To,
Dr BN Saxena,
Addl Dir Gen.
ICMR,
Ansari Nagar,
New Delhi

14.4.99

Sub: Public Debate on Ethical Guidelines

Dear Dr Saxena,

This is with reference to the Public Debate on Ethical Guidelines for Biomedical Research involving Human Subjects held on 23.3.99 at the IIC.

We would like to register our strong protest at not being invited to this meeting. As you are well aware, we have been working on issues related to women's health and medical ethics for about 15 years. We had also initiated a meeting with you on 18.12.97 following the controversy over the Cervical dysplasia study conducted by ICPO. During this meeting, you had circulated Draft Guidelines which were open to public debate. We had been assured that we would be invited to participate in a public debate before the Draft Guidelines were finalized. In fact, in November 1998, on reading press reports of such Public Debates held in Mumbai, we had in writing requested you to invite us to the forthcoming Public Debate in Delhi. A telephonic conversation with your office in December notified us that such a meeting was expected sometime after December. To our surprise, we find that you did not see it fit to invite us to this meeting, nor inform us of its occurrence.

We are interested to know the details of the proceedings of the Public Debate. Please send us the minutes of the meeting. If there were any papers presented, we would like to have copies.

We have gone through the Draft Guidelines and provisions especially pertaining to women's health, and would like these to be given careful consideration. We will shortly be sending our comments to the Committee in charge of the Draft Guidelines. Kindly keep us informed about any meeting/seminar or new development concerning the above matter.
Thanking you,

Sincerely yours,

Laxmi Murthy
(For Saheli)

use of trial observers and others assessing the fairness of an individual case. It covers pre-trial rights, rights and trial and during appeals and special cases including death penalty trial, cases involving children and fair trial rights during armed conflict. Unfortunately we do not have the resources to send a copy to each and every one of you free of charge. We are trying to organize for copies to be made available to people in India at the reduced cost of Rs300. We will let you know as soon as these are available.

Many of you may be aware of a decision made by the International Executive Committee of Amnesty International last year to de-recognise the Indian Section (membership chapter) of Amnesty International. The decision was based on the assessment that the section had not been fulfilling the requirements and expectations of an Amnesty International section. The section was given full opportunity to represent its case and the decision was upheld by an Independent Membership Appeals Committee of Amnesty International in November last year. The de-recognition is now complete. While de-recognizing the section, the International Executive Committee also made India a high priority for its future membership development. Individuals in India can still be members of Amnesty International through international membership. At present, international members are serviced by our Asia-Pacific Regional Office in Hong Kong (for details contact: Amnesty International - Asia-Pacific Regional Office, Unit D 3F, Best-O-Best Commercial Centre, 32-36 Ferry Street, Kowloon, Hong Kong, Tel no. + 852 2385 7187, Fax no: +852 2782 1143). Through a reorganization of our work in India we hope to develop through close cooperation with old and new AI members, as well as other human rights and non-governmental organizations (NGOs) and institutions.

Finally, I want to notify you of changes to the staff working on India at the International Secretariat once again. I am personally very pleased to tell you that following an international recruitment, I was appointed as researcher on India at the end of December. I am looking forward to working with many of you in this new capacity and ensuring continuity of the work of the team addressing human rights concerns in India in consultation with people throughout the country. Susan Batley also continues in the team and we are currently recruiting a third member of the team.

With best wishes from myself and the team.

Yours sincerely,

Emma Blower

Emma Blower
South Asia Team

team e-mail: **iteam@amnesty.org**

INTRODUCTION OF THE HAZARDOUS CONTRACEPTIVE NOR-PLANT INTO THE NATIONAL FAMILY PLANNING PROGRAMME :

(Report of the meeting held on the 6th & 7th of December 1991 by the Indian Council of Medical Research, at the ICMR head quarters New Delhi for what they termed "Health Advocates").

PARTICIPANTS:

Invitees: Dr. Saroj Pachuri (Ford Foundation), Ms Ena Singh(UNFPA), Dr. Saramma Mathai (address given as St. Stephen's Hospital, but is an ex USAID person; now free lancing for international agencies with explicit pro-population control policies), Dr. Banoo Coyaji (KEM Hospital Pune), Ms Kamla Bhasin (FAO), Dr. Promila David (Centre for population Concerns), Dr. Shanti Ghosh (not representing any organization), Dr. Kaushalya Devi (Gandhi Gram Institute), Dr. Rani Rang (Search, Gadchiroli), Dr. Mira Shiva (VHAI), Dr Vibhuti Patel (SNDT, Bombay), Dr Veena Mazumdar (CWDS, Delhi), Ms Gauri Choudhary (organization not mentioned),

(Kamla Bhasin, Mira Shiva, Saramma Mathai, Veena Mazumdar and Gauri Choudhary did not attend the meeting)

Uninvited participants: Sathyamala, Kalpana Mehta and Laxmi Murthy representing Saheli and Medico Friend Circle, though uninvited attended the meeting. This was possible because of the timely information sent out by the "Forum Against Sex Determination and Sex Pre-Selection," Bombay.

We report, briefly, the main points of I M's presentation (this includes the Chairperson Dr. Banoo Coyaji's remarks), followed by our own 'sub-missions', and our recommendations.

SALIENT FEATURES OF THE ICMR PRESENTATION:

1. The meeting has been called because we want to know what women want.
2. An ideal contraceptive that is 100% effective, 100% safe, and which has 100% return of fertility on discontinuation with no side-effects does not exist as of today.
3. The reasons for carrying out more research on the female methods of contraception is because of the fact that the physiology of male and females are different (truism?) and it is easier to intervene (interfere?) with the female physiology.

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4. Contraception is necessary for the well being of women and not merely for population stabilization. The primary concern is to improve the quality of life for the women; if there is a demographic spinoff, it would only be a consequance of the primary objective.

5. Women Health Advocates should spread the message widely and be actively associated with the introduction of the newer contraceptives.

6. The future belongs to Science and those who make friends with science (Jawaharlal Nehru).

7. A list of ICMR projects on "Psycho-Social Research Programme in FP", "Reproductive Health Care," and "Fertility Regulating Methods" were presented. (Since the presentation was rapid and the written list was not made available, it is not possible to list them out).

8. Terminal methods have not had an impact on birth rate and therefore more emphasis needs to be made on spacing methods.

9. ICMR has conducted trials on "newer" IUDs, Injectable Contraceptive, the Triphasic pill, Subdermal implants, menstrual regulating agents, and the vaginal rings.

10. The newer generation IUDs have no added advantage over the earlier IUDs in terms of their continuation rates (no mention of complications).

11. Due to an inadequate follow up, the IUDs are not generally accepted; Good 'counselling' can ensure a higher continuation rate.

12. The continuation rate with NET-EN during the phase IV trials was 22.9/100 users. Discontinuation due to pregnancy was 2.1% and that due to menstrual abnormality was 41.2%. Continuation rate was less than that with IUD or NOR PLANT.

13. The big difference between the continuation rate of NET-EN during the Phase III and Phase IV trials was perhaps due to a lack of 'motivation' The pregnancies during the Phase IV trials were insignificant because they were terminated and the products of conception were not examined.

14. The ICMR has recommended to the Drugs Controller that NET-EN should be made available only at the urban health centres where comprehensive care is avilable, where a doctor is present and that no targets for achievement should be fixed.

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15. Pre-Programme Introduction study with NOR PLANT (2) on 1466 woman, initiated during Jan 1986 and completed in Sept 1991, showed a discontinuation rate of 36 to 40% at 36 months of use. The method has been found to be safe, and the return of fertility was not affected adversely on discontinuation.

16. Although trials with NOR PLANT (2) have been completed, the production of NOR PLANT (2) has been discontinued. Since it is no longer available in the world market, it cannot be introduced into the FP Programme.

17. The real reason for withdrawal of NOR PLANT was pulled out of ICMR by Rani Bang when she enquired if the withdrawal was not because of doubts regarding the teratogenic and carcinogenic potential of the elastomer used in NORPLANT (2). (In August 1987, new trials of NOR PLANT (2) were suspended because the manufacturer of the silicone component used in the core of the contraceptive implant discontinued its production. This was following the request made by the Environmental Protection Agency (US) for additional animal studies on the 2 -ethyl hexanoic acid, a byproduct of the catalyst used to vulcanize the "Medical Grade Elastomer 382", the silicone component of NOR PLANT (2). The earlier studies had shown it to be carcinogenic and teratogenic in rats and mice. The USFDA however declared that it had no objections to the carrying out of trials with NOR PLANT (2). The WHO also gave a green signal and stated that exposure to the amount of 2 - ethyl hexanoic acid in NOR-PLANT (2) posed no toxicological risk to human beings. The manufacturer, Dow Corning Corporation, however decided that it was uneconomical to conduct additional studies and discontinued production of the elastomer).

18. Dr B.N. Saxena of ICMR however took great pains to explain that discontinuation with the NOR PLANT (2) was not because of the carcinogenic and teratogenic potential of the elastomer but because of the unavailability of NOR PLANT (2) in the market.

19. Still, according to Dr. B.N. Saxena, all was not lost because ICMR & the Ministry of Health & Family Welfare now planned to introduced NOR PLANT (6) into the FP Programme. This decision was based on the fact that the levonorgestrel the chemical component was the same in both the NOR PLANTS and both had similar clinical and pharmacokinetic profile and therefore it was not unscientific or unethical to introduce NOR PLANT (6) in the place of NOR PLANT (2) in the FP Programme.

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20. NOR PLANT (6) will be introduced into the FP Programme through hospitals attached to medical colleges in the country and for the time being will be confined to these. In the next six months the staff of 17-20 medical college hospitals will be trained in the insertion and removal of NOR PLANT (6) and will recruit 200 women each for insertion. In the next six months another 50 medical college hospitals will be trained and the target is that the 100 medical college hospitals in India will recruit a total of 20,000 women.

21. Monitoring and Evaluation will be carried out by the HRRCs and the Ministry of Health and Family Welfare. There are also plans to involve women health advocates and NGOs into this process.

22. ALL contraindications that apply to hormonal contraceptives in general also applies to NOR PLANT (2) & (6). i.e., the first six months of lactation, women with irregular cycles, genital and breast pathology, hypertension, diabetes etc.

23. The reason for confining it to medical college hospitals is because NOR PLANT is a medical method (whatever that means). A review will be carried out at the end of 2 years and then a decision will be taken as to whether it can be introduced into the FP Programme.

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IN COUNTER WE PRESENTED THE FOLLOWING:

1. The manner in which this meeting was being held was unacceptable because (a) none of the petitioners who have filed the Supreme Court case against NET-EN have been called and (b) the group that has been invited is not broad based enough to be representative.

2. In 1986, Saheli along with several other petitioners filed a case against NET-EN. This case is still pending in the Supreme Court and the injectable contraceptive NET-EN cannot be introduced anywhere in the country without the resolution of this case.

3. In Dec. 1990, the scope of this case was broadened to include the introduction of NOR PLANT (2) & (6), antifertility vaccine,

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vaginal rings nasal sprays etc, as they share with NET-EN certain similarities and ethical concerns for all remained the same.

4. Therefore in view of the pending case none of these contraceptives can be introduced into the FP Programme.

5. The presentation made by the ICMR was too rapid to be meaningful. The studies especially that related to the completed Phase III trials, Phase IV trials, and return of fertility with NOR PLANT (2) have not been made available and therefore on the face of it, the ICMR's statements cannot be accepted.

6. The information presented in Phase III trials (Interim report) of NOR PLANT (2)[Contraception Vol 38, No. 6, PP659 - 673] suggest that the method is hazardous on even short term use with life threatening complications (eg subendocardial infarction, Deep Vein thrombosis). These should be considered not as morbidity alone but as mortality if they occur in areas with inadequate medical facility. The quantum of mortality/morbidity the use of NOR PLANT will add to the women's ill health roughly works out to be ten times the maternal mortality rate. Given this, NOR PLANT (2) is clinically unacceptable.

7. The ICMR has tried to underplay the significance of certain information generated during the Phase III trials both at the time of their presentation and in the reporting of Phase III trials in Contraception.

For instance, out of the 907 women who were exposed to NOR PLANT (2) for 24 months, 5 showed dysplasia on cervical cytology (i.e., possible cervical cancer). Two of these women had abnormal cytology even on repeat examination. This is unacceptably high and raises questions about the real possibility of cervical cancer occuring in women using NOR PLANT even for as short a period as two years. This important information has however been presented under discussion and not under findings.

8. The effect of NOR PLANT in the menstrual cycle is very similar to the effect of NET-EN on the menstrual cycle. In a large number of women NOR PLANT produces irregularity of the cycle, increased blood loss, spotting, shortening of the cycle and amenorrhoea. This could indicate a possible irreversible damage to the hypothalamus, pituitary ovary and endometrium.

9. The contraceptive levonorgestrel is passed into the breast milk and is absorbed from the gut of the infant and enters the circulation of the child. NOR PLANT is therefore unsuitable for breast feeding women for the duration of breast feeding.

10. All the contentions against NET-EN presented in the Supreme Court petition apply to NOR PLANT and since NET-EN is clinically unacceptable NOR PLANT too is unacceptable.

11. From 1972 onwards, more than 15,000 women have been subjected to several hormonal contraceptives as part of the clinical trials carried out by the ICMR. These contraceptives include NET-EN, DMPA, NOR PLANT. ICMR should provide information regardingthe current status of health of these women and whether any adequate follow up measures have been undertaken to monitor their health.

12. The percentage of women 'lost to follow up' in the NORPLANT trials is more than 10%. This is totally unacceptable and indicates negligence on the part of the researchers. These women need to be contacted and the devices should be removed immediately.

13. What are the trade agreement and licensing agreements between the population Council (Manufacturer of NOR PLANT) and the ICMR

14. It is a matter of concern that the population Lobby has been invited to this meeting which is supposedly meant for initiating a dialogue between the ICMR and the "Women health advocates."

IN REPLY, ICMR STATED THAT :

1. It was not as 'oversight' on their part that the petitioners in the NET-EN case were not invited. It was for some wishy washy reason (the logic of which quite escaped us) that they were not invited.

2. NOR PLANT has been in use in Thailand for more than 20 years and has not shown any teratogenic effect.

3. The 'best' scientific minds have been involved in the study design and research methodology of the studies conducted by the ICMR and therefore they cannot be faulted.

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4. The procedure for informed consent was introduced into the programme after Dr B.N. Saxena came on the scene. This was in 1979. Ethical committees were set up in 80-81. ICMR is concerned about the potential for abuse and that is why ICMR has recommended that no targets should be fixed for NET-EN.

5. Long term surveillance is not possible because there are too many confounding variables. Even in the US where resources is not a constraint, it is not possible to follow up women participating in clinical trials. In India it is almost next to impossible, both because of financial constraint and the non-existence of record keeping system.

6. Recently there have been discussion regarding the transfer of technology. Population Council members have visited certain business houses in India to discuss the possibility of setting up manufacturing units in India.

7. None of the women who have participated in the clinical trials with any of the hormonal contraceptive have been followed up because this was not included in the research design. Therefore ICMR has no knowledge of where these women are, and whether their health has been affected. This includes women who 'participated' in the trials after 1986 (When the petition against NET-EN which raised these questions was filed).

8. In future, ICMR can consider the possibility of giving Insurance coverage to women who are in the trial.

9. The complications listed in the published report of NOR PLANT (2) is not significant because they are not drug related. (When we fished out the product information sheet on NOR PLANT published by Population Council to show that disturbances of the liver function, migraine type of headache, acute disturbance of vision, symptoms of thrombophlebitis, thromboembolism increase in blood pressure have received special mention under "Reasons for immediate removal", Dr. Shanti Ghosh replied that one should not believe everything in the product information sheets because they were written merely to escape litigation. She also gave the example of aspirin which no one will have the courage to prescribe if they were to read the product information sheet. We pointed out that Phase III trial is meant for studying toxic effects and that our experience has shown that Pharmaceuticals underplay the seriousness of side effects because they want their product to sell).

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10. In the past, all the methods have not received equal promotional efforts. The new programme envisaged is to promote a 'single package system' which will give equal weightage to all the methods.

11. This package will contain condom, IUD, Oral pill, injectables, implants and vaginal ring. (A massive argument took place because ICMR did not consider diaphragm as a suitable method for promotion because of a one-centre study conducted in Gandhigram on the acceptability of the diaphragm. ICMR also felt that diaphragm cannot really be considered safe because the failure rate is high and as everyone knows pregnancy is the greatest risk a woman faces.)

12. ICMR will plan to go ahead with the 'programme introduction' of NOR PLANT (6) because it is similar to NOR PLANT (2). This in no way contravenes any of the provisions of the Drugs & Cosmetics Act.

13. Finally, ICMR and the Health Advocates must work together and must trust each other. In order to build up trust and initiate the process of working together, ICMR plans to hold regional level meetings with health advocates. ICMR would also like the women health advocates to call a meeting where ICMR can present their point of view.

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The meeting also passed certain recommendations. We read out our own set of statements which had the agreement of Rani Bang and Vibhuti Patel.

1. While we welcome the ICMR's initiative to attempt a dialogue with 'health advocates' we object to the manner in which this meeting has been called. Firstly, none of the petitioners who have filed a petition in the Supreme Court against the introduction of NET-EN has been informed or called for this meeting, Secondly, the material presented in this meeting was not circulated in advance for the participants to react to in an informed manner. If these meetings are to serve their stated purpose, it is essential that these meetings are held regularly, that ICMR provides information in time, and that a broad based participation is ensured. Further for such meetings to be made meaningful, the chief investigators of the HRRCs are to be included.

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2. Since it is in the interests of ICMR to inform Health Advocates about their on-going research, we suggest that all ICMR publications pertaining to contraceptive research be made available free of cost to all health advocates on a continuing regular basis and that the ICMR library be opened for public use.

3. We wish to place on record that the respondents which includes ICMR have not responded to the petition against NET-EN in the Supreme Court. Such an act neither serves the interests of women nor the interests of the national FP programme.

4. Based on the existing state of knowledge regarding NET-EN and the inability of ICMR, Drugs Controller, Ministry of Health and Family Welfare to refute our contentions as exhibited by their continuing silence of over 3 years, there is no basis for introducing NET-EN in the National FP programme even on restricted basis.

5. As the ICMR presentation has made clear, only Phase II trials have been conducted with respect to Norplant (6). In accordance with the law of the land, it is only proper that Phase III trials are conducted before a programme introduction study is carried out on the 20,000 women which puts norplant (6) on par with other approved methods of contraception.

6. Nor Plant (2) has been withdrawn from the world market following doubts raised by the Environmental Protection Agency of US regarding the possible teratogenic and carcinogenic properties of the catalyst 2 ethyl hexanoic acid used in making medical grade elastomer 382 which forms part of the Norplant (2) system. Under these circumstances ICMR must make every effort to locate each and every woman who has the implant in her and remove the same expeditiously. Also the health of all subjects of this experiment (all phases) be monitored. This case should be treated as analogus to that of withdrawal of the Dalkon Shield.

7. It is a cause of great concern that ICMR has no provisions for following up women subjected to contraceptive trials in the past.

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Taking just the case of NET-EN, Norplant (2), Norplant (6) the number of women (experimental subjects) is of the order of 20,000. We don't know what miseries some of these women have undergone or are suffering at present. It is imperative that all these women are followed up for 10 years and all long term adverse effects are reported. In furture follow-up should be a mandatory aspect of all studies.

8. Barrier method such as diaphragm and condoms have not been given adequate attention and diaphragm have been dismissed on the basis of 1 - 2 micro studies. Barrier methods are free from hazard and in order to give woman better control over their fertility, diaphragms have to be brought back into the FP programme.

We dissented on one of the ICMR's and other 'health advocates' recommendation regarding the farming out of contraceptive research to NGOs and women's groups.

(Minutes prepared by Sahali and Medico Friend circle)

23.12.91.

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