INFECTION AND IMMUNITY, June 1988, p. 1407–1413
0019-9567/88/061407-07$02.00/0

Vol. 56, No. 6

MINIREVIEW

Idiotypic Vaccines and Infectious Diseases

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INTRODUCTION

The discovery of vaccination by Jenner, as well as the development of the principle of vaccines by Pasteur, had an enormous impact on the eradication of many infectious diseases. These developments opened the road to the development of attenuated (i.e., live) or inactivated (i.e., noninfectious) vaccines; however, such vaccines are not without problems and can have detrimental effects. Indeed, attenuated vaccines can revert to a more virulent form, and inactivated vaccines may produce serious side effects. There also are several infectious diseases for which no vaccines are available. For example, many parasitic infections cannot be prevented by vaccination. These facts, together with recent developments in the fields of molecular and cellular biology, have led to the creation of a new generation of vaccines (73): recombinant-DNA vaccines, synthetic-peptide vaccines (63), and idiotypic vaccines (3, 13, 46). In this paper, I review the principle of idiotypic vaccines, the experimental systems in which they have been used, and their potential advantages over other vaccines.

THE PRINCIPLE OF IDIOTYPIC VACCINES

Jerne has described the immune system as a web of interacting variable-region domains, i.e., the idiotypic network (30). He considers the network to be a logical necessity resulting from the dual character of the antibody molecule, which recognizes an antigen through its antigen-binding site and also is immunogenic by virtue of its idiotypic determinants (38, 48). In Jerne's description of the network, the antigen-binding site is called the paratope and the antigenic structure associated with the variable region is called the idiotype. An idiotype is public or cross-reactive (IdX) when it is detected in the sera of all individuals responding to a well-defined antigenic challenge. If it is only detected in the serum of one or a few individuals, the idiotype is defined as private (IdI). Each idiotype is composed of a set of distinct antigenic structures called idiotopes. The T-cell receptor is likewise dual in character; it can bind antigen in a major histocompatibility complex (MHC)-restricted fashion, and anticlonotypic antibody can be raised against antigenic determinants present in the variable portion of the α,β heterodimer constituting the T-cell receptor (29). According to Jerne's picture of the network, antigen-binding antibody and anti-idiotypic antibody belong to the same family. This implies that each antibody molecule can bind both an epitope on an antigenic molecule and an idiotope. The latter appears as the internal image of the foreign epitope. Nisonoff and Lamoyi (46) have proposed that such internal-image determinants could be used as vaccines for infectious diseases. This proposal is based on the idea that such determinants can substitute for antigenic determinants displayed on infectious organisms.

If we accept the view that idiotypic interactions play a role in the regulation of the immune response to infectious agents, various types of idiotypic manipulations (the injection of internal-image-bearing antibody being one of them) could influence ongoing regulatory processes. On the basis of the idiotypic-network hypothesis, the idiotypic cascade presented in Fig. 1 can be developed. Figure 1 follows Jerne's original assumption that paratopes and idiotopes are distinct functional entitites. This allows us to deduce which interactions can potentially occur within the idiotypic cascade. For the sake of simplicity, I only present some of the members of the cascade and consider one or two idiotopes associated with the variable region. According to this cascade, the antigenic epitope elicits an immune response, resulting in the production of Ab_1 antibody. Ab_1 antibody can, in turn, trigger an anti-idiotypic response consisting of distinct subsets of Ab_2 antibodies (4, 31). $Ab_2\alpha$ recognizes framework-associated idiotypes (i.e., $Ab_2\alpha$ cannot interfere with the binding of antigen by Ab_1), $Ab_2\gamma$ recognizes idiotopic determinants closely associated with the paratope (i.e., $Ab_2\gamma$ inhibits the binding of the antigen to Ab_1), and $Ab_2\beta$ bears an idiotope mimicking the antigenic epitope (i.e., it is an internal-image Ab_2). $Ab_2\alpha$ and $Ab_2\gamma$ are induced because their paratopes recognize idiotopes expressed by Ab_1. By contrast, $Ab_2\beta$ antibodies represent a unique subset of Ab_2 because their induction results from the fact that they bear an idiotope complementary to the paratope of Ab_1. Therefore, immunization with Ab_1 does not always elicit the $Ab_2\beta$ subset. Ab_2 antibodies belonging to the different subsets can elicit an anti-anti-idiotypic (Ab_3) antibody response. The Ab_3 response can be extremely complex, especially if it is elicited against a polyclonal Ab_2 consisting of the various subsets, e.g., $Ab_2\alpha$, $Ab_2\beta$, and $Ab_2\gamma$ (Fig. 1). If a monoclonal antibody belonging to one of those subsets is used, the nature of the Ab_3 response will be determined by the nature of this Ab_2. Each type of Ab_2 is potentially able to induce Ab_1-like antibody, because Ab_1 bears the internal image of the antigen recognized by $Ab_2\alpha$ and $Ab_2\gamma$ (in this case, the internal image is the immunogen itself), whereas $Ab_2\beta$ bearing the internal-image determinant of the epitope recognized by Ab_1 should naturally induce an Ab_1 response. Thus, $Ab_2\beta$ can be considered to be an ideal candidate for idiotypic-vaccine development. Indeed, in the first two cases, the induction of an Ab_1-like response might constitute only a minor component of the Ab_3 response, because it results from the fact that the paratope of the Ab_2 is complementary to the idiotope of the Ab_1-like antibody. An additional complexity is due to the fact that antibodies of different antigenic specificity can share a common idiotope. Therefore, $Ab_3\beta$ antibodies induced by $Ab_2\alpha$ and $Ab_2\beta$ can include an Ab_1-like subset as well as antibodies bearing the same idiotope and expressing a different antigenic specificity. By contrast, the Ab_1-like response should be a major compo-

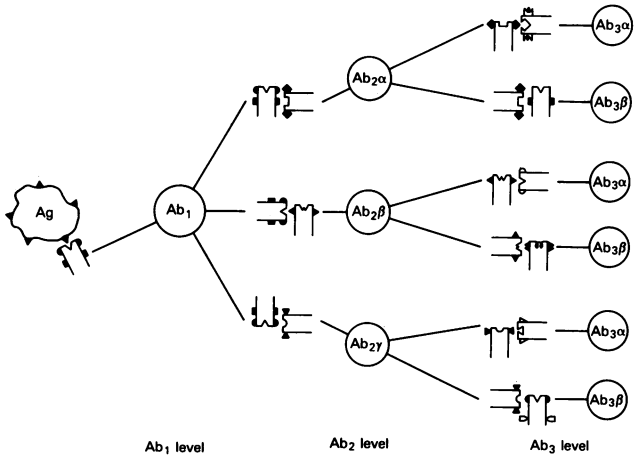

FIG. 1. Idiotypic cascade. A foreign epitope (▲) induces an immune response characterized by the production of Ab_1 antibody. Ab_1 elicits an anti-idiotypic response (Ab_2) which contains three subsets: $Ab_2\alpha$ recognizes a framework-associated idiotype (■) on Ab_1; $Ab_2\gamma$ recognizes an antigen-combining site-related idiotope (◑) on Ab_1; and $Ab_2\beta$ presents the internal image of the original antigenic epitope. Each subset of Ab_2 can trigger an anti-anti-idiotypic response (Ab_3). The Ab_3 response is fairly complex, and the nature of the Ab_3 depends on the inducing Ab_2. Some of the Ab_3 subsets are shown. $Ab_3\beta$ presents an internal image of the epitope inducing the corresponding Ab_2; a subset of $Ab_3\beta$ antibodies induced by $Ab_2\alpha$ or $Ab_2\gamma$ are Ab_1-like. $Ab_3\alpha$ antibodies are directed against the idiotopes of the various Ab_2 antibodies; $Ab_3\alpha$ antibodies induced by $Ab_2\beta$ have the same antigen-combining site as Ab_1. For each type of antibody molecule, one V region is shown.

nent of the anti-$Ab_2\beta$ immune response. The existence of the idiotypic cascade, as well as the characterization of some of its elements, was first demonstrated experimentally by Cazenave (6) and Urbain et al. (69). In the antigenic systems used in their studies (RNase and *Micrococcus lysodeicticus*), it seems that the polyclonal Ab_2 did not contain significant amounts of $Ab_2\beta$, because they did not detect Ab_1-like antibody in their Ab_3. Nevertheless, they showed that animals producing Ab_3 were primed for a response to the original antigen, to which they had never before been exposed.

The first demonstration of the existence of an $Ab_2\beta$ came from the work of Sege and Peterson (61). They showed that anti-idiotypic antibodies prepared against bovine anti-insulin mimics the action of insulin, in that they are able to interact with insulin receptors on tissues and to stimulate the physiological action of insulin itself. Since then, several investigators have produced anti-idiotypic antibodies against anti-ligand antibodies, which are able to bind the receptor of the corresponding ligand (for a review, see reference 21); however, $Ab_2\beta$ generally represents a minor fraction of a polyclonal anti-idiotypic response. Moreover, the characterization of an $Ab_2\beta$ is not easy when a functional test such as receptor binding is not available. $Ab_2\beta$ should bind Ab_1 from various species, recognizing the epitope it mimics. Nevertheless, this binding test does not allow one to discriminate between Ab_2 recognizing an interspecies (cross-reactive idiotype) IdX and a true internal-image $Ab_2\beta$.

In two instances, the immunodominant peptidic structure of the antigen has been found in the primary amino acid sequence of the $Ab_2\beta$. Using the GAT antigen, a $(Glu^{60}Ala^{30}Tyr^{10})_n$ copolymer, Ollier et al. (47) have shown that the D_H segment of the heavy chain of a monoclonal $Ab_2\beta$ presents a GAT-like epitope. In the reovirus type 3 system, a homology has been found between a portion of the hemagglutinin of the reovirus and the light chain of a monoclonal $Ab_2\beta$ (5). Homologies like those are found at the primary-structure level and do not ensure that the three-dimensional structure will be comparable. If the antigenic epitope includes a carbohydrate moiety or is a polysaccharide, this approach becomes impossible. Nevertheless, potential $Ab_2\beta$ antibodies have been found in the polyfructosan system (56).

In summary, the idiotypic-cascade concept leads to different idiotypic-vaccine possibilities. The most promising candidates for vaccine development in outbred species are $Ab_2\beta$ antibodies. $Ab_2\alpha$ and $Ab_2\gamma$, which do not mimic antigen, can prime the immune system to respond to the original antigen by virtue of the fact that their paratopes are complementary to one idiotope of Ab_1. Priming can thus involve the activation of the Ab_1-like B-cell clones within the $Ab_3\beta$ subset (Fig. 1). In an outbred species or in distinct strains of inbred animals, the priming antibodies can activate the silent part of the repertoire. The silent part of the repertoire designates the B-cell clones which are not activated in the course of an antibody response, although their immunoglobulin receptors recognize the challenging antigen. For example, strains of mice expressing different allotypes produce distinct Ab_1 characterized by different idiotypes in response to a given antigenic challenge (39). Those allotype-restricted idiotypes can be expressed in some strains and be part of the silent repertoire of other strains (44, 49). Priming with an anti-idiotypic antibody can activate silent B-cell clones (2, 44, 49, 69).

EXPERIMENTAL MODELS OF IDIOTYPIC VACCINES

Several experimental models involving viral, parasitic, or bacterial infections have been developed to examine the basis of the regulatory properties of the idiotypic cascade. Table 1 gives an overview of most systems studied so far.

The first application of idiotypic manipulation for infectious diseases was developed by Sacks and co-workers (57) for *Trypanosoma brucei rhodesiense*, the causative agent of African sleeping sickness. They produced murine polyclonal anti-idiotypic antibodies against protective murine monoclonal antibody. One of the Ab_2 antibodies was able to induce protective immunity when given to allotype-matched mice without adjuvant (59). This particular anti-idiotypic antiserum contained a large fraction of $Ab_2\gamma$ and an undetectable amount of $Ab_2\beta$, which might explain the ineffectiveness of such treatment in non-allotype-matched mice which do not express this idiotype after parasite infection. Nevertheless, it can be argued that this idiotype is part of the silent repertoire of those mice and could be activated by suitable treatment (i.e., the use of adjuvant or the coupling of the Ab_2 to a carrier). The induction of an allotype-restricted idiotype in mice expressing the wrong allotype (i.e., in mice expressing an allotype which is not associated with the expression of this idiotype) has been observed with suitably manipulated animals (44, 49); these restricted idiotypes were found to be part of the silent repertoire of the nonexpressor strains. In another case, a rabbit idiotype has been induced in mice not normally expressing that idiotype (19). In the course of the activation of a silent clone, the treatment with Ab_2 primes the animals, and Ab_1-like antibodies are usually detected after antigenic challenge.

More recently, with the *Trypanosoma cruzi* system, Sacks et al. have produced an $Ab_2\beta$ mimicking a carbohydrate

determinant of a major cell surface glycoprotein of the parasite (58). This $Ab_2\beta$ can induce Ab_1-like antibody in various species. Unfortunately, it did not elicit protective immunity. By contrast, protective immunity against *Schistosoma mansoni* has been observed with Ab_2-treated rats (25).

The principle of idiotypic vaccination has been applied successfully for several viral systems (Table 1). In the case of the hepatitis B virus system, Kennedy et al. (35) have produced a rabbit anti-idiotypic antibody which can induce virus-neutralizing antibody in mice. This Ab_2 reacts with anti-hepatitis B surface antigen Ab_1 from various species, suggesting that it is an $Ab_2\beta$ or an $Ab_2\gamma$ recognizing a highly conserved interspecies idiotype (37). Recently, Kennedy et al. reported that this Ab_2 can induce protective antibody in chimpanzees (36). This is a particularly exciting result, since chimpanzees and humans are the only two species susceptible to hepatitis B virus.

In the reovirus type 3 system, the reovirus hemagglutinin (HA) directs tissue binding and cell tropism and is the major target for the cellular and humoral anti-reovirus type 3 immune responses. An anti-idiotypic monoclonal antibody raised against an anti-reovirus type 3 monoclonal antibody bearing the IdX of the anti-HA response appears to be an $Ab_2\beta$ by several criteria: it binds to the receptor of the virus on target cells (the receptor has been characterized, thanks to the production of a rabbit polyclonal $Ab_2\beta$ [8]) and mimics its biological activity; it prevents the infectivity of reovirus particles and their binding to target cells (12); it triggers an Ab_1-like immune response in various species (22); and it can trigger T-cell immunity to reovirus type 3 in naive mice (62). As mentioned in the previous section, there is homology between part of the primary amino acid sequence of the reovirus HA and part of the $Ab_2\beta$ light chain (5).

The fact that the $Ab_2\beta$ of the reovirus system can elicit both B-cell and T-cell immunity is particularly exciting from the immunological point of view. It indicates not only that this $Ab_2\beta$ mimics the three-dimensional structure of HA, as indicated by its ability to bind to the HA receptor, but also that it can even mimic the immunological functions of HA. T-cell activation is usually MHC restricted and requires the processing of high-molecular-weight stimulating antigen. T-cell activation by an $Ab_2\beta$ can either result from its processing and MHC-restricted presentation or be a consequence of receptor cross-linking, if the $Ab_2\beta$ behaves as an anticlonotypic antibody. In the reovirus system, the fact that optimal cytotoxic-T-lymphocyte activation was obtained by injecting irradiated B-cell hybridomas, displaying class I and class II MHC molecules as well as the $Ab_2\beta$ on their surface, argues in favor of the first hypothesis (62). Recent studies using *Mycobacterium tuberculosis* provide clear-cut data on the activation of T-cells by $Ab_2\beta$. Indeed, it was shown that a monoclonal $Ab_2\beta$ raised against a monoclonal Ab_1 recognizing a protein antigen can stimulate T-cell proliferation (54). This stimulation requires the processing of the $Ab_2\beta$ and is MHC restricted (55).

In two other viral systems (poliovirus type II and rabies virus), Ab_2 immunization led to the production of virus-neutralizing antibodies but did not confer protective immunity (52, 71); however, different immunization schedules, as well as the use of other doses of antigen with or without adjuvant, might yield different results.

In the Sendai virus system, a monoclonal anticlonotypic antibody recognizing the T-cell receptor of a virus-specific T-helper cell clone was used for the first time (15, 16). Immunization with this anticlonotypic antibody induces protective immunity against Sendai virus infection by eliciting T-cell and B-cell immunity (18). Interestingly, from the point of view of vaccine development, the T cells induced by the virus are MHC restricted, whereas the T cells activated by the anticlonotype do not express MHC restriction (15, 16). A similar approach has been developed to induce protective immunity against the intracellular bacterium *Listeria monocytogenes* (32). Here, a syngeneic murine polyclonal anticlonotypic antibody was raised against the receptor of a T-cell hybridoma recognizing a protective antigen of *L. monocytogenes*. Immunization of syngeneic or allogeneic mice with the anticlonotype induced protective immunity.

Another area of interest for the development of idiotypic vaccines is bacterial infections. The immune response to bacterial antigens presents an ontogenic delay, and the vaccination of children with classical vaccines is not very effective (for a review, see reference 64). Obviously, the use of synthetic-peptide or recombinant-DNA vaccines are of no advantage with respect to antipolysaccharide responses. In fact, in some of the early work on the role of the idiotypic cascade, bacterial antigens were used. Urbain et al. (69) showed that it is possible to prime rabbits to respond to *M. lysodeicticus* by immunization with Ab_2 antibody. Earlier, Eichmann and Rajewsky (14) had found that the injection of an immunoglobulin G1 guinea pig Ab_2 could enhance the immune response to group A streptococcal carbohydrate. Finally, the work of Bona and collaborators (2, 27) has shown that the anti-β-2→6 polyfructosan response can be enhanced by treating adults or neonates with Ab_2. They even found one monoclonal Ab_2 which mimicked bacterial levan (56). Those studies indicate that idiotypic manipulations can prime the immune system to respond to polysaccharide antigens. Stein and Söderström (65) subsequently showed that protective immunity against *Escherichia coli* K-13 infection can be obtained by injecting a monoclonal anti-idiotypic antibody into newborn mice. This Ab_2 was raised against the idiotype of an anticapsular protective antibody. McNamara et al. (42) have observed that adult mice immunized with a monoclonal Ab_2 coupled to keyhole limpet hemocyanin are protected against *Streptococcus pneumoniae*. In that case, Ab_2 recognizes a determinant of the major IdX of antiphosphorylcholine antibody.

All the examples cited above demonstrate that idiotypic vaccines can be successfully used to confer protective immunity against viral, parasitic, and bacterial infections and that successful idiotypic priming can be elicited for peptidic as well as for carbohydrate antigens. Nevertheless, the injection of an Ab_2 does not always induce or prime for an Ab_1 response. In some cases, Ab_2 injection actually induces the suppression of the Ab_1 response, leading to expression of the corresponding idiotype (for a review, see reference 50). In the case of the infectious-disease models, idiotypic suppression might lead to increased pathogenicity (34). The mode of Ab_2 injection also can influence its outcome: in the arsonate system, treatment with monoclonal Ab_2 leads to idiotopic suppression in A/J mice (28), whereas injection of the same monoclonal Ab_2 coupled to keyhole limpet hemocyanin in CFA leads to increased idiotopic expression and primes the A/J mice for the Ab_1 response (J. Marvel, unpublished observations). This suggests that one must be very careful in designing idiotype vaccines or in using idiotypic manipulation to induce protection against infectious diseases.

TABLE 1. Experimental systems for which the role of anti-idiotypic antibody has been studied[a]

Infectious agent	Disease	Anti-idiotype antibody			Adjuvant	Result of injection	Reference(s)
		Specificity	Type	Classification			
Herpes simplex virus	Encephalitis						
Type I		IdI	Rabbit polyclonal	—[b]	None	Induction of DTH in mice	23
Type II		IdI	Rabbit polyclonal	—	Alum precipitate	Increased pathogenicity in mice	34
Hepatitis B virus	Hepatitis	Interspecies IdX	Rabbit polyclonal	$Ab_2\beta$	Alum precipitate	Induction of IdX^+ protective Ab_1 in chimpanzees	33, 34, 36
		Interspecies IdX	Rabbit polyclonal	$Ab_2\alpha$	Alum precipitate	Induction of a silent clone in mice	60
		Interspecies IdX	Mouse monoclonal	$Ab_2\beta$			66, 67
		Anti-anti-polymeric human albumin	Mouse monoclonal	$Ab_2\beta$		Induction of virus-neutralizing Ab_1 in rabbits	9,10
Poliovirus type II	Polio	Interspecies IdX	Mouse monoclonal	$Ab_2\beta$	None	Induction of virus-neutralizing Ab_1	70, 71
Rabies virus	Rabies	IdI	Rabbit polyclonal	$Ab_2\gamma$	CFA	Induction of virus-neutralizing Ab_1	52, 53
		IdX	Mouse monoclonal	$Ab_2\gamma$	None	Induction of virus-neutralizing Ab_1	70
Reovirus type 3	Encephalitis	IdX	Mouse monoclonal	$Ab_2\beta$	CFA	Induction of virus-neutralizing Ab_1 in mice, rats, rabbits, and guinea pigs	22
					None	Induction of T-cell immunity in mice	62
						Prevents infectivity of target cells in vitro	12
Sendai virus	Systemic infection	T-cell receptor of a T-helper clone	Mouse monoclonal	—	None	Induction of protective immunity in mice	15, 16, 18
		IdX	Mouse monoclonal	—	CFA	Induction of virus-neutralizing Ab_1 in mice	17
Listeria monocytogenes	Meningitis	T-cell receptor	Mouse polyclonal	—	With and without CFA	Induction of protective immunity in mice	32
Mycobacterium tuberculosis	Tuberculosis	Mouse monoclonal antibody binding mycobacterial protein antigen	Rabbit polyclonal	$Ab_2\beta$		Stimulation of proliferation of human PBL in vitro	54, 55
Escherichia coli K-13	Infantile diarrhea	IdX	Mouse monoclonal	$Ab_2\gamma$ (or $Ab_2\beta$)	None	Induction of protective immunity in mice by neonatal injection	65
Streptococcus pneumoniae	Pneumonia	IdX	Mouse monoclonal	$Ab_2\gamma$	CFA	Induction of protective immunity in mice	42
Schistosoma mansoni	Schistosomiasis	Rat monoclonal antibody binding a schistosomulum glycoprotein	Rat monoclonal	$Ab_2\beta$	None	Induction of protective immunity in rats	25
Trypanosoma rhodesiense	African sleeping sickness	IdX	Mouse polyclonal	$Ab_2\gamma$	None	Induction of protective immunity in allotype-matched mice	57, 59
Trypanosoma cruzi	Chagas' disease	IdX	Rabbit polyclonal	$Ab_2\beta$ (or $Ab_2\gamma$)	CFA	Induction of parasite-binding antibodies in mice, rabbits, and guinea pigs	58

[a] DTH, Delayed-type hypersensitivity; —, undefined.

DEVELOPMENT OF IDEAL IDIOTYPIC VACCINES

In the two preceding sections, consideration was given to how the concepts of the idiotypic cascade and of the internal image ($Ab_2\beta$) can be applied to the development of idiotypic vaccines. Obviously, much more needs to be done before the results obtained with experimental animal models can be applied for use in humans. Nevertheless, such studies have helped to define the criteria which need to be considered in the development of successful vaccines. Most of these criteria have already been reviewed by others (3, 13). Ideally, an idiotypic vaccine should be able to confer protective immunity. From the data reviewed in the previous section, it is clear that $Ab_2\beta$ are the best candidates for use as vaccines. The following criteria permit one to define a true internal image: (i) $Ab_2\beta$ should mimic the three-dimensional structure of the antigen (antigen essentially means the antigenic epitope recognized by Ab_1); (ii) $Ab_2\beta$ should induce the same immune response as the antigen (i.e., it should activate the same B-cell clones); (iii) the affinity of an Ab_1 for the antigen and the $Ab_2\beta$ should be of the same order of magnitude; (iv) if the mimicked antigen stimulates both T-cell and B-cell immunity, $Ab_2\beta$ should do the same; (v) $Ab_2\beta$ should mimic the physiological properties (for example, receptor binding) of the antigen; and (vi) $Ab_2\beta$ should bind Ab_1 antibody of any species.

When the original epitope is a peptide, there is clear evidence that $Ab_2\beta$ can mimic the physiological and immunological properties of this epitope and thus fulfill most of the criteria given above. These criteria lead to a conservative definition of the internal image. Indeed, an $Ab_2\beta$ can still function as a surrogate antigen, without presenting the same tertiary structure (see reference 68 for a detailed discussion of this point). Here, immunological efficiency would be the main criterion to define an $Ab_2\beta$. This is most likely the only way in which the internal image of a carbohydrate antigen can be defined. Potential $Ab_2\beta$ antibodies mimicking carbohydrate antigen have been studied experimentally. In one system, Ab_2 immunization induces protective immunity (65); in another, Ab_2 immunization activates the production of epitope-binding antibodies in various species (58). In the polyfructosan system, a monoclonal anti-idiotypic antibody mimicking bacterial levan has been observed (56), although the rationale for $Ab_2\beta$ mimicking a carbohydrate epitope is not understood. A clear understanding of the way $Ab_2\beta$ mimics a carbohydrate epitope requires that one knows the physicochemical basis of the binding of the $Ab_2\beta$ and of the carbohydrate to the Ab_1 molecule. An analysis performed by Greenspan and Davie (24) indicates that the carbohydrate epitope and the $Ab_2\beta$ might bind to distinct, although closely associated, contact residues.

If an $Ab_2\beta$ is not available, I would argue that $Ab_2\gamma$ (or eventually $Ab_2\alpha$) antibodies could be used as potential idiotypic vaccines. Indeed, if the silent repertoire of an individual contains Ab_1-like antibody, a suitable idiotypic manipulation should permit one to activate it. The fact that a rabbit idiotype which has never been detected in mice immunized with the same antigen can be activated in the mouse clearly illustrates this point (19).

Another issue of concern with vaccination is the use of adjuvants. The latter have been used in several instances (Table 1). In some studies no effect was observed without the use of adjuvants, which stresses the need to develop suitable nontoxic adjuvants. In this context, the fact that Ab_2-pulsed dendritic cells induce an enhanced Ab_3 response is particularly interesting, because dendritic cells can be considered as a natural adjuvant (20).

So far, very few experimental studies have compared the magnitude, as well as other parameters (e.g., affinity, idiotypic profile, isotypes), of the antibody responses induced by anti-idiotypic antibodies and by the corresponding nominal antigens. If the latter are unavailable, the comparison is obviously impossible. In the case of hepatitis B virus, a single injection of alum-precipitated Ab_2 does not induce an antiviral immune response, although it efficiently primes the immune system (i.e., induces immunological memory) (33). Multiple injections of alum-precipitated Ab_2 induce an antiviral immune response comparable to the one induced by a single injection of hepatitis B surface antigen (33). Also in this system, multiple injections of Ab_2 induce protective immunity in chimpanzees (36). In the case of reovirus type 3, multiple injections of multivalent Ab_2 (i.e., cross-linked or coupled to an immunogenic carrier) with adjuvant induce antiviral antibody titers similar to the ones obtained after several injections of the inactivated virus (22). Recently, McNamara et al. (41) compared the immune response induced by phosphorylcholine (PC), an immunodominant epitope located in the cell wall of *S. pneumoniae*, coupled to an immunogenic carrier (PC-carrier 1) with the antibody response elicited by two different Ab_2 antibodies coupled to another immunogenic carrier (Ab_2-carrier 2). Previously it had been shown that one of those Ab_2 coupled to a carrier can induce protective immunity as well as PC coupled to the same carrier can (42). The antibody response elicited by PC-carrier 1 has a higher titer than the response induced by $Ab_2\gamma$-carrier 2. Nevertheless, a precursor analysis indicates that $Ab_2\gamma$-carrier 2 stimulates a larger proportion of B-cell clones able to produce a protective antibody (41). The priming with this particular $Ab_2\gamma$-carrier 2 also modifies the profile of the antibody response to PC-carrier 1 by increasing the proportion of protective antibody. This leads to the concept that, in some cases, priming with an Ab_2 can induce a most effective protective immunity. More studies need to be done to compare conventional vaccines with idiotypic vaccines.

Since the injection of nonhuman antibody into humans might have toxic effects, an ideal idiotypic vaccine should be prepared by creating hybrid antibody molecules combining an animal V region with a human constant region. Such chimeric antibody molecules can be created by gene transfection (43). Alternatively, $Ab_2\beta$ could be produced by in vitro immunization and fusion of human cells.

CONCLUSIONS

The experimental studies reviewed here indicate that idiotypic vaccines are promising alternatives to conventional vaccines. This is especially the case when the protective antigen of the infectious agent is a polysaccharide or the carbohydrate moiety of a glycoprotein. It is also an interesting approach when the antigen involved is either difficult to isolate or unavailable, as well as when a synthetic peptide results in unsuccessful vaccination because it does not present the tertiary structure of the antigen.

It is worth mentioning that the application of idiotypic vaccines is not limited to the field of infectious diseases. In tumor immunology, anti-idiotypic antibody mimicking tumor-associated antigens may be used (11, 26, 45, 51). The use of anti-idiotypes to control autoimmune reactions (72), enteric intoxication (1), and the rejection of allograft (40) has also been suggested.

The possibility of using anti-idiotypic antibody to immunize against human immunodeficiency virus, the causative agent of acquired immunodeficiency syndrome, is currently being explored in several laboratories (74). One approach consists of producing an Ab_2 capable of preventing the binding of the human immunodeficiency virus to its receptor (the CD4 molecule) on CD4 cells. Chanh et al. (7) have shown that an Ab_2 directed against the idiotype of anti-CD4 antibody binds the human immunodeficiency virus and partially inhibits the infection of human T cells in vitro. Another approach might consist of producing an $Ab_2\beta$ mimicking a protective epitope of the virus in order to induce virus-neutralizing antibody and, it is hoped, protection.

ACKNOWLEDGMENTS

I am indebted to P. Baker and D. Sacks for critical reading of the manuscript and to B. Marshall for expert editorial assistance.

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