Private prescription:

A thought-provoking tonic on the lighter side

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Please note that these are the personal opinions of the author and do not necessarily represent those of AstraZeneca.

The age of peers

This year marks the centenary of the birth of Linus Pauling, winner of the 1954 Nobel Prize for Chemistry and the 1962 Nobel Prize for Peace. He has been called one of the two greatest scientists of the 20th century (the other being Albert Einstein), and the greatest chemist since Antoine-Laurent Lavoisier. However, as noted in a recent biography[1]:

'In spite of his intensely rational and analytical mind, he could abandon himself to being driven by irrational emotions, especially during his later years when his combativeness and defensiveness increasingly overcame his brilliance and creativity.'

Reading this reminded me of an old English proverb: 'You can't teach an old dog new tricks', implying that the older a person is, the more likely they are to be set in their ways and unable to cope with new ideas. Proverbs, of course, do not always have to be true and perhaps it is a mistake to regard them as a source of accumulated wisdom. However, they do contain elements of truth applicable to the whole population, including scientists.

Isaac Asimov, the popular scientist and science-fiction writer, once observed[2]:

'It is sometimes the fate of scientists who, in their youth, forge new trails and who led the way towards new concepts, to pass their last days bewildered by still newer developments they cannot accept.'

He was commenting specifically on the career of William Thompson (1824–1907), the famous Victorian mathematician and scientist who later became Lord Kelvin. In his youth, William was a brilliant scholar. He entered the University of Glasgow at ten years of age, wrote his first scientific paper in his teens, and became a professor of mathematics and natural philosophy at the age of 22. In a career of astonishing versatility, he combined pure and applied science to solve problems in electrostatics, thermodynamics, geomagnetism and hydrodynamics, while also inventing various electrical instruments, a tide predictor, a siphon recorder and many other devices. This is generally where the majority of short biographies of this great scientist end. However, the end of his life was not quite as illustrious as the beginning, for as Asimov comments:

'Old scientists do not change their minds, they just die off'

'With almost his last breath, as an old man in his 80s, he who had been so brilliantly a revolutionary in his youth, set his face against novelty and bitterly opposed the notion that radioactive atoms were disintegrating or that energy they released came from within the atom.'

Similar observations are widespread in the scientific community. For instance, there is a cynical saying among young, innovative scientists that 'old scientists do not change their minds, they just die off'. Even the eminent physicist Max Planck is reported as saying[3]:

'New scientific truth usually becomes accepted, not because opponents become convinced, but because opponents die, and because the rising generation is familiar with the new truth at the outset.'

Implications in peer review

Such observations have implications in our present system of peer review of publications and, more importantly, the granting of research funds. If such a system had been in place in the late-19th-century, Lord Kelvin would undoubtedly have been a peer reviewer, and would probably have rejected funds for research into radioactivity. This is not to suggest that the same thing could or does happen today. However, we generally associate our peers with those of the older age group, and it is widely suspected by younger scientists that work considered unorthodox by this group will have little chance of receiving support. Of course, peer reviewers must be leading figures and, as such, must be conversant with the prevailing circumstances in their subject. The question is one of how does one minimize the level of bias and vested interest found in these reviewers because of the natural progression of age, as age and experience are often directly related – a cursory glance at the age range of any editorial advisory board of a journal or any research committee would confirm this. One way would be to use younger reviewers. However, even this strategy has problems, not least in their identification and selection, because the process

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would undoubtedly involve others, more often than not their elders, making recommendations.

My aim is not to propose a replacement for the present system, but to highlight a need for a wider discussion of possible bias. At present no one can halt the progression of age, and all must live with its consequences.

Food for thought for those involved in peer evaluation!

References

1 Kaufman, G.B. *et al.* (2001) Linus Pauling: scientist of the century. *Chem. Ind.* 4, 106–109
2 Asimov, I. (1948) *Biographical Encyclopedia of Science and Technology*. Doubleday, New York, USA
3 Planck, M.K.E. (1946) *Naturwissenschaften* 33, 230

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Can smart bullets penetrate magic bullet-proof vests?

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Ehrlich's concept of a 'magic bullet' has long been a powerful focusing metaphor for the technology of treating infectious diseases. Magic bullets are usually considered to be agents with low toxicity to humans, high toxicity to microbes and with the ability to be delivered at efficacious concentrations to the site of infection. Ehrlich's idea has become ubiquitously associated with antibiotics and other modern antimicrobial agents: chemotherapeutics that unfortunately fall short of his grand concept. Rather than attempt to wrestle apart the magic bullet and antibiotic, here I discuss 'smart' bullets, that is, hypothetical agents that could build on the qualities of the magic bullet that have not been successfully designed into conventional antibiotics.

Antimicrobial agents have always dominated the modern infectious-diseases drug-discovery programme for good reason: it is self-evident that patients are rid of infections concomitantly with the organisms that cause the disease. These agents are not smart bullets, however, because they are toxic to both disease-causing and benign microbes. More importantly, they contribute directly to the evolution of resistance. Are antimicrobial agents the best approximation of the smart bullet we can achieve? Are we incapable of finding drugs that will treat infectious disease without incurring the ecological side-effects common to antibiotics, that of killing normal flora and selecting resistant pathogens?

Despite some 50 years of successful application of antimicrobial agents, their primacy in infectious disease management is increasingly being questioned[1–3]. Many researchers are asking whether drugs with alternative properties could be developed that could productively augment the use of antimicrobial agents[4,5].

Although an emphasis on the quick elimination of pathogens in acute infections is justified, there is also reason to develop drugs according to other priorities. Drugs developed for long-term use and longer-term efficacy, possibly at the expense of rapid effect, could enhance our other disease-management tools. Disappointingly few alternative concepts to antimicrobial agents are being discussed and even fewer technologies and proven alternatives have been offered. With the exceptions of some vaccines directed against the virulence determinants of pathogens, rather than the viability of the microorganism, hygienic practices and most vaccines are still effectively antimicrobial.

Although there are alternative agents in development, the number is small and the rationale for their development is not broadly understood. I would argue that a change in our understanding of microbial evolution is necessary to fully appreciate why conventional antimicrobial agents have limited lives, and why industry and academia should be trying harder to replace them.

A better understanding of evolutionary mechanisms will allow us to fruitfully invest in new kinds of drug-discovery strategies for truly new kinds of drugs. The truly novel drugs discussed here

