Genealogy of a Controversy

Development of an Anti-Fertility Vaccine

This paper reconstructs the controversy over the development of an anti-fertility vaccine in order to understand how scientific facts are constructed. It examines issues of ethics, clinical trials, the role of organisations such as the WHO and the positions of women's rights and health activists.

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The history of the development of a new scientific or medical technology is a story of science in the making. In this paper we attempt to trace the development of the anti-hCG vaccine over the past 20 years, using controversy as a methodological entry point into the history. The anti-hCG vaccine is one of the range of immunological contraceptives that is being researched and developed in laboratories around the world. There are two teams which have been working on this research since the early 1970s – Talwar and his team at the NII in India, and Stevens at the University of Ohio.[1] Both the vaccines have gone in for phase I trials and Talwar's vaccine has also completed phase II clinical trials.

The history of the development of this vaccine is closely linked to the competition between these two teams and is more clearly understood in the context of the controversy over Talwar's research in the 1970s. Through the process of tracing the controversy, we will also see the role that different national and international institutions play in vaccine research and development. The relations between these different institutions and the pressures that they are able to exert on the different actors clearly bring out the dynamics that are involved in any scientific endeavour. In the case of anti-hCG vaccines, other than the scientists, the different actors include the WHO, the Indian government and ICMR, other scientists and the women's health movement which has been a strong critic of these developments.

Latour (1987) posits that in order to study techno-science, we need to look at science in the making. Scientific and technical facts that are available to us as readymade black boxes need to be opened up and explored in order to understand how they are created. "Uncertainty, people at work, decisions, competition, controversies are what one gets when making a flashback from certain cold, unproblematic black boxes to their recent past" [Latour 1987:4]. It is thus important for us to enter into these black boxes to see how they have been constructed. In the case of anti-fertility vaccines we are fortunate because the black box has not yet been closed. It is thus an opportunity to see science in the making. It is through the process of following the controversy and the way in which it is settled that we can gain an insight into the process of how scientific facts get constructed. Studying the progress of technoscience through a controversy provides the advantage that the scientists themselves "offer rich material by transforming one another's statements in the direction of fact or fiction. They break the ground for our analysis"(25).

The controversy thus becomes a way to get a foothold into the process of the making of a scientific fact which becomes invisible once a black box of science is created. These black boxes are created both within and outside the laboratory. The process by which a box gets closed is one of gettng it accepted by more people. In the case of the anti-hCG vaccines this process has not happened due to several reasons. Firstly the controversy that erupted in the 1970s over the clinical trials that were conducted by Talwar's team caused more discussion around the issue. Secondly, because there were two similar preparations that were being worked on by different groups of scientists the competition prevented any crystallisation of the issue. Thirdly the campaign of the women's health movement against many of the new contraceptive technologies in general and the anti-fertility vaccines in particular has broadened the terms and the terrain of the debate. Finally neither of the teams working on developing the vaccine has come up with a product that is ready to be marketed.

The main players in this controversy are the WHO, Stevens, Talwar and women's health advocates. In 1972 the WHO set up the Human Reproduction programme to support research in the field of reproduction. The programme stressed different aspects of family planning from research to delivery and service, acceptability, processes of contraceptive research and introduction especially of clinical trials on human beings and safety aspects, and strengthening the different institutions that were supported by the programme. The WHO has played a very significant role in the development of immunological contraceptives. It has supported research on different anti-fertility vaccines, and has given long-term support to the anti-hCG vaccines being developed by Stevens and his team at Ohio University. Stevens has been working on developing immunological contraceptives since the 1960s and he was the first to work on hCG for purposes of developing a contraceptive vaccine. He continues to have financial and institutional support from WHO for the research on anti-hCG vaccine. The Task Force on Immunological Contraceptives has also been the pioneer in setting up guidelines for research in this area. WHO also supported Talwar's research in the early stages of development.

Talwar is one of the pioneers in this area of research. Research on developing immunological contraceptives was carried out at the AIIMS where he was working till 1982. After that it moved to the National Institute of Immunology (NII) which was set up by him. Along with his team, he has been researching the possibility of several immunological contraceptives, but development has reached the furthest stage with the anti-hCG vaccine, which has

completed phase II trials with women. He began research in this area in the early 1970s and is probably one of the better known scientists in this field. But some of his work has been critiqued and his early clinical trials with the anti-hCG vaccine has been at the centre of controversy.

After trials were conducted in 1974 there was a controversy over whether Talwar and his team had conducted the necessary animal trials and the fact that two women got pregnant caused some alarm. The controversy over the vaccine being developed by Talwar has focused on three specific areas.[2] The first pertains to the use of the whole beta hCG which was seen as carrying a very strong possibility of cross reaction with hLH which shares a similar beta subunit. This cross reaction could lead to antibodies being raised against the hormone LH and could cause side effects such as disturbances in the menstrual and ovulatory cycles. Since the principle of immunological contraceptives itself is a novel approach within immunology where the body is made to raise antibodies against a self protein, the WHO strongly stressed the safety aspects of the vaccines. WHO has been the strongest critic of Talwar on this issue. But WHO (Stevens' research) is also the direct competitor of Talwar in the development of this vaccine and these two roles of WHO cannot be seen independently of each other.

A second criticism has been directed towards the fact that Talwar conducted clinical trials on humans too soon without completing the necessary range of animal tests. Any new drug or vaccine has to undergo a complete range of animal tests before it is allowed to be tried on humans. While some tests on animals were conducted and the research was published, there were allegations that the trials on humans were commenced in haste. Human trials had been conducted by Talwar and Stevens in the early 1970s. The situation is complicated because the WHO guidelines for toxicology and animal studies specifically for immunological contraceptives were drawn up only in 1978. Thus the question is whether standards arrived at later could be applied to earlier practices. It is also interesting to see how far the controversies around animal trials themselves stimulated the formulation of the WHO guidelines.

Finally criticism has been levelled against Talwar on his neglect of ethical issues in the process of conducting clinical trials. He has been accused of not giving complete information to the women participating in the trial about the experimental nature of the trial and the possible risks. The issue of ethics has also come up in the context of the pregnancies that occurred because all the women who were involved in the trials were not previously sterilised. All phase I trials that were conducted subsequently only included women who were sterilised and therefore were not in danger of getting pregnant. But since Talwar conducted trials very early, there were no explicit guidelines. Some of the scientists at that time and women's activists later on point to these pregnancies as proof of Talwars' haste and poor ethical standards.

The women's health movement has been another very significant player in this controversy. Initially the critique of Talwars' research came from the scientific community and from WHO. From the late 1980s women's health advocates have also begun critiquing not only Talwars' research but all researches on immunological contraceptives. Some groups have initiated a worldwide campaign to call for a ban on all further researches on immunological contraceptives.

In the 1970s, the international women's movement campaigned strongly for expanding contraceptive choices to increase women's freedom and control over their bodies. However, over the last decade or so there has been growing perception that in the name of providing more contraceptive choices and in their zeal to check population growth, many governments are promoting the use of contraceptives, which in the long run may actually harm women's health.

Therefore, in recent years women's groups have been stressing the need to view new contraceptive technologies, including the anti-fertility vaccine, in the context of coercive population policies. New contraceptive technologies such as the hormonal injectables, Norplant and the anti-fertility vaccine are criticised for having high abuse potential, being invasive, long-acting, not easily reversible, provider controlled and mainly directed towards women, especially women in developing countries. Further, these contraceptives also have higher associated health risks and are not oriented towards the realities of women's lives, local health care conditions and the position of women in society. In addition to these reasons the anti-fertility vaccines are further criticised because they are interfering with the immune system and treat pregnancy as a disease.[3]

There is no single way to write the history of this controversy. It has to be reconstructed by looking at the different written records of it and the testimonies of the different personnel involved in it at that time. This will be further complicated by the fact that the testimonies will change over time and depending on who is the audience. Our aim is to provide an ethnography of the processes by which controversies are brought to the centrestage, the role played by different actors and the manner in which it is presented as a public debate. Through the study of the development of this vaccine, we look at issues of clinical trials, ethics and the role of different organisations and institutions. Controversies also provide the space for the interaction between scientists and society thus providing us with science that is perforce demystified.

Development of hCG Vaccine

Before we begin a discussion of the details of the controversy, it is necessary to have an overview of the history of the development of the vaccine and the various clinical trials that have taken place.[4] This history began in late 1960s when advances in biochemistry made it possible to isolate the hormone hCG. HCG is a hormone that is secreted by the body as soon as conception takes place and is essential for implantation and for the continuation of the pregnancy. It consists of two subunits, the alpha and the beta, of which only the latter is unique to hCG. Stevens conducted a preliminary clinical trial on six women using the whole hCG that had been chemically altered. The results showed that antibodies against LH were also raised to immunisation against hCG [Stevens and Crystle 1973]. Since it was realised that the beta subunit was unique, with further development in technology and the ability to isolate smaller units of the hormone, work shifted to a contraceptive based on the beta subunit of the hormone. But this also was viewed with caution as the beta subunits of hCG and hLH were both very similar.

During this time G P Talwar and his team in the department of biochemistry at AIIMS also began working on a vaccine based on beta hCG. Since hCG is a self protein it is not antigenic and needs to be conjugated to another substance which will be able to evoke an antibody response. Talwar

conjugated it to tetanus toxoid which was a known antigen. In 1974, phase I clinical trials were conducted at AIIMS on 12 women. All the women produced antibodies to hCG, but they varied in amount and duration [Talwar et al 1976 a,b]. Four women became pregnant, though all were terminated. These pregnancies happened when the antibody titres were low [Hingorani and Kumar 1979].

In the late 1970s, a four-country study of the same vaccine was carried out in Finland, Sweden, Chile and Brazil under the auspices of the International Committee for Contraception Research (ICCR) of the Population Council. The results showed that the antibody response varied among the subjects, with two women having very low response and one woman showing no response [Nash et al 1980].

Along with the four-country study, a phase I trial was carried out in Bombay by Talwar and his colleagues to further test the vaccine on human subjects. In most of the subjects the antibodies against hCG were produced after the second injection and reached a peak only after 4 to 6 months. Three women were non responders – one did not respond at all and two had very low responses. There were 10 pregnancies of which only one was carried to term.

These studies and their results reflect two areas of concern – the variability of responses in different women and cross reactivity with LH. A number of studies were done to determine the nature and level of cross reactivity to LH.[5] The studies showed that there was some degree of cross reaction but Talwar claimed that they were not significant as they did not affect ovulation or the menstrual cycle in the women.

To deal with the problem of variability Talwar and his team went back to the laboratory to work out aspects of the vaccine so as to improve the immunogenecity of the formulation. In 1986 they initiated phase I clinical trials with an improved formulation. Follow-up was done on 88 women who were immunised.[6] It was recorded that all the women generated antibodies against hCG above 20 ng/ml, which had been set as the theoretical level above which the vaccine was efficacious.[7] However, the antibody response was still variable among the participants, though less than with the earlier formulation.

In 1991 phase II trials were initiated with the same formulation on 148 women [Talwar 1994]. Of these 119 (80 per cent) generated antibody titres that were clearly above 50ng/ml. Only one pregnancy occurred above 50ng/ml. The phase II trials provided evidence that the principle of anti-hCG vaccination is workable but the titres produced were still too variable for it to be an acceptable product. Since 20 per cent of the subjects did not produce titres above the neccesary level, it was too high a level of failure to be an acceptable contraceptive measure. The delivery system of three injections and the lag period of approximately three months also posed significant obstacles to its acceptance. Taking all these into consideration, the scientists have gone back to the laboratory to work on ways to improve the formulation.

Dangers of Cross Reactions

The research conducted in the early 1970s by Stevens and Talwar showed that there was considerable structural similarity between the hormones hCG and hLH. This meant that there was a possibility that the beta hCG vaccine could also cause antibodies to be raised against LH. This cross reaction between hCG and LH carried the risk of side effects such as disturbances in the menstrual and ovulatory cycles. As an outcome of this the WHO decided to support the development of a vaccine which was based on a unique antigen. It was found that a portion of the beta subunit of the hCG was completely unique – a 43 amino acid carboxy terminal peptide (CTP). Stevens with the support of the WHO began research on a vaccine based on the CTP in the mid-1970s.

The WHO which had been supporting Talwar through the Research and Training Centre (RTC) at AIIMS began to distance itself from Talwar's research after the trials in 1974. While WHO continued to give funds to Talwar till 1978, in each of its reports of that time they stress that the formulation used by Talwar is different from that being developed by the Task Force.

In the WHO Annual Report of 1975, there is a section on the development of vaccines for fertility control. The clinical trials conducted by Talwar are mentioned in the report, without using names.

> Although recent short-term observations by two non-Task Force scientists indicated no obvious acute toxicity or disturbance of ovarian function accompanying the production of circulating anti-hCG antibodies when previously electively sterilised women were immunised with either the 39 amino acid peptide or whole beta hCG bound to TT, the need for extreme caution and full evaluation of any new procedure cannot be overemphasised (52).

In the WHO annual reports of that time the nature of safety testing, especially with regard to cross reactivity are reported in detail. Thus in the 6th annual report of 1977, two paragraphs are devoted to reporting on the results of the different tests done by the scientists at AIIMS to investigate the nature of cross reaction with hLH. All the results reported indicated that the level of reaction to LH was significantly lower than that for hCG. Some studies showed that there was no interference with LH action. From the report it would seem that the nature and amount of cross reaction with LH was not significant as shown by a number of different laboratory and animal studies. Yet the WHO position on the vaccine based on the whole beta subunit was that it is very likely to be unsafe. The same document also reports in detail the safety guidelines that have been drawn up by the Task Force.

These safety guidelines which were published as an article consist of two sections; one, which discusses safety issues relating to the research and development in the area of anti-fertility vaccines, and the second section which focuses specifically on the issues of safety related to the hCG vaccine. In this it is clearly mentioned that the whole beta subunit is structurally similar to hLH and thus may be "a cause of undesirable immunological side effects" [WHO/HRP 1978: 368]. Among the criteria specified for selecting the antigen for the vaccine, it is mentioned that it should be restricted to the intended target and it should not be present continuously in the body.

However, despite the guidelines' stress on avoiding cross reaction and a consensus at the HRP meeting in 1979 that substances that could cause cross reactions were to be avoided, Population Council and Talwar went in for the vaccine based on the complete beta hCG arguing that a moderate degree of reactivity with LH is not considered undesirable.

The vaccine being developed by WHO continues to be viewed as the safer vaccine. Stevens while comparing the two vaccines points out that the synthetic hCG peptide vaccine has no cross reaction with LH, though it has low immunogenicity compared to the other vaccine. He however feels that if lower levels of antibodies are required to establish a state of infertility in women, then the peptide immu-

nogen may be as effective as the other types of vaccines while being safe for the recipient [Stevens 1986].

Other members of the scientific community also expressed concern about the possibility of cross reactions using the vaccine based on the whole beta unit. Talwar and his colleagues have both anticipated and responded to this criticism. During both rounds of trials in the 1970s and 1980s they have published results of various tests done to show the lack of significant cross reaction with hLH. During the trials in the 1970s they carried out several tests to see the nature of cross reactivity and its effects which were published in the July 1978 volume of *Contraception*.

During the phase I trials in 1986, the scientists infer from the menstrual diaries that women kept that there were no serious disturbances in the cycles or in the process of ovulation. They state on the basis of all these studies that the degree of cross reaction is not significant enough as it does not impair ovulation [Talwar 1994, Kharat et al 1990].

Futher the Indian vaccine has gone through phase I and phase II clinical trials and the results have validated the principle of hCG immunisation and shown no significant alteration in menstruation and ovulation patterns. The problem of cross reactions with hLH is itself beginning to be questioned by the scientific community. It is interesting to note the change in the relationship between the WHO and Talwar. Thus Talwar was a member of the WHO Task Force for Immunological Methods Of Contraception in 1993. The results of the phase II trials of the NII can be seen to be a validation of all research on anti-hCG vaccines and that is why the WHO also acknowledges it as a positive development. It reinforces the fact that research along this line should continue.

It is interesting to understand this process of how the criticism of Talwar and research into the beta hCG vaccine took place and how the controversy has, in a sense, been settled. It is the results of the animal studies and the clinical trials that has actually led to the change in WHO perceptions. The Population Council study on 63 monkeys is an oft quoted one to prove the safety of the vaccines and the lack of significant cross reactions with LH [Thau 1986].

The results of the clinical trials conducted with the whole beta subunit are also seen to provide evidence of the safety of the vaccine and lack of significant cross reactions. After the phase I trials in 1986, Talwar and his team wrote a paper that specifically looked at the menstrual cycle and ovulation of the women who took part in the trial. It is the results of these that are seen to prove that the cross reactions with LH are not significant enough to jeopardise the safety of the vaccine. It is interesting to note that the normal range of the menstrual cycle is taken to be 22-35 days and on this basis, they conclude that 90 per cent of the women had normal menstural cycles. It was found that both women in the control group and in the vaccinated groups had some percentage of short and long cycles. But this data does not give details of the cycles within this range. For example, if a woman had a regular 22-day cycle before immunisation and this changed to 32 days post-immunisation, would this be a significant issue in the data. According to their method of analysis, this woman would fall within the range of normal. Five women in the high dosage group with one of the formulations all experienced irregular cycles and the analysis of the doctors and scientists is:

> The event was unrelated to the prevailing anti-hCG titres. Many factors contribute to the fluctuations in menstrual cycle length. These trials were conducted in women who, after completing their families, had opted for tubal ligation. This operation is reported to cause ovarian dysfunction in some women. It is possible that the five women in whom the frequency of irregular cycles is high belonged to this category [Kharat et al 1990:298].

The results of the phase II trials indicate similar results with the range of normal menstrual cycle being kept at 22-35 days. Here too 85 per cent of the women are seen to have normal cycles and it is concluded that there is no relationship between "degree of cross reactivity with human LH and menstrual length" [Talwar et al 1994:8533]. Similarly the trials in the 1970s showed that 79 per cent of all the women had cycles of duration 25-35 days (which was seen as normal). Here too the 21 per cent of irregular menstrual cycles were attributed to "insertion of IUD, irregular use of contraception or lactation" [Shahani et al 1982].

These trials are seen as evidence that the cross reaction with human LH is not significant enough to cause alteration in menstrual cycle and it is interesting to note that at this point of time the WHO is also accepting that the cross reactions are not significant. In an article written in 1996 about the current status of the development of the hCG vaccines, the results of the phase II clinical trials of the HSD vaccine of the NII is reported on. Stevens, the principal scientist of the WHO vaccines now views these cross reactions differently.

> No serious side effects were experienced by the study subjects, and despite cross reactions of antibodies raised by beta hCG-TT and HSD-TT-DT vaccines with human LH no effects of immunisations on ovulation or menstrual cycles patterns were reported. Serological and clinical assessment of the women in these trials revealed no health hazards from the use of any of these vaccines (Stevens 1996:149).

It is also important to note that the WHO vaccine was not able to complete phase II trials so it has not yet been ascertained whether the vaccine will be immunogenic enough to be used. Phase II trials were initiated in 1993 in Sweden but had to be terminated because all the women receiving the injection developed reactions at the site of the injection.

Some feminists and women's health advocates have also expressed their views concerning the possible harm that can be caused due to cross reactions, but have not focused on this. However, in this context it is interesting to note that the feminist criticism of the vaccine has not been directed so much at the issue of cross reaction as at unethical trials and abuse potential of the vaccine. Their criticism and concerns are located in the broader context of the women's health campaign against all 'long acting, provider controlled, invasive' contraceptive technologies.

It is clear though, that from the scientific point of view the criticism of the hCG vaccine in terms of safety is no longer as strong. The results of the various animal studies and clinical trials conducted over the past 20 years have led to the acceptance of this line of development by the WHO and other scientists.

Insufficient Animal Studies

Another central point of the controvery was whether Talwar had conducted sufficient animal studies before embarking on clinical trials on humans. The WHO felt that Talwar had gone into clinical trials with humans prematurely and doubted whether he had conducted all the necessary animal tests.

In an interview with David Griffin of the WHO in 1996, he states:

The WHO HRP centre at AIIMS was a research and training collaboration (for

IUDs and other contraceptives). We were funding the basic research on animals. Around 1974-75 there was a request from Talwar for material for lab tests. The beta hCG was sent with strict instructions that it was to be used only in animals. Six months later he sent information regarding clinical trials on four women who showed antibody response. That was a difficult period. We felt that human trials could not be done till a group of WHO consultants were sent to see if all the basic research was done and it was ok. We felt that the full range of animal tests may not have been done . But Talwar said he had all the necessary tests and published the results in the 1978 issue of *Contraception*. By this time he was also beginning to get support from other places such as Population Council. We offered to support the animal studies and helped set up a primate colony. After that we ceased to be involved.

Though there were no guidelines or rules about the necessary safety tests for immunological contraceptives at this time, the WHO was suspicious of the tests and clinical trials being done at AIIMS and this is reflected in their reports. Thus till 1978 the WHO was still giving funds to the research on the anti-hCG vaccines, though the money was earmarked for animal trials. WHO was aware that Talwar had conducted clinical trials on humans and that he had been collaborating with Population Council. It is clear from the annual reports of that time that the WHO was uncomfortable with the way that Talwar was progressing and in every report it is mentioned that WHO support was restricted to animal trials.

It was only in 1978 that WHO laid down a set of safety guidelines for conducting research on anti-fertility vaccines. These guidelines give details about the various tests that need to be carried out on different animals before each phase of clinical trials on humans. Before conducting phase I trials toxicity studies are to be done on animals such as the mouse, rats, rabbits and if possible on higher primates such as monkeys and baboons. During this time animal studies to evaluate the immunological safety, cross reactivity, tissue damage and toxicity of the vaccine should also be studied in higher primates. Further the guidelines stipulate that before initiating phase II trials, animal studies using higher primates should be conducted to study the efficacy, teratological effects, long-term toxicity and effect on pregnant females of the vaccine.

The need for safety guidelines and importance of animal studies have been stressed in the case of the anti-fertility vaccine particularly due to the fact that immunological contraceptives are a very new area of research. It was also felt that due to the risk of cross reactions with the use of the whole beta hCG, extensive animal studies needed to be conducted before human trials were initiated.

Griffin of WHO has mentioned that Talwar's team most probably went in for clinical trials before conducting all the necessary animal tests. Talwar did conduct animal tests after this, which WHO clearly states that it supports, and the results of these are published in the 1978 issue of *Contraception*. This is not clearly mentioned in any of the WHO reports or publications. But it is obviously an important reason leading to the withdrawal of WHO support to the research being done at AIIMS.

Criticism regarding insufficient animal studies has also come from the women's health movement. The WGNRR press release of 1995, the press release from the Women's Health Interaction, Inter Pares and the National Action Committee on the Status of Women of 1995 critique Talwar for not conducting sufficient animal studies before going in for clinical trials on humans.

Judith Richter comments that the way the trials of the hCG vaccine were conducted is reflective of a shift in the fundamental logic of clinical trials. While quoting from the Declaration of Helsinki and the CIOMS and WHO guidelines she says:

> The onus should be on researchers to ensure that there appears to be an acceptable risk and benefit balance before human trials are carried out...This means that only after a thorough review of the available theoretical knowledge and 'adequately performed laboratory and animal experimentation' are researchers allowed to start clinical trials (1993:58).

In response to this criticism and other reservations expressed by women's groups, Talwar in a letter to these groups in 1994 states:

> There have been more trials on animals with the hCG vaccine than any other contraceptive, because it is a conceptually new approach. The trials have gone on for over 10 years in both laboratory animals and on subhuman primates. Confirmatory toxicology and independent safety studies have been conducted on the AFV and its analogue by the Population Council. In fact, life long toxicology and safety studies lasting over seven years in monkeys were conducted and the lack of untoward reactions on tissues carefully examined by some of the top immunopathologists of the world. In Delhi, we have data on not only classical toxicology and special toxicology studies as per the guidelines of the ICMR, but also have data on the regain of fertility by baboons and monkeys on decline of antibodies and furthermore on the normalcy of the progeny of these monkeys to produce normal offspring when they attain adulthood. The WHO Task Force has similarly carried out extensive safety studies in rodents and baboons on the anti-hCG vaccine funded by them.

Clearly the issue of lack of sufficient animal studies was more valid a critique of the research conducted in the 1970s during the early trials with Pr beta hCG TT. It is now over 20 years since the research began and in the intervening time many more animal studies have been conducted by all of the groups involved in the development of the vaccines and also clinical trials by the NII team, Population Council and Stevens [*Contraception,* 1976, 1978; Thau 1986]. The results of these various studies have changed the tone of much of the scientific critique against Talwar as we saw in the earlier section.

Ethical Concerns on Vaccine Development

Issues of ethics in medical research and clinical trials have been part of debates on scientific and experimental methods. From the early trials of the small pox and cow pox vaccines and the administration of the rabies vaccine by Pasteur on human subjects, there has been an interest in these issues [Geison 1995]. The development of vaccines for fertility regulation has raised its own set of ethical concerns, some from the scientific community but more from the women's health activists. Within the scientific community, some ethical questions were raised when Talwar used women who were not previously sterilised in his phase I experiments in 1974 and two pregnancies occurred. Women's groups on the other hand have raised a whole set of questions regarding the development of fertility regulating vaccines and about the conduct of clinical trials.

Their critique strides two levels – on the ideology behind the development of particular kinds of contraceptives and of the way the process of research and clinical

trials are carried out. They critique the development of many of the new methods of contraception on the grounds that they are long acting, provider controlled and invasive. They state that it is not the needs of women that guide research, but rather the need for population control and demand a reorientation in research to focus on methods that are safe and user controlled.[8] In relation to clinical trials, they question the processes that are used to get the consent of women to participate in trials and whether it is really informed. In addition they critique the fact that trials are often carried out in the developing countries and mostly on poor women. Looking at the WHO position through the various documents and articles we can see that the two main areas of criticism of Talwar's research have been around the issues of conducting clinical trails too early without completing the necessary animal tests and the possibilities of cross reactions with hLH. There is no mention of ethical issues. In fact there is a conspicuous silence about these issues. These two issues are highlighted in the literature of the women's health movement. It is interesting to probe the reasons for the silence on the part of WHO. One reason could be that they actually have no problems with the way that clinical trials were conducted and only with the fact that it was too soon. Other reasons for not criticising Talwar for his neglect of ethical questions in clinical trials and resulting pregnancies could be due to either lack of evidence or that these issues are not of great importance. It could also be that all scientists are aware that ethics is a grey area.

While the exact nature of the controversy and reasons for withdrawal of WHO funds for Talwar's research on the hCG vaccine remain unclear, it is interesting to note that the issue of inadequate animal studies and unethical trials is often cited in feminist critiques and writings. The Joint Press Release from Women's Health Interaction, Inter Pares and the National Action Committee on the Status of Women (May 1995) to demand IDRC withdrawal of financial assistance to Talwar, states that:

> The Indian trials and the Indian researcher who has headed the trials NII, with funding from Canada's IDRC, have been previously censored by the WHO and the Indian scientific colleagues for insufficient attention to ethical standards and for pursuing human trials in the absence of adequate animal studies (1995).

The Forum for Women's Health, Bombay, argue that:

> This team has also been at the centre of controversy, having injected two fertile women with the vaccine developed early on in the mid-1970s as part of the phase I trials (which are only to be conducted with sterile women). Research funding was then coming from the WHO which later, after protest from the medical community in India itself, withdrew research support from Talwar's team [Yanco et al 1995:39].

Jayaraman[9] states that it was the pregnancies that brought the issue of ethics to light at that time. He states that both the WHO and the Indian government were concerned with the safety of the vaccine and with the trials. The government of India which was supporting Talwar's research at that time asked Talwar to conduct more animal trials before moving ahead. The WHO as we saw continued to support Talwar but had begun expressing reservations.

Women's groups both international and national have critiqued the trials in India as not being sufficiently ethical. The WGNRR in a press release state that:

> The clinical trials do not meet international standards of ethics. Enrolment is not based on fully informed consent. In the Indian trials women were not even told that they were participating in a trial. Besides this there has been insufficient data collection about adverse effects to women and the children born to them during the trials (1995).

Saheli, one of the Indian feminist groups that has been in the forefront of the campaign, submitted a petition in 1990 to the Supreme Court demanding information about the condition of the women who had been involved in the trials and the nature of follow-up in the various trials on different contraceptives that had been done over the past 20 years. They alleged that large numbers of women had been part of various contraceptive trials over the past 20 years and demanded information on their status and proper follow-up.

Women's groups have also seen the use of fertile women in the early clinical trials as an important critique of the way that scientific research and clinical trials are conducted. The critique is of the processes of development and evaluation processes of new medical technologies [Hardon 1992:754]. Interestingly, though women's groups attribute this as the reason why WHO withdrew support from Talwar's research, the WHO itself never mentions this as a reason for parting ways.

Conclusion

It is interesting to ask to what extent the critique from these different sources has affected the course of development of the vaccines. Neither of the two groups has taken a decision to halt the research on the basis of the call from women's groups. David Griffin of the WHO HRP has said that if he receives enough letters from women all over the world and is convinced that women do not want this kind of contraceptive, WHO would withdraw from the research. On the basis of this women's groups from around the world have started a postcard campaign to involve as many people as possible to register their protest against the research and development. The development on the Indian vaccines continue even though the funding from IDRC has stopped and from the Indian government has reduced.

In the meanwhile though the development of the vaccine continues at both the sites of research – Stevens at Ohio and the Indian group at NII. The NII team having completed phase II trials with the improved formulation and Stevens having completed phase I trials, are both now back in the laboratory working on ways to improve the vaccines. They are both working on finding ways of improving the immunogenicity of the vaccine, to improve the delivery system through encapsulation in microspheres and ways of producing beta hCG through recombinant methods. In trying to improve the immunogenicity of the vaccines, the NII team is not giving up on the whole beta hCG, but is experimenting with conjugating it with short peptides of viruses or bacteria in order to improve the immune response from women with a variety of genetic backgrounds [Talwar et al 1997:4]. Stevens is also working on isolating other peptides of beta hCG to use along with CTP in order to make it more immunogenic [Stevens 1996:151]. This could mean that it is been realised that the CTP alone is not immunogenic enough to make a vaccine that would be efficacious. In order to improve the delivery system both groups are working towards encapsulating the vaccine in microspheres which would mean that the vaccine would be released into the body slowly and that the woman would have to come for one injection instead of three.

These lines of research are being done

by both groups and quite obviously both are working towards improving the vaccine in ways that would make it more effective and easier to administer. They are certainly not responding to criticisms of the principle of immunological methods of fertility regulation or the potential for abuse inherent in the method. Their efforts in fact are an affirmation of both the principle and the method. The difference between the two groups lies in the nature of their relationship to the WHO. The WHO has played the role of mediating with the women's health groups and other voices of protest against the development of the vaccines. WHO has portrayed itself as responsive to the demands of groups representing women. The WHO has been having dialogues with representatives of women's groups and other human rights groups and has set up a gender advisory panel within the HRP.

It is therefore interesting to understand the role of the WHO as an international body, a funding agency and as a research organisation. In the case of the anti-fertility vaccine it can be seen to play three sometimes conflicting roles – first, as an organisation providing financial and material support for research; second, as an agency conducting independent research (in this case, the HRP) and thus working in competition with other agencies; and finally, as an international institution which lays down guidelines and parameters for research and attempts to objectively review research and trials carried out by different people. In playing this role the WHO is seen as being representative of the international science community.

The guidelines published in 1978 by the WHO were written to settle the controversy as it clearly stated that research with the whole beta hCG was not acceptable. Those guidelines are an important scientific paper because they were written in the midst of the controversy and WHO clearly gave its support to Stevens. The Indian researchers feel that WHO was unhappy because they didn't expect the research on the whole beta hCG vaccines to continue after this. Talwar and his associates chose to find other allies to support their work and thus came into direct conflict with WHO.

The roles of WHO can be contradictory at times. As an international body setting guidelines, they did not approve of the research being done by Talwar and his group. On the other hand because they were also supporting another team that was in competition with Talwar, their interest in halting the research on the whole beta hCG could be seen as more than just an ethical issue.

Women's groups in India have been more critical of the role of WHO in the research into the vaccine than women's health advocates in the west who seem to be more critical of Talwar on the grounds that the trials conducted in India are unethical and view the WHO as a forum open to negotiation and as a means to stop Talwar's research.

> They are all jealous of Talwar. Given half a chance, do you think that Population Council gives a damn about women's bodies. But it got left behind because of the abortion lobby. So for many years they could not do any research on post-coital methods. They are jealous. And WHO which declared Depo Provera a beneficial drug for cancer, do you think they are bothered? They just can't get their act together. I do not think Talwar is any worse than any of these characters, and I kept harping on that in Germany. Do you think the WHO trials in India are any more ethical, or Population Council the trials they had done with RU486. They have not still released the results. They used RU486 with cytotech, but it is not approved for abortion purposes. It is only approved for treatment for cancer in India. So they can do this on Indian soil. They are just whiter than Talwar (interview with women's activist 1996).

The role that the competition between the two groups played in the controversy cannot be overestimated. From the early 1970s the two groups have been moving neck to neck in their research on this vaccine. The two teams have constantly tried to prove that their prototype is better. The WHO team and Stevens have tried to show that though their vaccine was less certain of efficacy than the whole beta hCG vaccine, it was a much safer preparation. Talwar and his team have had to defend their research because of all the criticism that they have faced. They have been able to show the efficacy of their prototype vaccine but have been critiqued on safety. The WHO and Stevens on the other hand have not faced much critique in terms of safety of their vaccine.

Talwar has put his argument against the WHO vaccine mostly in terms of its low efficacy [Talwar and Gaur 1987]. Both teams clearly recognise that it is the whole beta vaccine that is more efficacious. Yet Talwar also realised that he cannot afford to only show that his vaccine is superior in terms of efficacy as the WHO has been very vocal about issues of safety. He has stressed the fact that the CTP vaccine has very poor immunogenicity and therefore needs to be conjugated to a very strong adjuvant.[10] In addition to this they have also tried to show specific drawbacks of the vaccine based on the CTP.[11]

Anti-fertility vaccines and the principle of immunological contraceptives are still in the process of becoming a black box. As we noted in the introduction, there are several reasons for this – the fact that it is a new principle that is being tried out and therefore needs to undergo stringent testing, the critique from the women's health movement, and that neither team has come to the stage where they can show an artefact that can be used, both in terms of efficacy and safety.

We can see that all the different participants in this area of development have contributed to the construction of the controversy over issues of research into and ethics of anti-fertility vaccines. Many of the issues have changed over the years and the controversy itself begins to get viewed in different ways over time. Both the results of the research and external factors have contributed to this. Only time will tell if the anti-hCG vaccine will become another black box of scientific technology. EPW

Notes

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1 The vaccine being developed by Stevens has been supported by WHO since the beginnning, and is known as the WHO vaccine.
2 We will focus in greater detail on each of these criticisms in the relevant sections.
3 Vaccines have traditionally been directed against infectious diseases. According to women's health advocates,by giving a vaccine against pregnancy, the danger is twofold. Firstly, it makes pregnancy seem like a disease that needs to be prevented and secondly, it may affect adversely the acceptance of traditional vaccines.
4 For a more detailed history of the recent developments in anti-fertility vaccines, especially in India, see Viswanath and Kirbat 1996.
5 This is discussed in greater detail in the following section.
6 They were now using an improved formulation

to the earlier beta hCG TT. Now the formulation was annealed to alpha subunit of ovine LH to both increase immunogenicity and decrease cross reactivity.

7 This level was theoretically derived. This was the level that was used by both Talwar and Stevens until phase II trials took place and it was possible to empirically set the threshold. During phase II trials it was revised to 50ng/ml.

8 There is a large body of work on this issue over the past decade which is critiquing the ideology of population control [see e g Hartmann 1987, Correa 1994, Bhate et al 1986].

9 Jayaraman is a scientific journalist who has been following the development of this vaccine since the 1970s. He also published an item in *Nature* in 1986 where he has written about the WHO withdrawal of support to Talwar in the 1970s and attributes it to hasty clinical trials and the pregnancies that resulted. This has been used as a reference by women's health groups in critiquing Talwar's ethics. It is interesting to note that Jayaraman now thinks that the research that Talwar has continued to carry out shows that the vaccine can be seen as a safe preparation.

10 This could lead to its own set of side effects. In fact the phase II trials with the CTP vaccine that were conducted in Sweden had to be stopped because all the women who received the first injection had inflammation at the site of the injection and some even developed abscesses. This was due to the instability of the adjuvant that was used [Stevens 1996].

11 In an article they state, "At times unexpected cross reactions occur, even when devising a strategy that obviates anticipated cross reaction with a hormone. For example the vaccine based on the CTP of the beta hCG engenders antibodies free of cross reactions with human LH; however the antibodies cross react with pancreatic cells and pituitary[Rose et al 1988]. The long-term effects of such cross reactions, if any, are not known" [Talwar, G P, O Singh, R Pal and K Arunan 1990:582].

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