



## HAZARDOUS CONTRACEPTIVES AND THE RIGHT TO LIFE

C. Sathyamala\*

### Introduction

India has the dubious distinction of being the first country to adopt the Population Control policy as a national programme as early as 1951. Since then, despite the several changes, i.e., other parties coming to power at the centre and changes in the nomenclature of the programme from Family Planning to Family Welfare to the current Reproductive and Child Health programme, the central purpose has remained essentially the same. Thus the “demographic” goal of 1951, spelt out in so many words, still holds true in the 1997 declaration that “the main objective ... for the country has been to stabilise population at a level consistent with the needs of national development”.<sup>1</sup>

The welfare nature of the Indian State leads one to suppose that the needs of “national development” are (must be?) in consonance with the interests of the individual citizen. That it is not necessarily so when it comes to the Population Control Policy has been clear right from the beginning; persuasion through incentives, often in the form of hard cash, had to be tied to the various contraceptive methods in order to demonstrate ‘people’s acceptance’. ‘Persuasion’ in the country reached its peak during the 1975 ‘Emergency’ when brutal force was used to geld the country’s male population.<sup>2</sup> The forcible sterilisations, reminiscent of the Social Hygiene drives of the Nazi Germany, was aimed at sections of the population whose presence was considered not just redundant but actually detrimental to the progress of the Indian nation. That these citizens thought otherwise was brought home in no uncertain manner when they exercised their franchise in the next election to bring down the government for their mistaken notion.

Lessons were learnt. It became clear that when it came to fertility control, no government could afford open, blatant force and no government of this patriarchally male dominated society could afford to alienate its male population, obedience to ‘gender-sensitivity’ notwithstanding. Yet, population control continued to be a very important agenda of international funders and national policy makers and needed to be pursued with as much commitment as possible. Data from behavioural research called for a change in tactics, subtle and sophisticated. It was in this atmosphere that a new contraceptive technology - the injectable contraceptive, which appeared to fulfill the necessary qualifications, came to be introduced into the country.

---

\* Epidemiologist and Public Health Consultant.

1. Department of Family Welfare, Ministry of Health and Family Welfare, GOI, *Reproductive and Child Health Programme, Schemes for Implementation 1* (1997).

2. It has been argued that, that was an ‘extraordinary’ period of the post-independent era, when in the interests of “national good” as perceived by the then ruling party, several other rights of the individuals were also suspended. However, for the ordinary citizen, it was the infringement of the individual’s rights, in particular that of the males’, to procreate that was considered the deepest cut of them all. In the history of the Family Planning Programme in India, this is the first and the only time that the number of males who were sterilized exceeded that of the women.



Primarily for the use of women, the injectable contraceptive had already demonstrated its potential for coercion in a manner where the recipient herself need not be aware. The fact that in the process, it was a threat to the life and health of the 'acceptor' and her progeny and made mockery of her fundamental rights as a citizen was not taken cognizance of till women's organisations, as concerned women and citizens of the country, raised the matter in the highest court of the land.

### History

DMPA<sup>3</sup> and Net-en<sup>4</sup> are the two main injectable contraceptives available in the national and international market. From the early fifties, when the parent company began synthesising the drug, to the late sixties, when they were ready to be marketed, the development of the two contraceptives proceeded almost neck to neck. But within a space of few years, Schering AG on its own, withdrew Net-en from the market, and Upjohn was ordered to withdraw Depo-provera by the American Food and Drug Authority (USFDA) because the animal models on whom the drug was tested developed cancer (see tables I and II).

In the seventies, India was one of the countries that participated in the clinical trials with the injectables. Under the aegis of the Indian Council of Medical Research (ICMR) the Injectable Depo-Provera was tested on 131 and Net-en on 225 Indian women as part of Phase III trials.<sup>5</sup> In 1975, ICMR reported the discontinuation of clinical trials with Depo-Provera because of the serious side-effect of heavy and/or prolonged bleeding or amenorrhoea it caused in more than 50% of women. In 1977, the World Health Organisation (WHO) reported a multi-centric Phase III clinical trial with these two injectables to which India had 'contributed' a total of 270 women from two of its centres, Bombay and Chandigarh respectively.<sup>6</sup> However, this trial had to be curtailed midway because of an unacceptably high number of pregnancies (high failure rate) from two of the centres, one of them being Chandigarh. Despite this 'Indian' experience with Net-en, in 1981-83, ICMR initiated a Phase III trial of its own with Net-en for which 3100 women were recruited from 16 centres all over India.<sup>7</sup> In 1983-84, Phase IV (pre-programme introduction study) was initiated in selected post partum centres and primary health centres in rural areas. The plan was to recruit 4000<sup>8</sup> and 2250<sup>9</sup> women respectively.

In March 1985, members of a Hyderabad based Women's organisation, Stree Shakti Sangatna, read in a local daily that for the first time in the State of Andhra Pradesh an

3. DMPA : Depot medroxyprogesterone acetate, brand name Depo-Provera, Upjohn Co., USA.

4. Net-en : Nor-ethisterone enanthate, brand name Noristerat, Schering AG, Germany.

5. ICMR, *Annual Report* New Delhi, 45-46 (1975).

6. WHO, Expanded programme of Research, Development, and Research training in human Reproduction, Task Force on long-acting Systemic agents for the Regulation of Fertility, "Multi National Comparative Clinical Evaluation of two long-acting Injectable Contraceptive Steroids, Net-en and MPA". 15 (5) *Contraception* 513 (1977).

7. ICMR in collaboration with the Ministry of Health and Family Welfare, *Introduction of Injectable Contraceptive (Net-oen, 200mg) in National Family Welfare Programme through Post-Partum Centres, Study Protocol* (monograph undated).

8. *Ibid.*

9. Introduction of injectable contraceptives (Net-en 200 mg) in selected primary health centres attached to medical colleges (Rome scheme)- a pilot study



injectable contraceptive (Net-en) was to be introduced into the rural areas. The contraceptive was to be distributed through a family planning camp to be held at the primary health centre in Patencheru village, nearby Block Head Quarters. To mark the special occasion, none less than the District Collector was to attend the inaugural ceremony organised for the launch. The large advertisement then went on to extol the virtues of the contraceptive. What the advertisement however, did not make clear was that the contraceptive was still under clinical trial, and that the launch at Pattencheru was the final or the fourth phase of the trial, a necessary pre-requirement before the drug could be submitted for approval by the Drugs Controller.

Members of Stree Shakti Sangatna who were aware of some of the controversy surrounding the injectable contraceptives decided to attend the family planning camp at Patencheru that was to be held on 1.4.85. At the camp, it became clear that the village women had been beguiled into attending the camp under the false propaganda that the injectable was an approved method of contraception. All that they had been told was that if injected every two months, it would prevent pregnancy. The members of Stree Shakti Sangatna voiced their concern about the lack of informed consent and spoke about the hazardous nature of the contraceptive. The District Collector on his part invited the members to present their view point to the audience alongside with that of the medical staff of the PHC. Most of the 'motivated' women who had come to receive the injection exercised their option and chose to leave without participating in the clinical trial.<sup>10</sup>

Consequent to this, members of Stree Shakti Sangatna wrote to the Union Minister for Health and Family Welfare and the Drugs Controller of India informing them of the violation of ethics in holding phase IV part of the clinical trials under the guise of such camps.<sup>11</sup> On the basis of literature published in medical journals they underlined the hazardous nature of the contraceptive and urged the Drugs Control authority to ban the use of the contraceptive in India. When there was no response forthcoming from the Drugs Controller's office or from the ministry, the women's group took recourse to legal remedy.

On April 7, 1986, a public interest litigation, signed by three women's organisations (Stree Shakti Sangatna, Hyderabad; Saheli, New Delhi; and Chingari, Ahmedabad) and several concerned individuals, was filed in the Supreme Court of India.<sup>12</sup> This was against the Ministry of Health and Family Welfare, Indian Council of Medical Research, and the State of Andhra Pradesh. When the case was admitted, the court ordered the inclusion of the Drugs Controller of India as a respondent.

Initially, the plan was to emphasise the lack of informed consent and the unethical manner in which clinical trials were being carried out in the country. However, delving into the medical literature on the drug, it became clear than an independent case could be made against the use of the drug per se in the Indian context, thereby broadening the scope of the case.

---

10. Subsequently, the recruitment for phase IV trial did take place in this PHC but without the earlier fanfare. However, only 32 women could be recruited and they received their first injection on 23.7.85. Out of them, 15 did not turn up for the next injection and by the third injection, there was a 70% drop-out rate.

11. Letter dated 18.10.85, sd/ Dr Suzie Tharu, Convenor, Stree Shakti Sangatna, Hyderabad, Andhra Pradesh.

12. *Stree Shakti Sangatna and 8 Ors v Union of India and Ors* Writ petition (civil) No. 680 of 1986.



The contentions against the injectable contraceptives can be divided broadly into three areas, viz.,

1. Safety of the injectable contraceptive;
2. Unethical manner of the trials on Indian women; and
3. Potential for abuse in a hitherto largely anti-people (anti-woman) Family Planning programme of India.

### Safety of the Injectable Contraceptives

Contraceptive drugs are somewhat different from other drugs used in clinical practice. Drugs in clinical practice are to be administered to diseased persons for therapeutic purposes and they act by altering/changing/ or correcting an abnormal pathological process or situation in the body. Thus, most of the drugs used in clinical practice are administered to, relatively speaking, a small number of individuals and the duration of use, again relatively speaking, is short till relief or cure takes place. In contrast, contraceptive drugs are used by normal healthy individuals to prevent a normal physiological process of pregnancy. Contraceptive drugs interfere with normal body mechanisms and convert them into abnormal processes i.e., a normal process of ovulation (production of egg) in a woman's body is converted into the abnormal process of shrivelling of the egg. Since contraceptives are to be used for preventing pregnancies, hypothetically speaking, the contraceptive drugs are targeted at all sexually active persons for the duration of their reproductive life, which is also the most productive healthy years of the adult part of life. For women it is approximately from the age of fifteen to forty five years.<sup>13</sup>

The weighing of risks and benefits for the individual is different for these two groups of drugs. For instance, in a potentially fatal disease such as cancer, the serious Adverse Drug Reactions (ADR)<sup>14</sup> of an anti-cancer therapy may be acceptable, both medically speaking and to the individual, as long as there is a possibility of prolonging

---

13. In reality, the drugs may not be ingested throughout the reproductive life of 30 years. In India, the Injectables are being promoted as temporary method for spacing children. The duration of use, as recommended, could be upto ten years with breaks in between for pregnancy.

14. When a drug is administered to a human being, two types of action may occur: (1) *desired* drug actions which are the preventive, diagnostic, prognostic or therapeutic effects that are the being primarily sought and (2) *undesirable* drug reactions which are the effects which are not sought. No drug is precisely specific for receptors or potent in its effects that it is effective in exactly in the desired manner to each person to whom it is administered. Thus, no drug is absolutely free of some capacity (in varying degrees) to produce unsought reactions in a certain percentage of patients. These unsought reactions may be harmful or harmless. The USFDA has given the term *Adverse Drug Experiences* for all harmful reactions associated with any given drug therapy. These include those occurring during as well as subsequent to the administration of the particular drug. Adverse experiences definitely shown to be caused by a drug are termed *Adverse Drug Reactions* (ADR). The term Serious Drug Reactions are reserved for those reactions which are definitely harmful to the person and/or possibly life-threatening (E.W. Martin *et al.*, *Hazards of Medication: A manual on Drug Interactions, Contraindications, and Adverse Reactions with other Prescribing and Drug Information.*, JB Lippincott Co., USA, 298-99 (1978).



life. A drug used for a simple skin condition such as scabies, on the other hand, will not be acceptable if it has any life-threatening complications.<sup>15</sup>

Depending on the potential number of users, computation of risks and benefits is different at the population level as well. From a public health point of view, it is important to assess the potential number of individuals who could develop a side-effect<sup>16</sup> as a consequence of using a particular drug. To assess this, one would have to look at the rate of risk and the number of potential users. For instance, a high risk of 1 in 100 for a certain adverse effect with a drug (i.e., out of 100 individuals using the drug, 1 will develop an ADR) would result in only 10 individuals thus affected if the potential users are only 1000. In contrast, a ten times low risk of 1 in 1000, would produce ten times higher number of diseased persons (100) if a population of 100,000 users were to use it. Therefore, even a small risk of adverse effect can assume great public health importance when the number of potential users is large as in contraceptive usage.

As drugs used by women in the reproductive age group, contraceptives are to be viewed with greater caution. The risk of administering a drug to women during their reproductive period assumes a greater significance because of the possibility of the drug affecting the progeny. The effect could be mutagenic due to the alteration of the genetic composition of the ovum which could lead to the birth of children with chromosomal anomalies such as Down's syndrome. Or the effect could be teratogenic with the drug passing through the placenta and directly affecting the foetus in-utero. Drugs could also pass through breast milk and affect the breast-fed infant. These effects could be of immediate nature and cause drug-induced abortions or congenital malformations (birth defects) or they could manifest as delayed effects some twenty-three years after the event. The history of drug development is replete with such tragedies.

In the sixties, congenital malformations induced in children born to women taking an anti-emetic drug Thalidomide during pregnancy shook the pharmaceutical world so to speak. Another drug, Diethylstilbesterol (DES), a drug prescribed to pregnant women for threatened abortions, left in its wake hundreds of young women afflicted with a rare form of the cancer of vagina. And these were not women who had ingested DES directly. They were the daughters of women who had taken the drug and who

---

15. Depo-Provera at a high dose of 400mg to 1000mg per week followed by a maintenance dose of 400mg per month, is used as a palliative therapy in inoperable, recurrent, metastatic endometrial and renal cancer. The risks of medication that would be acceptable when used for this (approved) indication is different than when it is to be recommended for contraception.

16. In drug literature, the term side-effect is used synonymously with ADRs. While this is technically correct, it conjures to the lay mind a minor effect of no consequence, perhaps just a nuisance value. The more precise method would be to categorise them into minor and major side-effects. For instance, an oral dose of the antibiotic, ampicillin may produce diarrhoea as a secondary (side) effect although its primary effect is anti-microbial. In the light of its primary effect, the diarrhoea may be accepted as a minor side-effect. On the other hand, the hypersensitivity reactions (anaphylaxis, allergy) with the drug which can lead to collapse and sudden death would be considered a major side-effect.



had become exposed to the drug as foetus in their mother's womb but developed the cancer later in adult life.<sup>17</sup>

It is for these reasons that in western countries, different norms and rigid rules of testing are applied to contraceptive drugs.

### **Safety of the injectable contraceptives as a chemical entering the woman's body**

In order to understand the health risk to the woman, it is important to understand both the normal physiology of the reproductive cycle and the mechanism of action of the Injectable contraceptive, which disrupts it.

The normal functioning of the reproductive system in the woman is maintained by two female hormones: estrogen and progesterone, both produced by the ovaries. The reproductive cycle of the woman as signified by her menstrual cycle is regulated by a finely tuned cyclical, controlled release of specific quantities of these two hormones, the levels rising and ebbing through the 25 to 30 days cycle to facilitate the maturation and release of the ovum (egg). Estrogen is necessary for the growth and development of the egg and progesterone for creating a favourable environment in the uterus for the implantation of the fertilized egg. If a sperm fertilizes the ovum and conception occurs, the ovary will continue to secrete estrogen and progesterone, which is necessary for the survival of the embryo in its early life. If there is no fertilization, the levels of the hormones will fall. As a consequence of this, the inner lining of the uterus (endometrium) will be shed and the monthly bleeding will occur. The cycle will begin once again and a new ovum will begin to mature.

---

17. DES is a synthetic estrogen (a female hormone) produced first in 1938. Between 1945 and 1970, in the USA, DES was prescribed widely to pregnant women to treat threatened abortions, premature labour, as preventive therapy in women with bad obstetrical history and even in cases of normal pregnancy as a general prophylactic measure. It was only in the late 70s, that it was discovered that it caused vaginal cancer (clear cell adenocarcinoma of the vagina, an extremely rare form of cancer in old women and unknown in young women) in young women barely out of their teens. They were the daughters of mothers who had ingested DES during their pregnancy. Virtually all the cases of cancer manifested after the onset of puberty, suggesting a complex interplay between in-utero exposure and the onset of endogenous secretion of estrogen at the initiation of puberty. Studies also showed that a significant number of male offsprings of women exposed to DES in pregnancy, had uro-genital abnormalities, particularly of the urethra. Evidence also seemed to indicate that DES exposed male offsprings had an increased rate of infertility.

Many parallels can be drawn between DES and the Injectable contraceptives. Firstly, DES was introduced into the market without adequate testing. Secondly, DES was marketed when animal studies had already shown potential teratogenicity (adverse effects on the developing foetus). Thirdly, even when the evidence piled up against DES, newer uses were being found for its use by the Drug company. Fourthly, the Drugs Control Authority of the country (USA) indicated its complicity by refusing to take a firm decision to ban the drug. And finally, it took twenty years before the delayed effects emerged and in a generation that was exposed to it in-utero.

But the parallel stops here. In the USA it was possible to detect the delayed effect because of the alertness of the medical community. An unusual clustering of cases of the rare cancer was observed in a small defined geographic region and the medical community decided to investigate. While investigating it was possible for them to associate the cancer with history of drug ingestion twenty years earlier because of prescription practices which does not allow for the sale of scheduled drugs over the counter. In India neither of these two conditions exist. There is no cancer registry maintained for monitoring prevalence rates and almost all drugs, including injectable contraceptives, are sold over the counter.

In India the drug DES is now being promoted as a morning-after-pill for emergency contraception.



The release and maintenance of the optimum blood levels of these hormones at the different stages in the menstrual cycle are controlled by a complex and delicate feed-back system of other hormones released from higher centres in the brain (pituitary and hypothalamus). These are in turn controlled by the varying levels of estrogen and progesterone in the blood.

Net-en and Depo-Provera, the two injectable contraceptives are very similar to each other chemically, and therefore pharmacologically, in their actions. They are administered as a single shot in a highly concentrated form, once every two or three months through a deep intra-muscular injection.<sup>18</sup> From the 'Depot' in the muscle, the chemical enters the blood stream continuously for the next two to three months to produce the contraceptive effect in the woman's body. The injectables are thus termed long-acting and invasive<sup>19</sup> methods of contraception.

Net-en and Depo-Provera are synthetic steroid hormones, similar to the naturally occurring progesterone. But this is where their similarity begins and ends. On administering the injectable contraceptive, the high dose of progesterone like compound inhibits the secretion of the natural estrogen and other hormones necessary to maintain the normal menstrual cycle. The finely tuned feed-back mechanism of regulation is disturbed leading to the complete disruption of the natural hormonal balance in the body. Just one of the outcomes of this disruption is the contraceptive effect that the drug is being marketed for.<sup>20</sup>

### *bleeding disorders*

The effect of the injectables on the cyclical release and control of the natural hormones in the body results in the total disruption of the regular monthly menstrual, reproductive cycle, an effect that is termed in medical literature as menstrual chaos. Thus the woman may exhibit irregular bleeding, spotting of blood throughout the cycle,

---

18. Net-en (200mg) once every two months; Depo-Provera (150mg) once every three months. Net-en is in an oily medium and the injections can be very painful.

19. Depending upon the levels at which they act, contraceptive methods can be categorised as invasive (systemic) or non-invasive. Barrier methods such as condoms and diaphragms prevent the meeting of the ovum with the sperm by forming a mechanical barrier. Their use as a contraceptive method and their presence in the body does not therefore alter the physiology of the human body. In contrast, oral contraceptives (Pill) and the injectable contraceptives are both invasive methods. The Pill is taken orally and enters the blood stream through absorption from the intestines. The injectables are injected directly into the muscle and bypass the longer route of entry through the intestine. Both act by altering the physiology of the body. The difference between the two is however, in the quantum of the chemical that enters the blood stream at a time, the ability to regulate the daily dosage and in the possibility to interrupt the intake if needed. The Pill is given everyday in small doses and if any serious ADR is noticed, the next dose can be stopped immediately. The injectable contraceptive on the other hand is given in a massive dose of 150 or 200 mg to last for a total of 60 to 90+ days. Once injected, the chemical seeps into the blood with no regulation or control, and the peak level in the blood is reached at varying periods in different women. And most important, once injected into the body, there is no way by which the chemical can be removed if the woman develops any serious ADR.

20. The Injectables prevent pregnancy by acting at several levels in the body: (1) by preventing the maturation and release of the ovum; (2) by increasing the viscosity (thickness) of the secretions from the cervix (mouth of the uterus) to form a barrier to entry of the sperm; (3) by slowing down the normal velocity of ovum transport in the fallopian tubes; (4) and by making the inner lining of the uterus (endometrium) thin and unsuitable for the implantation of the embryo.



changes in the frequency, duration and amount of blood loss, heavy and prolonged bleeding or a complete absence of bleeding. All these effects are completely unpredictable and a large number of women may exhibit these effects with the injectables. 50% of the women in a clinical trial with Net-en carried out by the WHO did not have a single normal menstrual period.<sup>21</sup> A multi-national survey of 35 researchers in 20 countries found that 1 to 2 in 100 users developed heavy/prolonged bleeding.<sup>22</sup> As stated earlier, in 1975, the ICMR had discontinued the testing of Depo-Provera on Indian women because of heavy and prolonged bleeding in women receiving it.<sup>23</sup> The ICMR's Phase III clinical trial with Net-en found that 90% of the menstrual cycles recorded were abnormal.<sup>24</sup> In the Indian context, the bleeding problems assume a greater significance. If these injectables are given to women from the poorer sections of society who are already anaemic, their condition will be worsened because of increased number of bleeding days, excessive bleeding or shortening of the menstrual cycle.

Till date, there is no effective treatment for this 'side-effect'.<sup>25</sup> According to the WHO, the risk of excessive bleeding which needed to be treated surgically by Dilatation and curettage (D & C) was in the range of "less than 1 in 1000 users".<sup>26</sup> There are also reports that women who received these contraceptives sometime had to undergo hysterectomy (surgical removal of their uterus) as the heavy bleeding could not be controlled by any other means.

### *demineralisation of the bones*

When the high dose of synthetic progesterone enters the body, it suppresses the production of natural estrogen by the ovaries and the resultant state is termed hypo-estrogenic state. There are several serious consequences of hypo-estrogenic state for

21. WHO, "Facts About Injectable Contraceptives: Memorandum from a WHO meeting", 60 (2) *Bulletin of the World Health Organisation* 199 (1982).

22. Population information program, The Johns Hopkins School of Hygiene and Public Health, "New era for Injectables" Series K (5), *Population Reports* 11 (1995).

23. *Supra* note 5.

24. *Supra* note 7.

25. The reaction of the population control lobby is to minimise these effects. For instance, WHO urges the 'Health Provider' (an entity that is non-existent in rural areas) to counsel the woman about bleeding as "many women can accept bleeding irregularities provided that they are well informed about the underlying causes and are assured that bleeding is neither a sign nor a cause of disease". (WHO. *Injectable contraceptives: Their role in family planning care* WHO Geneva 76 (1990). Yet, the bleeding disturbances with the injectables were serious enough for the WHO to hold a special symposium on the subject. The symposium concluded with "... (our) data base is meagre, confusing and sometimes controversial... The bleeding problem appears to be complex and no simple solution is in sight". E. Diczfalusy *et al* (eds.), *Endometrial Bleeding and Steroidal Contraception* 423-24 (1980).

One definitive conclusion that was reached in this symposium was that the bleeding due to Injectables was not mere changes of normal physiology i.e., a mere increase or decrease of a normal menstrual pattern. The symptoms indicated alterations that were taking place in the blood vessels and the clotting/bleeding mechanism affecting the entire body. Three hypothesis were postulated to explain the cause of the bleeding disorders: (1) changes in the lining of the blood vessels; (2) changes in the coagulability of blood; and (3) hypersensitive or allergic reaction. Twenty years have passed since the symposium. The scientists are still unable to explain the causes of the bleeding problem.

26. *Supra* note 21. The phrasing "less than 1 in 1000" could mean 1 in 1001, or 1 in 1002 or... It does not appear to be 1 in 2000 because then it would have been stated as such. The risk of D & C lying somewhere between 1 in 1001 and 1 in 2000 of users is to be considered a high and serious risk.





the woman. Estrogen is necessary for maintaining the integrity of the bones. In a hypo-estrogenic state, the calcium in the bones begins to 'dissolve' out of the bones (Demineralisation of the bones) making the bones brittle and fragile. This increases the chances of spontaneous fractures and fractures due to minor trauma particularly of the hips and spinal column. In a normal population, Demineralisation of the bones and increased probability of fracture of bone occurs in post-menopausal women when the ovaries have naturally stopped producing estrogen, i.e., after fifty years of age. Depo-Provera is known to increase the risk of fracture by 10 to 15%.<sup>27</sup> In India, the risk becomes much higher. Due to poverty, the calcium levels in the bones of most of women from the low economic strata are already low due to inadequate nutritional intake (starvation or semi starvation) in childhood. Use of Depo-Provera in such a population would increase the chances of fracture to an unacceptably high level.

### *onset of early menopause*

The hypo-estrogenic state in the woman's body also gives rise to several other symptoms which are similar to that found in pre-menopausal stage. These are, hot flushes, headaches, nervousness, dizziness, asthenia (weakness and fatigue), decreased libido or anorgasmia, vaginal dryness, night sweats and alopecia (loss of hair).<sup>28</sup>

The continuous bombardment of the reproductive organs (ovary and uterus) by the synthetic progesterone leads to the atrophy of the tissue in these organs. The ICMR's Annual Report of 1975 stated that atrophy of the endometrium (inner lining of the uterus) was a common feature in women receiving net-en.<sup>29</sup> Endometrial atrophy is seen to occur much earlier with the injectables than with the combined pills. Ovarian atrophy has also been observed in women who received Depo-provera.<sup>30</sup> These conditions are irreversible and there is no treatment for them. The consequence for the woman is that she would develop early menopause with a resultant shortening of her life expectancy and life span. In effect a body of a 25 year old woman is being converted into the body of a 45 year old pre-menopausal woman.

### *adverse effect on future fertility*

In addition, the impact of the above mentioned changes in her body could mean that the woman may not be able to conceive after she discontinues the injectables.

The injectable contraceptive is being promoted as a temporary method for spacing i.e., to increase the number of years between two successive births. Inherent in this

27. T. Cundy *et al.*, "Bone density in women receiving depot medroxyprogesterone acetate for contraception" 303 (6793) *British Medical Journal* 13 (1991).

28. Drug Information on Depo-Provera, *Physicians' Desk reference* 2416 (1994). The risk of many of these side-effects is 5 in 100 users.

29. *Supra* note 5.

30. Goodman and Gilman's : *The Pharmacological Basis of Therapeutics* (seventh ed.) 1433 (1985). "Continuous administration of progestin in sufficient dose...and leads to ovarian and endometrial atrophy". P.C. Schwallie and J. R. Assenzo, "The effect of depo-medroxyprogesterone acetate on pituitary and ovarian function and the return of fertility following its discontinuation: A review" 10 (2) *Contraception*. 181 (1974).



promotion is the promise to the woman that the injectable contraceptive will not impair her fertility permanently and that she could conceive again if she so desires after she discontinues the injectable after the period of effectiveness is over. A study carried out by ICMR has shown that almost 50% of women who had developed amenorrhoea, failed to conceive even one year after discontinuing with Net-en.<sup>31</sup> There are no studies on Indian women with Depo-Provera. But the Upjohn literature admits that it is likely that more than 30% of women will not conceive even a year after discontinuing Depo-Provera.<sup>32</sup> Whether these women will conceive at all ever is not mentioned.

The adverse effect of infertility on discontinuation is not dose-dependent i.e., even a single dose of the contraceptive could cause secondary infertility for varying periods of time or make the woman permanently infertile. By promoting the injectables as a spacing method, a fraud is being committed on the woman by false promises.<sup>33</sup> The consequence of infertility (sterility) in a woman in a male dominated society like ours is too well known for elaboration.

### *effect on the higher brain centres*

Since the mechanism of action is not localised to the reproductive organs alone, disruption is also experienced in the functioning of the higher brain centres (pituitary and hypothalamus) which control the reproductive cycle. Regulation of body temperature, hunger and feeding, thirst, emotional changes and sexual functions<sup>34</sup> are affected and manifest as headaches, dizziness, weight gain,<sup>35</sup> anxiety, clinical depression, increased blood pressure, decreased libido etc. The continuous over stimulation of the higher brain centres could lead to hypertrophy, or tumor formation. In fact, Net-en was withdrawn from the market because experimental rats developed nodules in the pituitary gland. That this is not an unfounded fear can be seen from the drug information provided by Upjohn Co. It states that if there is a partial or complete loss of vision, or if there is a sudden onset of double vision, or migraine or if examination reveals papilledema, the injectable should not be readministered. All these symptoms are indicative of a brain tumor.

31. ICMR, "Return of fertility and Net-en" 34(6) *Contraception* (1986).

32. Drug information on Depo-Provera, *Physicians' Desk reference* 2415 (1994).

33. Goodman and Gilman's, *The Pharmacological Basis of Therapeutics*, eighth ed. II 1404 (1991). "Medroxy progesterone acetate (Depo-Provera)... should be used only if the possibility of permanent infertility is acceptable to the woman". No additional information was available after 1991 to change this statement. Yet this sentence is missing in the later edition of this standard text book of pharmacology used by medical students.

34. The injectable contraceptives are effective in men also. But they are not being recommended for contraceptive use in men because of their well known effects on sexual functions. When it comes to women, decreased libido is apparently an 'acceptable' side-effect for the promoters of the Injectables.

35. Women report an increased weight gain of upto 10 lbs over a six months period. This pathological weight gain is being promoted as a beneficial effect for under-nourished Indian women.

*thrombo embolic disorders*

The Injectable contraceptives are reported to cause the spontaneous clotting of blood inside blood vessels (thrombo embolic phenomenon).<sup>36</sup> In a clinical trial reported by the medical team of the Upjohn company (developers of Depo-provera) 11 women developed this complication of whom one died and the others were left with serious disability. Thrombo-embolic phenomenon is responsible for myocardial infarction (heart attacks), cerebro-vascular accidents (strokes that leads to paralysis etc) and pulmonary embolism (sudden death).<sup>37</sup>

*injectable contraceptives and cancer*

Toxicological studies have shown that synthetic progesterone is carcinogenic (cancer producing) in animals. Net-en for instance, is carcinogenic in every one of the several animal models it has been tested on (see table III). With Depo-Provera, it was the development of breast cancers in beagle dogs that caused the USFDA to withdraw its approval to the marketing of the contraceptive in the US. The population experts however tried to argue that even if there was a possibility of cancer risk in women, it was really no risk in the context of Third world women. In these countries, the longevity of women was so short in any case, they would die before reaching the age of getting cancer. Since this argument was not successful in allaying the concern of the scientific community, the WHO stepped in to provide evidence to support the injectable contraceptive by carrying out a multi-national study to assess the cancer risk with the injectable. The results were published in 1991 and showed that while there did not appear to be an

---

36. One of the main reasons for the oral contraceptives (Pill) for coming under disrepute was its association with the spontaneous formation of blood clots in the veins. Initially, it was thought that these blood clots were caused by the estrogen component of the Pill (The commonly used combined Pills have both estrogen and progesterone). In the newer preparations, the estrogen component began to be reduced to eliminate this life-threatening side-effect. It was thought that the progesterone part of the Pill did not cause the ADR. Hence, Injectables, which contain only progesterone were promoted as being superior to the oral Pill. However, current knowledge has shown that progesterone also has an independent effect on the clotting mechanism of the blood and cause thrombo embolism. The irony today is that WHO recommends the use of estrogen to reduce bleeding disorders with the Injectables!

37. Whenever potent drugs can be particularly dangerous to patients under certain conditions, warnings are included in the labeling. Such warnings generally pertain to extreme hazard. ( Hazards of medication...). Under Warnings, the drug information of Upjohn states "If any of these problems occur following an injection of Depo-Provera, call your health care provider immediately: Sharp chest pain... indicating a possible clot in the lungs; sudden severe headache... indicating a possible stroke; severe pain or swelling of calf... indicating a possible clot in the leg". It is another matter that there is very little a health care provider would be able to do. The irony is that while the Drug companies are willing to admit the possibility of such serious ADRs, their supporters like the ICMR and the WHO categorically refuse to accept it- a matter of being more loyal than the King perhaps!



overall risk, in a sub-group of women aged less than 35 years Depo-provera could increase the probability of breast cancer two folds.<sup>38</sup>

### *effect on progeny*

There is a definite likelihood of the injectable contraceptives affecting children born to women using them. Pregnancy is an absolute contraindication for the use of injectables. However, in a field situation, the medical team may fail to detect early pregnancy. Even if a woman is not pregnant at the time of the injection, the injectable contraceptives are not 100% effective in preventing the release of mature ovum. In case this happens it is hoped that the injectable would act in other ways to prevent conception. One way is to delay the speed of ovum's transport along the fallopian tube and another is to create a hostile climate in the uterus to prevent implantation thereby causing an early occult abortion.

Any contraceptive that delays ovum transport along the fallopian tube has the possibility of causing ectopic pregnancy,<sup>39</sup> potentially a life-threatening condition even in the best of situations. Under "Warnings", the Drug literature of Upjohn states "Health care provider should be alert to the possibility of an ectopic pregnancy among women using Depo-Provera contraceptive injection who become pregnant or complain of severe abdominal pain".

In case the fertilized ovum does not abort and the pregnancy continues, the developing foetus would be subjected to a high level of the synthetic progesterone contained in the injectable. The foetus would be exposed to the high dose of contraceptive in the first three months of its life, i.e., in the vulnerable stage of growth at a time when its vital organs are developing. The effects could be either teratogenic or mutagenic.

There are published reports to show that exposure to synthetic progesterone during early foetal life can cause masculinisation of external genitalia in female infants and uro-genital malformations (hypospadias) in the male infants. A study carried out in Thailand showed that in women who had a history of using Depo-Povera as a contraceptive, the prevalence of chromosomal anomalies was ten times higher than that

---

38. WHO Collaborative study of neoplasia and steroid contraceptives. "Breast cancer and depot-medroxyprogesterone acetate" 338 *The Lancet* 833 (1991). This study is methodologically flawed in many ways. Yet, it did show a clear association between Depo-Provera and breast cancer in sub-groups of women. Since the WHO could not deny their own findings, their paper ends in a convoluted note: "...that these results provide some assurance that women who have used DMPA for a long time and who initiated use many years previously are not at increased risk of breast cancer". The reverse of this statement was that there is a strong likelihood that a woman may develop cancer of breast soon after she starts using Depo-Provera. If she does not, then the likelihood that she will develop cancer at a later stage is low. For a full critique of this study, see C. Sathiyamala, "Depot-medroxyprogesterone acetate and breast cancer: A critique of the WHO's multinational case-control study" 220 *Medico Friend Circle Bulletin* 1 (1995).

39. Since the speed of transport is slowed, the fertilized ovum may implant itself on the ovaries, in the abdominal cavity, or the fallopian tube and begin to grow. Since these locations are not suited for the growth and development of the foetus, the growing embryo might burst through the tubes, for instance. It is generally a difficult condition to diagnose particularly if the physician is not aware of this complication. The only symptom might be pain in the abdomen. Treatment is surgical but the woman might bleed to death (internally) before she reaches the hospital.



of normal population<sup>40</sup> and Down syndrome was the chief anomaly. In many of these cases, the children had been conceived many months after an injection had been administered to the woman when the drug was no longer in active circulation in the body. The adverse effect of Depo-Provera on the foetus need not thus be due to direct exposure.<sup>41</sup>

Children may be exposed to the injectables in other ways also. The injectable contraceptives are recommended specially to breast feeding women because apparently they do not decrease the quantity of breast milk. However, in breast feeding women, the injectable contraceptive passes easily through the breast milk. Children being suckled on this injectable contraceptive-laced breast milk could have their future development affected adversely because the contraceptive can cross the blood-brain barrier and affect the vital brain centres of the infants. As in the case of the DES daughters and sons, the effects may become apparent during puberty when the child's body begins to produce its own hormones. The impact of such an effect would be manifested only when the child reaches adolescence when his/her reproductive system begins to mature.<sup>42</sup>

Thus the injectable contraceptive is hazardous<sup>43</sup> for both the woman and her progeny. These health effects could be immediate or delayed appearing after more than 15-20 years. Many of the ADRs associated with the Injectables are serious, life-threatening or lead to life-long disability.

### Safety Aspects in the Indian Context

Combined with the hazardous nature of the chemical, the mode of delivery of the chemical poses an added problem. Oral contraceptives too contain hormones similar to that of the injectable contraceptive. However, unlike the Injectables, the woman has to take the Pill daily in very small doses. In case the woman develops any complication she can discontinue the pill and the levels of the hormone in the blood will come down promptly. In the case of the injectable, the full dose of three months (Depo-Provera) or two months (Net-en) is given in the form of a single shot of injection to the woman. Once the contraceptive drug is injected into the body, there is no way by which it can be removed from the body. If the woman develops a serious complication with the Injectable

40. T. Pardthaisong *et al*, "Steroid contraceptive use and outcome of pregnancy" 3 *Teratology* 51 (1988). This study is referred to in the Upjohn literature. The congenital abnormalities are termed as "chromosomal anomalies" which is technically the correct term. But the fact that many of them were Down syndrome babies, an entity that is fairly well known to lay people, is not made clear.

41. According to a foetal risk summary which grades drugs on the basis of their effects on the foetus (A,B,C, D and X), the injectable contraceptives would fall under category X: "Studies in animals or human beings have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience or both and the risk of the use of the drug in pregnant women clearly outweighs any possible benefit. The drug is contraindicated in women who are or may become pregnant". (G.G. Briggs *et al*, *Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk*, x-xi (1983).

The injectable contraceptive is considered a second rate contraceptive. The recommendation of the Drugs Control authorities of some of the developed countries where it has been registered is that they are "to be used only when it is not possible to use any other contraceptive methods".

42. There is only one study from Thailand which followed children exposed to Depo-Provera uptill puberty. In girls there appeared to be delay in the development of secondary sexual character.

43. There are many more hazardous effects such as that on metabolism which I am not going into.



in the first week of its administration, she will have to continue to suffer the effects (which may progress to death) for the next three months till the body can slowly eliminate the contraceptive drug from her body. During the period of the three months her blood levels of the contraceptive chemical will continue to remain high.

It is precisely because of this that extreme levels of caution and precautions are necessary for the screening<sup>44</sup> of a woman before she is advised an Injectable contraceptive. She would require a pregnancy test to eliminate the possibility of inadvertently subjecting the foetus to the contraceptive, a complete physical check-up including breast examination and internal vaginal examination to eliminate pre-existing disease. Moreover, if any of the above stated side-effects<sup>45</sup> occur, the medical set-up should be equipped to deal with them effectively.

There are enough studies to show that the government set-ups at the primary health care level in the rural areas where 80% of our population resides is grossly inadequate to deal with even simple diseases such as malaria. These facilities are in no way equipped to either screen out women in whom the Injectable should not be used or treat complications when they arise.

In the absence of adequate facilities, to allow the recruitment of women for administering the hazardous injectable could only be termed as a total lack of concern and a gross negligence of responsibility.

### **Unethical manner of trials on Indian women**

The Helsinki Declaration on bio-medical research has very clear guidelines for clinical trials. Every biomedical research projects involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards it may entail. The consent of the subjects must be obtained freely and in writing.

From the early seventies clinical trials with hormonal contraceptives have been undertaken by scientific bodies such as the ICMR in a large way. Since then these scientific bodies have subjected thousands of women to hazardous contraceptives as part of clinical testing. The women who formed the 'material' for experimentation have been generally from the low socio-economic strata of the society and were recruited through family planning clinics or post-partum wards when they were admitted for delivery. By providing the contraceptives through such outlets, the experimental nature of the transaction was hidden. The women were neither informed of the fact that they were participating in a clinical trial nor was any written informed consent taken from them.

---

44. A minimum requirement of pregnancy detection kits, cervical pap smears, liver function tests, a laboratory technician and a lady doctor would be necessary to screen the woman for the Injectables. To handle the complications and the side-effects of the drug at least a secondary level hospital facility would be necessary.

45. It needs to be reiterated once again that even if medical facilities are adequate, it may not be possible to treat or arrest the complication because of the continued presence of the drug in the body.



This appears to have been the case for all the stages of clinical trials with hazardous contraceptives. In 1985, when the members of Stree Shakti Sangatna visited the Family Planning Camp at Patencheru they found that the women who had come to receive the injection did not know that they were participating in a clinical trial. As the trial was conducted in a family planning camp, the injectable was being offered as a tested and approved method on par with the other legally approved methods. In the other states too where the phase IV trial was being conducted, there was similar evidence. The phase IV trial was advertised through posters and pamphlets which confined itself to giving favourable information on the Injectables. In fact, the phase IV research protocol of the ICMR did not mention anywhere in its document that the woman needed to be informed or that her consent should be taken.

This was true for the earlier phase III trials also. Not just that, in the phase III trial of the ICMR there were many protocol violations as well, which indicated a total disregard these research bodies had towards the well being of the woman. In this trial, 54 women were above the stipulated age, and 41 women were anaemic with a haemoglobin of less than 8 gms. In all, 241 women were later excluded from the study because of protocol violations.

When the petition against the introduction of the hazardous contraceptives was filed in the Supreme Court, it is a matter of record that the Indian Drugs and Cosmetics Act 1940, did not contain any rules or regulations for drug testing on human subjects. It was only in 1987, a year after the PIL against the Injectables was filed that the Drugs Controller of India through an extraordinary gazette notification informed the formulation of a set of rules and regulations for drug testing. This was later (September 1988) incorporated into the Indian Drugs and Cosmetics Act as Schedule 'Y'.<sup>46</sup> Thus during the time before 1988, all the women who had been administered the Injectables (or for that matter any other drug) as part of clinical trials had no protection, legal or otherwise for participating in these trials.<sup>47</sup>

Apart from the extremely important question of informed consent, there was another serious contention with regard to the phase IV trial with the Injectables. The petitioners argued that it was unethical on the part of the scientific authorities and the scientific bodies to have proceeded with the phase IV trial with the Injectables when sufficient evidence existed to show that the Injectables were hazardous to both the woman and her progeny. This was based on the experience from other countries where the Injectables were in use and on the findings of the ICMR's own research on Indian women.

When the ICMR was planning to proceed with the phase IV trials with Net-en, the following information on Indian women was already available with them:

(i) That wide inter centre variation and population differences existed in terms of effectiveness;

---

46. Requirements and guidelines on clinical trials for import and manufacture of new drugs, Drugs and Cosmetics Act 1940, 394 (1996).

47. The situation has not changed even after the inclusion of Schedule 'Y' in the Drugs and Cosmetics Act. The ICMR and the other research bodies continue to subject women to even more hazardous contraceptives without any informed consent, as will be seen later.



- (ii) Indian centres tended to give high failure rates; and there was a high failure rate in the first six months of contraceptive use particularly in thin, under nourished women;
- (iii) 90% of the subjects had either excessive bleeding or amenorrhoea;
- (iv) Even at the end of one year, not more than 26% of women could be recruited; and one third of the centres had to be dropped; discontinuation was mostly after the first or second injection.
- (v) There was no information on reversibility of the contraceptive.

It was obvious that Indian women found the Injectable unacceptable. The injectable also appeared to be less effective in Indian women. No basis existed on which ICMR could promote the method as reversible. By giving permission to the ICMR to proceed with the phase IV trial the Drugs Controller had knowingly allowed thousands of women to be subjected to an unacceptable contraceptive. It appeared then that the real intent behind the trials was not so much to gather medical information but to go through the motions of completing the formalities of drug testing so that the drug could be expeditiously introduced into the Family Planning Programme of the government.

#### *potential for abuse*

World wide, the injectable contraceptives have the unenviable reputation of being used as a tool to control the fertility of 'undesirable' populations. The Injectables have been used on women in the refugee camps in Thailand, black population in South Africa, the Asian population in the UK, the indigenous population of the US, adolescents from poor households in the West and women in mental hospitals and asylums in Canada. In many of the instances, the women were not aware that the injection was a contraceptive. The Injectables have also been used in males to control deviant sexual behaviour.<sup>48</sup>

The concern that the Injectable would render women from active decision makers to passive recipients with regard to contraceptive choice seemed well-founded on the basis of this evidence. Women cannot "forget" the Injectable like they can forget the pill; nor throw it away if they cannot tolerate side-effects; nor can it be pulled out of the body as the IUD (loop) when it causes infection or bleeding. The Injectable ensures the transfer of control from the hands of the user to the hands of the health personnel who wield the syringe.

---

<sup>48</sup> In 1983, the State of Oregon, USA, passed a Bill directing the mental health Division to establish a pilot programme to administer Depo-Provera to persons convicted of any sexual offence involving forcible compulsion. In the USA, Depo-Provera is used to control sexual deviance in males. Although not included in the labelling, Depo-provera has been prescribed for the management of paraphilia, (homosexual, heterosexual or bisexual pedophilia; heterosexual voyerism; sexual sadism or exhibitionism; and transvestism as late as 1994. In an ironical twist, Roger Gauntlett, heir to the Upjohn Company that manufactures Depo-provera, was sentenced to a year in jail and five years of 'chemical castration' with Depo-Provera by a Circuit Court Judge for the charge of sexually assaulting his step-daughter (Time, 1984).





### The Scope of Abuse of the Injectable Contraceptive in a Coercive Population Programme is Unlimited

The National Population Control Programme, euphemistically called the Family Welfare Programme, is not particularly known for having championed the cause of human rights. In fact, among the poor and the disadvantaged sections of the country, the Indian family planning programme has an anti-people particularly anti-women image. There is documented evidence of abuse with other methods of fertility control when they were propagated through this programme. In the past, different methods of contraception have been pushed at different points in time. In particular abuses with the IUDs (Loop) and female sterilisations are well documented. While the latter did not take the form of physically dragging women to the operating table as did happen in the male sterilisation camps during the 'Emergency', in effect that is what it did by linking it with the accrue-ments of benefits during a famine situation as in Rajasthan.

It was felt that if an injectable contraceptive, which is a provider controlled technology, were to be distributed/administered through the target driven family planning programme it would mean unchecked and uncontrolled use of it on women from the poorer sections without their knowledge or consent.<sup>49</sup>

For all these reasons, the testing of the injectable contraceptives and the plan to introduce them in the national family planning programme was considered to be in violation of several rights of the woman and her present and future progeny<sup>50</sup>

#### Why this enchantment with hazardous contraceptives?

To the reader it may appear illogical that the medical, scientific community represented by the ICMR and WHO should persist with the promotion of these contraceptives given their hazardous nature. To understand this unseemingly irrational and anti-women behaviour, one has to go back some thirty years.

Following the tragedies with Thalidomide and DES, (mentioned earlier in this paper), and reports of deaths and life-threatening complications with the oral contraceptives that began to appear in the medical literature, the USFDA formulated special regulations for establishing safety of drugs to be used by women in the reproductive age group. This was particularly with regard to the hormonal contraceptives as they were to be used by normal population. Emphasis was placed on toxicological studies with animal models and each step in clinical trial had to be proceeded by the mandatory animal studies (see table IV).

49. In India, the medical establishment has been extremely successful in creating an 'injection culture'. For the largely non-literate population in the country, anything that comes through the needle is considered 'superior' medicine. Unethical medical practitioners including fully qualified allopathic doctors are known to encourage this profit-making practice by giving unnecessary injections of vitamins, distilled water etc., as "*Takat ki dawa*". It is feared, and rightly so, that in a coercive population control programme among a non-literate population injectables may be given as a shot of *Takat ki dawa* through all the government health care outlet.

50. Article 14 (Equality before law); Article 21 (protection of life and personal liberty read in the light of the Directive Principles of State Policy 39 (b), (c), and (f); Article 47 (relating to Public health); Article 19(1) (a) pertaining to informed consent; Article 32 (Right to constitutional remedies) and Article 46.



These new regulations meant that the cost of contraceptive testing became prohibitive both in terms of money and lengthened duration of drug development. In the seventies to develop a single drug the cost was estimated to be anywhere between \$40 to \$70 million in the US, the toxicology studies alone cost 5 to 7 times more for contraceptives. This prolonged period of testing also meant that there was a decrease in the average effective patent life of a contraceptive drug. In addition, product liability issues, increasing litigations and high awards and compensatory damages<sup>51</sup> and collective action by women's groups and consumer fora made the pharmaceutical companies increasingly disenchanted with the development and marketing of contraceptive drugs.

The impact was that pharmaceutical companies began to withdraw their contraceptive products from the American market,<sup>52</sup> and to withdraw from contraceptive drug research and development. To reduce costs and bypass strict drugs regulatory norms, higher proportion of drug testing began to be shifted to the third world countries. With regards to contraceptive drugs, the public sector began to emerge as the important funder and increasingly 'non-profit' organisations began to get involved in research and development. For instance, in the post seventies, the American government provided 70 to 84% of world wide funds for contraceptive research and development with American and European pharmaceutical firms providing only 10 to 20%. The motives of the Western governments' interventions in contraceptive promotion is not difficult to understand. The western countries, particularly, the USA have never made a secret of their reasons for its aggressive involvement in the control of Third World population. To maintain operation of the US commercial interests and to prevent revolutions have been cited as two of the important reasons by R T Ravenholt, the Director of USAID, in 1977.

With the withdrawal of pharmaceutical firms from contraceptive research, the 'neutral' scientific bodies such as the WHO,<sup>53</sup> Population Council<sup>54</sup> etc., stepped in and became the developers of contraceptive drugs and devices. With their entry into the field of contraceptive development, the vested interests in drug development or population control have become obfuscated. For instance, Norplant, another hazardous contraceptive, is being manufactured by a pharmaceutical company in Finland and the clinical trials are carried out under the umbrella of Population Council with support from the WHO. Population Council and the WHO collaborate with research bodies of the different countries (ICMR in India) for recruitment of human subjects and for carrying out the study in the respective country. Funding is provided

---

51. AJ Robins, the company that developed Dalkon shield, an intra-uterine contraceptive device which was associated with the death of many women and the cause of permanent infertility due to septic abortions was ordered by the American courts to pay damages for death, disability etc to all claimants. By April 30, 1986, a total of 320,000 claims were filed for damages. AJ Robbins were also ordered to 'recall' every single device they had sold over the years.

52. Schmid Laboratories Inc., (saf-t-coil), 1983; Ortho Pharmaceutical Corporation (Lippes Loop), 1985; GD Searle & Co., (Copper 7 and Tatum 7). The oral pill has not been withdrawn because these products continue to be highly profitable despite litigation costs.

53. The Special Programme of Research, Development and Research Training in Human Reproduction of the WHO was set up in 1971 to plan, carry out and monitor studies on contraceptive methods.

54. The International Committee for Contraception Research of the Population Council was set up in 1971



by International donors such as the USAID, UNFPA, International Planned Parenthood Federation, Ford Foundation etc.<sup>55</sup>

Riding high on the credibility an organisation like the WHO has garnered for itself through its good works in the last fifty years in other areas of health, these organisations are able to give an ethical and scientific 'face' to contraceptives they develop and promote. It seems almost blasphemous to suspect such organisations of duplicity. A stamp of approval from the WHO, for instance, even if it is not based on hard scientific evidence is taken as irrefutable "truth". That the 'neutral' scientific bodies appear to lose their perspective when it comes to contraceptive research can be seen from their own documents. For instance, as early as 1982 the WHO published a document declaring Net-en and Depo-Provera to be reversible and safe for use in the general population. This was long before studies were initiated to examine their reversibility (return of fertility), effects on progeny, or their carcinogenic effects. The return of fertility study (which showed an adverse effect) with Net-en was published in 1986; the study on chromosomal anomalies and Depo-Provera was published in 1988 and the WHO study on Depo-Provera and breast cancer was published in 1991.<sup>56</sup>

When it comes to clinical trials, the WHO appears to be as much a violator of ethics as the ICMR. For instance, in the report of the multi-national phase III trials on 3,172 women (2,760 from developing countries and 412 from developed countries), published in 1986, 4 women were reported to have died during the trial: one due to cancer (metastatic chorio carcinoma, had received two doses of Depo-Provera), two due to tuberculosis (one had received 2 doses of Net-en and the second one had received 8 injections of Net-en), and one due to 'unknown' causes (had received 3 doses of Depo-Provera). Apart from stating that these deaths were unlikely to have been due to the injectables,<sup>57</sup> the report is silent on the ethical and legal questions regarding the death of these women.

The worldwide contraceptive market is very large particularly in the third world countries. If we take India alone, in 1990 there were approximately 100 million 'eligible' couples who were not using any effective contraceptive methods. This is the group at whom the Injectables are targeted. This represents at a conservative level a market worth more than 1000 million US \$ per year for the promoters of the injectable contraceptives. However, this remains merely a potential market even if the Injectable is

55. There is an important question with regard to liability. With so many actors involved in drug testing, if a woman 'subject' from India wants to file for damages and compensation, who should be held liable? Mr Sunil Sehgal, representative of the Upjohn Co. in India stated that in the US generally the cases of liability were settled out-of-court and both the company that sold the drug and the doctor who prescribed were held liable. In India, he felt that liability was not going to be a problem. (Interview with R Anandan and C.Sathyamala, 11.3.94, at Max India office, New Delhi).

56. And yet the 1982 WHO document was entitled "Facts about the Injectable Contraceptives . Memorandum from a WHO meeting".

57. It is technically not correct to call these deaths unrelated to the Injectables. Steroid hormones are known to decrease the immune response of a person and this could have led to the fulmination of the pre-existing tuberculosis. Moreover, the drug literature of Net-en states that interaction between Net-en and Rifampicin ( an anti-tubercular drug) reduce the efficacy. The fourth woman who died of "unknown" causes had the following history: after a two week period of generalised illness, including cough, malaise, fever, she was hospitalised for a day. There were no abnormalities on general physical examination. She became unconscious on the way home and died the following day of undetermined causes. No autopsies were performed on any of these women



registered and can be bought in the open market. This is because of the exorbitant cost of the Injectables. Each dose costs approximately Rs150/- and a woman would require 4 doses in a year. The cost alone would prevent a woman from the poorer sections of the population, at whom it is targeted, from using the Injectable. The Injectables in order to be 'available' to this population will therefore have to be distributed 'free' through the national programme and the Indian government will either accept a loan or grant from one or several of the donors such as the World Bank.<sup>58</sup>

### The Situation Today

Among the several prayers in the PIL filed by Stree Shakti Sangatna and others, was one for a stay on the phase IV part of the trials. The Supreme Court however, refused to grant an ex-parte stay and ICMR<sup>59</sup> went on to complete phase IV with Net-en. Following this, in the absence of any restraint from the Court, on 30.4.86 (23 days after the petition was filed), the Drugs Controller of India gave his approval to German Remedies (the Indian Subsidiary of Schering AG) to market the contraceptive in India.<sup>60</sup> Despite this 'legal' approval, Schering AG and German Remedies however decided against the marketing of Net-en in India although Schering was reported to be distributing it in 34 other countries.

With regard to the use of Net-en in the Family Planning Programme, the ICMR advised the Drugs Controller of India it should not be distributed in the rural set up.<sup>61</sup> The recommendation was that the Injectables should be available only from those urban centres which had adequate medical staff including a woman gynaecologist and the necessary facilities to screen women as well as handle the complications that could occur due to its administration. The Drugs Controller however, withheld his permission for its administration from any of the government health centres, rural or urban, well-equipped or otherwise.

In 1992, internationally, the climate became favourable for the approval of the Injectables for broader use in India. Firstly following the publication of the WHO's multinational study on breast cancer and Depo-Provera, which appeared to disprove any association, the USFDA granted approval for the use of Depo-Provera in the US.<sup>62</sup>

---

58. The UNFPA, the largest supplier of the Injectables provided about 12 million doses in 1992 and 20 million doses in 1994, including shipments from the World Bank. International Planned Parenthood Federation is another donor. (*Supra* note 22). It is not clear how the profits are shared.

59. This refusal to give ex-parte stay was reported by an ICMR representative as "The Supreme Court overruled the request and the ICMR completed the introductory study of Net-en". WHO, "Creating common ground in Asia" Geneva 35 (1994)

60. Although the Supreme Court ordered the inclusion of the Drugs Controller as a respondent in the PIL, the Drugs Controller did not file any response. The Court thus did not have on its record information regarding the registration and the licensing of the Injectable.

61. Personal communication, Dr BN Saxena, ICMR

62. In the context of India, the approval from the USFDA was essential because according to the Drugs and Cosmetics Act 1940, drugs banned from use in the parent country could not be imported into the country. The approval of USFDA was important for the US government also because official aid for the purchase of Depo-Provera through USAID could not be used as it was not permissible legally to promote a drug that was banned in the US.



Secondly, according to the Drugs Controller of India, India having accepted the package of liberalisation had to loosen its various controls on the market and one of them related to the marketing of pharmaceuticals in the country without their having to go through the mandatory trials in the country.<sup>63</sup> Thus, it came about that in 1992/93, the Drugs Controller allowed the registration and sale of Depo-Provera in India. It is to be noted that Depo-Provera has not gone through the mandatory clinical trials in the country. Instead, the companies have been asked to carry out post-marketing surveillance of the Injectables with the help of the doctors from the private sector. Today they are both available as 'approved' drugs for the contraceptive use of Indian women.

However, the availability of the Injectables in the open market has in no way changed or modified the contentions in the PIL that was filed against them thirteen years ago. The fact that German Remedies considered it ill-advised to market their injectable Net-en for eight years despite grant of approval from the Drugs Controller was largely due to these same contentions<sup>64</sup>. Further, the current approval is limited to its distribution through the private sector and the Ministry of Health and Family Welfare has not included either of the injectable contraceptives in its national family planning programme.<sup>65</sup> This only goes to show indirectly the reluctance of the concerned authorities to open themselves to attacks that they know are difficult to defend.

In the contraceptive scene other developments have taken place. With no deterrence constraining them, the ICMR went on to test newer, even more long-acting and even more dangerous contraceptives such as sub-dermal implants<sup>66</sup> Norplant(2) on 1925 women from 15 centres in India, again, with no informed consent. In 1989, this trial was prematurely terminated because the product was withdrawn from the International market because of the possibility of teratogenic effect of the elastomer contained in it. On the advice of the WHO and the Population Council, the ICMR then proceeded to replace Norplant(2) by another sub-dermal implant, Norplant®, and carry on phase IV without the mandatory phase III. While the substitution of phase IV in the place of phase III was against the Drugs and Cosmetics Act 1940 the ICMR was more concerned about opposition from the women's groups. In December 1991, the ICMR called a meeting of what they termed "Women's Health Advocates"<sup>67</sup> to gain consensus and approval of women representing the NGO sector for the substitution of the trials. Representative of the women's group raised serious objections to such moves.

63. Interview of Dr P Dasgupta, the then Drugs Controller of India, by Rukmani Anandani and C Sathyamala, on 11.4.94. *Medico Friend Circle Bulletin* 12 (Jan 1995).

64. German Remedies marketed Net-en in India in April 94, although they had registered it in 1986.

65. According to the Drugs Controller, he was waiting for "acceptability" studies to be completed. These studies have been completed by ICMR but the Injectables have still not been let loose on the Indian women.

66. The Norplant system consists of 2 silastic rods which contains the contraceptive chemical levonorgestrel, a synthetic progesterone. The rods are inserted under the skin through an incision. They continue to release the chemical as long as they are under the skin. This system was supposed to be effective for three years. In 1991, Norplant2 was replaced by Norplant ® which consists of six rods to be kept in the body for five years. The system was developed by the ICCR of the Population Council, Registered under the Population Council Trade Mark, manufactured under licence from the Population Council by Huhtamaki Oy/Leiras Pharmaceuticals, Finland. In 1985, the UNFPA requested the WHO to evaluate proposal for the introduction of the contraceptive into the family planning programme.

67. The attempts to get consensus (or coopt women) on contraceptive testing and introduction is a new trend. WHO has also called several meetings to get the support of the women for their trials.



It became clear that the ICMR was once again repeating past mistakes. The ICMR's own published report had shown that the contraceptive Norplant was hazardous to women. Among the women who were recruited for the phase III trial with this contraceptive 9 women developed serious, some of them life-threatening, complications.<sup>68</sup> 12% of the women in the study were "lost-to-follow-up" i.e., they could not be contacted after the device was put under their skin. This was a gross medical hazard because these women will continue to harbour within them the contraceptive chemical till the sub-dermal rods are removed from the body.

Today, there are several other institutions in the country, both governmental and non-governmental, which are carrying out covertly and not-so covertly, experimentation with contraceptive drugs on both male and female citizens of the country without the constraint of informed consent.<sup>69</sup>

### Concluding Remarks

While it is true that the organisations representing women and other ethical scientists, medical professionals have not been successful in getting the scientific bodies to stop unethical trials, or monitor such trials, or prevent the availability of hazardous contraceptives in the 'free' market, they have been quite successful in preventing their entry into the Family Planning Programme. Seeing the strength of these organised response, the state is now moving towards the privatisation of contraceptive research. There is also an attempt to reduce the mandatory steps of clinical trials by substituting post-marketing surveillance for phase III trials. This is in order to do away with the need for an approved protocol or informed consent necessary for the trial.

Till the seventies, contraceptive drugs and devices formed a lucrative market for pharmaceutical companies. While in the West, the Pill (oral contraceptives) enabled women to make real choices about their lives, today in the third world countries, provider-controlled contraceptives are being used as tools of control for subjugating women, the 'visible' cause of population explosion. It is not surprising then that the opposition to this oppressive medical technology has also come from the women themselves. Introduction of long-acting, invasive, hazardous contraceptives have been opposed by feminists, consumer and health groups alike. Keeping pace with this growing dissent, the promoters of the hazardous contraceptives have also changed their strategies. There

---

68. One woman developed deep vein thrombosis; one, sub-endocardial infarction; one, thyrotoxicosis, and one, depression. In five women there was mild dysplasia of the cervix (pre-cancerous condition). In one woman the rod broke. The study was funded by Population Council (free Norplant and travel grant). No informed consent was taken from the women who participated in the trial. We do not know what happened to the women who developed complications or the other women in the study who should have been followed up for a longer time even after the period of study was over. In this study, the women who were 'lost to follow up' is a group for special concern. These women numbering over 300 will continue to carry in their bodies the implants with the contraceptive drug in it thereby subjecting them to the risk of ectopic pregnancy. Without any follow-up, the fate of these women is unknown. Ethical concerns should have made the ICMR try its utmost to trace these women and get their rods removed.

69. These are the anti-fertility vaccines, vaginal hormonal rings, nasal sprays, abortifacients like the RU 486, hormonal nasal sprays etc.



are now attempts to do away with the 'problematic' toxicological studies on animals and test directly on women. Attempts are on to substitute post-marketing surveillance (an impossibility in countries like India ) for phase III clinical studies. And there are attempts to privatise contraceptive research using non-governmental organisations.

The most serious development today is that we have the scientific bodies lending their 'neutral' faces to mask the real intents of eugenics and profit motives behind the promotion of hazardous contraceptives. It is time that we begin to treat them on par with the pharmaceutical companies. They should be made responsible for the violations of human rights of the women on whom clinical trials were carried out and made liable for the damages they have suffered. Only then will they realise that women from third world countries are not toxicological models for contraceptive testing.

**Table I****History of Net-en**

- 1953      Injectable progestins developed.
- 1958      Net-en synthesised by the West German Firm Schering AG.
- 1963-65   Field trials.
- 1967      Marketed in Peru.
- 1971      Withdrawn from the market because of pituitary and liver nodules in rats 7 year Beagle dog study and 5 year monkey study initiated.
- 1977      Multi-centric phase III clinical trials under the aegis of the WHO (two of the centres were from India).
- 1981-83   Indian Council of Medical Research (ICMR) carries out phase III clinical trials on approximately 2,400 Indian women.
- 1982      Unconditional approval from the Toxicology Review panel of the WHO.
- 1983      West Germany, the country of Schering AG gives unconditional approval.
- 1984      West Germany revises its approval and terms the contraceptive "Second rate".
- 1983-84   ICMR proceeds with phase IV clinical trials on Indian women.
- 1984      Members of Hyderabad based women's group, Stree Shakti Sangatna observe the unethical manner in which phase IV trials are being conducted in the rural Primary Health Centre at Pattencheru.
- 1985      Members of Stree Shakti Sangatna communicate in writing to the Drugs Controller of India and the Ministry of Health and Family Welfare about the unethical manner of conducting phase IV trials and urge them to withdraw the injectable because of its known hazardous nature.
- 07.4.86   Writ petition filed in the Supreme Court by three women's groups (Stree Shakti Sangatna, Saheli and Chingari) and several individuals against the testing and introduction of Net-en into the National Family Planning Programme.

**Respondents:**

- The Health and Family Welfare Ministry, The Drugs Controller, ICMR and the State of Andhra Pradesh.
  - 30.4.86   Drug Controller gives approval to German Remedies (Indian Subsidiary to Schering) to market Net-en in India. German Remedies decide not to market Net-en in India.
  - 1987      Through an extraordinary gazette notification, the Drugs Controller of India communicates the formulation of Rules and Regulation for testing Drugs in India (later incorporated as Schedule 'Y' in the Drugs and Cosmetics Act in Sept 1988).
  - 1994      German Remedies decides to market Net-en in India.
- Current status of the PIL: Still pending in the Supreme Court.



**Table II****History of Depo-provera**

1950s	Upjohn, the American company develops Depo-Provera.
1960	USFDA gives approval for the use of the drug in treating endometriosis and in preventing abortions.
1963	Clinical trials to test Depo-Provera as a contraceptive.
1964	Field trials by Upjohn in 70 countries.
1967	Upjohn applies (New Drug Application) to the USFDA for use of Depo-Provera as a contraceptive drug Depo-Provera used in Thailand as an approved contraceptive.
1971	Upjohn Company withdraws Depo-Provera for use to prevent abortions. This is because of reported birth defects with the drug.
1972	USFDA Advisory Committee approves use of Depo-Provera as a contraceptive.
1975	ICMR reports the discontinuation of clinical trials in India because of heavy and prolonged bleeding in women. Beagle dogs and rhesus monkey studies raise the question of cancer.
1978	USFDA withholds approval because of the drug's potential to cause Upjohn Company requests for a public hearing to review the drug's status.
1982	The Toxicology Review Panel of the WHO gives unconditional approval.
1983	Public Board of Inquiry is constituted in the US.
1984	Public Board of Inquiry refuses to grant approval.
1985	Upjohn Company withdraws its NDA in the US. Upjohn however sells the drug as a contraceptive in other countries.
1991	The WHO publishes the multi national study on Depo-Provera and breast cancer. USFDA requests Upjohn Co to submit fresh NDA.
1992	USFDA grants approval to Upjohn to market Depo-Provera as a contraceptive.
1993	The Drugs Controller of India gives "No Objection " certificate to Max-Pharma to market Depo-Provera in India and to carry out post-marketing surveillance.

**Current situation in India:**

Depo-Provera for the use of contraceptive is available freely in the market and can be bought over-the-counter. The contraceptive is being prescribed by private practitioners and non-governmental organisations such as Marie-Stoppes' clinic. The contraceptive is not being distributed through the Family Planning Programme.

**Table III****Findings of Animal Toxicology studies with Net-en**

Rats	Breast tumors, pituitary tumors, and benign and malignant liver tumors.
Beagles	Benign and malignant breast tumors.
Monkeys	Breast nodules and endometrial (lining of the uterus) tumors.

**Table IV****Animal Toxicology Studies Pre-clinical Requirements USFDA***Contraceptives*

\* 90 day studies in  
rats, dogs, monkeys  
must be completed

*Other drugs*

2 to 4 week studies in  
2 animal species

*Phase I clinical trials on in 10 to 20 human subjects for upto 10 days*

\* One year studies in  
rats, dogs, monkeys  
must be completed.

90 days studies in.  
2 animal species.

*Phase II clinical trial in 50 women for 3 menstrual cycles*

\* Two year studies in rats, dogs,  
monkeys must be completed.

No requirements.

\* Seven year studies in dogs,  
monkeys to be initiated .

*Phase III clinical trials on a large number of individuals*

Progress reports on long term  
studies in dogs, and monkeys  
required.

Chronic toxicity studies of  
one year dog,  
18 months mouse and  
two year rat to be completed.

New Drug Application for approval.