep making an impact on the education of (bio)medical students.

On behalf of the eight board, I as chair also want to thank you for reading and I want to thank the seventh board. Strengthened by the news that lecture halls are reopening, we are looking forward to the beginning of another beautiful academic year filled with more educational editions and —hopefully physical— RAMS activities.

Stay safe and see you soon!

On behalf of the seventh and eight board of RAMS,

Lotte van der Net
Chair of the seventh board of RAMS 2020-2021

Jarno Baars
Chair of the eight board of RAMS 2021-2022

General Board

RAMS is directed by the general board, which consists of four (bio)medical students. As members of the board, they frequently meet to make sure all activities run smoothly. Moreover, they are in close contact with the supervisory board and the editorial staff. If you have any questions on general, promotional, or financial subjects, please contact the general board of RAMS via voorzitter.rams@ru.nl.

Editorial Board

The editorial board, which consists of three (bio)medical students, is responsible for the contents of the journal, from reviewing the submitted papers to their rejection or publication. Furthermore, the editorial board is in charge of writing editorials and determining the general layout. For questions concerning the content of the journal, please contact the editorial staff via hoofdredactie.rams@ru.nl. To submit papers, consult the 'for authors'-section on our website or mail to submit.rams@ru.nl.

Reviewers

Reviewers have been trained with the help of masterclasses given by professors and teachers at Radboud university medical center. With their knowledge, the reviewers are able to judge the submitted scientific and editorial articles.

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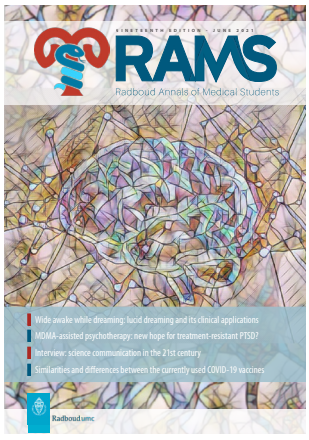

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