

"Getting Risk Right": An Interview with Geoffrey Kabat Seeking To Learn From Epidemiology At Its Best And Worst

This month The Epidemiology Monitor re-interviews Geoffrey Kabat, cancer epidemiologist at Albert Einstein College of Medicine, following publication of his latest book – Getting Risk Right, a thoughtful examination of the scientific process involved in identifying and assessing health risks. The Monitor interviewed Kabat earlier in 2009 when he published his first book entitled "Hyping Health Risks". (See <https://tinyurl.com/huv6vpb>)

Kabat has long been concerned with the challenges facing epidemiologists in doing solid research and having these results represented accurately in the public domain. Beginning with the basic question "Why do things that are unlikely to harm us get the most attention?", Kabat makes use of detailed case studies to explore the factors that contribute to epidemiology both at its best and its worst. The public, the media, and the scientists all appear to contribute to

- Kabat cont'd on next page

Lychee Fruit Identified As Culprit In Mysterious Illness Plaguing Indian Children

A frightening and mysterious outbreak that has plagued Muzaffarpur, India for over 20 years has been attributed to lychee consumption according to a recent article in *Lancet Global Health*. Each year between May and July, hundreds of children who went to bed seemingly healthy would awake with acute neurological symptoms. Forty percent of them would die. The illness was unique in that a single child in a village could be struck leaving

siblings spared. Going back to 1995, the mysterious illness has been attributed to everything from heat stroke to infection to pesticides. "They were in a kind of panic," said Dr. Rajesh Yadav, an investigator with the India Epidemic Intelligence Service, speaking to the New York Times. "Their children were dying, and it was an unknown thing."

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the problem Kabat highlights. His analysis should be of interest to those epidemiologists in the public health community hoping to contribute to meaningful scientific advances.

EM: The over-hyping of health risks is something you have been studying closely for some time and explored in your previous book *Hyping Health Risks*. What specifically motivated you to write this new book and how does it pick up where the last one left off?

GK: The first book, *Hyping Health Risks*, took a critical look at 4 prominent environmental exposures that received a great deal of attention in the 1980s and 90s. What I tried to show, and explain to myself, was how in each case a scientific question in the area of public health could get distorted and inflated as a result of limited or flawed epidemiologic studies combined with what was made of published results by the media, advocacy groups, regulators, and scientists themselves.

As I was finishing the first book, there were other questions, like cell phones and particulate air pollution, that caught my interest. And my editor suggested other topics, such as BPA. But my strongest feeling, as I thought about another book, was that I didn't want to repeat myself. To spend years writing a new book, I had to find an animating idea that felt new and exciting.

As I grappled with new topics, it came to me that I wanted to contrast instances where risks were hyped with examples of what science at its

best can achieve in the area of public health. And the HPV story came to mind because I knew people at Einstein who had worked on HPV since the early 1980s and because I noticed that epidemiologists got a gleam in their eye when we talked about this success story. What struck me, above all, is that the general public hears little about the process that led to the development of a vaccine – how long it took and how many twists and turns there were in the path leading to the identification of the specific types of HPV that cause cancer and then to the development of a vaccine -- and that achievements like this tend to be taken for granted. On the other hand, there is enormous attention rooted in fear that is directed at potential risks that often turn out to be of little or no consequence. So that idea – of the contrast between instances where scientific research relating to health risks gets enormous attention but fails to uncover important new knowledge or make progress, and those where unimaginable progress is made – provided the central tension of the book. These represent two extremes. Most research lies somewhere in the middle. But I felt that we could learn something by contrasting the two extremes.

EM: You devote roughly the first third of the book to discussing issues of bias and methodologic and disciplinary pitfalls. Can you summarize the thrust of this introductory section?

GK: The first third of the book lays the groundwork for the remainder of the book – the case studies that

- Kabat cont'd on page 11

National Academy Releases Report On Incorporating Emerging Science In Risk Assessment

In the current age of big data sets and increased computational power, many scientific fields are now faced with new tools and the challenges that come along with them. In the context of human health risk as a result of chemical exposure, risk has historically been assessed using animal models extrapolated to human scenarios. Many of the limitations to this approach are being addressed by recent advancements in a host of technologies that allow researchers to ask entirely new and complex questions to better assess the risk posed by environmental and chemical exposures.

Addressing the Advancement of Chemical Risk Assessment

Published in early January, a National Academies of Sciences, Engineering, and Medicine report outlines the very advancements that are improving and complementing the data from whole animal models such as new genetic techniques, high-throughput *in vitro* tests, and computational modeling. Chair of the report committee, Jonathan Samet, epidemiologist at the University of Southern California, says the report "... identifies critical challenges to be addressed in using 21st century science to better characterize the risks of chemicals for human health." Data from these new approaches can improve risk evaluations by doing a better job of accounting for the high degree of disease complexity related to exposure and causation.

Building on Increased Awareness

The report comes on the heels of two

previous reports (*Toxicity Testing in the 21st Century: A Vision and a Strategy* and *Exposure Science in the 21st Century: A Vision and a Strategy*). Written at a time when many began to realize how the advancements in biology and basic science might improve our understanding of chemical risk, these two reports spurred the scientific community to apply more advanced methods to chemical risk evaluation. Knowing the full potential of the new techniques and data now rapidly being generated, last month's National Academy Report was commissioned to "recommend the best ways to incorporate the emerging science into risk-based evaluations." Sponsored by the U.S. Environmental Protection Agency, U.S. Food And Drug Administration, National Institute of Environmental Health Sciences, and National Center for Advancing Translational Sciences, the report focuses on the scientific advances impacting several related fields: Exposure Science, Toxicology, and Epidemiology. Within each field, technology is driving new directions with respect to integrating emerging evidence that will improve the four elements of risk assessment: hazard identification, dose-response assessment, exposure assessment, and risk characterization.

Examples of 21st Century Science

Molecular advancements in *-omics* technologies are allowing scientists to get a better understanding of the mechanistic basis of biological

"Data from these new approaches can improve risk evaluations..."

"...the report focuses on the scientific advances impacting several related fields..."

"...these advanced techniques necessitate a host of new solutions in and of themselves."

responses, and identify biomarkers of exposure that are critical in connecting the dots from exposure to outcome. Computational advances are improving the ability to estimate risk from novel chemicals and exposures and probe chemical interactions, as well as helping model the intricacy of individual responses based on multi-route exposure and physiological variability. Lastly, new analytical techniques and assays are helping characterize chemical and environmental exposures by both broadening the scope of chemical exposure data (non-targeted analyses) and also improving targeted analyses.

Impact on Epidemiology

Epidemiology, due to its interdisciplinary nature, is benefiting from developments in all of the above areas. Molecular advancements in the -omics technologies (in particular) are changing the way epidemiology is practiced and strengthening our understanding of the biological plausibility of exposure and disease. While genome wide association studies have been helpful in understanding the genetic basis disease in some situations, now epigenomics, proteomics, transcriptomics, and metabolomics are adding enormous amounts of additional data for epidemiologists to consider in their efforts to improve public health.

Integration of Advanced Approaches

Advanced approaches can be combined with powerful results, but as the field matures these advanced techniques necessitate a host of new

solutions in and of themselves. For example, new statistical methods must be used to properly analyze and interpret the data. Infrastructure needs to be in place to handle the loads of samples and biobank data produced by these integrative studies. Harmonization and validation of platforms and results is required to not only assist with basic data comparison but also to potentially allow for better data-sharing and powerful meta-analyses. And perhaps more importantly, it also requires collaborations between experts to complete the picture.

A Multidisciplinary Path Forward

The report summary concludes by emphasizing this last piece; the necessity for a multidisciplinary approach. "Exposure scientists, toxicologists, epidemiologists, and scientists in other disciplines need to collaborate closely to ensure that the full potential of 21st century science is realized to help to solve the complex environmental and public-health problems that society faces." Data generation and collection is occurring at an unprecedented pace and the only way to keep up will be for the experts to work together to tackle these challenges. "Although the challenges to achieving the visions of the earlier reports often seem daunting, 21st century science holds great promise for advancing risk assessment and ultimately for improving public health and the environment."

EurekAlert! Coverage:

<https://tinyurl.com/jhw4m3m>

Link to Report:

<https://tinyurl.com/jyvdaq9> ■

"...the only way to keep up will be for the experts to work together to tackle these challenges."

Numerous Studies Point to Neurotoxic Effects of Air Pollution

In a recent article, *Science* highlights the growing body of evidence suggesting that inhalation of fine and ultrafine particles commonly found in air pollution can damage the brain and increase the risk of developing dementia and Alzheimer's disease. The potential for cognitive impairments is added to the long list of established health issues attributable to air quality such as asthma, lung cancer and heart disease.

Air Pollution and Dementia

One paper cited in the article and published last month in *Translational Psychiatry* was an 11-year epidemiological study of the effects of particulate matter (PM) exposure on women. The class of PM they studied is PM_{2.5}, specifically particles with an aerodynamic radius less than 2.5µm. According to Arian Saffari, an author on the study that came out of the University of Southern California, "The smaller the particles that cells are exposed to, the higher their levels of oxidative stress." Ultimately, the study found that "... airborne PM exposure promotes pathological brain aging in older women, with potentially a greater impact in ε4 carriers." The authors "estimate that ~21% of accelerated cognitive decline and all-cause dementia are attributable to residential exposure to high ambient PM_{2.5}." The second finding is particularly interesting because Apolipoprotein E (APOE) ε4 is among the loci implicated in Alzheimer's disease (AD) and yet these genetic alterations have so far accounted for less than half of AD cases. The present finding suggests the need for synergy between genetic and

environmental factors to increase risk.

Another study referenced in the article was published last month in the *Lancet*. Based on existing evidence that living in closer proximity to a major roadway might have negative effects on cognition, a team from the University of Toronto set out to investigate more closely the associations between proximity to roadways and Parkinson's disease, dementia and multiple sclerosis. Their finding? "In this large population-based cohort, living close to heavy traffic was associated with a higher incidence of dementia, but not with Parkinson's disease or multiple sclerosis." Interestingly, persons living in less than 50 meters from a major road showed a 7% increased risk of developing dementia. That risk disappeared completely for individuals living greater than 200 meters from a major road. For those living in major cities at less than 50 meters from a major road, their risk increased to 12%.

Relating Animal Model Insights to Humans

Many of the other studies linking pollution exposure to damage in the brain have used animal models and translation to meaningful insights for humans is still necessary. The *Science* article notes this will be difficult as long-term data on pollution are lacking globally. Some work has been done to date however such as a review of 18 studies in 6 countries, including the US and China, where all but one showed correlation

"...living close to heavy traffic was associated with a higher incidence of dementia.."

"...long-term data on pollution is lacking globally."

Differing Impacts Across Socioeconomic Groups

On a final note, the *Science* article highlights the differential effects across socioeconomic groups. Because they more commonly live in areas with higher PM2.5 levels, the poor will be disproportionately affected. Additionally, recent studies have demonstrated a synergistic effect between pollution levels and other environmental stresses like litter and crime. This means that policy changes might be most effective if focused specifically on the most vulnerable communities. In the end, air pollution may end up an even bigger villain than originally predicted. According to Caleb Finch, a neuroscientist who works with the USC team, "I think [air pollution] will turn out to be just the same as tobacco - there's no safe threshold."

Science News Article

<https://tinyurl.com/j9mclkg>

Translational Psychiatry Article

<https://tinyurl.com/gq1he2n>

Lancet Article

<https://tinyurl.com/z6r69u7> ■

between dementia and high exposure to a component of air pollution. More work needs to be done, however. And it's clear that more data are necessary. Only a third of US counties monitor pollution and PM2.5 has only been monitored since 1997.

Using Simulation to Fill in the Missing Pieces

One solution to the lack of data may be simulation, and one study underway in Seattle will use modeling data to estimate lifetime exposures to PM2.5 allowing for correlations with dementia incidence. Participants in the study have already been monitored for cognitive changes for 20 years. All that's missing is the PM2.5 data. Lianne Sheppard, a biostatistician at the University of Washington, says that combining the data set with genetic studies will allow their research group to understand "not just the epidemiology of the relationship between air pollution and cognition, but start drilling down to mechanisms" for interactions between pollutants and the brain.

"...the poor will be disproportionately affected."

"air pollution may end up an even bigger villain than originally predicted."

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Mathematical Correction Dramatically Increases Cervical Cancer Mortality Rates

A recent study found that a simple calculation error has led to a gross underestimation of cervical cancer mortality rates. The authors of the paper, published in *Cancer*, argue that prior studies failed to account for the prevalence of hysterectomy in the calculations of cervical cancer incidence. As lead author Anne Rositch, assistant professor of epidemiology at Johns Hopkins School of Public Health told the New York Times, "We don't include men in our calculation because they are not at risk for cervical cancer and by the same measure, we shouldn't include women who don't have a cervix." After estimating the overall prevalence of hysterectomy among women in the U.S. to be 20%, this correction has a profound effect, increasing the mortality rate to 10.1 per 100,000 among black women and 4.7 per 100,000 among white women. These numbers were previously calculated at 5.7 and 3.2, respectively. In addition to increases in overall mortality rates, the study found that the disparity in death rates between white and black women is much greater than previously thought, with age-specific rates in black women increasing by as much as 125% following the correction, compared to an 83% increase in white women of the same age. Most concerning, the corrected mortality rates for black women living in the U.S. are as high as those seen in much of the developing world, including sub-

Saharan Africa.

See the study in *Cancer* here:
<https://tinyurl.com/zwy29qv>



Time Magazine Tackles the Epidemiology of Hate

"It is neither partisan nor opinion to suggest that the rhetoric surrounding the Trump campaign was definitionally hateful, misogynistic, xenophobic, and racist." Following the election, *Time* magazine asked some tough questions about the state of hate crimes and the toll they may take, not just on politics, but also on public health. The piece explores data demonstrating a rise in hate crimes and anxiety levels and questions how the Trump administration might change the way the Department of Justice tackles or even acknowledges these issues. The authors of the piece, including physician and journalist Akash Goel, urge "Given that the downstream health effects of hate crimes and discrimination are so dramatic, public health and medical systems should join these efforts." Following their call to action, we are also reminded that, "When faced with the threat of pandemic, our public health systems are a fortress. Now, more than ever, they should be leveraged against our time's most virulent strain: hate."

Read the article from *Time* here:

<https://tinyurl.com/jnkm8la>

"...the corrected mortality rates for black women living in the U.S. are as high as those seen in much of the developing world..."

"The piece explores data demonstrating a rise in hate crimes and anxiety levels..."

*"...two-year
medical detective
story..."*

Who was on the Case?

A joint investigation by India's National Center for Disease Control and the India office of the Centers for Disease Control and Prevention in Atlanta set out to crack the case. The results of the investigation that carefully tracked the outbreak in the year 2014 were published last month. Investigators identified consumption of the lychee, also known as litchi, fruit as the culprit - particularly consumption of the underripe fruit on an empty stomach. According to the New York Times, "The *Lancet* article walks through a two-year medical detective story, as epidemiologists like Dr. Yadav closely examined the lives of hundreds of afflicted children, trying to understand everything they had eaten, drunk and breathed." Below are key findings that helped unravel the mystery.

No signs of Infection

The first puzzling result was that these children showed no evidence of infection. Many outbreaks of this nature are immediately assumed to be caused by infection. Yet, the sick children were not febrile nor did they have elevated white blood cell counts, both common indicators of infection.

Abnormally Low Blood Glucose Levels

Next, investigators assayed for a large number of markers, casting a wide net for hints. They found one in the form of strikingly low blood glucose levels, and they found further that children with the lowest levels were twice as likely to die.

Similarities to a Previous Outbreak

The final piece of the puzzle fell into place when investigators recognized similarities to a previous outbreak in the West Indies. In that case, the outbreak had been tied to a toxin found in the ackee fruit. This toxin, hypoglycin, as well as a similar toxin, methylenecyclopropyl glycine, are both found in the lychee fruit. The toxins in the fruit can cause acute hypoglycemia through inhibition of glucose synthesis. Following the development of a urinalysis test for hypoglycin, remarkable abnormalities were found in the affected children, strongly implicating consumption of lychee fruit on an empty stomach as the cause of extreme hypoglycemia.

Limitations of the Findings

According to the study, "Parents in affected villages report that during May and June, young children frequently spend their day eating litchis in the surrounding orchards; many return home in the evening uninterested in eating a meal." This common behavioral pattern coupled with the finding that only a single child from a village might be affected suggests that more factors than simply lychee consumption and a missed meal might contribute to susceptibility, including as yet unidentified genetic differences. The authors also concede that, "causality is considerably more difficult to establish," but they believe their, "findings reflect a plausible, but not necessarily sufficient, causal pathway between lychee consumption and illness.

*"... investigators
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What We're Reading

Are Opioids Behind a Cluster of Unusual Amnesia Cases?

Appeared in *The Atlantic Online* January 30, 2017

Doctors in Massachusetts have found a surprising link between 14 cases of amnesia and opioid use. Going beyond the usual memory loss associated with use of the drug, the patients showed acute, complete and bilateral ischemia of the hippocampus, a brain region critically involved in memory. That this condition is very rare and usually isolated is why experts are still stumped as to what would cause such a profound and specific effect.

<https://tinyurl.com/hy3uvjz>

Cancer Epidemiology Today: "Not Strengthening the Value Proposition" and "Science is an Iterative Process"

Both appeared in *HemOnc Today* January 25, 2017

An interesting debate has unfolded in the pages of *HemOnc Today*. In his editorial for the month titled "Not Strengthening the Value Proposition", [Derek Raghavan](#), MD, PhD, started asking some tough questions about the basic motivations behind studies in cancer epidemiology. Raghavan set his critical sights on what he considers to be an excess of pointless and redundant studies identifying only mild associations. He specifically cites a study by [Amanda I. Phipps](#), MPH, PhD and colleagues linking prediagnostic consumption of alcohol to modestly improved outcomes in colorectal cancer. In the same issue, you can find a direct response from Phipps titled "Science is an Iterative Process", defending her own studies and arguing that what may appear to be duplicative research is actually the iterative scientific process functioning as it should.

Editorial

<https://tinyurl.com/jz4qr2n>

Response

<https://tinyurl.com/j96utn3> ■

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How Long Would it Take Zombies to Wipe Out Humans?

Zombies are making public health headlines again. This time, undergraduate students at the University of Leicester have applied an SIR model to simulate the spread of a Zombie virus. SIR models are a

class of epidemiological models that predict the spread of disease. The name derives from equations describing the numbers of susceptible, infected and recovered people. The results of the zombie SIR model? In just 100 days, the human population would be reduced to less than 300, though the authors concede the original study had limitations. First, they did not allow humans to kill any

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Notes on People



Died: Shalon M. Irving, PhD, MPH, MS, Lieutenant Commander and epidemiologist in the Surveillance Branch of the CDC. An alumni of the Epidemic Intelligence Service ('12), Dr. Irving's dedication to public health was evidenced through her commitment to the prevention of child abuse and violence against women and the elimination of racial disparities in health. More information can be found at the following link: <https://tinyurl.com/zxs5ley>



Died: Hans Rosling, MD, PhD, Professor of International Health at the Karolinska Institute and Co-Founder and Educator at Gapminder Foundation, from pancreatic cancer. Recently the subject of a fascinating profile in *Nature*, Rosling had a long and varied career as a physician, epidemiologist and statistician, influencing the thinking of leaders including Melinda Gates, Al Gore, Mark Zuckerberg and even Fidel Castro. In his later years at Gapminder, Dr. Rosling became a self-described "Edutainer" and was well known for his TED talks.

See the *Nature* profile here: <https://tinyurl.com/z6357ck>

Watch one of his most famous TED talks here: <https://tinyurl.com/aj8upkt>



Profiled: Stephen H. Gehlbach, MD, MPH, former Dean of the School of Public Health and Health Sciences at the University of Massachusetts, Amherst, in *The Sentinel*, upon the release of an updated edition of his classic epidemiology text, American Plagues. "The lure of epidemiology for me is rather simple. It's about solving puzzles. That's an activity that many people find engaging but when it involves finding solutions to health problems, it's particularly compelling ... Challenging questions, important answers and the stuff of a career that has been most satisfying." The profile can be found at the following link:

<https://tinyurl.com/gue9dx5>



Lecturer: Katherine Fleming-Dutra, MD, on antibiotic stewardship as part of a lecture series organized by Southwest Health Systems in Montezuma County, CO. Dr. Fleming-Dutra, a medical epidemiologist with the Office of Antibiotic Stewardship at the CDC explained, "(This is) a very clear target for us to go after" when describing the 10% of antibiotic prescriptions that are incorrectly used to treat bronchitis and upper respiratory infections in the US.

<https://tinyurl.com/henjadn>

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Further Implications of the Study

The authors of the study also reference similar outbreaks in other lychee cultivation regions of India as well as Bangladesh and Vietnam that have yet to be investigated as exhaustively as the outbreak in Muzaffarpur. They suggest their findings may shed light on these similar illnesses. In general, the Muzaffarpur outbreak truly highlights the need for thorough investigation of unexplained illnesses in resource-limited settings. The application of similar systematic approaches has the potential to dramatically improve public health outcomes.

Lancet Global Health Article
<https://tinyurl.com/jdn8wqu>

New York Times Coverage
<https://tinyurl.com/z5a6nm3> ■

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zombies, and second, they did not account for the diminishing population of humans increasing the amount of time it took zombies to find their prey. According to *LiveScience*, a follow-up paper addressing these limitations resulted in a much rosier outlook for mankind. After a rapid decline in the human population, the zombies eventually died off and the human population began to recover.

Read the original article here:
<https://tinyurl.com/z6e6bfy>

Coverage on *LiveScience* here:
<https://tinyurl.com/zoe5kwm>
■

are the heart of the book. I start with the question, "Why do things that are unlikely to harm us get the most attention?" and refer to the large number of contested issues involving things that might be adversely affecting our health, including vaccines, GMOs, pesticides and other chemicals in the environment, cell phones, salt, obesity, smokeless tobacco, e-cigarettes, "fracking," etc. But rarely does the quality of the studies enter into the public discussion. You would never know from the media that there is a lively discussion going on the quality of scientific research in the biomedical field. Specifically, there is increasing recognition within the scientific community of what has been referred to as a crisis characterized by fierce competition for funding and professional advancement, a lack of reproducibility of published papers, and a lack of transparency.

EM: What was your main goal for this introductory section of the book?

GK: My goal in the first 3 chapters was to provide a framework for understanding the many factors that can influence published findings and how they get reported to the public. I cover methodological biases inherent in observational studies, as epitomized by the work of John Ioannidis and colleagues, cognitive biases such as those described by Daniel Kahneman, professional and political biases, and "bandwagon effects." These different biases can interact and reinforce each other. My intention in this section was to provide a description of the landscape in which research is

"Why do things that are unlikely to harm us get the most attention?"

"...rarely does the quality of the studies enter into the public discussion."

conducted and the kinds of pitfalls it is subject to.

EM: Do you feel these pitfalls apply equally across all areas of public health research?

GK: No, a crucial point, which rarely gets attention, is that all areas are not equal when it comes to the reproducibility of findings. This is shown nicely in a 2012 analysis by Tsilidis et al. that showed that among studies using biomarkers to assess associations with cancer, infectious agents (HPV, *H pylori*, HBV) had robust findings. In contrast, studies examining IGF/insulin and markers of inflammation had considerably lower reproducibility. Finally, studies of diet and environmental exposures had very poor reproducibility.

EM: Having set the stage, can you encapsulate the contrast between your two sets of cases studies?

GK: In the first two case studies I retell the story of roughly twenty years of research devoted to the issues of cell phones and brain cancer, and the possible health effects of exposure to “endocrine-disrupting chemicals” in the environment. In my view, both questions have their origin in dramatic findings that galvanized the attention of scientists but were misleading.

EM: What specifically were the dramatic findings that led scientists down the wrong path for so many years?

GK: The cell phone question arose

due to a man in St. Petersburg, Florida, who, after his wife died from brain cancer, brought a lawsuit against a wireless company and went on *Larry King Live*. The endocrine disruption hypothesis came about in large part in the early 1990s due to three observations: incidents in which exposure to industrial runoff affected the sex of alligators and other wildlife; the DES experience in the middle of the last century; and the alleged decline in sperm counts. None of these findings turned out to be relevant to the general population, as I explain in detail. But they led to a line of hundreds of research studies, which sometimes produced “suggestive” results and kept the bandwagon going.

EM: What were the main factors that contributed to the propagation and continued study of these misleading hypotheses?

GK: Importantly, the results of studies generated concern in the public and led to regulatory attention. I think one must acknowledge that the fact that these two issues were so much in the public eye and caused so much concern helped to perpetuate a line of research that has failed to produce solid evidence in favor of either hypothesis. Being in the spotlight helped to keep what was a weak and poorly-justified hypothesis alive and consume scarce funding.

For me, when I had a back-and-forth with the eminent expert on male reproductive function, Richard Sharpe, who is one of the originators of the endocrine disruption hypothesis, he put the issue in a way that sheds a glaring light on how a

"...all areas are not equal when it comes to the reproducibility of findings."

"Being in the spotlight helped to keep what was a weak and poorly-justified hypothesis alive..."

field can go wrong. "In retrospect, I consider that circumstances helped me because I ended up disproving my own hypothesis/ideas early on in the ED saga. Plus, I was lucky that the question that drove me was 'what causes these disorders,' not 'how do EDCs cause these disorders?' Such a simple difference, but it takes your thought processes in a very different direction."

EM: Were there clues at the time that the original hypotheses were poorly justified? Would you suggest that these situations could be avoided if hypotheses are more solidly justified before being pursued?

GK: That's an interesting question. I think, to some extent, the degree of distortion could have been reduced. Scientists are supposed to be skeptical and to be critical of the evidence, and, I think that regarding cell phones, and the earlier question of EMF, there was a tendency to have a narrow focus on weak epidemiologic studies and difficult-to-interpret in vitro studies. What I think should have gotten more attention was the nature of the type of energy involved (i.e., microwaves and extremely low-frequency electromagnetic fields) and the plausibility that these types of very weak energy could be inducing biological effects. I'm not saying that this consideration should have been determinative, but it should have been taken into account. Certainly, as time passed and more robust studies were done (particularly, involving whole animals exposed to radiofrequency emissions), there was a tendency for this strong null evidence to not receive the weight it

deserved and to latch on to weak findings from a minority of epidemiologic studies. So, to an extent, yes we could have been more skeptical from the outset, but, of course, the picture becomes clearer as more high-quality studies are done. Similar considerations could have helped put the endocrine disruption hypothesis in a critical perspective.

EM: And what about the second set of case studies?

In contrast, the second set of case studies tells of work that was carried out over decades to understand 1) a mysterious disease involving irreversible kidney damage in the Balkans and 2) the etiology of cervical cancer. Both questions were difficult and required considering multiple hypotheses, excluding explanations that did not fit with the evidence, confirming findings, and refining one's hypothesis. Over time, there were false leads, methodological and technical obstacles that had to be overcome, and disputes between different disciplines. But over time, scientists in different parts of the world collaborated and overcame obstacles and confirmed the links in a chain of causation. In both cases the work led to new knowledge but also to undreamed of consequences for public health.

EM: What were those consequences?

GK: In the first case, we now know that an herb used in traditional medicine in major cultures going back two thousand years (*Aristolochia*) causes irreparable kidney damage and cancer of the upper urothelial tract, and the

"...the picture becomes clearer as more high-quality studies are done."

"...the work led to new knowledge but also to undreamed of consequences for public health."

"...we should give greater attention to the hard work of science..."

mechanism of cancer induction is now known (i.e., it is a highly specific signature mutation in TP53). In the second case, work over more than 30 years has led to the development of vaccines that protect against HPV infection and have the potential to virtually eliminate cervical cancer, with over half a million new cases and over a quarter of a million deaths each year, mostly in countries in south Asia and Africa.

EM: So what do you believe is the main contrast between the two sets of studies?

GK: The stories highlight how science that tackles an important question typically only makes progress by dint of painstaking work by different groups of scientists over time. As Harald zur Hausen has said, there was "no eureka moment." Furthermore, because forging the links in the chain is painstaking and unglamorous, it is not newsworthy. Rather than the reports of the latest threat or breakthrough, we should give greater attention to the hard work of science that, if it pursues an important problem, can make life-changing advances.

"...we need much higher standards for what gets published..."

EM: It seems a key distinction between these sets of case studies is whether or not the media got involved early on and played a role in influencing the research before the scientific process had enough time to play out and reach solid conclusions. Would you say the media or the scientists shoulder more of the blame in these situations?

G.K. The media is the media. What sells is what is unexpected, startling,

and novel. That is not going to change. There is actually a good deal of high-quality reporting, if you know where to look for it, but that is not going to reach the vast majority of the population. So, I don't think one can have great expectations about the mass media changing. As a scientist, I'm more concerned about the quality of scientific studies and the seeking out of media coverage for results that really have very little claim on the public's attention. There is a pretense that the public needs to know about studies, but often the results really are so uncertain that one has to question what use they are to anyone. So, I come down on the side of feeling that we need much higher standards for what gets published and to stop utilizing the public to boost the stature of our work.

EM: Today more than ever, scientists are under tremendous pressure to publish or perish. Do you think systemic reforms are needed within academia in order to balance such a desire for higher standards in publishing with the increasingly competitive modern academic environment?

GK: I definitely think that systematic reforms are in order. These issues have been widely discussed, for example, in an informal survey of scientists conducted by Vox <https://tinyurl.com/joyw7xx>, and, most recently in a paper entitled "A manifesto for reproducible science." <https://tinyurl.com/jcya7f7>

- Kabat continues on next page

(The Epidemiology Monitor covered the results of the Vox.com survey mentioned above in detail in our September 2016 issue:

<https://tinyurl.com/z6sfj5s>)

EM: What is the key lesson that can be taken from these case studies about how to best investigate and report on scientific results?

GK: Having in mind models of what science can achieve at its best can provide a standard by which to judge the extravagant claims based on flimsy evidence, which get so much attention.

EM: How does having a standard of what science can achieve actually help us to determine that some claims are extravagant and others are reasonable to pursue? After all, isn't determining what is flimsy evidence from what is promising evidence the real challenge here? That is not always easy to determine in the early days of research findings.

GK: You are right, in the sense that the case studies that I recount only achieve maximum clarity in retrospect. In the 1970s virologists were dismissive of Harald zur Hausen's hypothesis that papilloma viruses might be the cause of cervical cancer. And Richard Sharpe put forward the idea in the early 1990s that "living in a sea of estrogens" might explain abnormal reproductive development. All one can do is to keep in mind alternative hypotheses and not develop tunnel vision, blocking out explanations that don't fit with one's hypothesis. As I emphasize in the book, quoting the

biophysicist John Platt, keeping in mind alternative hypotheses is the best way to protect against selecting data that appear to support a favored hypothesis.

EM: You describe a litany of factors contributing to misrepresentation of health risks. Is there any one factor you believe is most central to the problem? If not one, which do you feel are the most detrimental to promoting good science?

GK: Two things appear to me to be of paramount importance. First, we have to avoid becoming wedded to a particular hypothesis, even if it is in vogue and provides a source of funding. Once we block out alternative and possibly more promising hypotheses, we become prisoners of confirmation bias. Second, the politicization of science is a serious danger. By politicization, I mean allowing an ideological stance or policy considerations to influence one's interpretation of the evidence on a particular question. We need to continuously strive to distinguish good -- that is, reproducible -- science from politics and from policy. Jeremy Berg, the new editor-in-chief of *Science* magazine, has recently made this point.

<https://tinyurl.com/hm8yrln> ■

"...we have to avoid becoming wedded to a particular hypothesis..."

"...the politicization of science is a serious danger."

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The Department of Epidemiology and Biostatistics is located on UTHSCSA's main campus near its medical, dental, and nursing schools in the heart of South Texas Medical Center, 900 acres of medical-related institutions in San Antonio that employ 28,000 people with a \$3.3 billion budget. The Department has 20 full-time faculty (with additional affiliate faculty and 46 support staff) with expertise in translational scientific discovery, clinical- and population-based investigation, applying epidemiological and biostatistical principles to clinical problem-solving and health services organizational management, formulation of health policy, and developing epidemiological and biostatistical research methods. The mission of the Department is to: develop and enhance population-based, clinical and translational research in clinical and community settings; develop epidemiologic, biostatistical and medical informatics resources to enhance UTHSCSA researchers' ability to conduct novel research, promote health, deliver quality health care, and inform health policy decisions; and promote epidemiology and biostatistical education for all UTHSCSA medical students and staff.

The Department has close research and education collaborations with the San Antonio Campus of The UT School of Public Health and the Cancer Therapy & Research Center (CTRC) at UTHSCSA, the only NCI-designated center in South Texas, serving a multiethnic population of 4 million people in a 45,970-square-mile region. The CTRC is building on its strong reputation as a leader in population research, integrated multidisciplinary science and care, and translation of research findings into the diagnosis, treatment, and prevention of cancer while improving the quality of life of cancer survivors. CTRC's 77 researchers have more than \$29 million in extramural research funding and have a broad range of basic, clinical, and population science expertise in three research programs (Cancer Prevention and Population Sciences, Cancer Development and Progression, and Experimental and Developmental Therapeutics) that utilize eight shared resource facilities to reduce the cancer burden in our area.

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Contact: Brian Rogers MD, Director of the Institute on Development and Disability 503 494-7410 <mailto:rogersbr@ohsu.edu>



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Contact: eepe@eepe.org and <http://www.eepe.org>

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