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 pangs-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.1

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.1 Although most of these autoantibodies are not organ specific, and may be found in other diseases,2,3 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.1

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.4 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.5 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.6 More recently children with autoimmune hepatitis have been shown to have antibodies to alcohol dehydrogenase, which is the second well defined component of LSP.7

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 (Th2) cells become activated, differentiate into functional phenotypes, and initiate a cascade of immune reactions determined by the cytokines they produce. Th1 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
hepatocytes, which then become able to present the autoantigenic peptide to T<sub>H</sub> cells, thus perpetuating the immune recognition cycle. T<sub>H</sub>2 produce mainly IL-4, IL-5, and IL-10 which induce autoantibody production by B lymphocytes. Various components of this model have been investigated and some have been shown to be involved: hepatocytes from patients with active autoimmune hepatitis express class II HLA antigens, not normally expressed on liver cells, and can therefore present autoantigenic peptides. CD4<sup>+</sup> positive unactivated lymphocytes are present in areas of piecemeal necrosis, and a high proportion of circulating helper T lymphocytes express the activation marker IL-2 receptor (IL-2R).<sup>11</sup> Liver specific CD4<sup>+</sup> positive T cell clones obtained both from the peripheral blood and the liver biopsies of autoimmune hepatitis patients<sup>12</sup> stimulate autologous B lymphocytes to produce liver membrane specific autoantibodies and antibody to the ASGPGR<sup>13</sup> and high titre liver specific autoantibodies are present in the circulation of these patients, as mentioned above. Once the autoimmune reaction is initiated, hepatocytes can be destroyed through various mechanisms. These include direct T cell cytotoxicity, cytolytic action of cytokines, and autoantibody directed complement or killer (K) cell mediated lysis. Among these, evidence exists showing the involvement of both K cell<sup>14</sup> and T cell cytotoxicity,<sup>13</sup> and abnormal cytokine production,<sup>16</sup> while studies to investigate the possible role of complement in generating liver cell damage have failed to demonstrate any association between complement activation and biochemical evidence of hepatocyte injury in autoimmune hepatitis.<sup>18</sup> The engagement of these effectors of autoimmune damage is normally prevented by immunoregulatory mechanisms. These are defective in patients with autoimmune hepatitis.<sup>19, 20</sup>

**Genetic predisposition**

White patients with autoimmune hepatitis have an increased frequency of the histocompatibility antigens HLA A1/B8/DR3, a haplotype characteristically associated with other autoimmune conditions. A link between HLA antigen and a regulatory T cell dysfunction would explain both the increased immune responsiveness and the increased frequency of HLA B8 observed in autoimmune diseases. Indirect confirmation of this hypothesis is provided by the results of family studies showing high titres of autoantibodies in B8 positive patients and their first degree relatives. Curiously, although possession of HLA A1/B8/DR3 augments susceptibility not only to autoimmune hepatitis but also to a wide range of other autoimmune disorders, very little overlap exists among them, implying that HLA A1/B8/DR3 is a marker of impaired immunoregulatory activity but that other genetic and/or environmental factors must determine which organs or tissues are affected. In a reported family with multiple occurrence of autoimmune hepatitis, female sex and possession of DR3 was more important than B8 in conferring susceptibility to the disease, suggesting that a defective antigen recognition by T cells in the context of class II HLA molecules plays a central part in generating autoimmunity, in association with gender determined factors (genes and hormones).

Recent studies focusing on the susceptibility to autoimmune hepatitis conferred by HLA class II genes have shown that the disease is associated with DR3 in children,
with DR3 or DR4 in adults, and have indicated that the major predisposing role is played by DRB3*0101 and DRB1*0401, genes linked to DR3 and DR4 respectively. Both genes encode a six amino acid (Leu-Leu-Glu-Gly-Lys-Arg) sequence at positions 67 to 72 of the DRβ polypeptide. This motif is present in 94% of patients with autoimmune hepatitis and confers a ninefold increased risk for the disease in comparison with individuals negative for these genes. Further analysis suggested that the lysine residue at position 71 is the key element in this motif. As amino acid residues in the third hypervariable region of the DRβ molecule determine the ability of class II molecules to bind antigenic peptides and to present them to T cells, it is likely that this amino acid motif plays a critical part in the generation of liver damaging immune responses in autoimmune hepatitis.

The A1/B8/DR3 haplotype is in strong linkage disequilibrium with the complement loci on chromosome 6, collectively known as class III HLA genes. Children with autoimmune hepatitis have an isolated partial deficiency of the complement component C4, which is genetically determined and is associated with the possession of the silent gene C4AQ0 at the C4A locus. C4AQ0 either in linkage with A1/B8/DR3 or on its own has been reported in association with other autoimmune disorders and could represent the true disease susceptibility gene. C4 has a key role in virus neutralisation and failure to eliminate viruses might lead to the development of immunity and autoimmune reactions directed against antigens on persistently infected cells.

Clinical features
Two types of autoimmune hepatitis are recognised according to the presence in the peripheral blood of smooth muscle and/or antimuclear antibody (SMA/ANA) or liver kidney microsomal type 1 antibody (LKM1). While SMA/ANA positive autoimmune hepatitis affects both children and adults with two peaks of incidence between the ages of 10–20 and 45–70 years, LKM1 positive autoimmune hepatitis is rarely seen in association with ANA or SMA and usually affects children. The main target of SMA has been reported to be the actin of smooth muscle, while the main target of LKM1 is cytochrome P4502D6 (CYP2D6).

The observation that LKM1 antibody may be associated with hepatitis C virus infection has led to the suggestion that hepatitis C virus may cause autoimmunity. It is not clear, however, that anti-LKM1 positive patients fall into two distinct groups according to their hepatitis C virus markers. LKM1 positive subjects without hepatitis C virus markers are likely to represent the true autoimmune group and tend to be children, female, with either a family history of autoimmune disease or associated autoimmune disorders and respond to immunosuppressive treatment, while LKM1 positive patients with markers of hepatitis C virus infection come from endemic areas, are older, male, without a clear association with other autoimmune manifestations, and respond better to antiviral than immunosuppressive treatment.

In children, autoimmune hepatitis, whether ANA/ANA or LKM1 positive, is a severe condition. Early diagnosis, based on the presence of diagnostic autoantibodies, with or without increased IgG, and a compatible liver histology should be made to avoid severe morbidity and high mortality. Autoimmune hepatitis affects mainly girls (75%), with a wide age range, from a few months to adolescence (median 10 years). LKM1 positive patients tend to present at a younger age and more often with acute liver failure. Autoimmune hepatitis should be suspected in all children presenting with symptoms and/or signs of persistent liver disease in whom other known causes, such as Wilson’s disease, drug toxicity, α1-antitrypsin deficiency, or infection with hepatotropic viruses (A, B, C) have been excluded. Up to 60% of the patients present with a prolonged acute hepatic illness indistinguishable from viral hepatitis. Early diagnosis and treatment is particularly important for these patients as they can rapidly progress to fulminant hepatic failure. For the others the onset is insidious with a history of progressively increasing fatigue, relapsing jaundice, anorexia, and weight loss. Occasionally the diagnosis is made in hitherto asymptomatic children whose presenting manifestation is related to portal hypertension (for example, bleeding varices, florid spider naevi). A family history of autoimmune disease is common and often children with autoimmune hepatitis have other autoimmune manifestations, such as thyroiditis, insulin dependent diabetes mellitus, arthritis, vitiligo, or inflammatory bowel disease. In particular, children with LKM1 positive autoimmune hepatitis may develop a polyendocrinopathy with diabetes, thyroiditis and/or hypoadrenalism. It is therefore advisable to test for antithyroid, islet cell, and adrenal antibodies and to investigate thyroid function at presentation. Interestingly, despite this association with other autoimmune disorders, autoimmune hepatitis is not associated with lupus erythematosus. At diagnosis, LKM1 positive patients have biochemical evidence of more active disease, with higher bilirubin and transaminase levels, while ANA/ANA positive patients have more often low albumin and histological features of established cirrhosis. IgG and INR (international normalised prothrombin ratio) are similarly raised and C4 similarly decreased, but LKM1 positive have an increased frequency of IgA deficiency.

Treatment
Although autoimmune hepatitis usually responds satisfactorily to immunosuppression, the ‘fine tuning’ of treatment may be particularly difficult during the first year after diagnosis. In our unit, treatment is started with prednisolone 2 mg/kg/day (maximum 60 mg/day) and gradually decreased over a period of four to six weeks on the basis of weekly assessment of transaminase activity, the progressive decrease of which reflects the response to treatment. The aim is to reduce prednisolone to the minimal dose able to maintain normal transaminase levels, usually 5 mg/day. If too high a dose of prednisolone is required to maintain normal liver function or if the child does not go into remission (that is, the transaminase activity exceeds the upper limit of normal), azathioprine is added at a starting dose of 0.5 mg/kg/day which, in the absence of signs of toxicity, is increased up to a maximum of 2 mg/kg/day over a period of four weeks in an attempt to obtain biochemical control. Although an 80% decrease of the initial transaminase levels is achieved within six weeks in most patients, the complete normalisation of the liver function may take several months. In our own series of 52 patients, normalisation of transaminase levels occurred at a median of 0.5 (range 0.2–7) years in ANA/ANA positive children and of 0.8 (0.2–3.2) years in LKM1 positive ones. Relapse while on treatment is common, affecting about 40% of the patients, and requiring a temporary increase of the steroid dose. If after one year of normal liver function tests a liver biopsy specimen shows no inflammatory changes, cessation of treatment can be considered. Following these criteria, we have been able to stop treatment in 70% of the ANA/ANA positive patients, after a median of 3–2 years.
Autoimmune hepatitis

(range 1–11 years), but in none of the LKM1 positive. Patients who do not fulfil the criteria for cessation of treatment or fail a trial of treatment withdrawal will require lifelong immunosuppression with the lowest dose of steroid and azathioprine able to maintain normal liver function. Children presenting with an acute hepatitis illness or with acute liver failure are better treated in a specialised centre with facilities for paediatric liver transplantation. For those patients with established cirrhosis, liver decompensation, which may occur several years after diagnosis, should be treated by transplantation. The disease occasionally recurs after transplant.35

Treatment with steroids and azathioprine is usually satisfactory in controlling the inflammatory process damaging the liver; progression to cirrhosis, despite treatment, however, is frequent. In addition, such treatment may have serious and unpleasant side effects. New immunosuppressive agents such as cyclosporin and tacrolimus have been anaesthetically used in the treatment of autoimmune hepatitis. The role of these drugs, however, which have serious side effects such as nephrotoxicity and predisposition to the development of lymphoproliferative disorders and other malignancies, should be evaluated in trials conducted in specialised centres.

It is hoped that in the not too distant future a better knowledge of pathogenetic mechanisms of liver damage will lead to a more specific and effective therapeutic intervention.

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Hirschsprung’s disease

Although it is over a century since Harald Hirschsprung first described congenital megacolon, only relatively recently has research endeavour begun to throw light on its pathogenesis and pathophysiology. It is the purpose of this annotation to review some of this recent evidence. Hirschsprung’s disease is a common condition (one in 5000 live births) characterised by aganglionicom in the myenteric (Auerbach) and submucous (Meissner) plexuses of the distal colon and a sustained contraction of this segment. In the majority of cases (80%), the aganglionic tract involves the rectum and the sigmoid colon only (short segment Hirschsprung’s disease) while in 20% of cases it extends towards the proximal colon (long segment Hirschsprung’s disease). Enlarged nerve trunks are present...