100 YEARS AGO

Mr. G. Archdall Reid contributes to the current number of the *Monthly Review* an instructive and clearly written account of "the rationale of vaccination"… After passing in review the theories which have previously been held to explain acquired immunity, Mr. Reid shows that it is due to an habituation to the toxins of that disease. This result is brought about by the digestion in the blood of the toxins, so that there are present in the animal's blood toxins in all stages of attenuation, from those newly produced by the microbes, and extremely virulent, to those produced in the beginning of the disease and now in a state of great enfeeblement. Up that graduated scale the cells of the animal react till complete immunity is attained. The serum treatment artificially supplies digestive substances and, what is even more important, a scale of attenuated toxins. Applying these principles to the case of small-pox, the necessity for periodical vaccination is established. It is pointed out that, since small-pox is an air-borne disease, isolation, by itself, has no greater power of controlling small-pox than the historic old lady with a broom had of sweeping back the Atlantic.

From *Nature* 16 January 1902.

50 YEARS AGO

***Patterns of Marriage.* It is possible to give only a few of the results of this research. One point that soon became obvious was that like tended to marry like — the intelligent man, the intelligent woman; the neurotic, the neurotic. Sexual attraction played only a minor part in drawing two people together. Among the psychiatrically sound couples 45 per cent claimed to be happily married, 36 per cent considered their marriage satisfactory, 10 per cent unsatisfactory and 9 per cent admitted to being positively unhappy. In the neurotic group happiness or satisfaction in marriage was less frequent. It is clear also from the answers given that children ranked highest in bringing about marital happiness and that other factors, in diminishing order of importance, were as follows: "clerical rating of personality, economic status, intelligence, orgasm adequacy of the female, pre-marital chastity, good looks, stature, rating of personality by test, similarities between husband and wife and test responses". Frequency of intercourse and youth bore no relationship at all to marital happiness.**

From *Nature* 19 January 1952.

learning when people with partly conflicting interests interact with each other. For researchers in this field, these are exciting times, not least because we are witnessing a partial reunification of psychology and economics. ■

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AIDS vaccines

One step forwards, one step back

Jeffrey D. Lifson and Malcolm A. Martin

New AIDS-virus vaccines induce cellular responses that can contain, but not prevent, infection. Mutations can allow the virus to escape this immune control, emphasizing the challenges in developing an effective vaccine.

As someone accustomed to persevering on a long-term project in which repeated periods of hard work lead to modest progress, only to be followed by setbacks, Sisyphus would be well suited to a career in AIDS-vaccine research. Papers on pages 331 and 335 of this issue[1,2] illustrate the point. In the first paper, Shiver and colleagues[1] describe how they immunized groups of rhesus macaques against a protein from a monkey AIDS virus, the simian immunodeficiency virus (SIV), effectively stimulating antiviral cellular immune responses. The immunizations did not prevent, but did help to control, subsequent infection with a related virus. But Barouch and colleagues[2] show that AIDS viruses can mutate to evade such vaccine-induced, virus-controlling cellular immunity, calling into question a vaccination strategy based solely on such responses.

The aim of most vaccines that offer protection against viruses is to stimulate antibody molecules that can neutralize the virus or otherwise help clear the infection, and cellular immune responses, particularly by cytotoxic T lymphocytes (CTLs) that bear the surface marker CD8 and can kill virus-infected cells. But for the human AIDS virus HIV-1 it has proved difficult to generate vaccines capable of inducing antibody responses that neutralize the broad range of virus strains found in patients. CTL responses may be able to cope with a wider range of virus strains, and appear to help control HIV-1 in infected people, so much current attention in AIDS-vaccine research is focused on vaccines that stimulate CTL responses.

Pursuing this approach, Shiver *et al.*[1] systematically compared vaccination strategies using DNA molecules or engineered non-SIV viruses (a vaccinia virus or an adenovirus known as Ad5) to express a single SIV protein, Gag. After immunizing macaques with these potential vaccines, the authors detected strong and sustained responses by T cells that express CD8, most notably in animals immunized with the Ad5 vaccine — either alone or after 'priming' immunization with DNA.

To assess the efficacy of the vaccines, the authors[1] then challenged the macaques with a highly pathogenic chimaeric simian–human immunodeficiency virus (SHIV), SHIV 89.6P (ref. 3). This virus contains a gene encoding the viral glycoproteins from the HIV-1 outer 'envelope', as well as several SIV genes, including a Gag-encoding gene matching that used in the vaccines. Like HIV-1 and SIV, SHIV 89.6P infects and kills 'helper' T lymphocytes bearing the cell-surface marker CD4 (ref. 3).

Shiver *et al.* found that their vaccination strategies did not prevent infection with SHIV 89.6P, but did modulate its course, most strikingly in animals immunized with the vaccine based on Ad5. Early on, peak levels of virus in the macaques' blood were only slightly lower than in controls. But by 70 days after challenge, vaccinated animals showed markedly lower levels of virus and preservation of CD4-expressing T lymphocytes. This 'partial protection' is similar to that obtained with other vaccine approaches[4,5] against challenge with SHIV 89.6P. Used clinically, a vaccine that controlled HIV infection might result in a longer period of infection without symptoms, and a decreased risk of transmission.

However, Barouch *et al.*'s work[2] provides a cautionary counterpoint to these encouraging results, and raises questions about the strategy of controlling infection by using vaccines that stimulate CTLs alone. These authors describe the course of infection in a rhesus macaque that was at first partially protected from SHIV 89.6P by a DNA-based immunization approach[5]. This vaccinated animal showed high peak levels of virus after challenge, but viral levels eventually

declined to below the limit of detection, with no depletion of CD4-expressing T cells[5]. However, during a year of follow-up[2], virus replication increased to measurable, albeit modest, levels, in association with the emergence of mutations that allowed the virus to elude a dominant CTL response. An acute loss of CD4-expressing T cells and progressive disease ensued.

This is perhaps more disappointing than surprising. Such escape mutations have been detected before in SIV-infected animals[6], and there is also evidence of HIV-1 evolution in the face of 'effective' anti-retroviral therapy[7]. So we might have expected, in the setting of similarly 'controlled' viral replication in a vaccinated animal, the emergence of mutations that allow the evasion of immune responses. But this nonetheless represents a fundamental and potentially ominous challenge to the idea of containing, rather than preventing, AIDS-virus infections. The frequency and kinetics of such escape will affect the ultimate usefulness of vaccines that are based on this approach.

Moreover, interpretation of the studies[1,2] is complicated by the fact that the SHIV 89.6P challenge virus produces a course of infection that is very different from that typical of HIV-1 and SIV. Infection with HIV-1 and most pathogenic SIVs is generally characterized by the gradual, progressive destruction of CD4-expressing T cells. In contrast, infection with pathogenic SHIVs such as SHIV 89.6P typically results in the rapid, systemic and irreversible destruction of nearly all of these cells[3].

SHIVs that include the HIV-1 envelope gene were originally developed to evaluate how well monkeys are protected by vaccines that target the HIV-1 envelope glycoproteins[8]. But pathogenic SHIVs, particularly SHIV 89.6P, have been more widely used of late, even for studies in which the HIV-1 envelope glycoprotein is not a vaccine component. Although the vaccines have not completely blocked infection, they have generally lowered the post-peak viral load and prevented the rapid, almost complete destruction of CD4-expressing T cells that is characteristic of SHIV 89.6P infection[4,5]. This alteration of such a dramatic consequence of infection has been interpreted as evidence of an important advance in the development of an effective HIV-1 vaccine.

However, accumulating data indicate that it is comparatively easy to prevent the loss of CD4-expressing cells and to bring about the sustained control of infection through partial inhibition of SHIV replication early in an infection, whether by vaccination[4,5,9], passive immunotherapy[10], short-term drug treatment[11], or limiting the amount of challenge virus used[12]. Moreover, although rigorous head-to-head comparative vaccine studies have not yet been reported, the results obtained with pathogenic SHIV challenges contrast markedly with those obtained when pathogenic SIV strains are used to challenge similarly vaccinated monkeys. In such studies, sustained control of SIV infection and its consequences has rarely been achieved[9,13,14]. So we should be cautious when using alteration of the unusual course of disease caused by pathogenic SHIVs, rather than prevention of infection, as a major test of vaccine efficacy.

All in all, the two studies[1,2] provide both an encouraging step along the road towards an effective AIDS vaccine and a sobering reminder of how long and difficult the road is likely to be. They do provide some direction along the road, suggesting that successful vaccines will need to induce immune responses that are both durable and broad, recruiting both antibodies and cells[15]. Unfortunately for sisyphean AIDS-vaccine researchers, it is likely that the signposts on this road will continue to indicate an uphill grade for the foreseeable future. ■

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Condensed-matter physics

Eavesdropping on spin talk

Jay Kikkawa

Taking advantage of nuclear and electron 'spin interactions' to store and process information is a long-standing goal. A systematic technique for manipulating spin in a semiconductor provides a low-temperature solution.

The currency of mainstream electronics has always been the movement of electric charge. Building blocks of technology, such as resistors, capacitors and transistors, all rely on the position of charge for their action. But electrons are like tiny magnets with north and south poles, a quantum mechanical property referred to as 'spin', and many scientists believe that harnessing spin could push back the frontiers of information processing[1]. This endeavour could be revolutionary because 'spintronic' devices can, in principle, function in a manner that has no charge-based counterpart. One example is the ability of electron spins to exchange magnetic information with nuclei in a solid.

Nuclei have weaker spins than electrons and might behave as stable storage elements because they are better isolated from their environment than electron spins. A fundamental trade-off between information storage times and transfer speeds means that optimizing both in a single material would be difficult. But on page 281 of this issue, Smet *et al.*[2] circumvent this obstacle and show how complex changes in electronic behaviour can both control and monitor the flow of spin information into and out of the nuclei in a semiconductor.

What lies behind this nuclear–electron crosstalk? Electronic and nuclear spins in a solid are coupled through the 'hyperfine interaction', which allows a pair of spins to undergo spin-reversal or flip-flop (Fig. 1a, overleaf). This means that an electron can flip its spin by simultaneously flipping a nuclear spin in the other direction, provided that energy is conserved. In a solid material such as a semiconductor, 'information' transfer occurs in the form of a change in net nuclear spin. Both electron and nuclear spins tend to align themselves with an external magnetic field, just as an ordinary magnet would. But nuclear spins are almost always overwhelmed by thermal energy to become randomly orientated, so they contribute virtually no net spin within the material.

The nuclear system can acquire a net spin from the electrons through flip-flop as long as energy is conserved. This requirement can be difficult to satisfy because the energy associated with the orientation of a nucleus is much smaller than that associated with an electron. Accordingly, flip-flop requires a compensatory change in, for example, the electron's kinetic energy (Fig. 1b). Smet *et al.*[2] chose to study a collection of electrons confined to move in a two-dimensional plane by their host semiconductor and subjected to a perpendicular magnetic field. In the absence of electron–electron interactions and in a strong magnetic field, the electrons in such a system typically cannot