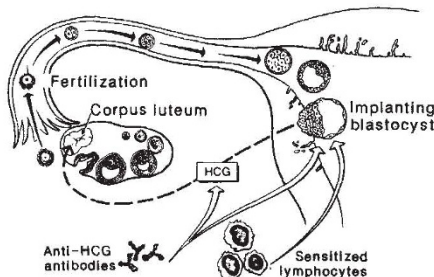


techniques; (4) restricted to gametes and/or the early products of fertilization (full functional characterization of the antigen being desirable, but not essential).

To be acceptable, the vaccine should have an efficacy rate of at least 90 per cent; elicit a reproducible immune response of the desired magnitude, nature and duration, irrespective of genetic background and health/nutritional status of recipients; be free of side-effects; exert an anti-fertility effect which is potentially reversible, either spontaneously or by manipulation; and be suitable for widespread use. To satisfy many of these requirements, safety and efficacy testing in an appropriate animal model is necessary before the initiation of human studies.

A decade ago WHO decided to coordinate and sponsor the development of a vaccine which was based on the carboxy-terminal polypeptide of the  $\beta$  subunit of human chorionic gonadotrophin (hCG),



Possible modes of action of anti-hCG vaccine. Antibodies capable of neutralizing hCG may inhibit its luteotrophic action on the corpus luteum. Cytotoxic anti-hCG antibodies or sensitized lymphocytes may disrupt the early peri-implantation blastocyst (reproduced from Jones W.R. *Immunological Fertility Regulation*, Blackwell Scientific, Melbourne, 1982).

a protein hormone produced by the early trophoblast. One of the functions of this hormone is the maintenance of progesterone production by the corpus luteum in a conceptual cycle (see figure). Abrogation of this role by vaccination mimics physiological luteolysis and results in menstruation, thereby preventing pregnancy in what otherwise seems to be a normal non-conceptual menstrual cycle. A prototype vaccine on which preclinical toxicity and safety evaluations have already been completed is now ready for clinical testing. It is a multicomponent formulation consisting of (1) an oligopeptide corresponding to the amino-acid sequence 109–145 of the carboxy-terminal region of the  $\beta$  subunit of hCG; (2) a protein carrier, diphtheria toxoid, to which the oligopeptide is conjugated; (3) a synthetic adjuvant based on muramyl-dipeptide which seems to be as potent as the clinically unacceptable Freund's complete adjuvant, but without the ability of the latter to generate extensive tissue reactions.

The peptide-carrier conjugate and adjuvant are suspended in saline and emulsified with arlcel A in squalene. Active immunization with this preparation has

been effective in inhibiting fertility in baboons (Stevens, V.C. *et al. Fertil. Steril.* 36, 98; 1981), even though there is only 3–15 per cent cross-reactivity between antibodies to the carboxy-terminal region of hCG and baboon CG. Toxicity studies in rodents, rabbits and baboons have failed to demonstrate any adverse side-effects of this treatment and extensive screening of immunized baboons has failed to reveal significant titres of auto-antibodies or evidence for immune-complex deposition in tissues. On the basis of these encouraging results, WHO plans to carry out a clinical trial to assess the immunological efficacy and safety of the vaccine as soon as approval from regulatory authorities has been obtained. At the same time, work has been progressing on the synthesis of the corresponding oligopeptide from baboon CG to allow further studies with a baboon CG vaccine that will more closely approximate to the clinical situation in which the hCG vaccine will be used.

During the past decade significant progress has been made in the search for additional vaccine candidates. Sperm antigens comprise one possibility for both males and females, as they are present only transiently in the female reproductive tract and are sequestered in the male, where their expression is restricted to testicular germ cells and sperm. Immunization of females with whole sperm or two preparations of isolated sperm antigens — the sperm-specific enzyme lactate dehydrogenase (LDH-4) and a germ-cell antigen (GA-1) derived from spermatocytes — has been effective in reducing fertility in animals. Such studies, together with evidence of anti-sperm antibodies in healthy but infertile men and women and vasectomized men, suggest that naturally occurring sperm antibodies with adequate anti-fertility properties have no deleterious effects on the host. In animals, fertility, has returned after sperm antibody titres waned. Of the sperm antigens identified to date, only LDH-4 has been well defined; however, it should be possible to produce this and other suitable polypeptides by modern techniques. In the female, access by antibodies to the target may be a problem and further consideration should be given to the use of mucosal as well as systemic routes of immunization.

Immunization with well-characterized zona pellucida (ZP) antigens can inhibit fertility in several species. Some antibodies to ZP glycoproteins inhibit sperm-ZP interaction *in vitro* (both binding and penetration). However active immunization with ZP seems to result in an unacceptable alteration in ovarian function. Whether other ZP antigens can elicit anti-fertility antibodies with without such side-effects must be determined before such antigens become candidates for vaccines.

Trophoblast surface antigens have the

## 100 years ago

ADDRESS BY FRANCIS GALTON, F.R.S., ETC, President of the Anthropological Institute.

THE object of the Anthropologist is plain. He seeks to learn what mankind really are in body and mind, how they came to be what they are, and whither their races are tending; but the methods by which this definite inquiry has to be pursued are extremely diverse. My data were the Family Records entrusted to me by persons living in all parts of the country, and I am now glad to think that the publication of some first-fruits of their analysis will show to many careful and intelligent correspondents that their painstaking has not been thrown away. As the popular views of what may be expected from inheritance seem neither clear nor just, the subject of my remarks will be "Types and their Inheritance." I shall discuss the conditions of the stability and instability of types, and hope in doing so to place beyond doubt the existence of a simple and far-reaching law that governs hereditary transmission, and to which I once before ventured to draw attention, on far more slender evidence than I now possess. My experiments have shown that the mean filial regression towards mediocrity was directly proportional to the parental deviation from it. from *Nature* 32 507, 24 September 1885.

advantage of being expressed only at one anatomical site following fertilization and of being in intimate contact with maternal blood at a very early stage in pregnancy, perhaps within 10 days of ovulation in the human. Studies with human tissues indicate the existence of potentially suitable tissue-specific and possibly stage-specific cell-surface antigens, but a relevant animal model for efficacy studies is required.

Embryonic antigens, some carbohydrate, are transiently expressed in low concentration on early embryonic cells in several species. As they may also be present in sperm, antibodies specific to them could have two targets. The pattern of temporal expression of these antigens in the embryo needs to be established before this target satisfies the criteria of a vaccine antigen.

Based on data already available, together with the rapidly expanding potential of recombinant DNA technology and other techniques of molecular biology using synthetic vaccines, an appropriate iso-immunogen has considerable promise for the development of a safe, effective and cheap fertility-regulating vaccine. There is, therefore, an urgent need for further research, particularly because of the probability that the user population will increase if vaccination against common infectious diseases in the developing world is successful. □

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