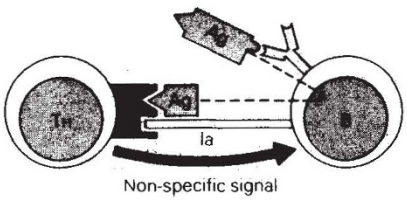
from the work by Gefter, Gray and coworkers[5], they clearly demonstrate that the importance of a carrier protein for a hapten is its ability to stimulate a helper T-cell response. The relative molecular mass of the carrier is unimportant, other than the larger the protein, the more likely it is to contain helper determinants for a greater number of histocompatibility types.

Perhaps a more important issue that these experiments collectively highlight is the problem that MHC restriction of the immune response poses for peptide vaccines. For although the non-responsiveness can be overcome for individual strains of mice, it is clearly a greater problem when considering the outbred human population. This concern also extends to proposed vaccines composed of individual viral proteins, because any one sequence is not guaranteed to contain regions recognized by all histocompatibility types.

One potential solution would be to generate a cocktail of peptides that can bind to most MHC class II alleles. Proponents of such a strategy can argue that such a cocktail would not necessarily be prohibitively large, both because the diversity of antigen-combining sites of class II proteins is limited and because certain sequences could be recognized by various histocompatibility types. Furthermore, most vaccines protect on the level of the population by reducing the rate of transmission and do not rely on protecting each individual. Consequently, a cocktail of peptides that would be recognized by a significant proportion of the population might be quite beneficial. But if I were going to an area where malaria was endemic, I would want to be vaccinated with a mixture that assured protection on the level of the individual.



Possible mechanism for T–B cooperation. T-helper (T_H) cells are primed to antigen (Ag) associated with an MHC molecule (Ia) on antigen-presenting cells. The primed T cells then help B cells. Cooperation is restricted to the I region because of a requirement for the same type of MHC either on the T and B cells or on the T cell and the antigen-presenting cell that primes the T cell. (From ref. 14.)

Another possible solution to the problem of MHC restriction of the immune response was proposed recently[10] by Milich and colleagues, who demonstrated that an antibody response to the nucleocapsid protein of hepatitis virus can be generated in mice primed with synthetic peptides corresponding to helper T-cell determinants. Although there have been many unsuccessful attempts to generate similar stimulation using peptides corresponding to areas recognized by B cells, the success of Milich and colleagues is not surprising because T cells naturally recognize peptide antigens, whereas B cells bind proteins with their conformation intact. What is noteworthy in the experiments of Milich *et al.* is that by priming with a single T-cell determinant from the nucleocapsid, and subsequently boosting with the intact virus, the authors could generate antibodies against a second protein comprising the viral envelope.

Similar examples of such aberrant help have been seen previously in two other systems[11,12]. The proposed mechanism does not violate cognate recognition of protein antigens by B and T cells. Rather, it postulates that immunogens that are aggregates, such as viruses, are treated by the immune system as single molecules. The polymeric structure is bound and internalized as a unit by B cells specific for any of the sterically available proteins of the virus, in this case, both the nucleocapsid and the envelope. Consequently, T-helper determinants from each of the viral proteins will be displayed on the surface of each B cell in association with MHC class II antigens (see figure). Helper T cells specific for the envelope protein generated from the priming with peptide then bind to B cells specific for each of the viral proteins, not just the envelope protein, resulting in the production of antibodies against both proteins. The aggregation of the two proteins is essential, shown by experiments in which primed mice generate antibodies only to the nucleocapsid when boosted with an equivalent mixture of the individual proteins.

The relevance of this work[10–12] to MHC restriction of the immune response is the demonstration that by priming a non-responding strain of mouse with a helper determinant from the nucleocapsid, antibodies against the envelope protein that the mouse normally cannot recognize are generated. Thus, priming with T-cell epitopes could be generally useful not only because the presence of pathogen-specific helper T cells will increase the kinetics of the immune response during an infection, but also because such a procedure might allow non-responsiveness to particular proteins to be circumvented by providing an alternative source of T-cell help.

In their latest work[13], the Wellcome group has examined the usefulness of protein aggregates in immunization. The group greatly improved the immunogenicity of the foot-and-mouth peptide discussed above by fusing it to the hepatitis B nucleocapsid protein. This complex forms virus-like aggregates with the peptide displayed on its surface, and such aggregates are significantly more potent than when the peptide is administered in liposomes, emulsified in Freund's adjuvant or when fused to β-galactosidase. The authors do not know why their complex is more immunogenic than the other forms of the antigen, but the ability of hepatitis nucleocapsid to elicit a strong T-cell response distinguishes it from the other forms of polymerization. □

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100 years ago

The scientific world, in the Duke of Argyll's opinion, has been for some time bowing down to the idol of Darwin and the theory of evolution, which is the fundamental dogma of that cult. Like a prophet of old the Duke raises a warning voice, and points out that the feet of the golden image are in part composed of clay.

Among the results of Mr Darwin's labours during the voyage of the *Beagle* in 1831–36 was a theory of the formation of Coral Reefs and Atolls. These are the Duke's words (*Nineteenth Century*, September 1887, p.305):

"Mr Murray's new explanation of the structure and origin of coral reefs and islands was communicated to the Royal Society of Edinburgh in 1880, and supported with such a weight of fact and such a close texture of reasoning that no serious reply has ever been attempted . . . The overthrow of Darwin's speculation is only beginning to be known. Can it be possible that Darwin was wrong? Reluctantly, almost sulkily, and with a grudging silence so far as public discussion is concerned, the ugly possibility has been contemplated as too disagreeable to be much talked about."

Prof. Huxley asserts that Darwin's confidence in the accuracy of his own theory was not seriously shaken, as the Duke alleges, and quotes as conclusive evidence a letter from Prof. Judd, who gives the results of a conversation which he had with Darwin no long time before the death of the latter. Prof. Huxley also intimates that Prof. Dana, "an authority of the first rank on such subjects," has pronounced against the new hypothesis.

So the "great lesson" has been read, and the scientific world, I fear, has not repented or rent its clothes. But it has heard, and not without indignation. The Duke of Argyll has made grave charges against the honour and good faith of men of science, and they ought to be grateful to Prof. Huxley for his prompt repulse of the attack and his stern rebuke of the assailant.

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