

SJM Commentary

007 meets The Lancet

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Ten years after becoming international news as the KGB-cum-British spy, taken out by shady Russian operatives using new radioactive poisonings, Alexander Litvinenko has made it back into the (medical) news in a recent case study in the Lancet. His doctors are free to describe his case, now that any state secrets involved have been exposed in the court of law. Thus, The Lancet brings us the closest thing I've seen in a medical journal to a spy thriller. Alright, perhaps not quite so suspenseful, since we know the tragic outcome from the get-go. Still, a fascinating toxicology tale describing the natural history of Po-210 poisoning. There are interesting parallels to be drawn to the effects of chemotherapy: first nausea and vomiting (though possibly attributed to a potential concomitant *C. difficile* infection), then alopecia, then bone marrow failure, and finally multiple organ failure and death (Figure 1). The treating physicians note that, at the dosage with which he was poisoned, there was never any hope of his recovery, though they raise the possibility of treatment of lower Po-210 doses and raise interesting questions about hospitals' ability to recognize cases of this poisoning. A worthy read, both for the sake of geopolitics and for a good primer in radiotoxicology.

Nathwani A. C., Down J. F., Goldstone J., et al. (2016). Polonium-210 poisoning: a first-hand account. Lancet, 388(10049), 1075-80.



Karen Arane: *No Comment*

Mindfulness in Medicine – Helping Community and Physician Health

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Mindfulness is a form of meditation that focuses on nonjudgmental present moment awareness. The study by David S. Ludwig MD, PhD, and Jon Kabat-Zinn, PhD, titled “Mindfulness in Medicine” suggests that the practice of mindfulness is not only beneficial for patients who may experience chronic illness, pain and substance abuse, but also to the physician’s ability to be more compassionate and make better clinical decisions that may prevent medical error. Medical students selected at random to participate in mindfulness-based, stress reduction training showed decreased stress levels and increased empathy compared to those that did not participate in the study. The study analyzed cases where patients with cancer, type 2 diabetes, psoriasis, sleeping disorders, ADHD, obesity and other conditions showed a positive increase in mood, perception and acceptance of pain, overall stress reduction, better physical functioning, increased overall well-being, and ability

to cope better with everyday life.

Another study titled “The Neuroscience of Mindfulness” aimed to analyze the effects of mindfulness on the brain and reveal specific neural pathways involved during mindfulness meditation. MRI data suggests that mindfulness meditation might lead to increased cortical thickness and increased activity within the white matter. Eight different brain regions were shown to be involved in mindfulness meditation: the frontopolar cortex, involved in meta-awareness; the sensory cortices and insula, involved in body awareness; the hippocampus, involved in memory; the anterior cingulate cortex, mid-cingulate cortex and orbitofrontal cortex, areas involved in emotion; and the superior longitudinal fasciculus and corpus callosum, areas involved in communication within and between cerebral hemispheres.

Both of these studies suggest that cultivating present moment awareness through the practice of mindfulness can have major positive benefits with regards to the quality of life of patients and physicians alike.

Ludwig D. S., & Kabat-Zinn J. (2008). Mindfulness in medicine. *JAMA*, 300(11), 1350-2.

Tang Y. Y., Hölzel B. K., & Posner M. I. (2015). The neuroscience of mindfulness meditation. *Nat Rev Neurosci*, 16(4), 213-25.

Zika Virus: Looking Back and Forward

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The authors of a recent publication in *The Lancet* examined whether or not a correlation exists between infection with Zika virus, an emerging arbovirus, in pregnant mothers, and microcephaly in the developing fetus. After gathering data from an epidemic that took place in French Polynesia prior to the outbreak that occurred in the Americas, the authors found an increased risk for microcephaly, and resultant brain/mental damage, in infants born

to mothers infected with Zika virus during the first trimester. This risk was estimated to be about 1%. The statistical significance of their findings should be taken into account by health professionals worldwide. Although further prospective studies need to be done to establish stronger connections between maternal infection and microcephaly, these data indicate that significant correlation likely exists. Emerging viruses present the potential to cause devastating epidemics, and thus should be tackled with full force in order to prevent morbidity and/or mortality. Zika virus, being an emerging virus, thus has direct effects on healthcare personnel, who need to be aware of the potential risks associated with maternal infection, and to ensure that their patients are adequately informed. By doing so, medical professionals can limit the number of diagnosed cases of congenital microcephaly. Medical students and young doctors need to be made aware of the variety of emerging viruses, as well as their potential treatments and methods of containment, as they will be the ones that will treat those patients who are unlucky enough to become infected.

Cauchemez S., Besnard, M., Bompard P., et al. (2016). Association between Zika virus and microcephaly in French Polynesia, 2013–15: a retrospective study. *Lancet*, 387(10033), 2125-2132.

PD-1 Blockade in Melanoma

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The authors examine the use of pembroluzimab, a monoclonal antibody designed to block the PD-1 pathway in metastatic melanoma. PD-1 ligand has been found to be expressed on several cancer cells, including metastatic melanoma, and when bound to the PD-1 cell-surface receptor on T-cells, functions to reduce immune mediated destruction of those cancerous cells. Blockade of this pathway has the potential to promote T-cell mediated cytotoxicity and reduce tumor burden. The authors note that further studies need to be done to establish which patients should receive treatment with pembroluzimab and

whether this treatment should be started after initial therapy with other monoclonal antibodies directed against differing cell surface receptors (i.e. BRAF/MEK). The use of monoclonal antibodies shows great promise as a future treatment option for a wide variety of diseases, and thus medical students, and all medical professionals, should be made aware of the amount of potential of such therapy.

Bhatia S., & Thompson J. A. (2016). PD-1 blockade in melanoma: a promising start, but a long way to go. *JAMA*, 315(15), 1573-5.

What is Precision Medicine?

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The emerging and rapidly progressing field of precision medicine, in which treatment is tailored to patients on an individual basis, is examined by the authors. Advances in the fields of genetics, proteomics, diagnostic imaging, and several others have allowed physicians to establish treatment options for patients that show greater efficacy and fewer unwanted side effects in comparison to administration of broad-spectrum therapy. The authors note that it will likely be difficult for the desires of patients, physicians, insurance companies, and pharmaceutical industries to align. More than likely, there will have to be a joint effort carried out so that precision medicine can become the norm in patient care. As an emerging field, medical students and other training physicians need to stay well informed as any changes in regards to precision based medical approaches will likely affect how they practice medicine in the future

Jameson J. L., & Longo D. L. (2015). Precision medicine—personalized, problematic, and promising. *N Engl J Med*, 372(23), 2229-34.

E-Cigarette Policy

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This paper examines the ever-increasing use of electronic cigarettes as a possible alternative to the use of combustible tobacco products. The authors note that many anti-tobacco advocacy groups tend to focus on the adverse effects of electronic cigarette use, rather than noting the potential benefits of these nicotine delivery systems. The authors argue that electronic cigarettes can provide an excellent outlet for smokers who are unable or unwilling to quit smoking. With the use of electronic cigarettes, smokers are able to intake the desired nicotine, whilst avoiding the harmful tar and other byproducts introduced into the body with combustible tobacco products. Due to the major side effects and deaths associated with combustible tobacco products, the possibility of appeasing smokers' addictions using a less harmful delivery system can dramatically reduce medically related symptoms, including morbidity and mortality. This has an incredible amount of potential, with the possibility of greatly reducing healthcare costs associated with tobacco use. Young physicians should take note of the potential benefits of using e-cigarettes as they may be employed to appease addictions while avoiding the toxic effects of inhaling combustible products.

Green S. H., Bayer R., & Fairchild A. L. (2016). Evidence, policy and e-cigarettes — will England reframe the debate? *N Engl J Med*, 374, 1301-1303.

NEJM: Betamethasone for Late Preterm Births

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This April 2016 article in the New England Journal of Medicine raises lots of new and interesting questions as it answers some existing and important ones! The authors, on behalf of the NICHD, present results of an RCT giving antenatal betamethasone to women at high risk of late-preterm delivery (W34-W36) to see if this would lessen adverse respiratory events among these preterm newborns. Steroids are regularly given when early pre-term birth is expected, but the data has been unclear about what to do with the late pre-term pregnancies.

And it continues to be unclear! I love this study for its classic methodological elegance. Double-blind, randomized controlled trial; relatively large sample sizes (~1400 in each group); beautiful symmetry between groups; immediate and relevant primary and secondary outcomes.

And the results? I confess I'm not sure what to make of them. For mitigating the primary outcome (respiratory distress of a variety of different flavors, within 72 hours), the Number Needed to Treat (NNT) represents the predicted number of patients treated for one patient to see benefit. For example, if the NNT is 100, then—on average—out of one

hundred patients treated, one is expected to receive the benefits of the therapy described in the trial. The NNT for this study was 35, with a 95% confidence interval from 19 to 259. Various secondary outcomes had more clearly meaningful margins, and, as the authors (and Crowther & Harding's commentary) point out, the best test will be in late follow up, several years from now. The authors point out one particularly interesting subgroup: there was a significantly meaningful reduction in risk in those patients for whom a cesarean delivery was planned. It would be interesting to see how the NNT played out in that group.

Overall, given a relatively mild adverse reaction profile (the authors note a need to follow the newborns for hypoglycemia), I am curious to see how this plays out in terms of recommended practice. Perhaps we'll have to wait to see the long-term follow-up before we know, though I wouldn't be surprised if this starts to become common practice in the c-section group sooner, at very least.

Gyamfi-Bannerman C., Thom E. A., Blackwell S. C., et al. (2016). Antenatal betamethasone for women at risk for late preterm delivery. *N Engl J Med*, 374, 1311-1320.