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The WHO Task Force on Vaccines for Fertility Regulation. Its formation, objectives and research activities

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Over the past 18 years, the WHO Task Force on Vaccines for Fertility Regulation has been supporting basic and clinical research on the development of birth control vaccines directed against the gametes or the preimplantation embryo. These studies have involved the use of advanced procedures in peptide chemistry, hybridoma technology and molecular genetics as well as the evaluation of a number of novel approaches in general vaccinology. As a result of this international, collaborative effort, a prototype anti-HCG vaccine is now undergoing clinical testing, raising the prospect that a totally new family planning method may be available before the end of the current decade.

Key words: vaccines/birth control/immunocontraception

Introduction

This account of the activities of the Task Force on Vaccines for Fertility Regulation summarizes the research supported by WHO over the past 17 years in an effort to develop safe, effective and acceptable birth control vaccines. It indicates how valuable such vaccines are perceived to be as a novel addition to the options available to the users of family planning services and reflects the long-term, high risk nature of this line of new product development which combines two of the most difficult and sensitive areas of biomedical research, namely, the development of novel vaccines and of new methods of birth control. Also explained are the financial constraints that have affected these studies and the major influence these factors have had on determining whether research lines were continued or abandoned.

Formation of the Task Force

The Special Programme of Research, Development and Research Training in Human Reproduction was established by the World Health Organization in 1972 in response to demands from its Member States that the Organization take a more active role in the development of a greater variety of family planning methods to meet the needs of reproductive age couples in widely different cultural, religious, service and personal settings, particularly in the developing countries. These demands were prompted by the rapidly expanding population in many parts of the world and the increasing dissatisfaction being expressed about the inconvenience of use, the unacceptability of side effects and the possible health risks associated with the long-term use of some of the existing methods available at that time.

To launch this major research and development effort, the Programme formed a number of Task Forces, each consisting of an international, interdisciplinary group of scientists and clinicians collaborating in research orientated towards a specific set of predetermined goals and objectives. At the time the Special Programme was established in 1972, one of the most often expressed needs was for a safe, effective and acceptable birth control method which could be taken by women as an anti-implantation agent. Therefore, one of the Task Forces established in the first year of operation of the Programme, was on Methods for the Regulation of Implantation which included, in its research strategy, studies on the inhibition of implantation by immunological means. During 1973, it was recognized that the successful development of anti-implantation vaccines required specialized immunobiological expertise that was not directly relevant to the other objectives of the Task Force. Furthermore, an increasing amount of information was becoming available to indicate that there were other molecules and tissues, apart from those involved in implantation, that were both specific to and essential for the process of reproduction and which represented, at least theoretically, candidates for antifertility vaccine development. It was decided, therefore, to establish a separate Task Force on Immunological Methods for the Regulation of Fertility to investigate the feasibility of developing immunological methods to: (i) prevent or disrupt implantation; (ii) prevent sperm transport and fertilization; and (iii) prevent blastocyst hatching through interference with the zona pellucida.

Exploratory programmes of research were initiated in each of these broad areas.

Identification of research priorities

In 1974, the Programme convened an international symposium on immunological approaches to fertility control in conjunction with the Karolinska Institute in Stockholm (Diczfalusy, 1974). The opening paper at that symposium reviewed the steps in the human reproductive process susceptible to immunological interference. During the ensuing discussion of that paper, and throughout the rest of the symposium, it was agreed that although there are a large number of reproduction-specific molecules against which antifertility vaccines could be directed, not all of them represent attractive options, in that the immunological removal or neutralization of some of them can result in endocrine or other metabolic disturbances and could possibly lead to long-term immunopathological *sequelae*. Therefore, in selecting

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candidate immunogens for subsequent development into vaccines that will be safe, effective and acceptable for clinical use, the Task Force has used the following criteria: (i) molecules which are restricted to the intended target; (ii) molecules which are sequestered in the lumen of the male or female genital tracts or are located in a site where the desired immune response does not produce immunopathological or other unacceptable side-effects; (iii) molecules which are present transiently and in low amounts compared to the expected immune response; (iv) molecules whose elimination or neutralization by immunological means will result in a clinically safe, effective and acceptable antifertility effect; and (v) molecules which are (or can be) chemically well characterized, to facilitate eventual large scale manufacture at low cost.

These criteria are met by molecules found in or produced by the gametes (spermatozoon and ovum) and the trophectoderm of the preimplantation embryo. However, there are a large number of sperm-specific, ovum-specific and trophectoderm-specific molecules that could be used for vaccine development, and it was obviously not feasible, in terms of time or cost, to carry out studies simultaneously with all of them. Parallel studies in all of these areas were funded initially and then a progressive reduction was made in the number of leads supported depending on the results obtained and the relative degree of advancement in each area.

Research and development—past and present studies

Anti-sperm vaccines

Task Force studies in this area have focused on two types of sperm-specific antigens: (i) functional antigens such as the enzymes known (or suspected) to be required for sperm metabolism (lactic dehydrogenase-X) or involved in sperm–egg interactions and the processes leading to fertilization (acrosin and hyaluronidase); and (ii) structural antigens such as the molecules expressed on the sperm cell membrane and against which the naturally occurring agglutinating and immobilizing antibodies found in some infertile individuals were believed to be directed.

Sperm enzymes. Between 1973 and 1977, sufficient quantities of lactic dehydrogenase-X (LDH-X or LDH-C4), acrosin and hyaluronidase were prepared to permit both passive and active immunization experiments to be carried out in several animal species.

Varying degrees of fertility reduction were observed in mice and rats (55%), rabbits (70%) and baboons (30%) actively immunized with mouse LDH-X and with a synthetic peptide based on a portion of the molecule (Goldberg *et al.*, 1981). Unfortunately, studies to dissect further the molecule and identify additional immunogenic epitopes for synthesis were prevented by funding constraints experienced by the Programme in the late 1970s. Although the Task Force was obliged to terminate its studies on an anti-LDH-X vaccine at that time, work on this molecule has continued with support from other funding agencies and has progressed to the point at which a cDNA expression library, derived from human testis, has been screened with polyclonal and monoclonal antibodies raised to murine LDH-C4 (Millan *et al.*, 1987). As a result, the nucleotide sequence coding for human LDH-X has been deduced and engineered into an expression vector system. A sufficient quantity of this material is being prepared to conduct a preliminary efficacy trial in baboons (Goldberg, 1990).

Although encouraging data were produced by the Task Force to indicate that anti-acrosin antibodies could inhibit the action of the enzyme on substrates *in vitro* and that anti-hyaluronidase antibodies could inhibit rabbit in-vitro fertilization, active immunization of rabbits and sheep with these two enzymes, either alone or in combination, did not result in a reduction in fertility (Morton and McAnulty, 1979).

Sperm membrane antigens. By virtue of their relatively low abundance and often labile nature, many of the molecules forming integral components of the sperm membrane prove difficult to isolate in pure form and in sufficient quantities for meaningful immunization experiments. Some preliminary studies were carried out in this area by the Task Force between 1975 and 1978 with the lipoprotein sperm immobilizing antigen (SIA), the T and S antigens and microbial antigens which had antigenic similarities with molecules in the sperm plasma membrane. Although all of these antigens were capable of eliciting antibodies which bound to and immobilized spermatozoa *in vitro*, they had no effect on the fertility of rats, guinea pigs or monkeys when used for active immunization experiments and this line of research was terminated.

Reference Bank for Reproductive Immunology. Another approach to the identification of novel molecules which might form the basis of antifertility vaccines, is to exploit the 'experiments of nature', in which naturally occurring immunity to reproductive antigens, particularly sperm antigens, is associated with infertility.

Although it was known that anti-sperm antibodies could be detected in the sera of some infertile men and women, the tests used to measure these reactions often yielded conflicting and confusing information. In an attempt to resolve this problem, the Task Force convened a series of workshops and planning meetings, between 1974 and 1977, to standardize the various techniques used for the detection of iso- and auto-antibodies to spermatozoa (Rose *et al.*, 1976). In addition, a Reference Bank for Reproductive Immunology was set up to serve as a central reference facility for a multi-centre study involving the examination, calibration, standardization and selection of reliable and repeatable tests for antibodies to spermatozoa and other reproduction-specific antigens (WHO Reference Bank, 1977).

The primary objective of the bank was to collect and evaluate sera from 16 clinical categories of donors. However, major problems were soon encountered in collecting the sera due to the very strict criteria for assignment to each donor category, the substantial workload required to screen and select the donors, the large volumes of sera required (200 ml), and the comparative rarity of some of the clinical conditions listed. A total of 21 university and hospital departments in 10 countries contributed sera to the Bank project and a total of 18 collaborating laboratories received panels of sera, coded in a blind manner, for investigation. The sera were tested using a variety of classical and novel procedures for anti-sperm and anti-zona pellucida activities, including gelatin agglutination, tray agglutination, immobilization, immunobead binding, ELISA, cytotoxicity, radioimmunoassay

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and immunofluorescence. The data obtained in this ambitious project indicated inter- and intra-laboratory, test and sample variations in the procedures used for the detection and quantitation of anti-gamete antibodies with some tests performing better than others in terms of repeatability and correlation with other procedures. The results were reviewed at a Task Force workshop in 1983 and considered to be an important step in selecting reliable laboratory procedures for measuring and characterizing antibodies associated with infertility and which might be appropriate reagents for the isolation of antigens suitable for vaccine development (WHO Task Force, 1985).

Anti-ovum vaccines

Because of its crucial role in the gamete interactions leading to fertilization, the majority of the research directed at developing an anti-ovum vaccine has focused on the zona pellucida (ZP) as a source of potential candidate antigens.

Following the observation that the fertility of the females of several species of laboratory animals is reduced following either active or passive immunization with crude preparations of whole ZP (Gwatkin *et al.*, 1977), the Task Force carried out, between 1974 and 1978, a number of experiments which showed that: (i) passive immunization with anti-ZP antisera produced a pronounced antifertility effect in guinea pigs, lasting up to four oestrous cycles without any apparent disruption to ovulation; (ii) anti-ZP antibodies could be detected on the surface of the ZP within five days of administration of the antisera in the marmoset, and that these antibodies persist for up to 3 weeks; and (iii) active immunization of a small group of fertile female baboons with solubilized whole porcine ZP resulted in a reduction in their fertility.

In the baboon experiments, amenorrhoea, of variable duration, was observed in the majority of the immunized animals, suggesting possible intraovarian complications and anovulation. In order to overcome this problem, the Task Force proposed to isolate sufficient quantities of porcine ZP to permit the identification and characterization of antigens expressed on the surface of the ZP only during the peri- and post-ovulatory period and that were involved in sperm–ZP interactions. These studies were to have begun in 1979, but the same funding constraints that had curtailed work on sperm vaccines, led to the termination of Task Force funded work in this area also. Fortunately, as with the LDH-X vaccine, this work is being supported by other national and international funding sources and has now reached the stage at which the chemical structure of the ZP has been partially determined and the role of specific saccharide residues have been shown to be involved in sperm–ZP binding (Macek and Shur, 1988). In addition, amino acid sequence data on some of the protein components of the ZP have also been obtained and mice immunized with a 16 amino acid peptide of one of the ZP proteins have produced anti-ZP antibodies and exhibited reversible infertility with no evidence of ovarian damage (Millar *et al.*, 1989).

Anti-placenta vaccines

The Task Force has investigated a number of placenta-specific antigens that might be suitable for development into anti-implantation vaccines. As with its studies on sperm antigens, both structural antigens, forming part of the trophoblast cell membrane, and functional antigens, such as placental hormones, were evaluated.

Structural placental antigens. These studies, carried out between 1974 and 1978, largely involved a preliminary evaluation of the antifertility effect of active immunization with two placental-specific proteins, SP-1 and PP-5, that had been identified at that time (Bohn and Weinmann, 1974).

SP-1 is a rapidly secreted placental protein which can be detected by immunofluorescence in the cytoplasm of the syncytiotrophoblast as well as on the plasma membrane of this tissue. Although an antifertility effect was observed when female baboons and cynomolgus monkeys were actively immunized with human SP-1, in the majority of cases (50–80%) this effect was manifested as a late abortion. In contrast, no antifertility effect was observed in similarly treated rhesus monkeys nor in rhesus monkeys immunized with rhesus SP-1, even in the presence of high titres of anti-SP-1 antibodies. Similar studies in baboons indicated that the rate of secretion of SP-1 in early pregnancy was probably too high to be neutralized by the antibody in the maternal circulation. Unlike SP-1, PP-5 is not found in the cytoplasm of trophoblast cells but appears to be an integral component of the cell membrane. It is present in a low concentration in trophoblast tissue, is not secreted into the maternal circulation and is very difficult to isolate from placental tissue. However, a sufficient quantity of human PP-5 was prepared to permit the active immunization of a small group of female monkeys. Although a substantial reduction in the fertility of these animals was observed, attempts to extend these studies, by immunizing rhesus monkeys with rhesus PP-5, were thwarted by the major difficulties experienced in obtaining a sufficient number of rhesus placentae from which the protein was to be isolated (Botev *et al.*, 1979).

Hormonal placental antigens. The Task Force has carried out studies to determine the potential of the two principal placenta-specific hormones, chorionic somatomammotrophin and chorionic gonadotrophin, as candidates for antifertility vaccine development.

Chorionic somatomammotrophin (HCS). Although earlier studies had shown an antifertility effect in baboons resulting from passive immunization with antisera raised against HCS (Stevens *et al.*, 1971), further studies, carried out in 1974, in which a group of fertile female baboons was actively immunized with a preparation of baboon chorionic somatomammotrophin (BCS) failed to show a reduction in the fertility of the treated animals.

Chorionic gonadotrophin (HCG). By far the greatest amount of work carried out by the Task Force over the past 10–12 years has been concerned with the development and clinical testing of a prototype vaccine directed against the glycoprotein hormone, HCG. The principal function of HCG, produced by the trophectoderm of the preimplantation embryo within a few days of fertilization, appears to be the maintenance of the corpus luteum thus ensuring its continued production of progesterone. Since progesterone is needed for the successful completion of

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implantation of the blastocyst, if the production or function of HCG can be inhibited immunologically, the corpus luteum would regress, its production of progesterone would decline and menstruation would occur at or about the expected time thus mimicking the natural events that occur in a non-conceptual cycle.

To avoid the risk of producing immunity cross-reacting with the pituitary glycoproteins (luteinizing hormone, follicle stimulating hormone and thyroid stimulating hormone), the Task Force focused its efforts on the development of an anti-HCG vaccine based on the apparently HCG-unique carboxyterminal peptide of the beta subunit of HCG (β-HCG-CTP). Between 1975 and 1980, the Task Force carried out a series of studies to define the optimal composition of an anti-HCG vaccine (Stevens *et al.*, 1981a,b) using, as its criterion for selection of the various components, their ability to elicit high-titre antibodies specific for HCG. These studies involved: (i) the comparative evaluation of numerous synthetic peptides of various lengths within the β-HCG-CTP; (ii) the potency of a variety of different macromolecules to act as carriers for the β-HCG-CTP; (iii) the development of a chemical coupling methodology that would permit the production of β-HCG-CTP: carrier conjugates of predictable and predetermined composition and characteristics; (iv) the selection of a potent but potentially clinically acceptable immunostimulant; and (v) the identification of a suitable vehicle in which the vaccine could be administered.

By 1979, a prototype vaccine consisting of the above components and satisfying the appropriate criteria had been developed and tested for antifertility efficacy in fertile female baboons (Stevens *et al.*, 1981c). A significant reduction in fertility, to $<5\%$, was observed in the immunized animals compared to 70% in a control group. Furthermore, no alterations to the menstrual cycles of the immunized animals were observed, suggesting that the antifertility action of the vaccine was effective prior to completion of implantation, an important consideration in terms of the use of this vaccine for birth control purposes.

Between 1980 and 1983, priority was given to conducting the appropriate preclinical toxicity and safety studies with the prototype vaccine that would enable a Phase I clinical trial with the prototype vaccine to be carried out at the earliest opportunity (Stevens and Jones, 1983). A total of 21 different preparations, consisting of the complete vaccine and various combinations of its individual components, were evaluated at a number of dose levels in acute and sub-acute toxicity studies, muscle irritancy studies and in a 5 month hyperimmunization study in baboons.

The data obtained in these preclinical studies amounted to >1300 pages of tabulated information which, together with supporting information from the suppliers of the vaccine components and a phase I clinical trial protocol, were compiled into an Investigational New Drug (IND) application and submitted to the United States and Australian drug regulatory authorities in mid-1984. The primary purpose of this trial (Jones *et al.*, 1988), initiated in late-1985, was to evaluate the tolerability of the vaccine. As the study was carried out in previously electively sterilized women volunteers, no direct information could be obtained on the efficacy of the vaccine although anti-HCG antibody levels were measured as an index of potential efficacy. The subjects consisted of 30 women aged 26–43 years who had been surgically sterilized, who met the inclusion criteria for the study and who gave their written and informed consent to participate in the trial.

The amount of HCG present in the maternal circulation at the time of implantation in the human, 135 mIU/ml, approximates to 0.26 nmol/l of HCG binding capacity *in vitro*. Preliminary data indicate that the biological neutralizing capacity of the anti-HCG antisera is ~50% of its *in-vitro* binding capacity for the hormone, suggesting that an antibody titre of at least 0.52 nmol/l will be needed to achieve an antifertility effect if the vaccine works by this mechanism alone. The mean values of the antibodies in all of the volunteers reached this threshold level by 6 weeks and persisted for up to 6 months or more in some cases. The antibody titres attained in the higher dose groups reached 5–7 times the level estimated to confer antifertility efficacy. No unacceptable side-effects were reported or observed during this phase I trial.

This clinical study was the first to demonstrate that a synthetic peptide, based on a portion of a self-like molecule to which the body is immunologically tolerant, can be made iso-immunogenic and that the resulting immune response is both free of unacceptable adverse side-effects and of sufficient magnitude, theoretically, to confer antifertility efficacy on the recipient.

Research and development—ongoing and future studies

Anti-sperm vaccines

The recent advances that have occurred in the field of molecular genetics and in the production of monoclonal antibodies (MAbs) now provide an opportunity to identify, isolate and synthesize peptides, representing part or all of the primary structure of selected protein molecules, which can be subsequently evaluated as antifertility immunogens. The Task Force is currently supporting a project to classify sperm membrane-specific MAbs, and the molecules they react with, as a means of identifying relevant candidates for development into prototype anti-sperm vaccines.

Anti-trophoblast membrane antigens

Similarly, the Task Force has established a research programme to classify trophoblast-specific MAbs, and the molecules with which they react.

The studies being supported by the Task Force in this area include: (i) the production of new monoclonal antibodies and polyclonal antisera (PAbs) raised to carefully prepared and selected trophoblast tissue extracts; (ii) the screening of these MAbs and PAbs in terms of their tissue-specificity; (iii) the intra-tissue localization of their reactivities in human and primate placentae; (iv) the isolation of putative protein antigens from human placentae; (v) the production of MAbs and PAbs to these isolated antigens; (vi) the evaluation of the ability of these MAbs and PAbs to lyse and/or inhibit the growth of trophoblast cells *in vitro*; and (vii) the evaluation of the antifertility efficacy of active immunization of relevant animal models with these antigens.

To facilitate and accelerate definition of the chemical structure of the more promising candidate antigens, trophoblast-derived gene libraries are being screened with appropriate MAbs and

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PAbs to isolate and subsequently sequence the gene coding for these molecules. From the nucleotide sequence thus obtained, the primary structure of the antigen can be deduced and corresponding peptides synthesized for evaluation as candidates for vaccine development.

The Task Force convenes workshops at regular intervals to review the data obtained in these sperm and trophoblast studies and to decide on the direction of future studies in these areas (Anderson *et al.*, 1987).

Anti-HCG vaccines

The Task Force has initiated studies in the following areas as a continuation of its programme to develop a safe, effective and acceptable anti-HCG vaccine that can be manufactured on a large-scale and that will be suitable for wide-scale clinical use.

Preliminary clinical efficacy of the prototype vaccine. As a result of the encouraging outcome to the phase I clinical trial undertaken between 1986 and 1988, the Task Force is proposing to conduct a phase II clinical trial to determine if the immune response raised to its prototype anti-HCG vaccine is capable of preventing pregnancy in fertile women volunteers (Griffin and Jones, 1991). The proposed study will be the first evaluation of the antifertility efficacy of this particular vaccine in humans and its outcome will greatly influence the nature and direction of future work in this area.

Development of an improved prototype vaccine formulation. The prototype anti-HCG vaccine developed by the Task Force is a complex preparation consisting of a peptide–carrier conjugate mixed with a synthetic immunostimulant and formulated as a highly viscous water in oil emulsion. The limited depot effect of the emulsion vehicle necessitates booster injections every few months to maintain an effective level of immunity.

The Task Force has been conducting pilot studies aimed at the development of an improved version of the prototype vaccine in which the peptide–carrier conjugate and immunostimulant are incorporated into microspheres formed from biodegradable and biocompatible polymers and administered in low viscosity emulsions. The objectives of these studies are three-fold: (i) to produce a delivery system capable of releasing immunogen and adjuvant over an extended period of time in order to maintain an effective level of immunity lasting between 12 and 24 months; (ii) to produce a delivery system that will permit effective immunization to be achieved as a result of a single injection of vaccine; and (iii) to produce a stable form of the vaccine that can be stored under a wide range of conditions, and over long periods of time, and easily reconstituted prior to injection.

A number of co-polymer formulations have been prepared and evaluated, in rabbits, as delivery systems for the prototype anti-HCG vaccine and some are capable of maintaining theoretically effective levels of immunity of HCG for periods in excess of 12 months. Subject to a satisfactory outcome to ongoing formulation work and planned baboon immunogenicity and antifertility efficacy studies, a proposal to conduct a phase I/II clinical trial with this improved prototype anti-HCG vaccine formulation will be drawn up.

Development of an optimized (pre-product) vaccine. Although the improved prototype version of the anti-HCG vaccine will have a number of advantages over the first generation prototype, there are several areas in which further improvements can be foreseen which, if successful, will yield a pre-product form of the vaccine suitable for large-scale manufacture and clinical use (Griffin, 1988).

The hapten in the prototype and improved prototype vaccines is a comparatively long peptide of 37 amino acids. If one or more shorter peptide epitopes could be identified within the parent structure, which retained the ability of the long peptide to elicit an adequate level of immunity specific for HCG, greater ease of vaccine production and quality control would be possible which would be reflected also in reduced cost of the product.

One such short peptide epitope has been identified and a variety of analogues prepared and evaluated. Further work in this area is planned in order to find additional HCG-specific sequence and conformational determinants on the β-HCG molecule using techniques such as X-ray crystallography, computer modelling and the sequential synthesis of artificial epitopes constructed as a result of progressively selected reactivity with monoclonal antibodies.

The carrier is a chemically ill-defined, although purified, sub-fraction of clinical grade diphtheria toxoid (DT). The amount of DT used in the prototype and improved vaccine formulations represents several times the adult therapeutic dose. Although no significant adverse effects of the DT were seen in the phase I trial, it is not unlikely that such reactions would occur after several administrations of the vaccine to a larger number of individuals.

A number of alternative T-cell stimulating molecules have been evaluated by the Task Force as alternatives to the DT carrier. The possibility of using recombinant DNA techniques to produce hapten-carrier complexes as fusion proteins is also being investigated, both as a means of obtaining small amounts of test materials as well as an alternative means of large scale production of the immunogen.

The adjuvant must be capable of attracting, to the injection site, the relevant cells of the immune system needed for the generation of an effective immune response and of stimulating the production of the appropriate cytokines needed for the development of effective immunity. However, the difference between the dose of adjuvant required to elicit these desired responses and that which causes unacceptable side-effects is small and if potent but 'safer' immunostimulants could be identified they would represent an important advance in the development of all vaccines.

The delivery system currently under development for the improved prototype vaccine formulation will provide a slow release of immunogen and adjuvant over a period of several months. Theoretically, it should be possible to develop a range of customized biodegradable and biocompatible co-polymer delivery systems which provide (i) the same release kinetics for different immunogens and adjuvant combinations, thus permitting different vaccines to be prepared with the same duration of effect and (ii) different durations of release for the same immunogen and adjuvant combination, thus permitting a given vaccine to be offered with a range of pre-determined durations.

The vehicle employed in the prototype vaccine is a highly

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viscous emulsion serving the dual purposes of a suspending medium permitting injection of the vaccine and of a depot for delayed release of the vaccine. Subject to a satisfactory outcome to the delivery system studies described above, appropriate vehicles will need to be developed in which the vaccine proper can be injected. Such vehicles will need to have the following properties: (i) biocompatible to ensure clinical acceptability; (ii) chemically compatible with the vaccine components; (iii) low viscosity to facilitate injection; and (iv) chemotactic to ensure infiltration of the injection site by the appropriate cells of the 'afferent' arm of the immune system.

Conclusions

The work carried out by the Task Force over the past 17 years has coincided with a period of major technological transition in the biomedical sciences. During the 1970s, the classical biochemical methods being used to isolate molecules of potential interest for vaccine development were often too harsh to permit the isolation of labile molecules or molecules that occurred only transiently or in low concentrations in cell membranes. During the past decade, however, a number of major advances and technological developments have occurred in the fields of immunology, molecular biology and vaccinology which now permit the molecular structure of potential immunogens to be deduced from the genes encoding them and from algorithms predicting their secondary and tertiary structures. These modern technologies offer the opportunity to develop a new generation of synthetic vaccines, either as replacements for existing preparations or as vaccines for totally new applications. The Task Force has played an important pioneering role in this area by initiating, applying and further developing many of these new procedures, particularly in the development of vaccines based on synthetic peptides.

In addition to WHO, there are a number of other institutions and public sector agencies that have made, and are continuing to make, a major contribution to the field through dedicated research programmes in immunoreproduction and the development of birth control vaccines. These include the National Institute of Immunology (Delhi, India), the Population Council (New York, USA), the Contraceptive Research and Development Programme (Norfolk, USA) and the National Institutes of Health (Bethesda, USA).

To ensure the optimal utilization of the limited funds available for research in this area, WHO and these other institutions and agencies have formed an informal global partnership for coordinated, collaborative research in this area. The Task Force is confident that this partnership will strengthen and facilitate the continuation of this important work and will expedite the development of a range of safe, effective and acceptable birth control vaccines, specifically designed to meet the expressed needs of the users of family planning services.

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