the recipient became infected with HIV-1 when the immune responses were near peak levels), the host responses generated had no perceptible effects on the nature or progression of the infection.

Why did these vaccines fail? One intriguing possibility, as noted by Berman *et al.*[5], is that the subjects became infected with HIV-1 isolates bearing envelope proteins that differed from the vaccine immunogen at several neutralizing antibody-sensitive sites. But Connor *et al.*[3] (and others[6]) reduced this possibility by comparing contemporary infections in matched controls. Therefore, vaccination with viral-envelope subunits alone did not exert overt selective pressure on the HIV-1 strains with which the patients became infected. Although this conclusion weakens the case for further development of these gp120 products, it is not possible to infer anything about their efficacy from these studies[3,6] — except that the subunit vaccines are not 100% protective — because the results stem from relatively small studies.

The viral gp120 is one of two glycoproteins that make up the HIV outer envelope. It targets the virus to certain cells in the body by binding to specific cell receptors, and it initiates the early steps of virus entry into these targeted cells. Recombinant gp120 subunits emerged as candidates for vaccine development based on their ability to raise antibodies that effectively neutralize laboratory strains of HIV *in vitro*. Moreover, defined thresholds of such antibodies prevented infection of chimpanzees by the HIV strains from which the vaccines were derived. Studies for safety and immunogenicity in humans were successful, laying the foundations to test whether levels of neutralizing antibody correlated with immunity against HIV infection. But first, researchers tried to show that the neutralizing-antibody response would be effective against the viruses circulating in populations where the trial was to be carried out. In laboratory assays using field strains, however, no neutralizing activity was detectable[7].

Why are laboratory strains of HIV sensitive to antibody neutralization, whereas primary viruses are resistant? There seem to be substantive differences between the envelope structures of these two viral phenotypes, which also use different co-receptors for infectivity. Phase I trials of several candidate vaccines that use the gp120 subunit derived from primary virus isolates are already underway (Table 1). But many researchers doubt that the simple substitution of one gp120 subunit for another will be enough to cause these constructs to act any differently from the early prototypes based on laboratory strains. Nor is there enough knowledge to design immunogens that can effectively induce neutralizing antibodies with sufficient potency and breadth against primary viruses. Insights to this end could emerge from increased understanding of the HIV envelope, its multimeric nature, the shielding of antibody targets by carbohydrate, and the structural transitions of HIV during receptor/co-receptor binding, fusion and entry into the target cell.

The main vaccine concept currently under development is a combination of a multicomponent canarypox viral vector and one of the original gp120 envelope subunits. Such combined vaccines induce detectable cytotoxic T lymphocytes in about 60% of vaccinated people[8]. These lymphocytes can recognize and lyse target cells infected by field strains, even from distantly related virus families (clades)[9] — in contrast to the narrow specificity of the antibodies induced by the gp120 vaccines. The antibody responses induced by the canarypox vector alone are limited, but they are substantially improved when combined with the gp120 subunit boost. Although these antibodies do not neutralize primary HIV isolates, they induce antibody-dependent cell cytotoxicity, which is detectable in 50–70% of vaccinees. Moreover, T-cell proliferative responses are more potent and durable when the two vaccines are combined[8], and the response of CD4-positive T cells has been highlighted as a possible correlate for disease progression[10].

The HIV-vaccine field remains at a crossroads. Development of an effective vaccine entails a proper balance between the growing information about HIV and empirical principles that have guided the successful production of vaccines against other agents. Correlates of protection, although useful in guiding preclinical studies, can only be established retrospectively from the results of appropriately designed clinical trials. Combining studies such as that of Connor *et al.*[3] with sufficiently powerful clinical trials should allow the immunological and virological parameters that correlate with the success or failure of a vaccine to be dissected. Experiments are critical for the advancement — and, ultimately, development — of an effective vaccine against HIV. □

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100 YEARS AGO

The War of the Worlds.
By H. G. Wells. Pp. 303.
(London: William Heinemann, 1898.)

Many writers of fiction have gathered material from the fairy-land of science, and have used it in the construction of literary fabrics, but none have done it more successfully than Mr. H. G. Wells. It is often easy to understand the cause of failure. The material may be used in such a way that there appears no connection between it and the background upon which it is seen; it may be so prominent that the threads with which it ought to harmonise are thrown into obscurity; or (and this is the worst of all) it may be employed by a writer whose knowledge of natural phenomena is not sufficient to justify his working with scientific colour. Mr. Wells makes none of these mistakes. Upon a groundwork of scientific fact, his vivid imagination and exceptional powers of description enable him to erect a structure which intellectual readers can find pleasure in contemplating.

From *Nature* 10 February 1898.

50 YEARS AGO

A new high-altitude research laboratory for cosmic ray work at a height of 11,500 ft. on the upper slopes of Monte Rosa was opened by the Italian Centre for Research in Nuclear Studies on January 11. The laboratory portion of the station at present consists of one large experimental room, and a small fully screened room for a Wilson cloud chamber. The equipment is very complete, and includes a three-phase 30 kW. power supply, a separate lighting supply, and two high-capacity battery sets with a petrol generator in case of main power failure. The station is also equipped for two-way direct radio contact with the parent laboratory at Rome, a useful facility at all times, but particularly necessary when the Laboratory is likely to be cut off from the outside world for days at a time in midwinter. ... The work at present going on in the Laboratory includes the exposure of nuclear plates, which in suitable weather can also be carried out up to 3,000 ft. above the Laboratory. Experiments on meson decay are also being carried on, and it is expected that later some Italian geneticists will be undertaking work at the station on mutations induced by cosmic rays.

From *Nature* 14 February 1948.