

## A prank too far

To promote responsible driving, the catch phrase widely promoted was, and is, 'Think before you drink before you drive'. The key word is 'think'. It is a tragedy when thoughts die of loneliness but they do, and thinking of others does not always equate to understanding how others may perceive and react to a sequence of events.

A prank is defined as 'A mischievous trick; a practical joke' – and originates from the 16th century. We are familiar with the proverb 'laughter is the best medicine', but it remains essential that we think (that word again) how others may react to what may be considered to be innocent jesting. Humiliation is, by definition, degradation leading to disgrace and shame. The thick-skinned will hardly be disturbed, but the sensitive can be extremely traumatised, and probably feel isolated and bullied.

The death of the nurse Jacintha Saldanha has deeply affected many people, occurring shortly after a hoax phone call from Australia tricked her into putting the callers through to the nurse looking after the Duchess of Cambridge. Clearly, no one thought (that concept again) that the outcome would be so tragic, but that it was identifies and illustrates how intentions and actions can be interpreted so differently. The repetitive international playing of the 'interview' boasting about its content compounded the humiliation and almost certainly the sense of shame. The fact that she was blameless and unbelieving that anyone would seek to use deception to obtain confidential medical information reflects on her innocence of the media and its methods – verbal hacking in this case.

Where do we go from here? A husband and two children have the intense pain of it all, and it will be a pain that never completely goes. The two Australian presenters did not think (again) about the potential consequences of their 'fun', but that does not mean they are bad people. There is no doubt that they will need support for some time to come – they have lost their broadcasting innocence as well as their social innocence and no one wants any more tragedy. The media need to think (!) much more about the follow through of their actions. When there are no winners, focusing on the philosophy to change and improve the process is the only way to stop it happening again.

*A still small voice spake unto me,  
 'Thou art so full of misery,  
 Were it not better not to be?'*

Alfred, Lord Tennyson (1809–92)  
 – 'The Two Voices'

It need not and should not be like this. Jacintha – rest in peace.

### Disclosures

None.

Graham Jackson  
 Editor  
 Email: gicardiol@talk21.com

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**It need not be  
 like this**

## Infectious diseases: a call for manuscripts in an interdisciplinary era

*Nothing is built on stone; all is built on sand,  
 but we must build as if the sand were stone*  
 – Jorge Luis Borges

Visualising paradigm shifts and following the temporal succession of concepts that define and shape various disciplines represent a fascinating feature of the biomedical world. In many respects, this is ideally exemplified by the field of infectious diseases,

which historically has represented one of the most challenging and dynamic medical areas. In recent years, as the global distribution of pathogens witnessed significant changes, and the threat of existing, re-emerging, newly emerging and intentionally used pathogens increasingly permeated our collective awareness, this field has become more interdisciplinary than ever, opening the need for a novel framework to dissect the host-pathogen interface.



**An increasingly multi-disciplinary and interdisciplinary perspective is required to explore the complex and dynamic interface between hosts and microbes**

The epidemiology of infectious diseases has been marked by major transformations. Diseases, such as malaria, cholera, or yellow fever, once considered under control or eradicated from certain geographical areas, are re-emerging, and the geographical distribution of other, existing diseases, has been shifting. For example, while the altitude limit of *Ixodes ricinus*, an intermediate tick host of *Borrelia burgdorferi*, was considered to be 700–800 m above sea level in the Czech Republic, the bacterium was recently detected in ticks at 1065 m altitude, and its northern limit in Sweden expanded between the early-1980s and the mid-1990s, placing a larger percentage of the population at risk for Lyme disease (1,2). In the Bure District from northwestern Ethiopia, a region that has not seen the malaria outbreaks that regularly affected the rest of the country before 1998, people in many villages developed the disease around the time maize replaced more traditional crops. The first epidemiological link between maize cultivation and malaria in this region identified multiple categories of newly established conditions that favoured the survival of *Anopheles arabiensis*, the main mosquito vector (3). At the same time, known pathogens have been linked to new infections; for example, *Streptococcus pyogenes*, associated with scarlet fever until early in the 20th century, is increasingly implicated in new conditions, including toxic shock syndrome and necrotizing fasciitis (4). Furthermore, increasing numbers of pathogens have crossed the species barriers to cause human diseases. Pathogens from other species frequently and regularly cross into the human population, in a process termed 'viral chatter', which most often does not lead to epidemics, but enhances microbial diversity and adaptability and increases the likelihood that subsequent events will generate successfully established human pathogens (5,6). At least 75% of the emerging human pathogens are zoonotic, and 10–40 new viruses are estimated to emerge in the human population by 2020 (7,8). Many of these events were facilitated by anthropogenic changes that altered the interaction between species inhabiting various components of the ecosystems. The plantation of fruit orchards around pigsties in Malaysia attracted fruit bats, and the overlap between their habitat and that of farmers contributed to Nipah virus outbreaks in the local communities (9). The Diama Dam on the Senegal River, which was constructed to prevent the intrusion of seawater during the dry season and became operational in August 1986, provides another relevant example. The resulting changes in water pH and salinity provided a more suitable habitat for the freshwater snail *Biomphalaria pfeifferi*, the intermediate *Schistosoma mansoni* host, and led to an increase

in the prevalence of stools positive for schistosoma eggs from <1 to >71% between early 1988 and late 1989 (10,11). These events point towards an unmet need to devote enhanced attention to the global epidemiology of the host-pathogen interface.

The necessity to understand cross-species transmission at the molecular level emerges as an additional key facet of exploring the host-pathogen interface and has prophylactic and therapeutic relevance. The SARS outbreaks confirmed that minimal molecular changes are sufficient to modify the species tropism of a pathogen. Only four amino acids within the ~ 200 amino acid receptor-binding domain of the S protein were different between a SARS coronavirus strain infecting palm civets and the 2002–2003 human epidemic strain, but this accounted for an over 1000-fold difference in its binding affinity to the human receptor (12,13).

As opposed to the historical view that virulence is an exclusive attribute of the pathogen, a fundamental concept with significant research and clinical implications is the need to envision the host-pathogen interface as a complex and dynamic entity, shaped by contributions from both the host and the pathogen (14). HIV-1, which manipulates multiple host factors during the infection despite encoding only 15 proteins, provides an intriguing example (15). Four recent genome-wide RNA-based screens identified several sets of host genes that are critical for viral replication (16–19). One of these studies unveiled 267 host genes that were previously not linked to the infection (18).

Particularly in context of the limited number of newly approved antimicrobial agents, the emergence of resistant and multiresistant bacterial strains deserves increased attention. Resistant strains have emerged, without exception, to all commercially used antibiotics, sometimes within a year after these became available, often making the respective compounds ineffective in time. For certain pathogens, resistance has engendered global crises. The emergence of multidrug-resistant and extensively drug-resistant *Mycobacterium tuberculosis*, a pathogen that the World Health Organization declared a global emergency in 1993 (20), was followed by recent reports of totally drug-resistant strains that exhibit resistance to essentially all available antibiotics (21). Multiple lines of evidence point towards antibiotic use being a key selective force responsible for the emergence of resistance (22,23). The prescription of antibiotics for non-bacterial conditions, their frequently inappropriate clinical use, the extensive global use of certain compounds in agriculture, aquaculture and animal farming, and the circulation of resistance across ecosystem compartments are only

a few of the factors that promise to exacerbate an already existing crisis. Antibiotic resistance affects the most remote corners of the world, as revealed by the identification of *Escherichia coli* strains resistant to at least one antibiotic in 67% of the Guarani Indians inhabiting a very remote rural Bolivian area located at 1700 m altitude and characterised by minimal antibiotic consumption and very limited exchanges with the outside world (24). Defining the most effective interventions to limit the emergence of resistance and providing guidelines for judicious antibiotic use represent key tasks with public health relevance. In addition, as resistance can be mobilised between nonpathogenic and pathogenic microorganisms by horizontal transfer, the combined focus on antimicrobial resistance determinants from both pathogenic and nonpathogenic bacteria, collectively termed *the resistome*, is necessary to understand the global ecology of bacterial resistance (25). This is greatly facilitated by advances in metagenomics that opened the possibility to gain information about the genomes of unculturable microorganisms, which represent the overwhelming majority within bacterial populations found in most environments (26,27). Moreover, single-cell genomics offers the unprecedented opportunity to probe the biology of intercellular variability and to explore virulence factors, which in certain situations are known to be lost during the *in vitro* passage of pathogens (28,29).

A relatively neglected topic is the causal link between infectious diseases and other medical conditions, such as cancer and autoimmune diseases. The idea that certain microorganisms cause cancer, a concept known for approximately a century, was initially ridiculed and fell into oblivion for decades, but was subsequently rediscovered and is poised to become a key theme in microbial pathogenesis. As pathogens were causally linked to slightly over 20% of the human cancers, enhanced efforts are needed to understand the mechanistic details of this process, which recently started to emerge. This effort involves concerted contributions from several areas, including chromosomal biology, genomics and microbiology, and is facilitated by technological advances, such as next-generation sequencing and gene expression analysis. Mechanistically, microbial carcinogenesis was most thoroughly studied in context of certain carcinogenic *Helicobacter pylori* serotypes. The inflammatory process that accompanies the bacterial infection establishes an *epigenetic field for cancerization* or *epigenetic field defect*, an area in the gastric mucosa where CpG hypermethylation in the promoter of specific genes marks regions with increased risk for malignant transformation (30). This gene-specific aberrant methylation pattern provides a fin-

gerprint of exposure, which can unveil pathological modifications at a very early stage, preceding histopathological changes, and also provides a tool to monitor the therapeutic response (31). In gastric cancers, the inactivation of certain tumour suppressor genes was shown to more frequently occur by epigenetic changes, such as hypermethylation, than by genetic alterations, such as mutations, and similar findings were reported for other cancers (32). The reversibility of epigenetic modifications, one of their key distinctions from genetic changes, makes them particularly attractive prophylactic and therapeutic targets.

Another important stride came in 1993, with the first proof of molecular mimicry in a human autoimmune disorder, when it was revealed that an oligosaccharide protruding from the lipooligosaccharide core of the *Campylobacter jejuni* strain isolated from a patient with acute motor axonal neuropathy was identical to the terminal tetrasaccharide present on the GM1 ganglioside (33). The mechanism that explains why certain individuals develop post enteritis Guillain-Barré syndrome, whereas others develop its more rare variant, the Miller Fisher syndrome, was also elucidated with the discovery of a polymorphism at position 51 of the bacterial enzyme that transfers sialic acid to the lipooligosaccharide. When this amino acid is a threonine, the enzyme acts as a  $\alpha$ -2, 3-sialyltransferase and produces lipooligosaccharides that induce antibodies against gangliosides on motor neurons controlling the limbs. When the amino acid at this site is asparagine, the enzyme exhibits both  $\alpha$ -2, 3- and  $\alpha$ -2, 8-sialyltransferase activities, and the resulting lipooligosaccharides induce antibodies against gangliosides that exist mostly on oculomotor and primary sensory neurons (34). These findings define a new paradigm, that of a bacterial gene polymorphism shaping the clinical presentation of the postinfection autoimmune disease that it causes.

A topic expected to impact preventive medicine in the coming decades is vaccine design. Among viruses, bacteria and fungi, the latter are the only group of pathogens that, to date, lack an approved vaccine. Particularly as fungal infections rank among the top causes of infectious diseases, new vaccination strategies emerge as a public health priority. Vaccine design is challenging for other pathogen groups as well. As recently pointed out, only four HIV efficacy clinical trials, testing three candidate vaccines, were completed in the 30 years since the virus was discovered (35–38). This underscores the need to better understand the response to vaccination and to design and conduct more trials, a task that becomes particularly urgent for special segments of the population

such as children, the elderly people and pregnant women.

At the interface between biomedical and social sciences, the psychological and emotional impact of naturally occurring and intentionally caused outbreaks on patients, families, and health care professionals, represents a relatively underexplored area. The 1995 Ebola outbreak from Kikwit, the Democratic Republic of Congo, underscored the impact that an epidemic with a highly contagious pathogen, causing high mortality rates, may exert on health care providers and on the community (39). Both immediate and sustained psychological consequences were described in the aftermath of the SARS outbreak, which was regarded as a *mental health catastrophe*. Post-traumatic stress disorder and depressive disorders were the most frequently described long-term consequences among SARS survivors, and a study on the psychological impact of the SARS-related quarantine in Toronto found post-traumatic stress disorder and depression in approximately 30% of the respondents to a survey (40,41). A 59% cumulative incidence of DSM-IV psychiatric disorders was found among SARS survivors from Hong Kong 30 months after the outbreak, and high levels of stress, perceived by both low- and high-risk health care workers, persisted in the latter group even 1 year after the end of the outbreak (42). Amidst all the negative impact on mental health, SARS also exerted certain favourable effects on social and family support systems and helped implement positive lifestyle changes. Over 60% of the respondents to a telephone survey stated that they cared more about

family members' feelings, 35–40% reported a willingness to invest more time and financial resources into their health and > 13% admitted to engage less in risky behaviours, such as unsafe sexual relationships (43,44). Understanding the psychosocial impact exerted by past outbreaks will be critical for developing the framework required for future epidemic and pandemic preparedness efforts.

These are a few of the key aspects that redefined infectious diseases as a field and promise to shape it further. Concerted interdisciplinary efforts, no longer an option, but an absolute necessity, emerge as a hallmark of this vibrant field and assume critical roles in filling existing gaps and in catalysing the transformation of biomedical advances into clinical benefits. To achieve this, we are looking for manuscripts to help unveil prophylactic, diagnostic and therapeutic applications and ensure a better understanding of the complex, dynamic and multi-disciplinary interface between hosts and microbes, for which, as Stephen Jay Gould so relevantly stated, we are merely *transient and delectable islands ripe for potential exploitation* (45).

## Disclosures

No competing interests to declare.

R.A. Stein

Department of Biochemistry and Molecular Pharmacology, New York University School of Medicine, New York, USA  
Email: richardastein@gmail.com

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## EDITORIAL

# The obstructed flow of the prostate evaluation

**Linked Comment:** Montorsi and Mercadante. *Int J Clin Pract* 2013; **67**: 114–9.

I would like to commend Drs Montorsi and Mercadante for their article published in this edition of the IJCP titled *Diagnosis of BPH and Treatment of LUTS among GPs: A European Study* (1). The sheer magnitude of collecting that amount of information from 455 doctors in five different countries in and of itself is quite an accomplishment. Language barriers and time zones make it hard enough, getting providers to sit down with you . . . ugh! Even with all that, perhaps the most disconcerting reality came as they were performing the interviews and realised that how the doctors evaluated this problem was anything, but uniform.

I cannot speak for the authors on what they were thinking when they set out on this journey, but I imagine it was to find which symptom consistent with benign prostatic hyperplasia (BPH) the primary care provider (PCP) found to be important. Then to see how they went about evaluating it and finally, how they chose a medication, if warranted. Come on, this stuff is in the literature, so everybody should be pretty close, right? Wrong! What they found was

a tremendous array of inconsistencies. As I was contemplating the importance of this article, I was watching my son and his friends look at a model rocket he got for his 10th birthday. The box said for ages 13 years and up and Nathan reads at a 16-year-old level so no problem. A few moments go by and they tell me they are going to tie the propulsion device to a toy car and see what happens. Actually, they told me not because they wanted my opinion, but because they wanted some Scotch Tape. I looked at them like they are from outer space (as are most 10-year olds) and inquired if they had read the directions and it made mention of this 'opportunity'. You can guess the answer as no legal department in the US would advocate propelling small objects into the sky, unless it was their rocket. And then it hit me . . . have these 455 general practitioners been educated on the evaluation of BPH, are they aware of the guidelines? Probably, for many of them it was same answer that my son gave when I asked about how he got his information regarding sending a model Mus-