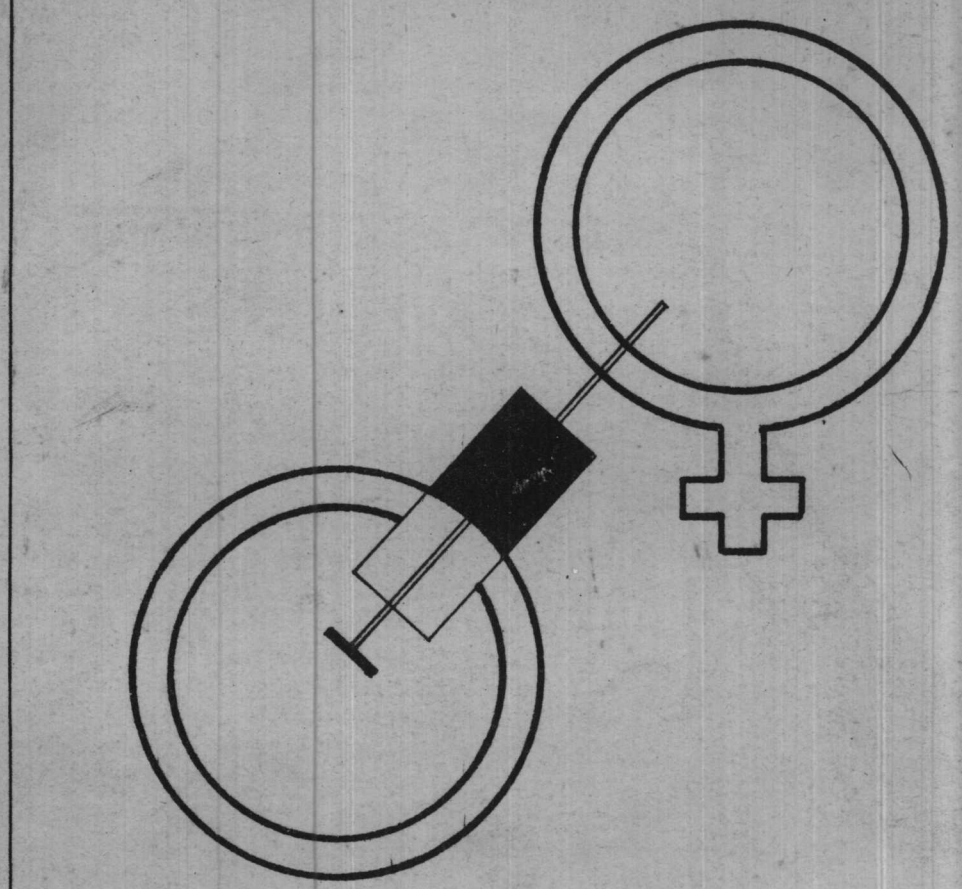

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NET-EN

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by Dr. Mira Savara

Updated, Revised & Edited by

Gouri Dange
John D'Souza
Nita Thomas

Centre for Education & Documentation

Composed & printed at M/s Off-Set, 16 Chitra, Nava Shrinagar, P.L.Lokhande Marg, Chembur, Bombay 89

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INTRODUCTION

Injectable hormonal contraceptives were conceived of as a long-acting and fail-safe method of contraception. Today, as nearly 1.5 million people in 80 countries use injectables, the drug has become an issue of international concern and interest. Its possible side-effects and the many contraindications and cautionary measures needed prior to its use, have led women's groups and health organizations to campaign against its widespread use.

Despite this the National Family Planning Programme in India may soon be using the injectable contraceptive NET-EN. The Indian Council of Medical Research in collaboration with the Ministry of Health has already introduced NET-EN in 40 post partum centres in India, as part of the Phase IV testing of the drug. Phase IV trials are used basically to test the feasibility of the drug under normal family planning programme conditions. This means that these injectable has already been medically cleared.

Considering the volume and extent of the FP Programme in India, several thousands of women from remote, backward areas will become victims of a drug that could change their reproductive cycle and with it affect the life and health of future generations.

In view of this, it becomes necessary to collate all relevant information regarding NET-EN, the issues arising from it, its social and medical significance, and, most important, its degree of safety.

In the chapter "What is NET-EN", we have included several boxes of the relationship between hormones and the menstrual cycle. Though these are not part of the main text on NET-EN and need not be read by the informed women, we have included them to restate the basic framework on which hormonal contraception rests.

We then discuss "development of injectables & origins of the controversy (Chapter III) before going on to summarise the known clinical facts about NET-EN vis-a-vis safety.

The test results of NET-EN in India are discussed in Chapter IV. Apart from confirming some of the doubts about safety, the trials in India raise serious questions about the testing procedures itself (see section "Comments on Testing"). All these point to the problems inherent in the introduction of an "easy to administer" and "long acting" drug on a mass scale in a country like India (Chapter V).

There is a special need for vigilance in the case of hormonal contraceptives since they affect the reproductive cycle of women and also potentially affect the health of future generations. It is essential to keep in mind that we are differentiating between hormonal contraceptions and other drugs used to cure diseases and illness. Contraceptive drugs are given to healthy women; they cause alterations in the reproductive cycle, and remain in the body not for a limited period, but for months.

I. WHAT IS NET-EN?

NET-EN (Norethindrone enanthate) is a progestin derived from testosterone, belong to the C-18 group of steroids. It is administered through an intramuscular injection in an oily solution. Once injected, NET-EN must be converted into norethindrone (NET) in the body before it can become biologically active. For this, hydrolysation must take place to release the active steroids. The concentration of NET-EN increases and decreases quite rapidly and it is usually untraceable after about 70 days following the injection.

However, the factors governing the rate of metabolism of NET-EN have not been clearly understood yet because women from different ethnic groups metabolise the drug at significantly different rates.

Injecting NET-EN requires a considerable degree of clinical skill. If the full prescribed quantity of the drug is not drawn into the syringe, the dosage may be inadequate. As NET-EN is in a viscous oily solution before being injected it is difficult to pour into a syringe; so, warming the vial helps. If the drug is not injected deep into the muscle, or, if the injection site is massaged, the drug's disbursion may be accelerated and its period of effectiveness shortlived.

It is presumed that NET-EN prevents pregnancy because:

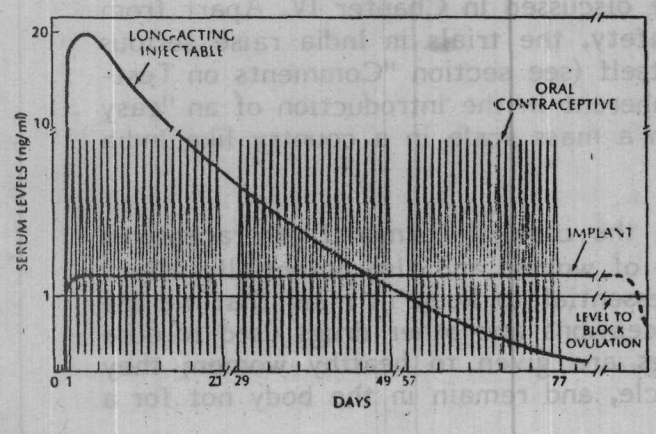
1) it inhibits gonadoptropin production in the pituitary gland, which, in turn, prevents ovulation.

2) it makes the cervical mucus thick and scant thus creating a barrier for the sperm

3) it makes the endometrium less suitable for implanting a fertilized ovum

4) it changes the rate of ovum transport to the oviduct.

Blood Serum Levels of Hormone in Users of Three Contraceptive Methods



Schematic representation of the levels of hormone in blood serum illustrates the differences among injectables, implants, and daily oral contraceptives. Just after an injection, the serum level rises quickly. Then it drops gradually as time passes. An implant releases hormone at a roughly constant rate, so serum levels remain constant. By contrast, oral preparations must be taken daily because the hormones are quickly metabolized. As a result, the serum level fluctuates each day.
(Courtesy of Henry Gabeinick)

II. THE DEVELOPMENT OF INJECTABLES AND ORIGINS OF THE CONTROVERSY[1]

History of Hormonal Contraception

One goal of contraceptive research has been to develop an effective, long-acting method that does not require action on a daily basis or at each act of coitus, yet is easily reversible. Voluntary sterilization provides long-term protection against pregnancy but it is not generally reversible. IUDs provide long-term protection and reversibility but are not suitable for all women. Female hormones offer another possibility for long-acting reversible protection against pregnancy, but the search for long acting hormonal method free from any suspicion of serious side-effects has proved a difficult one.

The first hormonal contraceptives, developed in the mid-1950s, were short-acting progestins administered orally. Although these progestins effectively prevented pregnancy by suppressing ovulation, they caused irregular menstrual bleeding. It was soon discovered that estrogen, present in the progestin as an impurity of the manufacturing process, could reduce menstrual disruption. Therefore estrogen was deliberately added to the progestin. The result was the combined estrogen-progestin pill, the first marketed hormonal contraceptive. Later, in the late 1960s low-dose, daily progestin - only pills - the minipills - were introduced.

The first injectable progestins were developed in 1953. In 1957 Karl Junkmann and his associates at Schering AG in Berlin synthesized long-acting injectable esters of the progestin norethindrone (also known as norethisterone including norethindrone enanthate (NET-EN). At about the same time the Upjohn Company in the U.S. developed medroxyprogestrone acetate in its depot or injectable form (DMPA) and gave it the trade name Depo-Provera.

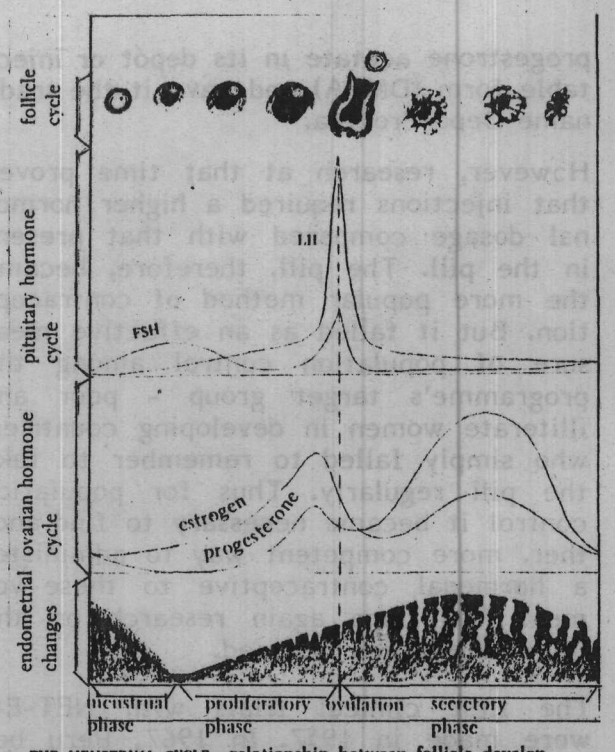
However, research at that time proved that injections required a higher hormonal dosage compared with that present in the pill. The pill, therefore, became the more popular method of contraception. But it failed as an effective measure of population control among the programme's target group - poor and illiterate women in developing countries, who simply failed to remember to take the pill regularly. Thus for population control it became necessary to find another, more competent way to administer a hormonal contraceptive to these women. And once again research on the injectable option resumed.

The first clinical trials with NET-EN were made in 1957. In 1967, Peru became the first country to register and market NET-EN. It was followed by Chile, Brazil and Argentina. **However, four years later, the drug was withdrawn from the market after pituitary and breast nodules were found in rats injected with Norigest in experiments for testing NET-EN.** Ironically, investigation reports concluded that findings in rats were not applicable to humans and after further clinical testing the drug was reintroduced.

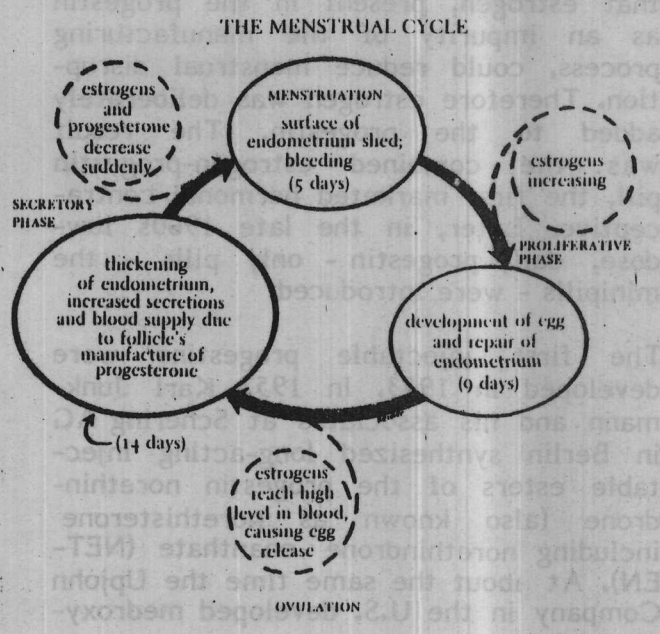
NET-EN is marketed commercially as Norigest, but the trade name Noristerat is used for distributing it through international donor agencies.

The Controversy

Meanwhile Depo-Provera (DMPA) a similar injectable contraceptive became the subject of a major controversy. By 1970, studies on progestins -- DMPA included -



THE MENSTRUAL CYCLE—relationship between follicle development, hormone cycles, and endometrial (uterine lining) buildup and disintegration. The cervical mucus gets progressively wetter from the menstrual phase to ovulation, then becomes drier during the secretory phase. *Peggy Clark*



Source: Our Bodies, Ourselves - Boston Women's Health Collective

Hormones of the Menstrual Cycle

During the reproductive period of a woman's life, low levels of all the sex hormones are being continuously produced. In addition to these base levels there are fluctuations which establish the menstrual cycle. The main organs in the cycle are the hypothalamus (a part of the brain) and the pituitary and the ovaries (both glands). The hypothalamus signals the pituitary, which then signals the ovaries, which in turn signal the hypothalamus. The signalling is done by hormones secreted by the different organs and carried from one part of the body to another through the blood.

The hypothalamus is sensitive to the fluctuating levels of hormones produced by the ovaries. When the level of estrogen drops below a certain level the hypothalamus releases FSH-RF — follicle-stimulating-hormone-releasing factor. This stimulates the pituitary to release FSH - follicle-stimulating hormone. This triggers off the growth of 10 to 20 of the ovarian follicles. Only one of these matures fully; the others start to degenerate sometime before ovulation. These are called atretic.

As the follicles grow they secrete estrogen in increasing amounts. The estrogen affects the lining of the uterus, signalling it to grow, or proliferate (proliferatory phase). When an egg approaches maturity inside the follicle that will develop fully, the follicle secretes a burst of progesterone in addition to the estrogen. This combination of progesterone and estrogen probably triggers off the secretion of FSH-RF and LH-RF, luteinizing-hormone-releasing factor by the hypothalamus. These releasing factors signal the pituitary to simultaneously secrete FSH and LH, luteinizing hormone. The FSH-LH peak probably signals the follicle to release the egg (ovulation). Under the influence of LH the follicle changes its function. Now called a corpus luteum, the follicle secretes decreasing amounts of estrogen and increasing amounts of progesterone. The progesterone influences the estrogen-primed uterine lining to secrete fluids nourishing to the egg if it is fertilized (secretory phase). Immediately after the peak that triggers ovulation. FSH returns to a base-line level. LH declines more gradually as the progesterone increases. If the egg is fertilized the corpus luteum continues to secrete estrogen and progesterone to maintain the pregnancy. However, the corpus luteum is stimulated to do this by HCG, human chrorionic gonadotropin, a hormone which is secreted by the developing placenta. HCG so far appears to be chemically identical to LH, so it's not surprising that it has the same functions.

If the egg is not fertilized, the corpus luteum degenerates until it becomes non-functional. This is called a corpus albicans. As the degeneration occurs, the levels of hormones from the corpus luteum decline. The declining levels fail to maintain the uterine lining, which leads to menstruation. When the level of estrogen reaches a low enough point, the hypothalamus release FSH-RF and the cycle strats again.

(Taken from: **Our Bodies, Ourselves**, Boston Women's Health Collective)

began to reveal startling facts. Research showed that some progestins caused breast nodules in beagles and the opinion against injectable progestins gathered strength.

In 1978, the USFDA (The U.S. Food and Drug Administration) formally **denied** approval of DMPA for use in U.S.A. because:

1) the questions raised by the development of breast nodules in beagles were still unresolved
2) there was the potential risk of birth defects in case of contraceptive failure
3) a significant need for DMPA for U.S.A. had not been conclusively demonstrated

Inspite of the popular national consensus against the use and sale of DMPA as a contraceptive in U.S.A., Upjohn was granted permission by the USFDA to export the drug. Today, DMPA can be found in active use in 80 countries around the world.

This double standard exhibited by U.S.A. drew the attention of health, consumer and women's groups from all over the world and there is, today, an international movement, 'Ban the Jab', against Depo Provera.

Despite this, use and sale of injectable contraceptives is on the rise. Between 1978-81, Upjohn sold about 7 million doses of DMPA and by 1982 million doses reached roughly 2 million women.

A significant portion of injectables has been supplied by various family planning government organizations, primarily in Asia. In 1983, NET-EN sales received new impetus when the International Planned Parenthood Federation (IPPF), which had previously supplied only DMPA, began to distribute NET-EN as well.

In U.S.A., NET-EN is neither registered nor permitted to enter the market; but recently, in the wake of toxicology test results in animals, the USFDA has approved a programme of clinical trials on women.

By 1983 only 4 developed countries had licenses to use NET-EN and that too only for a very limited group. The major market for the drug remains 'developing countries'. And, international agencies who believe that 'overpopulation' in the Third World must be controlled by whatever means available are the drug's major suppliers.

Mangal

Countries where NET-EN is available

Australia	Central Africa	Philippines
Bahamas	Germany (Federal Republic)	Sierra Leone
Barbados	Gautemala	Singapore
Belize	Haiti	South Africa
Bermuda	Indonesia	Surinam
Central America	Kenya	Thailand
Curacao	Liberia	Trinidad
Denmark	Pakistan	Zaire
France	Peru	Zambia

(Information from IPPF, 1983)

Table

Deliveries of Injectable Contraceptives

(in thousands of doses)

Year	Africa	Asia	Europe	Latin America	Middle East & N. Africa
1975-78	402.0	2599.5	-	422.4	68.5
1979	334.2	1757.4	29.1	539.7	12.0
1980	133.1	1429.7	3.1	56.9	15.0
1981	212.3	1583.3	3.3	116.1	18.0
1982	264.0	315.3	-	56.8	14.8
1975-82	1345.7	7685.4	35.5	1191.8	128.3

Source: Population Reports: Long Acting Progestins - Promise and Prospects, Series K, 2 May, 1983

III. EFFECTS OF NET-EN AND SAFETY

Animal Studies

One of the most significant questions that arise about the use of the drug is whether long-acting progestins in the system increase the risk of cancer. Certain laboratory tests on animals have shown that these animals developed more tumours in the uterus and breast **after** they were injected with progestin, as compared with those animals in the control group (not injected with progestin). Some tumours were found to be malignant.

The following is an extract from "Facts about injectable contraceptives: Memorandum from a WHO meeting, Bulletin of the WHO [60(2) pg.202, 1982]

Rodent Studies:
As part of routine toxicological testing, several hundred mice and rats were given NET-EN, **there was a drug-related increase in the incidence of tumours,** similar to that seen in studies where rodents were given other progestogens. Unlike DMPA, **NET-EN shows estrogenic activity in rodents, and breast tumours and eye changes attributable to this were found in the rats.** Neither the progestogenic effects observed nor the changes due to estrogenic activity were considered to have toxicological significance.

Beagle Studies:
A 7-year beagle study was begun in 1975 with 4 groups of 24 animals: a control group which received no drug, a group receiving the equivalent of the human dose, a group receiving 10 times the human dose, and a group receiving 50 times the human dose.

At 6-1/2 years, **more bitches in the medium and high dose groups had died than in the control and low dose groups.** However, the only deaths attributable to effects of the drug were due to complications of progestogen-induced diabetes mellitus among animals in the medium and high dose groups. As a result, the FDA requested that insulin treatment be given to some animals. Diabetes mellitus was not found in the bitches receiving the equivalent of the human dose. The development of the disease in some of the animals receiving the higher doses of NET-EN indicates a need for further research on the effects of NET-EN on carbohydrate metabolism.

It should be reiterated that the beagle is considered by the Toxicology Review Panel to be an unsuitable toxicological model for the study of progestogens.

Monkey Studies:
A 10-year study in sexually mature female rhesus monkeys was also begun in 1975. In addition to a control group of 24 monkeys who received no drug, there was low-dose, medium-dose and high-dose groups, each containing 24 animals, who received dosages of NET-EN equivalent to those used in the beagle study.

During the **first 5 years of the study, more monkeys in the control group died than in any of the treated groups.** Many of the deaths were attributed to pre-existing disease or aging. In addition to these spontaneous deaths, 31 monkeys were sacrificed at scheduled intervals. Except

for an endometrial carcinoma in one monkey, all findings were compatible with those expected after administration of any progestogen. Endometrial carcinoma has not been reported among women using NET-EN; in fact, progestogens are given as treatment for endometrial carcinoma in considerably higher doses than those used for contraception. However, it is important to look carefully for the development of neoplasis in monkeys and other animals given dosages close to human dose.

The Toxicology Review Panel concluded by endorsing their previous statement and recommended that current and planned studies of norethisterone enanthate could continue, and that it could be introduced into family planning programmes.

All the collated data so far has led to a fair amount of controversy. While WHO cleared NET-EN arguing that the results were not applicable to humans, opinions differ.

USFDA officials defend the agencies' general reliance on animal studies with the rationale that while evidence of tumorigenic effects in animals does not mean that the drug will cause tumours in humans, evidence that is **not** tumorigenic in animals allows a drug to be marketed with a 'certain measure of assurance of its safety for human use.

The very fact that tumours were found in all the species of the animals tested with different types of progestins (Depo, NET and the Pill), should make us, if anything, more cautious when analysing such animal test data because it points very definitely to a high-probability progestine-related risk of tumours and cancer.

The WHO report points out that **"No studies exist on the risk of cancer in humans using NET-EN. And studies are only now being undertaken on the potential long-term effects of NET-EN."**[2]

The uncertainty about whether or not the tumours, found in the animals' tests will show up on humans, will only be settled by long-term studies on humans themselves. But by then, the damage would already have been done.

The question therefore is, in view of the tentative unsure conclusion, is it ethical to continue with mass scale testing? Can the international voluntary agencies ethically justify their indiscriminate distribution of injectables on the negative statement that the "tumorigenic effects in animals is not relevant to humans?" Besides, since opinion on the relevance of animals tests are divided, shouldn't more caution be exercised about its use? Isn't it irresponsible that in the face of such divided opinion the drug is still deemed 'totally safe' and reaches millions of women?

The fact that NET-EN was registered for sale in several countries and subsequently withdrawn because of the tumour findings, also raises a disquietining question: was the drug allowed to be marked **before** the animal tests' findings were known? Or, the even more disturbing question: was the drug allowed to be marketed **despite** the animal tests' findings which happened to be made public later on?

Clinical Trials : Bleeding Patterns & Side Effects

The WHO multinational clinical trials, the largest undertaken so far on injectable contraceptive, indicate side effects like bleeding, change in blood pressure

and body weight, abdominal discomfort, anxiety, depression, fatigue, dizziness, headaches, etc.

The report[3] reveals that -

a) After the second injection, **32-34% of the women had no bleeding for 45-90 days**

b) **7% had no bleeding at all during the entire 3-month period**

c) **Only 15% had normal periods** - a normal period being defined as a cycle of 26-35 days with bleeding/spotting which lasted 2-8 days

d) For those women who did not previously menstruate, the average number of days of bleeding/spotting in the 3-month period was 6.4-6.7 days

d) The average number of days of bleeding/spotting for those who did previously menstruate was 2.6-3.2 days.

Table

Cumulative life table discontinuation rates

	NET (60 days)[a]		NET (84 days)[b]	
	Duration of use		Duration of use	
	12 months	24 months	12 months	24 months
Accidental Pregnancy	0.4	0.4	0.6	1.4
Amenorhea	6.8	14.7	8.4	14.6
Bleeding Problems	13.6	18.4	13.7	21.8
Other medical reasons	9.3	16.0	9.9	16.7
Personal reasons	24.5	42.6	22.8	40.2
Total discontinuation	49.7	70.7	50.3	72.8

[a]200 mg NET 60 days : Injection given every 60 days for 2 days

[b]NET 84 days : Injection given at 60 days for 6 months, thereafter every 84 days

Centres : Egypt, Thailand, Nigeria, Pakistan, Zambia, Philippines, Mexico, Brazil, Chile, Yugoslavia, Luxembourg, Italy, Netherlands

Sample : A total of 1587 women, 1377 from the developing countries, 210 from the developed.

WHO Multinational Comparative clinical trial of long acting injectable contraceptives: NET-EN given in two dosages Regimes and DMPA - Final report, Contraception, July 1983, Vol. 28, No. 1).

NET-EN users experienced a shift from relatively short 'cycles' during the first injection intervals to longer 'cycles' - of more than 45 days - during the third injection period (3 months).

The WHO study concluded: "If a normal cycle is narrowly defined as a cycle of 26-35 days' duration and two to eight days' bleeding, **then 47% of NET-EN users did not experience even one such normal cycle.** Furthermore, among those women who had one or more 'normal cycles', only a small minority had a consistent pattern. Thus the overwhelming majority of women experienced some abnormality in their bleeding pattern whilst using these drugs."

Women tended to have more than the normally expected blood loss during each episode i.e. though the number of days of the periods were fewer, the blood loss exceeded that lost during a normal period. Another study found that **approximately 3% of the women had bleeding episodes of over 21 days.**

Attempts to prevent menstrual irregularities caused by the injections have proved successful. If the bleeding does not stop within 24 hours, a dilation and currettage is usually resorted to. Estrogens were also often used in pills and injections, but with their connection to incidents of clotting and other side effects, only progestin-based contraceptives are in use currently.

Table[4]

Duration of Bleeding/Spotting Episodes & Standard Errors

Period of	Duration of Episodes of bleeding and/or spotting			
	NET-EN 60 days		NET-EN 84 days	
	Mean no. Days ± SE	Percentage of women with episodes of 21 days	Mean no. Days ± SE	Percentage of women with episodes of 21 days
0 - 6 months	6.9*** (±0.2)	4.1%	7.2 (±0.2)	4.4%
7 - 12 months	6.1 (±0.2)	2.4%	6.2 (±0.2)	3.3%
13 - 18 months	5.4 (±0.3)	1.8%	6.1*** (±0.2)	4.1%
19 - 24 months	4.7 (±0.2)	0.9%	6.6+++ (±0.5)	3.5%

** Significant difference relative to DMPA $p < 0.1$
*** Significant difference relative to DMPA $p < 0.001$
+++ Significant difference relative to NET-EN (60 days) $p < 0.001$

Table[4]

Period of observation	Percentage of Women with Amennorrhoea for more than 90 days' duration			
	NET-EN (60 days)		NET-EN (84 days)	
	No. of subjects*	Percentage	No. of subjects*	Percentage
0 - 6 months	645	14.0	652	12.7
6 - 12 months	453	27.4	453	30.9
12 - 18 months	328	33.5	317	28.7
18 - 24 months	241	40.7++	245	24.5

++ Significant difference relative to NET-EN (85 days) $p < 0.001$
* The number of women commencing each interval with complete menstrual diary and data for 90 days or more during each 6 month period.

The most common side effect and the main reason for discontinuation of NET-EN are disturbances in the menstrual cycle. A WHO study notes that "approximately one-half of the users report at least one normal cycle during the first year." In other words, approximately one half of the women do not have even one normal menstrual cycle during the first year.

The irregularities take two forms: either frequent bleeding or spotting; or an absence of bleeding (amenorrhoea). WHO notes that amenorrhoea or frequent bleeding, providing it is not heavy, are not likely to pose any health problems for women. Nonetheless, a woman who finds the disruption in the menstrual cycle intolerable in terms of her social or cultural environment, has little choice but to live with it: for once the injection is given, she will have to wait until the effect wears off.

Data on Indian Woman

- Two women were administered 200 mg NET-EN for a period of 56 days. In one, there was an immediate change in menstrual pattern and **the excessive bleeding could be controlled only by dilation and curettage.** The second woman **suffered prolonged bleeding** after the third injection.[5]

- In Delhi, **four out of six women injected with NET-EN suffered bleeding episodes of over 10 days.**[6]

- NET-EN (50 mg) and Oestradiol Valerate (5 mg) was injected once a month, in an effort to develop an injectable that would induce bleeding. In the three-month treatment period, 14 out of 15 women had evolved a regular pattern, **but 33% suffered continued and profuse bleeding in the 5th and 6th cycles.**[7]

- Seven women administered 20 mg of NET. One had **menstrual bleeding right through the cycle.**[8]
- Of 203 women tested on 20 mg of NET, 40% noted alterations in their menstrual cycles; 14.6% had intermenstrual spotting; and 4.6% suffered profuse bleeding.[9]
- For 50 women given monthly injections of 200 mg in three series, withdrawal bleeding in the first month was regular, but in 90% of the cases, irregular bleeding marked the second and third months.[10]

In the 1977 WHO multicentre trials, **52.5% of the women given NET-EN in Chandigarh dropped out of the programme because of bleeding irregularities.** This percentage was significantly different from that at any other centre.

On this the WHO report only says: "There was a typically high discontinuation rate for menstrual abnormalities in Chandigarh. The results from this centre was so different from all other centres, and had such a profound effect on the analysis of pooled data that a recalculation of the life tables including Chandigarh was considered necessary."

The report, however, does not question the extremely significant percentage of discontinuation at Chandigarh. It could, perhaps, be explained in terms of cultural ethos. In several communities in India, a menstruating woman is considered impure and contact with her is restricted. Consequently her work pattern changes. So the question now is whether an indiscriminate bleeding pattern could lead to hitherto unforseen social problems, especially for women in traditionally conservative rural areas?

Other Side Effects

Other side effects reported include headache, weight gain, dizziness and abdominal discomfort.

It is worth nothing that large numbers of women, approximately 50 per 100 discontinued using either DMPA or NET-EN within one year, according to the WHO study. WHO notes that these discontinuation rates are comparable to those reported for oral contraceptives in similar clinical trial settings, but notes that the pregnancy rates for injectables are generally lower than with oral contraceptives.

Table[4]

Selected Medical reasons for discontinuation by women in the WHO trial over two year observation

Medical Reasons	NET-EN (60 days)		NET-EN (84 days)	
	No.	Rate/100 woman-year	No.	Rate/100 woman-year
Abdominal distention or discomfort	5	0.6	3	0.3**
Weight gain	14	1.6	7	0.8**
Anxiety/depression	8	0.9	3	0.3
Fatigue	8	0.9	8	0.9
Dizziness	14	1.6	13	1.5
Headaches	17	2.0	18	2.1
Decreased libido	5	0.6	5	0.6
Hypertension	6	0.7	7	0.8
Total	77		64	

** Significant difference relative to DMPA P<.01.

Progestins have been associated with changes in many body functions and organs, but given the many processes of the human system which are still a mystery, it is unlikely that all of these changes or effects will ever be found or completely understood. A few effects which are of great concern remain, and they are:

- NET-EN has been associated with the decrease of high-density cholestrol which, in turn, **increases the risk of cardiovascular diseases.**[11]

- Following an injection of NET-EN, the serum zinc level in the system decreases significantly. As zinc is an essential component of blood platelets, a reduction in the zinc level could mean abnormalities of the blood platelets - a symptom common to Pill users. Researchers conclude that "It is assumed that **any contraceptive drug decreasing the serum content of zinc represents a potential risk to users."**[12]

- NET-EN reduces prothrombin activity (prothrombin is a substance present in the plasma and is essential for the clotting of blood). There is also a suspicion that NET-EN affects the hepatocellular function of the liver. This means that women suffering from jaundice or other liver ailments may not use the injection.[13]

The effect of NET-EN on lactation:

"In women who are breastfeeding their infants, it is not yet advisable to use NET-EN because there is little information on its effects during lactation".
(WHO, Injectable Hormonal Contraceptive, 1982)

"Progestins do pass into breast milk and are consumed by the infant. Whether the infant will suffer any long term ill-effects is unknown."

- Population reports

One study showed that seven days after an injection, the daily intake of NET-EN in 600 ml of breast milk ranged between 0.5-2.4 mg of NET (one millionth of a gram). Eight weeks later, when it was time for the next dose, 20% of the women had a detectable level of NET-EN in their breast milk.[14]

In India, where the majority of its women breastfeed their infants for anything upto three years, the potential risk factor facing both child and mother (if she has been injected with NET-EN) is alarming. To avoid the problem from arising, one testing centre in India asked its subjects **not to breastfeed their infants.** It is logical at this point to ask whether this will now lead to a situation familiar in developed countries with its well-recorded problems of the bottle-fed babies?

Specific side-effects concerning children consuming NET-EN have not been defined yet. A recent report[15] by the International Organisation of Consumer Unions lists the adverse side effects of anabolic steroids (a synthetic derivative of the hormone testosterone, from which NET-EN is also derived) on irreversible symptoms of masculinisation such as deepening of the voice, hirsutism (growing of hair on the body) and male-pattern baldness.

Other side effects include tumours of the liver, jaundice, fluid retention, ache and nausea.

The main question that now arises is - would the effects of NET-EN be similar?

Effect on Adolescents and Women over 40

The consequence to sexual development when a drug interrupts pituitary activity in the first few years of adolescence has not been fully understood yet. Therefore, medical caution advises against the use of NET-EN in girls, for two years atleast after the onset of menstruation. With reference to women over 40, the problems associated with the use of NET-EN concerns the body's hormonal changes. Since menopause is a hormonal change related phase, injectables could affect this process.

WHO Guidelines on Safety

"The history and physical examination necessary for a women either to start or to continue NET-EN should include at least the minimum information required to identify those who have contra-indications for its use or who present special problems that require medical intervention or supervision. Information should be obtained on age, recent menstrual history, history of jaundice, other liver disease, cardiovascular disease or diabetes. The obstetrical history should contain information regarding parity, abortions, date of last delivery, present lactational status, and gestational diabetes. The physical examination should include inspection for the presence of jaundice. When the local circumstances permit, examination of the urine for the presence of sugar, ausculation of the heart, blood pressure measurements, and breast and pelvic examination should be included. The Pap smear is an optional examination to be performed when indicated and when resourcs permit."
- WHO booklet on technical and safety aspects:

It is also suggested that NET-EN should not be used by a woman if she has had -

1) earlier phlebitis or thromboembolic symptoms (i.e. inflammation of the vein)

2) earlier depressions

3) high blood pressure

4) if pregnancy is not surely excluded because of probable foetal deformity

5) diabetes mellitus or fat-metabolism-disturbances because of metabolic disturbances by NET

6) herpes gestationis or pruritus or osto-clerose during an earlier pregnancy

7) any liver damage or liver-enzymatic disturbances

8) sickle cell anaemia

9) cancer of breast or uterus because of carcinogen effect of NET

10) during breastfeeding period because of possible androgen effects or disturbance of bilirubine-metabolism in the newborn baby

Schering AG, Germany, holds that NET should be discontinued if the following symptoms manifest themselves during treatment:

1) Significantly severe headaches or sight disregulation

2) Phlebitis or pain in the legs

3) Severe pain in the thorax or cough without reason

4) Increase in blood pressure

5) Alterations in liver function

A gynaecologist incharge of a testing centre in India advises against using NET if the woman was over 35, because following this period, hormonal changes for the onset of menopause in her system have begun, and this could lead to all types of endometrial changes in the uterus.

The checklist suggested by WHO to be used by paramedic staff:

Checklist for auxiliary workers for the prescription of injection contraceptives to eligible women

Check the following by history and examination:

	Yes	No
Above 40 years of age	....	....
Above 35 years of age and a heavy smoker	....	....
Seizures	....	....
Severe pain in the calves or thighs	....	....
Symptomatic varicose veins in the legs	....	....
Severe chest pains	....	....
Unusual shortness of breath after exertion	....	....
Severe headaches and/or visual disturbances	....	....
Lactating (Yes = for less than 6 months)	....	....
Intermenstrual bleeding and or bleeding after sexual intercourse	....	....
Amenorrhoea	....	....
Abnormally yellow skin, eyes	....	....
Blood pressure (Yes = above 140 mm Hg) (18.7 kPa) systolic and/or 90 mm Hg (12 kPa) diastolic	....	....
Mass in the breast	....	....
Swollen legs (oedema)	....	....

Instructions

If all the above are negative, the woman may be given injectable contraceptive. If any are positive, she must first be seen by a doctor.

(WHO, Injectable Hormonal Contraceptives: Technical and Safety Aspects, WHO Offset Publications, No. 65, 1982).

IV. NET-EN IN INDIA

Testing in India[16]

The Indian Council of Medical Research (ICMR) is the main organising centre for research and testing of contraceptives in India. The earliest trials of injectables that were conducted by it were with Depo Provera at 8 centres during 1967-68.

As part of the WHO multicentre trials, 225 women in India were administered 200 mg of NET-EN every three months, and approximately 50% of these women reported incidence of breakthrough bleeding, heavy bleeding and amenorrhoea.

Another group of 131 women who were on 150 mg of DMPA every six months also revealed a similarly high percentage (50%) of prolonged, heavy bleeding and amenhorroea. In order to reduce the bleeding, a long acting oestrogen (quinestrol - 0.5 mg) was administered once a month to those on DMPA, but this did not appear to have any significant effect on regulating bleeding patterns. Subsequently, further trials with DMPA were discontinued.

However, despite reported similarities between the trial results of both injectables, only trials of Depo Provera were discontinued. Since the test results of Depo and NET-EN are similar, NET-EN too should have been discontinued for use. Those involved in reproductive research indicate another reason for its continuing use. There is a law in India that holds that any drug which is not allowed for use in the country where it is manufactured, may not be used in this country either. This perhaps explains the discontinuation of only Depo Provera - because it has been unequivocally banned by the FDA for use in America.

Findings in Phase III Trials

The ICMR through its network of HRRCs initiated a randomized Phase III clinical trial, in March 1981, to evaluate the contraceptive efficacy and safety of injectable NET-EN (200 mg) given in two different treatment schedules of 60±5 days and 90±5 days.

The following are some extracts from the report.

The first four injections were given at an interval of 60±5 days to all study subjects and thereafter, either at 60±5 or 90±5 days depending on their allocation to either of the treatment schedule for two years.

Out of a total of 2602 subjects, 1290 for the 60±5 day schedule and 1312 for the 90±5 day schedule, 214 subjects were excluded from the study because of protocol violation. Thus, 2388 subjects - 1181 for the 60±5 day schedule and 1207 for the 90±5 day schedule were considered for analysis.

41 involuntary pregnancies were reported in this trial; of these 21 had occurred during the first six months. This gave unexpectedly high method failures during the first six months of treatment when compared with other published studies. Keeping in view the fact that average body weight of Indian women is lower than their counterparts in western countries, it is likely that the body weight may be an important causative factor.

Discontinuations due to menstrual distur-

bances constituted 7.4 per 100 users for the 60±5 day schedule and 8.8 per 100 users for the 90±5 day schedule at 6 months of contraceptive treatment. Thereafter, these **figures rose almost in geometrical progression to 21.2, 31.0 and 43.5 per 100 users** for the 60±5 day schedule, at 12, 18 and 24 months of NET-EN use. Discontinuations due to menstrual disturbances like amenorrhoea, excessive/prolonged bleeding and irregular cycles/spotting were the major reasons for drop-outs.

Discontinuations due to other medical reasons amounted to 3.2 and 4.4 per 100 users for the 60±5 day and the 90±5 day treatment schedule, respectively.

Of these, one subject was discontinued from the trial by the investigator because of hypertension at 18 months of drug use. None of the remaining study subjects in the present study showed any adverse effect of BP during the period of contraceptive treatment.

Changes in body weight of more than 5 kg was considered to be significant. **Gain in body weight (⩽ 5 kg) was observed in 3.1, 7.0, 13.3 and 22.6 per cent of subjects** respectively in I, II, III and IV reference periods of six months of drug use indicating a direct association between gain in weight and the period of drug use.

The overall continuation rates at the end of one year were 58.5 and 59.8 per 100 users, respectively, from the 60±5 day and 90±4 day treatment schedules. **These rates were marginally lower than those observed under similar conditions for intrauterine devices** in our country (69.9 per 100 users). At the end of the second year, the continuation rates were 31.4 and 32.6 per 100 users for the 60±5 day and 90±5 day treatment schedules, which are considerably lower than the continuation rates observed for CuT-200 IUD (52.6 per 100 users) at 24 months.[7] The decline in the continuation rate during the second year of drug use was mainly due to discontinuations due to personal reasons and amenorrhoea.

The results of the present study further indicate that the thin built women (⩽ 40 kg body weight) are at an increased risk of pregnancy while on NET-EN treatment. The effect of the body weight on hormone metabolism is incompletely understood.

In November 1983, the Indian Council for Medical Research disclosed that it was conducting Phase IV testing of NET-EN in 49 postpartum centres in India. In a letter to the Editor, Badri Saxena, its then Secretary General, also added that the ICMR had completed a Phase III clinical trial with 200 mg NET-EN injections; implying, thereby, that the drug had successfully passed three phases of field testing in India.

Since the three-month NET-EN injected was associated with a high rate of menstrual disorders, an addition of a suitable estrogen to reduce and regularise bleeding was thought necessary. Therefore, to work out the most effective, and least harmful - combination, a study was initiated, involving five centres and 70 women. The report collated a final series of quantities which would be tested. They are:

NET-EN 200 mg plus estrodiol valerate (0.5 mg)

NET-EN 200 mg plus estrodiol valerate (2.5 mg)

NET-EN 200 mg plus estrodiol benzoate (0.5 mg)

NET-EN 200 mg plus estrodiol benzoate (2.5 mg)

NET-EN 200 mg plus estrodiol cypionate (0.5 mg)

NET-EN 200 mg estrodiol cypionate (2.5 mg)

An ongoing study is investigating how long it takes women who have been on NET-EN for a minimum time of one year to conceive again. Meanwhile Phase IV testing has already begun.

Comments on Testing & Procedures

To find out how NET-EN is being tested in India, an initial interview with two women doctors incharge of two centres in India, testing the NET-EN 2-month programme and three social workers associated with the programme was conducted. Simultaneously, an interview with 10 women who had received the injection was also recorded.

According to the Central Drug Policy, no new drug may be tested in India without the prior approval of the Central Drug Controller, Government of India.

For this, initial toxicology, safety and efficacy tests, are made which, in turn, are reviewed by a panel of experts who qualify a drug's suitability for testing in India.

Once a drug has been found suitable for testing, it is released to specific medical institutions for further clinical research. Every such institution must have an Institutional Ethics Committee, made up of 5-6 persons representing the medical, legal and religious faculties. This committee reviews the protocol of the tests and formalise its method of execution. The review report is then sent back for suggestions or changes. We found in our investigations that in this case, the committee was only minimally involved. It did not even, for example, make the mandatory checks to ensure that the guidelines laid out for its testing were maintained.

Testing in India is done primarily at government-run public hospitals where the patients are mainly from the very low or no-income group, and the services offered are free. We found that most of the patients used in the trials were those whose initial visits to the hospital were related to family planning problems or abortions. They are asked to follow a spacing method, and, invariably a loop or injection is the first suggestion. If for some reason they reject the suggestion of the loop, they are encouraged to avail of the injection method. But do these patients know that the drug is being 'tested' on them? On the question of 'consent', doctors on the program insist that consent is sought before the injection is administered. It is more a matter of convincing the patient that the injection is a new method and that the government is providing it free. We found that **at no time are they explicitly told that the drug was being tested and that they are a part of the test.** The only possible side effect mentioned are irregular menstrual cycles. No potential danger/risks or unaswered questions are even mentioned.

Doctors say that "The class of people are like that, they won't understand." "Educated people would understand that there is nothing wrong with a trial, but not these ignorant people." "If we

PRINCIPLES FOR CLINICAL EVALUATION OF DRUGS

1) *Consent - "Subjects must usually (sic) be informed of the nature and purpose of the trial and of the potential risks and benefits. A fair presentation of the major issues should be given, but not an excessively detailed and technical discussion, which might simply confuse the subject." Written records are deemed desirable. Consent, freely given, should be obtained. "If at all possible, and in case of legal incapacity, consent should be procured from the legal guardian." Where the physician may aver that seeking informed consent would be either impossible or not in the best interests of the patient, "the patient's interests will be safeguarded by consultation with a review group of physicians and other medical scientists (peer group)."*

2) *Safety - although little risk of serious danger exists when competent investigators conduct trials, planning must include provisions for untoward effects and safety of the subject must take precedence; and on any suggestion of harm, halve the administration of the drug.*

3) *Reward - rewards to encourage participation should be such to induce submission to unreasonable hazards; a review by persons not involved in the research should be provided to "decide the advisability of the study independently of considerations of reward."*

4) *Payment of costs - trials during medical treatment, beyond routine costs should be supported by the sponsor, not the patient.*

5) *Compensation for Injury - "It is not possible under common law to absolve the investigator for liability for negligence, nor should he be so absolved. Liability for negligence remains a useful check on the incompetent or unscrupulous investigator. However, injuries nor mishaps with medical consequences may occur during the course of research in which there is no question of negligence... There is need for some process, such as an insurance system that will pay for medical care, when necessary, and provide appropriate compensation when research subjects sustain injury of death during investigation, regardless of possible negligence and with prejudice to liability. The cost of this protection should be considered part of the basic cost of the conduct of the clinical investigation."*

Source: WHO (1968) Principles for the Clinical Evaluation of Drugs (Report of a WHO Scientific Group) Technical Report Series No. 403, Geneva.

told them it's a trial, then no one would be willing to have an injection."

Every trial specifies what type of women must be recruited for what type of test. The Phase III NET-EN 2-monthly trial specified that the women had to be between 20 and 34 years; with a haemoglobin count of 8 gm and with more than one living child. They were not to breastfeed, which meant that their last child would be older than six months. Yet, at the time of the interview, **several among these women were still breastfeeding their child.**

At one centre, records show that several women selected for the tests had to discontinue it because earlier guidelines for selection had not specified that they should not be lactating mothers.

In India, written consent is required only for Phase I trials. No such formality binds subjects in the Phase II trials, although a monthly payment is made to these women. According to a doctor incharge of a Phase II NET-EN monthly injection trial, a provision to pay Rs.10/- per month to each patient has been made. However, the payments were not made every month "because then they could become suspicious". A lump sum is usually paid at the end of the trial period.

Phase III requires neither a written consent nor is any money paid to the patients participating in it. The test begins with a routine clinical examination to investigate the woman's medical history for diseases, hypertension and bleeding problems. A breast-pelvis examination and a pre-abdominal examination follows. A Pap smear is taken which, if normal, will be repeated only once every year. But, should there be any abnormalities, the smear is taken once every three months. Her blood is checked and she is supplied with a menstrual regulation card on which she must maintain a record of her bleeding pattern. The first injection is then administered to her during a menstrual period to ensure that she is not pregnant.

At the time of the next injection the weight, blood pressure is taken and pelvic exam is done. Her menstrual card is taken, and if she has had no bleeding for 50 days, a pregnancy test is performed. If she is pregnant, an abortion is done.

During our visit, we found that a woman is asked if she has any problems. No specific questions like do you feel depressed, have headaches etc. are asked. The doctor said "If we had a check list, the answer would be yes to everything." The tested women spoke to usually said they had no problems except irregular bleeding. On probing they said they had giddiness and backaches. When asked if this bothered them, they said that the doctors had told them it was alright. The doctors say "the women have so much faith in us, that they believe what we tell them."

We also noticed that there is no effort to keep track of the patient once the trial periods are over, but the doctors feel "that if there were any problems the women would come back to us."

Government of India
Ministry of Health & Family Welfare

GUIDELINES FOR USE OF NORETHISTERONE ENANTHATE, AN INJECTABLE CONTRACEPTIVE FOR ITS USE IN GOVERNMENTAL AND NON-GOVERNMENTAL FAMILY PLANNING CLINICS

Criteria for selection

Healthy informed women who seek Family Planning services to be selected if they fulfill the following criteria -

1. Age between 18 to 40 years.
2. Proven fertility.
3. Exposed to the risk of pregnancy.
4. Willing to rely only on NET-EN as a method of fertility regulation.
5. Regular menses (variation of not more than 10 days between the longest and the shortest menstrual cycle during the last 6 months). One cycle after M.T.P.

The following record of the woman to whom the drug is administered should be maintained.

1. Age of menarche.
2. Regularity and length of cycle.
3. Duration and amount of menstrual flow.
4. Occurence of abnormal bleeding.
5. Data of last menstrual period.

The obstetical history should contain the following information.

1. Regarding parity.
2. Abortions.
3. Data on last delivery.
4. Present lactational status.
5. Gestational diabetes.

Contra-indications to the use of NET Enanthate

1. Cancer of the breast.
2. All genital cancers (except as treatment for endometrial cancer).
3. Undiagnosed abnormal uterine bleeding.
4. Suspected pregnancy.
5. Should not be given to lactating women.
6. Cases which require medical supervision e.g. undiagnosed breast lump, abnormal liver function or recent history of liver disease including H/o Jaundice in pregnancy or jaundice during the last six months, H/o or evidence of cardiovascular disease, congenital hyperlipidaemia, H/o infrequent bleeding, amenorrhoea, diabetes mellitus or H/o gestational diabetes.

The following common side-effects to be explained to each women.

1. Irregular bleeding and spotting, sometimes prolonged.
2. Amenorrhoea.
3. Delay in becoming pregnant after discontinuing NET injection.
4. Headache and weight gain.

It is of great importance that adequate explanations of the long term effectiveness of the product, its possible side-effects and of the impossibility of reversing the effects of each injection are given to potential users.

Duration of use

If the periodic clinical evaluation does not reveal any adverse effects, the medication can be continued. NET-EN should be used primarily for spacing pregnancy in younger women. However, sterilisation or other forms of contraception should be considered for women not desiring any more pregnancies. Beyond 40 years of age, other forms of contraception should be considered.

An Annual examination of pelvis and the breast is recommended.

Administration of Norethisterone Enanthate

The initial injection of NET-EN should be given during the first 5 days of the menstrual period. The woman should be re-examined for the development of any problem and would receive the next injection after every 8 weeks of its use.

Mode of administration

Since NET-EN is a viscuous oily solution, special care should be taken while aspirating it into the syringe and during injection in order to ensure that all the material is ejected from the syringe and that no leakage occurs around the needle. If the vial has been stored in low temperature, it is advisable to warm it before giving the injection. The preparation should be given by deep intramuscular injection, preferably into the gluteal muscles. The injection site should not be massaged.

Precautions

If any of the contra-indications to use appear, further injections of the drug should not be given. Similarly, if any of the special problems requiring medical supervision should develop, the advice of the trained medical personnel should be sought prior to giving additional injections.

Warnings

Do not administer an injectable contraceptive when a pregnancy is suspected. It will not cause abortion but may interfere with the normal development of the baby.

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Appendix 1

TESTING PROCEDURE

The first stage in contraceptive testing is on animals and these tests are usually done by the manufacturer of the drug. Each country has its own required rules and guidelines about the tests.

The USFDA requires hormonal contraceptives to be tested in 3 animals species:

Rats
Must receive amounts of the drug equivalent, on the basis of body weight
1) 1 or 2 times the human dose for 7 years
2) 10 times the human dose for 7 years
3) 50 times the human dose for 7 years

Beagles
Must receive 1 or 2 and 10 and 25 times the human dose for 7 years.

Monkeys
Must receive 1 or 2 and 10 and 50 times the human dose for 10 years.

Based on an analysis of these results the USFDA decides whether the drug can be clinically tested on women.

The major organisation for testing is the World Health Organisation, the Special Programme on Research, Development and Research Training in Human Reproduction.

A doctor actively involved in testing contraceptives in India told us that there are various stages in the testing of contraceptives on women, in India.

Phase I
Has 6-10 women per group. The aim is to test the **safety** of the drug and the tolerance.

Phase II
Is on 6-10 women per group and tests (on a limited sample) the **dosage** and efficiency of the contraceptives.

Phase III
Tests the dosage and efficacy on an expanded number of women 25-50 a group.

Phase IV
Studies are conducted to assess the introduction of contraceptive methods in a national family planning programme. A variety of aspects are examined, including acceptability in terms of use, use effectiveness, side effects under usual family programme conditions and its programmatic implications, including logistic considerations, the need for reference services, additional staff training and supervision, and the acceptability of the method to clinic staff.

Currently Phase IV trials are underway in India on NET-EN injections.

Tests are carried out in various countries all over the world because the efficacy and side effects of the drug varies, depending on several variables including race, different nutritional levels etc.

Appendix 2

More and More Injectables

(Taken from: **Women's Global Network on Reproductive Rights**, Jan.-Mar. 1986)

In 1984 we reported that drug companies were taking advantage of the fact that the patent on DMPA (the progestogen used in Depo Provera) had run out. Since then, the number of injectable contraceptives has increased at an alarming rate, and more are being tested in centres around the world. The following is a list of those we have heard of.

Because a number of different progestogens and oestrogens are being used in these different brands, because the action of a progestogen alone would be different from the combined action of a progestogen and an oestrogen, and because the duration of use differs, it is not possible to assume that what we learn about one brand applies to the others. For example, Pheno M was meant to be a locally-produced substitute for Depo Provera, but an early study comparing it to Depo found a higher pregnancy rate in women using Pheno M.

In addition to the above brands, the World Health Organisation's Special Programme of Research, Development & Research Training in Human Reproduction is testing a number of one-month injectables, each containing a different oestrogen and progestogen combination. In addition, the director of Organon in the Netherlands said recently in an interview that Organon are planning to bring out an injectable as well.

There has been more research done on Depo Provera and Norigest than any of the other brands, though most of the compounds were first synthesised in the 1960s and 1970s. Less is known about any of the other brands because fewer studies in fewer women exist. In spite of this, they are on the market and often available over the counter, at prices which make them competitive.

In 1985 ISIS Internacional in Chile asked if we could find out anything about Agurin, Segura al Mes and Una al Mes, all of which are on sale in Chilean pharmacies. We wrote to a clinical pharmacologist in Britain, Professor M.D.Rawlins, and received a report and letter from him.

BRAND NAME	MANUFACTURER/ COUNTRY	DURATION OF USE	COMPOSITION
Depo Provera (Depoprodasone)	Upjohn/USA	3 months	progestogen
Norigest (Noristerat)	Schering/West Germany	2 months	progestogen
Pheno M	?/Thailand	?	progestogen
Farlutol	?/Italy	?	?
Perlutal	?/Mexico	?	?
Patector	?/Mexico	?	?
Una al Mes	Silecia/Chile	1 month	progestogen
Agurin	Recalsine/Chile	1 month	progestogen + oestrogen
Segura al Mes	Norgine/USA	1 month	progestogen + oestrogen
Injectable No.1	Chinese government	1 month	progestogen + oestrogen

UNA AL MES

About Una al Mes, Prof Rawlins said: "It would appear that Una al Mes...would be expected to have similar actions and effects as Depo Provera. However, there is considerably greater published work on the latter...There might be a case for using Una al Mes in favour of Depo Provera on cost grounds. If such a decision was to be taken, it would have to be done in the realisation that there is less good evidence to support its safety." According to ISIS Internacional, Una al Mes used for three months cost about US$4.20 in early 1985, while Depo Provera for 3 months cost about US$15.40.

AGURIN/SEGURA AL MES THE SAME

Agurin and Segura al Mes contain both progestogen and oestrogen. The progestogen in them could prevent pregnancy if used alone. However, progestogen-only methods often cause amenorrhoea and other effects on menstrual bleeding, which women don't like, and which are the main reason why women stop using them. Oestrogen seems to have been added to ensure that the woman gets menstrual bleeding, in the hopes that she will be more likely to continue using the method. The bleeding is the same as what happens on the pill; it is a withdrawal bleed, not a real period.

What is important about Agurin and Segura al Mes is that they appear to be identical to a product called Deladroxate, which was marketed by Squibb in the USA in the 1960s and was taken off the market by them in about 1970. Few women had amenorrhoea on Deladroxate; most had cyclic bleeding. One study showed that the length of different women's cycles was between 16 and 47 days. In another study, most cycles were between 20 and 32 days. The variation was because the speed of release of the oestrogen from the injection site into the body of the woman was different in different women. The length of women's cycles tended to increase with repeated doses of the drug, and the amount of bleeding decreased to spotting toward the end of the second year of use in one study.

Ovulation returned only after 4-10 months in one group of women who used Deladroxate for 2 years. In another study, it took up to 3 years for some of the women to get pregnant after stopping the drug, which indicates that the effect on the body is carried over after the woman stops using the method. The longer the drug was used, the greater the delay there seemed to be for a normal menstrual cycle to return.

Common adverse effects reported during 6-12 months of use included bleeding between periods, increased or decreased bleeding, headaches, breast pain, painful periods, weight changes, pain at the injection site, and altered libido. All of this sounds quite similar to progestogen-only methods. There was also a decrease in quantity and quality of breastmilk in breastfeeding women, due to the oestrogen.

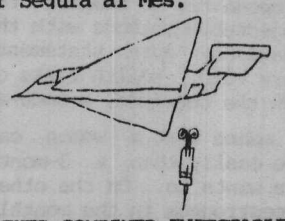
Overall, Deladroxate was more or less 100% effective in preventing pregnancy. The problem with this information is that few studies were done and only in small groups of women, so it is of limited value. Reliable information about longer-term effects on health is totally lacking.

The report from Prof Rawlins' unit says: "Deladroxate was abruptly withdrawn from sale in the USA at some time around 1970. No explanation is available, and Squibb UK are unable to elaborate. It has been suggested that a two-year toxicology study in dogs demonstrated 'an enormous number of breast cancers' and 'a very curious pituitary hyperplasia'." Beagle dogs were used in that toxicology study, the same kind of dogs which developed breast cancers in studies of Depo Provera.

Since then, an international meeting of scientists has declared that such toxicology studies in beagles do not provide accurate information about effects in humans. There was controversy over that declaration at the time, as well as over the validity of such studies as had been done.

If this was indeed the reason why Deladroxate was withdrawn from the market, then perhaps the manufacturers of Agurin and Segura al Mes felt there was no longer a reason to keep a product like Deladroxate off the market. They could expect few people to know about or remember Deladroxate. They would probably also take comfort from the fact that the WHO is testing similar progestogen-oestrogen compounds.

Having looked at the available evidence about Deladroxate, Prof Rawlins told us that he would not support the use of Agurin or Segura al Mes.



OTHER COMBINED INJECTABLES

In contrast, the WHO Special Programme seem to be keen on similar drugs. The 1984 Annual Report of the Programme says: "a major effort is being made to produce formulations which include little or no disturbance of menstrual bleeding." The only disadvantage they mention with these compounds is the need for monthly visits to a clinic. They expected to have recruited 3300 women at participating centres by the end of 1985 to test these compounds. The centres are in: Bangkok, Hangzhou, London, Mexico City, Szeged, Allahabad, Bombay, Calcutta, Madras, Madurai, Stockholm, Alexandria, Birmingham, Havana, Jakarta, Karachi, Leningrad, Santiago de Cuba, Huntingdon, and 4 other centres supported by Family Health International. They will be doing Phase I, II and III trials.

The Chinese government recently opened a factory in Shanghai with assistance from the UNFPA, which will produce an oestrogen-progestogen monthly injectable sufficient for 2.5 million users in China alone. The type of oestrogen and progestogen in this compound are different from those in the Chilean drugs.

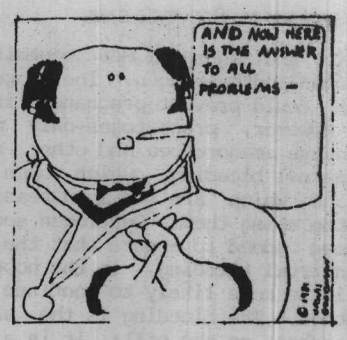
DISCUSSION

In terms of contraceptive safety, it seems we have come full circle. When it was discovered that the oestrogen in the pill was responsible for potentially serious risks to health, the big selling point of progestogen-only methods (both pills and injectables) was that they were free of oestrogen. The implication was that they were safer. Now oestrogen is being introduced into injectables in an attempt to eliminate effects on menstrual bleeding. Nothing is being said about introducing the risks of oestrogen, particularly of long-acting oestrogen which is used in injectables. Nothing is being said about the fact that the oestrogen does not add to the contraceptive efficiency of the injection. And to top it off, there seems to be little proof that the effects of the injectable, with the added oestrogen, on menstrual bleeding are any improvement over the effects of progestogen alone, if Deladroxate is any measure.

There are complicated issues involved here. Without sufficient evidence from research, it is impossible to compare the better studied injectable methods with the newer ones, or make any sure statements about their failure rate, health risks or adverse effects. On the one hand, a once-a-month injectable means that a woman can stop using it more easily than a 3-month injectable, if she wants to. On the other hand, the use of oestrogens in the monthly brands does not appear to be justified on contraceptive or health grounds.

This information is yet another example of the lack of international standards and controls on drugs. In the case of injectables, the market is clearly out of control. It seems clear that campaigns against Agurin and Segura al Mes would be justified, and this information has been sent to Health Action International in hopes that this will be taken up.

by Marge Berer



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-WHO Special Programme 1984 Annual Report, pp.2,4,5,12
-Letter and report to M Berer from Professor M.D. Rawlins, Department of Pharmacological Sciences, University of Newcastle upon Tyne, 31.10.85
-McDaniel, Edwin et al, "Method Failure Pregnancy Rates with Depo Provera and a Local Substitute," The Lancet, 9.6.84 (re Pheno M)
-Letter from ISIS Internacional, Santiago, 29.1.85 (re Una al Mes, Agurin & Segura al Mes)

Appendix 3

INTERIM STAY ON FURTHER TRIALS

SAHELI,
WOMEN'S RESOURCE CENTRE,
UNIT ABOVE SHOP 105 TO 108
SHOPPING CENTRE
DEFENCE COLONY BRIDGE (SOUTH SIDE)
NEW DELHI 110 024.

PRESS RELEASE

May 1, 1986

For the first time in India, the attempts of the Health Ministry and the ICMR to push a hazardous contraceptive for women has been challenged through a writ petition filed in the Supreme Court on the 7th of April 1986. The contraception in question is NET-EN.

The Court today (1st May 1986) issued notice to the respondents to show cause as to why the petition filed by Stree Shakti Sanghatna and others, should not be admitted and stay order granted on further trials of the contraceptive. In addition to the Health Ministry, the ICMR, and the State of Andhra Pradesh, the Drug Controller of India was also impleaded as a respondent. The notice is returnable on July 15, 1986.

The ICMR is currently engaged in the last stage of trials and the government plans to introduce it into the mass Family Planning Programme in a big way. Far from sharing the optimism of the government and the ICMR, the petitioners contend that there are several reasons for grave concern.

The drug is a definite hazard to women's health and a potential hazard to their progency. The high dose of NET-EN which is to be injected every two months, causes a complete disruption of the hormonal balance maintaining the reproductive system of women. Menstrual chaos, which is experienced by 90% of Indian women who were administered the drug, is just one of the ways in which this is manifested. Neither has the cause of this menstrual chaos been understood, nor has an effective treatment for it been developed so far.

WHO, though a proponent of NET-EN, admits that the safety of the drug is yet to be established with regard to aspects such as: effect on lactation and progeny, cancer-risk, long-term sequelea, effects on lipid metabolism and endometrial bleeding.

The drug has a long list of contra-indications ranging from breast-feeding in the initial six months after delivery, liver disease including jaundice, breast or genital cancer, undiagnosed vaginal bleeding, to suspected pregnancy. Women suffering from several other conditions such as diabetes and hypertension, need to be monitored closely. Given the present state of health services in India, the Primary Health Centres,

(through which the drug will primarily be administered), are not equipped to screen women with these conditions, administer the injection in a careful and safe manner and deal with complications as and when they arise. Hence, under Indian conditions, the potential hazards of this drug do not justify its introduction into the mass Family Planning Programme.

All the same, in their eagerness to complete the trials on the drug, the centres chosen by the ICMR have been recruiting women through unethical publicity campaigns. Women are being lured by incomplete and biased information which is designed to conceal the experimental nature of the exercise and are led to believe that the drug is already tried and tested.

One of the major fears of the petitioners is that, once introduced, this contraceptive has a high potential for misuse and can recreate the Family Planning scene of the Emergency era. Unlike then, the unwitting victims may not even be aware that they have become acceptors of this method of contraception because an injection can always be administered under false pretexts.

The petitioners therefore contend that all further experiments on Indian Women with this drug must be stopped and the drug be banned for use in India.

PETITIONERS

Stree Shakti Sanghatana, Hyderabad
Saheli, Delhi
Chingari, Ahmedabad
Dr. Shyama Narang, Dr. Kamala S.Jaya Rao, Dr. Davayani Dangoria,
Dr. A.K.Vasudevan, Dr.Raman Dhara, Ms. Vimal Balasubramaniam.

RESPONDENTS

Union of India through its Secretary, Ministry of Health.
Indian Council of Medical Researchg through its Director General.
State of Andhra Pradesh through its Secretary, Department of Health and Family Welfare, Drug Controller of India.

ADVOCATES

Petition filed by Mr. Venkataramani;
Appeared before Court: Mr. M.S. Ganesh.