

Drug Resistant Bacteria and the Global Economy

Bacteria are amongst the most adaptable organisms on Earth. Long evolutionary timescales, extremely short generation times, exposure to the most diverse and often hostile environments, together with the remarkable power of natural selection have made microorganisms the most resilient of life forms on this planet. In very large measure, many forms of bacteria are benign and beneficial to their animal hosts; most often colonizing the guts of animals, humans amongst them, providing key enzymes for digestion and producing metabolites that are essential for normal biological function. Bacteria and fungi abound in the soil; essential contributors to maintaining an ecological balance in our environment. Microbiology provides the bridge between the study of plants and animals on the one hand and the earth sciences and agriculture on the other. However, bacteria have a very poor public image; most commonly being associated with infectious disease. Human pathogens constitute only a limited fraction of bacterial populations; yet their impact on human health has been devastating over the centuries. Despite the apparent sophistication of animal immune systems, these natural defences can be breached with impunity by pathogens, which have learnt to evade and subvert the immune processes, that identify and destroy 'foreign' organisms. One of the most dramatic developments of the 20th century was the discovery of the antibiotics, with penicillin and streptomycin being the earliest members of an increasingly large battery of pharmaceutical agents used to combat the spread of infection. The structure determination of penicillin using X-ray diffraction by Dorothy Hodgkin, a landmark in the development of X-ray crystallography, revealed the beta-lactam, a ring of four connected atoms, for the first time. Penicillin's successors, and there are many, are generically called beta-lactam antibiotics.

In the last few days the term 'beta-lactam' has appeared repeatedly in the Indian press as a result of a paper entitled, 'Emergence of a new antibiotic resistance mechanism in India, Pakistan and the UK: a molecular, biological and epidemiological study' (Kumarasamy, K. K. *et al.*, *Lancet Infection* online August 11, 2010, doi: 10.1016/S1473-3099(10)70143-2). These authors examine the prevalence of a gene encoding the sequence of an enzyme that breaks down beta-lactams, named as the New

Delhi metallo-beta-lactamase-1 (NDM-1), in clinical isolates of bacteria. The presence of this gene (and the production of the enzyme beta-lactamase) permits bacteria to breakdown the beta-lactam antibiotic, rendering them resistant to the molecules designed to kill them. Resistance genes can be transferred through populations posing a public health hazard. There is little that is new or surprising in the *Lancet* paper. It is the conclusion that UK patients travelling to India for elective surgery (an interesting byproduct of globalization, which has added a new term to our vocabulary – medical tourism) are at risk of contracting drug-resistant, hospital-acquired infections, which has raised hackles. In a world dominated by commerce even scientific papers can be viewed with suspicion; especially in the medical arena where researchers, their journals and pharmaceutical companies often confront difficult, conflict of interest situations.

The phenomenon of antibiotic resistance was anticipated by Alexander Fleming, an inevitable consequence of Darwinian selection when bacterial populations are exposed to antibiotics (*Current Science*, 2008, **94**, 697). Several of the most successful agents in the fight against bacterial disease are molecules (secondary metabolites) produced by microorganisms; a curious example where both the enemy and the weapons to be used against them are products of nature. Synthetic molecules, the products of painstaking research in medicinal chemistry that have appeared on pharmacists shelves, have often been modelled on the structures of natural products with antibiotic properties. Why do microorganisms produce antibiotics, investing a great deal of genetic and metabolic effort? Are these secondary metabolites the true offensive weapons to be deployed in a battle for ecological space; elements in the 'survival of the fittest' scenario which so often intrudes into discussions of natural selection. Do bacteria (and other microorganisms) wage a sophisticated form of 'chemical warfare' as they battle over environmental niches? Defensive strategies to overcome an antibiotic onslaught are an inevitable biological consequence. Drugs, antibiotics among them, can be extruded from target cells by 'pumps'. Drug targets, most often proteins, can be altered rendering them impervious to the molecules flung at them. Even more directly, drug molecules can be chemically degraded by an enzyme that is geneti-

cally encoded in resistant bacteria. The beta-lactamase, now indelibly linked to New Delhi, is an example. It is the name which appeared to attract a great deal of adverse reaction in the popular press in India. The first report describing this gene in an isolate of *Klebsiella pneumoniae* from 'a Swedish patient of Indian origin' who had been 'admitted to a hospital in New Delhi' appeared in December last year (Yong, D. *et al.*, *Antimicrobial Agents and Chemotherapy*, 2009, **53**, 5046). These strains were shown to be resistant to the carbapenems, which at present are the last line of defense against many Gram negative, opportunistic bacteria that are unaffected by most commonly used antibiotics. The new antibiotic pipeline is far from being reassuring, raising the serious concern that bacterial resistance may soon approach alarming proportions. This report which, introduced the name New Delhi beta-lactamase, noted that 'the broad resistance carried on these plasmids is a further worrying development for India, which already has high levels of antibiotic resistance'.

Even before this detailed study on NDM-1 appeared, an alert had been issued in the UK, warning of the appearance of bacterial strains which seemed resistant to carbapenems (*Health Protection Report*, vol. 3, No. 26, July 3, 2009). The report stated clearly that 'a further metallo-beta-lactamase type – designated NDM-1 ("New Delhi Metallo-1") – is swiftly emerging. . . . Critically, at least 9/19 affected patients have had recent hospitalization in India or Pakistan'. This report also goes on to note that 'carbapenems are widely available in the Indian subcontinent, are widely used owing to prevalent cephalosporin resistance, and have doubtless exerted selection pressure'. There is also a mention of the fact that 'the population flow between the UK and the Indian subcontinent is larger (than other countries) with some elective medical tourism'. In an ominous note the report warns that 'most isolates with NDM-1 enzyme are resistant to all standard intravenous antibiotics for treatment of severe infections'. The UK report was followed remarkably quickly, in March, by a study from the P.D. Hinduja Hospital, Mumbai entitled: 'New Delhi Metallo-beta-lactamase (NDM-1) in Enterobacteriaceae: Treatment options with carbapenems compromised' (Deshpande *et al.*, *Journal of Association of Physicians of India (JAPI)*, 2010, **58**, 147). This study reports that of 24 carbapenem-resistant isolates, collected over the period August–November 2009, 22 were indeed NDM-1 producers. The authors draw attention to earlier work which suggests the possibility of using non-carbapenem antimicrobials in many situations, helping to 'preserve the efficacy of carbapenems against increasingly resistant organisms'. The *JAPI* report suggests that the spread of NDM-1 producing organisms 'may endanger patients undergoing major treatment at centres in India and this may have adverse implications for medical tourism'. Indeed the authors of the *Lancet* paper in August 2010 appear to

have gone further, presumably due to 'calls in the popular press for UK patients to opt for corrective surgery in India with the aim of saving the NHS money'. They argue that the data presented in the *Lancet* paper show that this 'might ultimately cost the NHS substantially more than the short-term saving' and 'strongly advise against such proposals'. While the authors of the *JAPI* paper worry about the adverse impact of NDM-1 on medical tourism, the *Lancet* authors warn 'tourists' away from undergoing hospitalization in India. Clearly, the furore in the media is a consequence of the greater 'impact' of the journal *Lancet* and its undoubtedly superior ability to ensure that papers likely to engage public attention are quickly released to the media. Despite the sensitivity about the propriety of naming the offending beta-lactamase after the city of Delhi and the suspicion that commercial interests may be involved in promoting studies that adversely affect the medical tourism industry, the problem of antibiotic resistance must be taken seriously by the community of physicians.

In an editorial that appears in the same issue of *JAPI* as the paper from the Hinduja Hospital, K. Abdul Ghafur (*JAPI*, 2010, **58**, 143) highlights the crisis in the management of infectious disease in India. His commentary is strongly worded, undoubtedly hoping to provoke a somnolent medical community into action. He notes: 'There is no restriction on the use of higher end antibiotics in India. Indian doctors need not justify their prescription. Any doctor can prescribe and in some cases even pharmacists can dispense without prescription, meropenem in a situation where ampicillin would have been adequate and at the same time prescribing ampicillin in a case where meropenem would have been the right choice'. Ghafur's may be a cry in the wilderness, since testing for antibiotic sensitivity of clinical isolates may hardly be an option in many situations. Microbiology is a discipline that is fundamental to the understanding of infectious disease. It is hardly an important subject in the medical curriculum in most institutions. Ghafur may touch many a raw nerve when he says: 'Indian medical community has to be ashamed of the NDM-1 ('New Delhi Metallo-1') gene. Even though we have not contributed to carbapenem development, we have contributed a resistance gene with a glamorous name'. The antibiotic pipeline in pharmaceutical laboratories is nearly dry. Bacteria have been quick to adapt and neutralize the molecules thrown indiscriminately at them. Holding the line in the war against infectious disease, in a globalized world, will need renewed focus on public health, hygiene and medical education, in addition to a concentrated effort to discover new antibiotics and beta-lactamase inhibitors. The prospect for an outright victory in the war against bacterial pathogens is very bleak. It will be a continuing struggle, in which nature sides with the enemy.

P. Balaram