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Editors' view

Sensitivity: real (interferons, odorants) and imagined (homeopathy)

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Fifty years of interferons

We recently passed the fiftieth anniversary of the description by Isaacs and Lindenmann of viral interference [1]. Interferons are a family of inducible proteins now classified with cytokines and growth factors. There are at least three types (α, β and γ) implicated in cell growth and regulation and in the modulation of immune responses. They have been hailed as potential 'wonder drugs' not once but twice first because it was anticipated that they would be therapeutically useful antiviral agents (before the advent of antivirals) and then, in the mid nineteen-seventies, as a 'cure for cancer'. Today, their actual clinical uses are relatively circumscribed (eg chronic viral infections including HBV, HCV, human herpes virus-8 – the causative agent of Karposi's sarcoma – metastatic melanoma and renal cell carcinoma, haemangiomas unresponsive to steroids, and some forms of multiple sclerosis). Their effectiveness is limited and much of their importance relates to their impact on the disciplines of molecular and cell biology: they were among the first proteins whose genes were cloned, and were important milestones in the development of cytokine and growth factor pharmacology.

Difficulties in their development reflect many generic problems posed by large molecules as therapeutic agents. Pharmacological methods have been key in overcoming these problems. The extreme potency of IFNs coupled with a 'dirty' biological source meant that bioassay was critical. Purified preparations of human IFN-α from buffy coat of donated blood of consistent quality and potency led to advances in understanding of mechanism and hints of therapeutic potential. Early studies of multiple sclerosis patients with partially purified human IFN-β administered by lumbar puncture (!) reported reduced exacerbations [2]. However, it was not until the genes coding the proteins were cloned that production of quantities of interferon sufficient to carry out definitive clinical trials became practicable. Given intravenously, IFNs have an elimination half-life of two to four hours and they do not cross the blood brain barrier. CNS efficacy when they are administered intravenously or subcutaneously presumably reflects indirect actions. Short half-life has been addressed by conjugation of IFN-α with polyethylene glycol as peginterferon. The fascinating interferon story is succinctly told in this issue by RM Friedman [3].

Homeopathy

We move from something that does work and has much to tell us about molecular mechanism, to something that does neither, but is (astonishingly) widely used in the NHS [4]. In the present issue Paris *et al*. describe a well constructed add-on randomised controlled trial with 3 arms: a double blind homeopathic remedy versus placebo, plus an open label non-interventional control group [5]. Treatment was administered the evening before knee ligament surgery and continued for three days. The primary endpoint was based on the amount of morphine delivered by patient controlled analgesia during the first twenty-four hours. Outcomes in treated and placebo groups were similar both for the primary endpoint and for secondary endpoints (subsequent morphine intake, visual analogue pain score and quality of life). These parameters were also similar in patients enrolled in the open label non-interventional arm. Proponents of homeopathy would probably object to the conclusion that homeopathy is not better than placebo in reducing morphine consumption after surgery, acceding only that a certain homeopathic remedy fails to be effective for a certain type of surgical pain. In an accompanying commentary, Edzard Ernst argues that if one were to accept such pleading, one would pointlessly divert considerable effort and resource. Instead, common sense and existing knowledge tell us that

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homeopathy is biologically implausible, that its predictions are incorrect and that the clinical evidence is largely negative. Observational data attesting to the apparent effectiveness of homeopathy are explained by the variable nature of the natural history of disease and the potential of homeopathy to act as a placebo. He concludes his commentary by referring to a strange historical episode relating to a research programme conducted during the Nazi era. The report survived the war but disappeared subsequently. Reference to this has perturbed one reader and we publish his letter together with a response from Ernst [6,7,8]. The question what to do when sound data are obtained in an unethical manner is an important and complex issue, and we may revisit it. What is, however, straightforward is that pharmacology is based in physics, chemistry, physiology, biochemistry and cell biology. Any future submissions to BJCP on this subject will require a scientifically plausible hypothesis as well as valid methodology if they are to be taken seriously: we do not anticipate a spate of publications.

Class activity versus individual drugs?

Different individual drugs that share the same main action may nevertheless differ importantly in kinetics and in ancillary actions. Examples include beta-blockers (differing degrees of selectivity; vasodilating action through α_1 blockade or β_2 action; ISA; antioxidant properties etc.), statins (endothelial actions; propensity to cause rhabdomyolysis), anti-inflammatory drugs (COX1 versus COX2 selectivity; lipoxygenase inhibition; nephrotoxicity etc.). Angiotensin converting enzyme inhibitors (ACEI) are no exception with drugs containing sulfhydryl groups such as captopril exhibiting distinctive toxicities, pro-drugs such as enalapril versus active parent compounds, short acting drugs (e.g. captopril) versus long acting ones (e.g. trandolapril) drugs metabolised by the liver and drugs eliminated by the kidneys. Individual drugs are licensed for defined indications, and while clinicians often assume efficacy across a class it is unwise to rely on this, an evidence-based medicine caveat that comforts the marketing departments of pharmaceutical companies. Members of formulary committees trying to obtain best value for money naturally regret this, especially when older compounds come off patent and their cost falls. In the present issue, Hansen *et al*. address the question of whether different ACEI have similar clinical efficacy following myocardial infarction. They identified, via registries, some sixteen thousand patients who had been hospitalised for their first MI between 1995 and 2002, had survived at least thirty days after discharge and had claimed at least one prescription of an ACEI. Reassuringly for pharmacologists there was evidence of a dose-response relationship and reassuringly for cash strapped trusts, clinical outcome with different ACEI was similar. The authors conclude that focus on treatment at the recommended dosage is the most important priority rather than which ACEI is used [9]. This is good news, but should not be extrapolated to other drug classes and other indications.

Pharmacoeconomics

Trading off duration of survival against quality of life raises issues about which many of us feel decidedly squeamish. Economists are exceptions, asking such questions as: 'how many years of life would you be prepared to sacrifice in order to live the rest of your life free of the disability you are currently experiencing?' or, even more disturbingly: 'if you could gamble on surviving free of disability for your normal lifespan, or (if you lose the gamble) dying immediately, what odds would you accept?' Imagine being asked this by your doctor. 'But I only wanted something for my sore throat,' you protest weakly [10]. It is easy to mock, but health economic assessments necessarily contribute to funding decisions for new treatments. Such assessments are often based on life years gained (LYG) or on the cost per quality-adjusted life year (QALY) gained. Neither of these measures adjusts for prognosis (hence the above absurdity). In the present issue Camidge and colleagues from Edinburgh demonstrate that information on untreated prognosis should be considered as a modifier during health economic assessments of new treatments for life shortening diseases [11]. NICE has always resisted providing an exact figure for cost per QALY at which a drug would be regarded as cost effective, so such qualitative modifiers could presumably be incorporated quite readily into their approach, which may also, one would surmise, come to be adopted in Scotland.

Smell of success?

Proust remarked that asparagus '. . . transforms my chamber-pot into a flask of perfume.' Some of the constituents of asparagus are metabolised and excreted in the urine, giving it a distinctive smell caused partly by sulphur-containing degradation products [12]. (We all produce these odorous compounds but only about 40% of individuals have the genes required to smell them). It comes as no surprise that such an emotionally laden sense as smell should influence autonomic function. However, odorant inhalation can induce a fall in blood pressure in anosmic patients as well as in healthy subjects. Umeno *et al*. therefore tested the hypothesis that the odorant Cedrol ((1S,2R,5S,7R,8R)-2,6,6,8-tetramethyltricyclo [5.3.1.0]undecan-8-ol, a major component of cedar wood oil) may act on the lower airway as well as in the nose. They investigated patients with total laryngectomy who inhaled vaporised Cedrol or blank air directly through the lower

airway via the trachea. Blood pressure decreased significantly during Cedrol inhalation demonstrating that it acts on the lower airway, and suggesting a possible new target for drug therapy of hypertension [13]. So perhaps aromatherapy (unlike homeopathy, see above) will be worth revisiting!

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