Jenner, romanticism, and research

The bicentenary of the inoculation by Jenner of 8 year old James Phipps with cowpox is an opportunity for medical scientists and researchers to reflect. Two hundred years is but a blink in the history of our planet yet in that short time the pace of medical discovery has been breathtaking.

If Jenner were to meet a group of thinking medical researchers who could explain to him ‘the way it is now’ we could only guess whether he would find today’s research environment more or less academically stimulating and enjoyable. A cynic might say that it was now more academically stimulating, but less enjoyable. It is this I wish to explore.

When one reads of Jenner and his discovery, so admirably reported by Peter Dunn in this months Fetal and Neonatal Edition of the Archives, one is struck by the romanticism of it all. Presumably a scientific discovery has recognisable elements which determine whether it will widely capture the imagination of people, create a sense of excitement, and inspire awe at the researcher’s achievement. A key feature determining this response is simply the practical importance of the discovery of course, but it is not the only one.

One element that endows a research finding with romanticism is serendipity. In 1768 Jenner overheard a dairy maid saying that she couldn’t develop smallpox because she had already suffered cowpox. Jenner listened, and perhaps we should all do more listening. The opportunity for serendipity by hearing a chance comment knows no bounds in clinical medicine which is practised within a framework of patients, relatives, nurses, doctors, medical students, and many others.

Yet the increasing sense of separation of basic science research from clinical medicine poses an awkward problem. A research team that operates within a closed network, divorced from clinical practice, has little chance of receiving inspiration from a serendipitous observation or remark at the patient interface. In contrast, researchers who practise within a truly interdisciplinary culture, where at least some members of the team have clinical contact, will be alert to and share chance observations and comments made in the clinical setting.

Jenner inoculated James Phipps with cowpox without prior consent from his parents and without approval from the local ethics committee. If he had presented his observation to the Archives as a single case report it would not have been published. Yet before conducting this experiment he had made meticulous observations, and discussed his ideas with others including the then President of the Royal Society, Sir Joseph Banks.

Where are today’s meticulous observers? No doubt they are out there but they remain unseen because the skill is not so much in the observing but in the literary expression of what is observed. Jenner and others of his era had wonderful opportunities to observe and express. A love of nature and a penchant for expressive and creative writing were characteristics of many researchers of his time, exemplified by descriptions of landscapes and plant and animal anatomy.

John Hunter, who was Jenner’s friend, may have written, albeit in a different context, ‘Why think? Why not try the experiment’, but Jenner both thought and observed carefully, and tried the experiment, thereby suggesting that this conduct for that time was not unethical.

Nowadays, of course, he would have to show that he was in a state of equipoise about whether the inoculation of cowpox protected against smallpox. He would need to organise a randomised placebo controlled trial, with defined primary and secondary outcome measures, and a prior power calculation to estimate the trial size.

We should be thankful for today’s tighter controls on the conduct of clinical research. For each famous name endowed with discovery in centuries gone by there were, no doubt, many others who failed to discover and in the course of trying harmed their patients. The extent to which this occurred cannot be estimated because, unlike today, the practitioner was accountable largely to himself and there were few to challenge him – he would certainly not be challenged through the media.

Today the media has a curious attitude towards medical research, based on the need to inform in a sensational way and to arouse public interest and concern. On the one hand we read exaggerated accounts of the clinical implications of research findings (a cure for cancer in two years’), and on the other hand nationalism is revealed when an important discovery is greeted with ‘why has it taken so long for this to come to light?’

Perhaps more to the point is why it takes so long for research findings to be put into clinical practice. The fruits of Jenner’s own meticulous observations came some 180 years later when smallpox was eradicated. There are
probably two main factors operating which govern the speed of integration of research findings into clinical practice. First, there is increasing difficulty in determining when a discovery is sufficiently proved and ‘clean’ for introduction. Jenner’s observations were initially met with disbelief and rejection – an understandable human response. Today’s medical scientist is more likely to be disbelieved because of contradictory observations from other research camps. Differences in experimental design, often quite subtle, may generate different results. In clinical research this leads, even after many years of investigation, to an inability to give a straightforward answer to the question: ‘Does this drug do any good for this group of patients?’

At what point then does the pendulum swing away from equipoise and hover to one side, and how is this decided? Efforts to clarify this by meta-analyses, systematic reviews, and more recently the notion of evidence based medicine certainly need our support, but we must guard against throwing the baby out with the bath water and creating a philosophy of therapeutic nihilism. None of the current research review methodologies is perfect but they are better than nothing.

Second, the speed of integration of research findings into clinical practice is also determined by the organisational structure required and its costs, set against the perceived benefits. These concepts were responsible for the delay between Jenner’s discovery and the eradication of smallpox worldwide.

When public money is involved in funding both research and the costs of service developments therefrom, we can anticipate an evolving political edge to medical research. In the United Kingdom the NHS Research and Development Initiative already influences the direction of research to some extent.

Given today’s setting, can romanticism still flourish in medical research, and is there a place for it, or is it simply the stuff of art and literature? The novelty of Jenner’s discovery at the time was that it was a preventative measure rather than a treatment. While there is no exact parallel today of a killer disease on a massive scale, caused by infection and awaiting prevention, the closest analogy is the spectrum of HIV, and AIDS related disease.

The romantics among us might well look forward to another Jenner style discovery leading to eradication of AIDS by immunisation. But realism dictates that instead the path will be strewn with many more years of pains-taking and uncertain research, at best culminating in further trials of treatment regimens, and perhaps trials directed at the efficacy of vaccines. Alas, there is no romance in discovery by meta-analysis.

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1 Dunn PM. Dr Edward Jenner (1749–1823) of Berkeley and vaccination against smallpox. Arch Dis Child 1996; 74: (Jan, in press).

Autoimmune hepatitis

Definition
Autoimmune hepatitis is an inflammatory liver disease characterised histologically by a dense mononuclear cell infiltrate in the portal tract and serologically by the presence of non-organ and liver specific autoantibodies and increased concentrations of IgG in the absence of a known aetiology. It usually responds to immunosuppressive treatment, which should be instituted as soon as diagnosis is made. The onset of the disease is often ill defined and the previously accepted requirement of six months’ duration of symptoms before diagnosis could be made has been abandoned.

Pathogenesis of liver damage
Patients with autoimmune hepatitis are mainly female and have high titre of circulating autoantibodies reacting against nuclear components, smooth muscle, liver/kidney microsomes, or a liver cell cytoplasmic protein called soluble liver antigen. Although most of these autoantibodies are not organ specific, and may be found in other diseases, they are important diagnostic markers of autoimmune hepatitis. In contrast to adults, these autoantibodies are very rare in healthy children and even low titres are compatible with the diagnosis of autoimmune hepatitis.

The first liver specific autoantibody described in autoimmune hepatitis reacted with a macromolecular antigenic complex called ‘liver specific lipoprotein’ (LSP) on the hepatocyte cell membrane. Patients with autoimmune hepatitis have high serum concentrations of anti-LSP, with a close relationship between the serum anti-LSP titre and the extent of histologically assessed liver damage. Later it was demonstrated that patients with autoimmune hepatitis have circulating antibodies against a component of LSP, the human asialoglycoprotein receptor (ASGPR) and that anti-ASGPR titres are also correlated with disease activity. More recently children with autoimmune hepatitis have been shown to have antibodies to alcohol dehydrogenase, which is the second well defined component of LSP.

Liver damage in autoimmune hepatitis is believed to be orchestrated by CD4 positive (helper/inducer) T lymphocytes recognising a self antigenic peptide, possibly derived from ASGPR (figure). To trigger an autoimmune response, the peptide must be embraced by an HLA molecule and presented to the helper/inducer T cells by professional antigen presenting cells. These cells belong to the monocyte/macrophage lineage. T helper (T4) cells become activated, differentiate into functional phenotypes, and initiate a cascade of immune reactions determined by the cytokines they produce. Tc1 secrete mainly interleukin (IL)-2 and interferon gamma (IFN-γ), which activate macrophages, enhance expression of HLA class I, increasing liver cell vulnerability to a cytotoxic attack, and induce expression of HLA class II molecules on