

Leading articles in medical journals in 1966

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In this issue of the *Journal*, Harold Ellis provides his perspective on contemporary topics of medical discussion 50 years ago. At this stage, he was already a professor of surgery, and has since had a distinguished career as a clinician, academic, and renowned and inspirational educator. Here, we provide our perspectives looking back at the leading clinical articles from 1966, as two academic clinicians early in our careers. This is the recent history of many of the medical advances we now take for routine in our day-to-day practice, and highlights how far we have (or in several cases, have not) progressed over the past five decades.

Therapeutics

The 1960s witnessed considerable progress in the disciplines of transplant medicine, and oncology. The concept of immune-mediated transplant rejection had been established by Peter Medawar in 1943 (Gibson and Medawar, 1943), but the cellular mechanisms were only fully understood in 1966. A study of two patients who experienced hyperacute rejection of renal transplants suggested that this might be mediated by antibody, as these individuals had previously received multiple blood transfusions and their sera contained complement-fixing antibodies against donor kidney antigens (Kissmeyer-Nielsen et al., 1966). Rejection occurred within an hour, and microscopic examination excluded the cellular infiltrates that would have been expected with cell-mediated rejection. This observation was crucial for the refinement of strategies to allow transplant organ engraftment. The same year, one of the major complications of immunosuppression associated with transplant was also recognised: that cytomegalovirus could be acquired from transfused blood, and that this could then infect both donor and native organs (Kaariainen et al., 1966).

There were life-saving advances of comparable magnitude in the development of chemotherapeutic regimens, particularly for haematological malignancies. Many of these agents remain part of the standard of care today (Kennedy and Yarbro, 1966; Stutzman et al., 1966). The utility of antimetabolites beyond cancer medicine, for immune-mediated disorders, was also beginning to emerge, with the first formal case series describing deployment of azathioprine in ulcerative colitis (Bowen et al., 1966). Nonetheless, it has only been over the last 10 years that we have begun to master the delicate balance between efficacy and toxicity of this agent, with assays to measure thiopurine methyltransferase activity, thioguanine nucleotides and toxic metabolites (de Wit et al., 2013).

Among the more every day examples of therapeutic advances were the development of allopurinol as a preventative for gout (Bartels, 1966), and heparin for prophylaxis and treatment of venous thromboembolic disease (described in depth in Harold Ellis's commentary). In the cardiology world the first demand pacemakers were implanted, and scanning through the letters pages of *JAMA* there was a flurry of correspondence on how to manage patients with difficult venous

access during cardiac arrests. Many contributors highlighted their own anecdotal success using the intraosseous route, a technique that has only recently found its way into routine guidelines.

Toxicology

Although paracetamol was first discovered in 1877, its use was initially superseded by the introduction of aspirin by Bayer. It was only reintroduced into the market at scale during the 1950s, when the risks of Reye's syndrome in children became apparent. Just over a decade later, the first cases of overdose and its impact on the liver were published in the *BMJ* (Davidson and Eastham, 1966). Paracetamol remains the leading cause of drug overdose, and acute liver failure, in resource-rich countries today. This paper paved the route for the mechanistic understanding of its metabolism, including characterisation of *N*-acetyl-*p*-benzoquinone imine (NAPQI), and strategies to detoxify this through restoring glutathione. That this was a major advance is reflected by the fact that treatment protocols for managing overdose have barely changed since the 1970s. It is only in the past few years that there has been a substantial re-examination of this field with concerted efforts to identify novel biomarkers that enhance risk-stratification, and abbreviated individualised treatment protocols (Bateman et al, 2014).

The epidemiology of poisoning was also reshaping. There was an increase in accidental deaths in children due to wider access to chemical pesticides, a rise in both accidental and non-accidental overdoses with sedatives and tranquilizers, but a reduction in completed suicides due to gas inhalation (attributable to conversion of the cooking supply to non-toxic natural gas).

New diseases, new mechanisms

A number of conditions now standard in basic primers of medicine were first described or consolidated in the 1960s. Jerome Conn had recently proposed a syndrome of secondary hypertension caused by aldosterone-secreting adrenal tumours. He amalgamated his cases in a report in *JAMA* in which he suggested that this was relatively common, and that affected individuals had a cluster of four features: hypertension, hypokalaemia, aldosterone overproduction, and suppressed renin (Conn et al., 1966).

The first recognition of an association between dermatitis herpetiformis and coeliac disease was a triumph of observational medicine. The authors embarked upon their study after appreciating that several other dermatoses were linked with gastrointestinal manifestations (Marks et al, 1966). This also established the importance of avoiding provoking food antigens in the management of dermatitis herpetiformis.

Although a descriptive association between alveolitis and contact with pigeons had already been identified, a paper in the *Lancet* extended the observation to include budgerigars, and prove that sensitivity arose to antigens present in excrement from both species (Hargreave et al, 1966). By performing both cutaneous and aerosol challenge, as well as demonstrating serum reactivity, this provided the causal basis and rational avoidance strategy to limit disease progression.

Chronic Granulomatous Disease (CGD) is a primary immunodeficiency first described in 1957, but it was not until 1966 that neutrophils from these patients

were demonstrated to have lost the ability to eradicate intracellular pathogens (Holmes et al., 1966). This seminal observation led to subsequent identification of the molecular mechanisms responsible for the respiratory burst, which underlies much of our current understanding of how the innate immune system kills bacteria.

Finally, a unique and particularly exciting debate took place regarding the medical implications of manned space travel. Although both the USSR and US had sent astronauts on orbital spaceflights, the current discussion anticipated the Apollo moon landing three years later.

Diagnostics and prognostication

Considerable effort over the past 50 years has gone into elucidation of risk factors that identify individuals at risk of ischaemic heart disease. Notwithstanding the tremendous amount of work that has since gone into refinement of these tools, it is noteworthy that a prospective study of bus drivers in 1966 concluded that four parameters were predictive: blood pressure, serum lipids, smoking, and obesity (Morris et al., 1966). In the same year, reports emerged that testing serum creatine phosphokinase in patients presenting with chest pain halved the number of missed myocardial infarctions. Emphasis was still placed on the value of clinical examination skills, such as the prognostic importance of fundoscopy in hypertension (Breslin et al., 1966), although there was already evidence that the autopsy was in decline (Wilson, 1966).

Reminiscent of comments recently emanating from the Department of Health, *JAMA* published a symposium on the new role of computers in medicine, including as aids to diagnosis. Their advent was likened to the agricultural and industrial revolutions (Ledley, 1966), although it would appear that the intervening 50 years has not been sufficient to replace the clinician at the bedside.

Service organisation

On July 1, 1966, the majority of American Hospitals qualified for the new Medicare programme, providing health insurance to those aged 65 or over, irrespective of race, colour or national origin (Stewart, 1966). Correspondence over subsequent months highlighted some of the teething issues with the programme, but nonetheless this was a major contributor to both socialised healthcare and racial desegregation in medical facilities.

Even in 1966, articles were discussing the emergency department “problem”, recognising that “for many years, the emergency service has been the most neglected and often the weakest department in the hospital. Administrators look on it as a drain of resources; physicians debate the proper staffing. Increased use, however, has created pressures on the hospital and medical staff to provide a more adequate service” (1966). The same authors noted that “the number of emergency department visits has increased faster than either hospital inpatient admissions or outpatient visits, and indications are that these trends will continue at a growing rate.” Plus ça change, plus c’est la meme chose.

Attitudes

An important topic of discussion in both the British and American literature was medical abortion, with the British Abortion Act passed the following year.

“Therapeutic” abortion was already on the radar, particularly in the aftermath of the thalidomide disaster, with a frequent view that “a doctor will, in all likelihood, refuse even to discuss the possibility of abortion and will usually offer only reassurances” (Niswander et al., 1966).

A picture of how other attitudes have evolved can be gleaned from the titles of a number of articles, a selection of which include: “Prevention of VD in the sexually promiscuous”; “Psychotherapy of the mentally retarded”; “The incidence of carcinoma of the prostate in Jews and Gentiles”; and “The theatre and the homosexual”. While some might bemoan the march of political correctness, in reality the medical profession has discarded many of its prejudices and made substantial progress towards embracing historically more vulnerable patients and their individual health needs.

A look back at the literature highlights how much research ethics have also evolved. For example, in one study, the aim was to determine whether a single drink was sufficient to provoke a relapse in individuals with alcohol dependence. Patients were recruited from an addiction unit and asked to participate in a trial investigating means to maintain their abstinence. They were unaware that the “vitamin” cocktail they received contained alcohol (Merry, 1966). Controls on use of animals for medical research were also more lax than today, although these too were starting to come under increasing political scrutiny (Visscher, 1966).

Medical publishing

One of the most striking qualities of articles from 1966 is that brevity was frequently the norm, both of their content and authorship. This provides a marked contrast to many manuscripts submitted today, with their ever-expanding cohorts of authors and reams of Supplementary data, often reflecting the increased technology available and subspecialist expertise required for its engagement. One illuminating feature, which we do not see enough of today, is that *JAMA* ran a regular article series called “Negative results”, providing a home for manuscripts that disprove important hypotheses. Such a resource, in a high impact factor journal, might go some way to reducing the publication biases that still plague evidence-based medicine.

Finally, reminiscent of the recent debate surrounding open access publishing, one letter in the 1966 correspondence pages lamented the economic impact of the newly available photocopiers on journals reliant on reprint sales for economic support.

Epilogue

This commentary can only provide a taster of the themes arising in the medical literature of 50 years ago, but for the more junior clinicians this is an important retrospective into how many of the practices we take for granted were innovated. Also informative, though sadly out of scope for this viewpoint, are the much greater number of studies describing interventions that have not stood the test of time. It is likely that the majority of trials published in high-ranking journals today will share the same fate. Finally, it is salutary to be aware of the areas where the medical profession has struggled to make progress. Without a radical rethink in the ways we

structure, deliver and consume healthcare, there is a real risk that, in another 50 years' time, A&E will still be a problem.

Conflicts of interest Dr DJB Marks is Associate Editor for the *British Journal of Hospital Medicine*, consultant in clinical pharmacology for GSK, and a junior doctor who thoroughly enjoys working in A&E and opposes the imposition of a non-negotiated contract in England.

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