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MEMORANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
CENTER FOR DISEASE CONTROL

TO William H. Foege, M.D.
Director, Center for Disease Control (CDC)
Through: Philip S. Brachman, M.D.
Director, Bureau of Epidemiology (BE)

DATE December 14, 1979

FROM Howard W. Ory, M.D., Chief
Epidemiologic Studies Branch
Family Planning Evaluation Division, BE

SUBJECT International Travel: Delhi, India, 11/22-11/30; Chandigarh, India, 12/1-12/2; London, England, 12/4-12/6, 1979

SUMMARY

I. DATES AND PLACES
II. PURPOSES
III. CHIEF CONTACTS
IV. ACCOMPLISHMENTS
A. India-United States meeting on reproduction and contraception as called for by the United States, India Science and Technology Agreement
B. Recruitment of candidates for Rockefeller Foundation traineeships
C. Finalize manuscript on Length of Hospitalization Stay Relating to Tubal Sterilizations in the United States, 1970-75

SUMMARY

A joint meeting of Indian and United States scientists was held on the subject of Reproductive and Contraceptive Research. The meeting was sponsored under the new Science and Technology Agreement between the two countries. A series of relatively detailed proposals for projects that could be immediately implemented was produced as the final report of the meeting. With respect to those that affect CDC we proposed a training program in the epidemiology of reproductive health and contraceptive safety to be put on in India by CDC epidemiologists. In addition, we proposed a work study assignment for Indian obstetricians to come to the United States and work in the areas of reproductive health and contraceptive safety for from three months to two years. (NIH also made a similar proposal.) Three obstetricians were specifically identified as being potential candidates for this traineeship. In addition, several of the leading Indian scientists in the field of reproductive health were informed about the existence of the Rockefeller Foundation traineeship. On the London portion of the trip the manuscript on Length of Hospitalization Relating to Tubal Sterilization in the United States, 1970-1975 was completed.

I. DATES AND PLACES

Dehli, India - November 22-November 30, 1979
Chandigarh, India - December 1-2, 1979
London, England - December 4-6, 1979

II. PURPOSES

Dehli: The Indian government is apparently more favorably disposed towards collaborative work with the United States than it has been in recent years. Under the new Science and Technology Agreement between the United States and India, reproductive biology and contraceptive technology are listed as priority areas. The Indo-U.S. Workshop on Reproduction and Contraception Research was set up as the first meeting under this Science and Technology Agreement. The purpose of the meeting was to develop concrete proposals for areas of future collaboration. Where possible, we attempted to develop projects that could be implemented immediately. Several that will need review before implementation were also developed.

Chandigarh: Dr. Ranjit Roy Chaudhury, Professor of Pharmacology and Dean of the Postgraduate Institute of Medical Education and Research in Chandigarh invited me to his Institute to speak to his group about epidemiology and to tell them about our Rockefeller Foundation traineeships.

London: To meet with Dr. Peter Layde to finalize a manuscript on The Length of Stay Associated with Tubal Sterilization in the United States.

III. CONTACTS

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Bomba-400 036

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Education and Research
Chandigarh

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Director
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Jehangir Merwanji Street
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Bombay-400 012

Dr. K. Prema
Assistant Director
National Institute of Nutrition
Jamai-Osmania
Hyderabad-500007

Dr. G. P. Talwar
Professor and Head
Department of Biochemistry
All India Institute of Medical Sciences
New Delhi

Dr. J. S. Bajaj
Professor
Department of Medicine
All India Institute of Medical Sciences
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Dr. K. R. Laumas
Head
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Dr. A. R. Sheth
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Dr. S. K. Mukherjee
Scientist-in-Charge
Division of Toxicology and
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Central Drug Research Institute
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Dr. Malini Karkal
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Deonar
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Dr. Badri N. Saxena
Deputy Director-General
Indian Council of Medical Research

Dr. Suman Mehta
Institute for Research in Reproduction
Jehangir Merwanji Street
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Bombay

Dr. Inov Gupta
Department of Ob/Gyn
Post Graduate Institute of Medical Education
and Research
Chandigarh

IV. ACCOMPLISHMENTS

A. The Indo-U.S. Workshop on Reproduction and Contraceptive Research

The final report of the Workshop is attached (Attachment 1). With respect to those accomplishments that relate specifically to CDC's work, a protocol was designed to study the long and short term effects of male and female surgical sterilization. With respect to vasectomy, the long term effects of vasectomy are not known at the present time and there is speculation that vasectomy may cause an increase in cardiovascular disease over long periods of time. A protocol to accomplish a study of this subject was outlined and presented to the group. Since this protocol will need NIH and ICMR approval it cannot be immediately implemented.

For immediate implementation, we proposed a three month to two year training program in the United States either at NIH or at CDC in the areas of the epidemiology of reproductive health and contraceptive safety. In addition, we proposed a two to four week training course in India on the epidemiologic study of reproductive health, contraceptive safety and effectiveness.

While contraception programs have suffered in India in recent years, the keynote speech of our meeting suggests a favorable change is occuring (see Appendix 2 of Attachment 1). Thus the projects I have outlined above do have some chance to be implemented. Of course, this could change depending on results of the upcoming elections.

B. Recruiting for the Rockefeller Foundation Traineeship

Dr. Sheldon Segal suggested that I contact Dr. Ranjit Roy Chaudhury, Dr. K. Prema, Dr. Badri Saxena, and Dr. V. Ramalingaswami. Since all these people were at the meeting, I was able to talk with each of them. I explained the Traineeship to them and gave them a draft of the brochure describing it. In addition, I talked to Dr. Suman Mehta. Dr. Chaudhury invited me to Chandigarh after the Workshop was over to address his group there and to meet an obstetrician on his staff--Indu Gupta. Mrs. Gupta was specifically interested in further training in the area of epidemiology. Dr. (Mrs.) Gupta, Dr. (Ms.) K. Prema, and Dr. (Mrs.) Suman Mehta are the three best prospects for the Fellowship. Drs. Gupta and Mehta have done a year's course at the London School in Statistics and Demography. Dr. Prema does mainly small-scale clinical studies of the metabolic effects of oral contraceptives but is a highly intelligent person who has interest in epidemiology.

C. Finalizing Manuscript with Dr. Layde

Dr. Layde and I met and worked out the remaining problems on our manuscript on The Length of Stay of Women Undergoing Tubal Sterilization in the United States, 1970-1975.

Recommendations

1. Support the training course in India and the work/study assignments of Indians to CDC and NIH.

2. The vasectomy follow-up study would be of importance to both the United States and India. If the Indians are interested in doing the project, a CDC epidemiologist and statistician each would need to spend about three months in Dehli to help the Indians complete the protocol and get the study started. The project is worthwhile enough that additional man power should be recruited for this task if the Indians desire to do it.

3. With respect to the Rockefeller Foundation Traineeships, Dr. Roy Chaudhury suggested to us that a two year fellowship that does not lead to a diploma or degree has limited usefulness. He strongly urged that we find a way to grant a degree with that traineeship. If any of the three mentioned Indian obstetricians are interested in that program, I would urge that they be accepted as they all appear capable and energetic.

4. The manuscript that was completed will be submitted for publication.

Howard W. Ory

Howard W. Ory, M.D.

ATTACHMENT 1

INDIAN COUNCIL OF MEDICAL RESEARCH

REPORT OF THE INDO-US WORKSHOP ON REPRODUCTION AND CONTRACEPTION RESEARCH

[illegible]
([illegible],1972)

REPORT OF THE INDO-US WORKSHOP
ON
REPRODUCTION AND CONTRACEPTION RESEARCH

The Workshop was convened by the Indian Council of Medical Research (ICMR) in New Delhi 26-29 November 1979 with the mandate under the Indo-US Sub-Commission Agreement to develop research plans and protocols in reproduction and contraception research. The list of participants is provided in Appendix 1.

The Workshop was opened by Prof. V.Ramalingaswami, Director-General, ICMR. He indicated that hopefully this workshop would enable us to develop a creative partnership for scientific exchange, new knowledge, information and technology between the two countries in the field of reproduction and contraception research. He also stressed that the workshop should have two categories of functioning - (1) a short-term view where existing knowledge and technology can be made available for better use and (2) a long-term view where the newer approaches in the contra- and reproduction may be developed keeping in mind the priorities and the needs of the country.

The inaugural address for the workshop was given by Mrs.Sarla Grewal, Additional Secretary & Commissioner(FW). She was optimistic that "this meeting will lead to fruitful collaboration between the Scientific Community in India and US." A complete copy of the Add.Secretary's inaugural address is provided in Appendix 2.

The Agenda for the whole meeting is placed in Appendix 3. The first day was then devoted to an overview of research undertaken in India and the US with particular reference to topics of special interest to the counterpart expert participants keeping the priorities of India in mind.

The remaining 3 days of the workshop were devoted to the development of research plans and protocols. Task Forces were formed on the following topics, with members as indicated:

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1.	Reagent Bank	...	Talwar, Dialy
2.	Workshop on Hybridomas	...	Talwar, Corfman
3.	Cooperative Drug Testing	...	Chaudhury, Khanna, Dialy, Harper
4.	Drug delivery systems	..	Chaudhury, Lauwas, Khanna, Kumar, Dialy, Harper
5.	Inhibin	...	Duraiswami, Sheth, Moore, Moudgal
6.	Male reproduction	...	Bajaj, Kumar, Sheth, Troen, Moudgal, Dialy
7.	Medical effects of contraceptives	...	Prema, Mehta, Merkal, Soonawalla, Dry, Berendes
8.	Receptor assays	...	Lauwas, Hoffman
9.	LHRH	...	Talwar, Bajai, Dialy
10.	Implantation	...	Lauwas, Chaudhury, Harper
11.	Primate resource exchange	...	Mukherjee, Kumar, Corfman
12.	Infertility	...	Sheth, Troen, Moudgal, Moore, Duraiswami

Each Task Force was asked to prepare two types of protocols:

i) Protocols suitable for immediate initiation, subject to final negotiations and concurrence under the Indo-US Agreement, if required

ii) Protocols in draft form which will require further preparation and review

The Task Force Protocols for immediate initiation are provided in Appendix A and those for further development and review in Appendix B.

Dr. P. Corfman
(Member-Secretary US side)

Dr. H.N. Saxena
(Member-Secretary Indian side)

Appendix 1

INDO-US WORKSHOP
ON
REPRODUCTION AND CONTRACEPTION RESEARCH

List of Participants

INDIAN PARTICIPANTS

Dr. T.C.Anand Kumar
Department of Anatomy
All India Institute of Medical Sciences
New Delhi.

Dr. J.S.Bajaj
Professor of Medicine
All India Institute of Medical Sciences
New Delhi.

Dr. Ranjit Roy Chaudhury
Professor of Pharmacology and
Dean
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Dr. S.Duraiswami
Professor of Zoology
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Dr. Usha Gupta
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Dr. N.R.Moudgal
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Dr. S.N.Mukherjee
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Dr. S.K.Mukherjee
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Dr. K.Prema
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Dr. Shanta S.Rao
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Dr. V.Ramalingaswami
Director-General
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Dr. Badri N.Saxena
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US PARTICIPANTS

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Bethesda, M.D. 20205.

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Dr. Philip Corfman
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Dr. Ruth Moore
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Dr. Howard Ory
Chief, EpidemiologicalStudies Branch
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Dr.Philip Troen
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FAMILY PLANNING PROGRAMME AND RESEARCH IN CONTRACEPTIVES IN INDIA

Paper presented at the Indo-US Workshop on Reproduction & Contraception Research

By

Smt. Serla Grewal, IAS
Additional Secretary & Commissioner (FP)
Government of India
Ministry of Health & Family Welfare
NEW DELHI

Dated : 26th Nov.,1979

The ups and down that India's Family Planning Programme has witnessed in recent times bring into bold relief one known fact there cannot be any short-cuts in a nation's journey in the area of social reform. And when the area is as sensitive as human reproductive behaviour, the need for caution is all the more. Time, of course, is of crucial importance. Every year India has 12 million more mouths to feed and 3.5 million more jobs to create as a direct consequence of the population growth phenomenon. This stark reality cannot be pushed under the carpet or brushed aside as a problem or situation which may find its own solution as man struggles to carve a brighter future for himself.

In 1977 the programme was rechristened - from Family Planning to Family Welfare, with maternal and child health care as its main base. Services relating to maternal and child health care were strengthened and extended and it was made clear to the people that the principal aim behind the programme was to improve the quality of life by creating conditions which could prove conducive to the promotion of positive aspects of health.

Apart from strengthening maternal and child health care services, several new measures were taken to bring about people's participation in Health & Family Welfare Programmes. The most important of these measures is the Rural Health Scheme which was launched on October, 2, 1977. Under this scheme, every village having a population of 1000 has to have a Community Health Volunteer of its own. This worker is not a government functionary. He is selected by the village community with the help of doctors of the nearby Primary Health Centre and is expected to be a certified Female worker who works for it in the area of health and family

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welfare. Nearly 1,20,000 such workers have already been trained and they are working in as many villages. They are given a small stipend for the part-time (nearly two hours) service which they render to the community. In them a new leadership is emerging on the rural scene in India in the sphere of health and family welfare. Through this leadership, greater participation of the community in health and family welfare programmes can legitimately be expected. By1982-83 there is likely to be no village in the country without a community health volunteer of its own.

We have also undertaken a massive programme of training indigenous midwives. The intention is to upgrade existing skills in the baby-delivery system in villages. These midwives, like the community health volunteers, are also not government functionaries. Nearly 2,00,000 of them have already been trained and the goal is to have one trained indigenous midwife in every village by 1982-83.

We have been trying to involve all departments of the Government, particularly those which are concerned with development, in the family welfare programme. The process has been initiated and is gathering strength gradually.

India has already made considerable headway in introducing population education the formal educational system. In many schools, population education is being imparted to students; it has been integrated with other relevant subjects. An ambitious project under which population education will be imparted to nearly 100 million students has been drawn up and is likely to be launched next year. We have also developed a series of twelve lectures on population education for university students. The University Grants Commission has accepted our request to introduce this series in the Universities.

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In revitalising the family welfare programme, we are making full use of the mass media. From the All India Radio alone, more than 50,000 programmes on health and family welfare subjects are broadcast every year. Films, print media, outdoor media, traditional media, folk songs and dramas - from sophisticated television to puppetry - there are no media which we are not utilising to promote the family welfare programme amongst the people. At the grassroots in villages, we have tried to break new ground through the organisation of orientation camps of village influentials. Nearly 9000 such camps were organised last year. This year's target is 40,000 camps. On an average, every camp is attended by about 40 prominent persons from villages adjoining primary health centres and sub-centres. These persons are given free refreshments. At the camps they have free discussions with doctors and extension education personnel. This new approach - reaching the people through the people - is yielding good dividends. It is helping us greatly in removing misgivings about the programme amongst villagers and should eventually increase its acceptance by them.

The objective of the Family Planning Programme is to bring down the birth rate to 30 per 1000 by March, 1983 from the present level of around 35. This would mean adoption of contraceptive practices by 44 millions eligible couples as against 24 millions at present. This is a stupendous task. The knowledge of contraceptives is wide and attitude towards practice highly favourable among Indian couples; yet the gap between knowledge, attitude and actual practice continues to be wide. Perhaps to a considerable extent the reason for this situation lies in the absence of appropriate contraceptive technology.

The national family planning programme provides all contraceptive services and supplies free to acceptors. Our experience however shows

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that Vasectomy is not accepted as widely as it ought to be. Tubectomy services are limited due to inadequacy of technical facilities and trained man-power. Continuation rate of IUD (Lippes Loop and Cu.T 200) and oral pills is only about 60% and 30% respectively after a year. The condom is getting popular but its larger acceptance and regular use are linked with a number of factors which are slow to build, particularly in villages. Creams and foam tablets have a high failure rate and natural methods are highly unreliable.

Scientists all over the world have been struggling to make a breakthrough in developing more acceptable, easier contraceptives. Large sums of money have been invested in this endeavour. Sometimes one wonders whether we are going along the right tract. Research in this field has to have a much wider base and sweep. It is not just a matter of achieving greater sophistication in science and technology. The contraceptives to be developed are to be used by common people with their known simple attitudes to life.

The task demands a combination of disciplines - that of the pure scientists and of the social scientists. Sophistication and technology are no doubt highly important. Equally important are two other factors - how far the new contraceptive will be acceptable to the common people and what is the delivery system for its use? Is any scientific know-how necessary before it can be made use of? Can it be used on the simple advice of the vast array of paramedicals who are closer to the scene in rural areas? Whatever contraceptive is developed must be available locally. Advice to use it must also not be far to seek. In the matter of use of existing contraceptives, the developing countries owe a heavy debt to the developed ones. Their reliance on borrowed technology cannot, however, remain unending.

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Nor do they have endless resources to be invested in something which may finally emerge but may not be easily usable. It is indeed a paradox that while the National Family Planning Programmes are suffering due to non-availability of appropriate technology in contraceptives, more and more information is coming on about rural population using local herbs, plants and traditional medicines for contraceptive effects. This information must be taken note of by our scientists. Ultimately their success will lie in developing contraceptives which the people can use without having to go to doctors for advice - contraceptives which they may be able to get easily through local, rural sources. The delivery system is of utmost importance and it must be taken into account as scientists intensify their efforts to evolve simple contraceptives.

India gives a high priority to Research in reproduction. A coordination Committee with Scientists from Government and non-Government research institutions as its members, has been constituted. In the light of our past experience, a new direction has been given to Reproduction research and priorities have been identified. High priority is given to applied research. New contraceptive development is a long process and takes anything from ten to twenty years. Time is crucial for the family planning programme and we cannot wait for years for new contraceptives. Keeping this in mind, we have given high priority for research which aims to improve the existing available methods. The results have been quick and greatly satisfying. Indian scientists have been successful in identifying an indigenous medicine, which controls bleeding after IUD insertion. Initial results are extremely encouraging. Potential local spermicidal action has been identified in one of the widely available local nut. This has been used in developing highly effective Jelly and Foam tablets. These products are also under clinical trials. In India termination of pregnancy is legal. A cheap Cervical Dilator Implant as a substitute to laminaria tent has been

developed and would be soon marketed in India. Now a low oestrogen content pill is being used in the National Programme, which is found to have comparatively less side effects. Clinical trials with centchroman, a sort of a morning after pill, are in final stages. Extensive trials are also going on in India with implants, injectables, vaginal rings and other promising new methods. Basic research, though given a low priority, is not neglected. India's lead in developing an antifertility vaccine and male pill have been well recognized.

This Workshop is being held as a follow up of one of the recommendations of the joint Indo-US Sub-Commission which had met in India two years ago to formulate collaborative research projects enabling the scientists from both India and US to work on mutually interesting topics which have relevance to their respective countries. It is expected that this scientific and technological collaboration between the scientists from the two countries will accelerate the progress of various research activities. From the Indian view-point, it is quite appropriate that the ICMR has been asked to host and coordinate this workshop since its pattern of functioning has considerably changed in the last one year. The ICMR has been rightly projecting its role as the national coordinating agency in the country in the field of biomedical research. The ICMR has constituted a Advisory Committee on Contraception/Human Reproduction Research which consists of scientists from various ICMR and non-ICMR institutions in the country and also includes representatives from the concerned departments in the Ministry of Health & Family Welfare as well as from sister research Councils, such as the Council for Scientific & Industrial Research and the Indian Council of Agricultural Research. This Advisory Committee has met and is utilizing the Task Force approach to deal with various problems which have relevance to the needs of the country. In addition, ICMR has set up a Toxicology Review Panel and a Central Ethical Research Committee which screen the

available information on various contraceptives for possible studies in and research on relevant subjects.

I would urge the participants in this Workshop that while they discuss and plan projects for possible Indo-US collaboration, they should keep the time factor in their view. Our country needs urgently research which will enable us to make existing methods safer and more acceptable for mass use in the immediate future; while we may keep on exploring newer avenues. For example, in the field of female contraception, it is imperative that we find out solutions to the bleeding problems which are associated with IUDs, as well as long acting injectable contraceptives. As regards oral contraceptives, the need perhaps is to find out a pill which does not require daily administration. In the field of male contraception, we have only one method available for the time being, which is vasectomy. The long-term effects of vasectomy needs to be investigat It is also necessary to explore and develop techniques which will make vas occlusion a reversible method. The same approach applies to female sterlization where newer tecaniques which would reduce complications following tubal sterilization as well as make the method reversible are also required. As regards Medical Termination of Pregnancy, we must realize that while sophisticated techniques can be and are being used in various teaching hospitals, the actual need lies in rural areas, where literacy rates are low, motivation is inadequate and socio-economic conditions are also poor.

I hope that the deliberations of this meeting will lead to fruitful collaboration between the scientific community in India and US. India considers any expenditure on research as sound investment.

I wish all success to this Workshop and take great pleasure in inaugurating this Workshop.

APPENDIX 3

INDIAN COUNCIL OF MEDICAL RESEARCH

INDO-US WORKSHOP ON REPRODUCTION AND CONTRACEPTION RESEARCH

Venue: ICMR Headquarters
New Delhi

Date: November 26-29, 1979

Tentative Agenda

MONDAY NOVEMBER 26,1979

0900 - 0910	Welcome	: Dr.V.Ramalingaswami : Director-General,ICMR
0910 - 0930	Inauguration	: Mrs. Serla Grewal, Addl. Secretary and Commissioner (FW)

0930 - 1300 SESSION I : BRIEF REVIEW OF RESEARCH WORK DONE IN INDIA

Chairperson : Dr. P.Corfman

0930 - 1030 SECTION A - REPRODUCTIVE BIOLOGY

1. Male Fertility Regulation (30 minutes)
   Overview - Dr.J.S.Bajaj (20 minutes)
   Inhibin - Dr.A.R.Sheth (10 minutes)
2. Female Fertility Regulation (15 minutes)
   Overview - Dr.K.R.Laumas (15 minutes)
3. General Comments and Discussions (15 minutes)

1030 - 1100 COFFEE BREAK

1100 - 1200 SECTION B - CONTRACEPTIVE DRUG & DEVICE DEVELOPMENT

1. Vaccine - Dr. G.P.Talwar (15 minutes)
2. Newer Drug Delivery Systems - Dr. G.N.Saxena (15 minutes)
3. Toxicological Studies - Dr.S.K.Mukherjee (15 minutes)
4. General Comments and Discussions (15 minutes)

1200 - 1300 SECTION C - MEDICAL EFFECTS OF CONTRACEPTIVES IN USE

1. Intrauterine Devices (20 minutes)
   IUD Induced Bleeding
   - Dr.R.R.Chaudhury (10 minutes)
   Pelvic Inflammatory Diseases and Newer IUDs
   - Dr.R.P.Soonawalla (10 minutes)

2. Metabolic Effects of Steroidal Contraception
   - Dr.K.Prema (10 minutes)

3. Epidemiological Studies (10 minutes)
   - Dr.Suman Mehta

4. General Comments and Discussions (20 minutes)

1300 - 1400 LUNCH BREAK

1400 - 1700 SESSION II : BRIEF REVIEW OF RESEARCH WORK DONE IN US

Chairperson : Dr. B.N.Saxena

1400 - 1500 SECTION A : REPRODUCTIVE BIOLOGY

1. FSH,LH and Folliculostatin - Dr.R.Moore
2. Testicular Function - Dr. P.Troen
3. Estrogen Receptor Assays - Dr.P.Hoffman

1500 - 1530 TEA BREAK

1530 - 1630 SECTION B : CONTRACEPTIVE DRUG & DEVICE DEVELOPMENT

1. The Drug & Device Program at NIH - Dr.C.Dialy
2. Prostaglandin and Implantation - Dr.M.Harper

1630 - 1730 SECTION C : MEDICAL EFFECTS OF CONTRACEPTIVES IN USE

1. IUDs and OCs - Dr.H.Ory
2. Sterilization & Abortion - Dr.H.Berendes

TUESDAY NOVEMBER 27,1979

0930 - 1730 SESSION III : DEVELOPMENT OF SPECIFIC RESEARCH PROPOSALS FOR INDO-US COLLABORATION

Chairperson : Dr. B.N.Saxena

0930 - 1300 *SESSION III(A): INDEPTH DISCUSSION ON POSSIBLE AREAS OF INDO-US COLLABORATION

0930 - 1030 SECTION A - REPRODUCTIVE BIOLOGY

1030 - 1100 COFFEE BREAK

1100 - 1200 SECTION B - CONTRACEPTIVE DRUG & DEVICE DEVELOPMENT

1200 - 1300 SECTION C - MEDICAL EFFECTS OF CONTRACEPTIVES IN USE

1300 - 1400 LUNCH BREAK

*Joint Discussion by participants from India & US

1400 - 1730 *SESSION III(B) WORKING GROUPS FOR DEVELOPING RESEARCH PROTOCOLS FOR SPECIFIC PROPOSALS OF INDO-US COLLABORATION

GROUP I : REPRODUCTIVE BIOLOGY
GROUP II : CONTRACEPTIVE DRUG & DEVICE DEVELOPMENT
GROUP III : MEDICAL EFFECTS OF CONTRACEPTIVES IN USE

WEDNESDAY NOVEMBER 28, 1979

0930 - 1700 *SESSION III(B) (Continued) WORKING GROUPS FOR DEVELOPING RESEARCH PROTOCOLS FOR SPECIFIC PROPOSALS OF INDO-US COLLABORATION

THURSDAY NOVEMBER 29, 1979

0930 - 1300 *SESSION III(B) (Continued) WORKING GROUPS FOR DEVELOPING RESEARCH PROTOCOLS FOR SPECIFIC PROPOSALS OF INDO-US COLLABORATION

1300 - 1400 LUNCH BREAK

1400 - 1630 SESSION IV : PLENARY SESSION (FINAL DISCUSSION AND RECOMMENDATION ON JOINT PROPOSALS OF INDO-US COLLABORATION

Chairpersons : Dr.P.Corfman
: Dr.V.Ramalingaswami

1630 - 1700 Concluding Remarks : Dr.V.Ramalingaswami

RAPPORTEURS

	Indian Side	US Side
Reproductive Biology	: Dr.K.R.Laumas : Dr.J.S.Bajaj	: Dr.Michael Harper
Contraceptive Drug & Device Development	: Dr.G.P.Talwar : Dr.S.K.Mukherjee	: Dr.Gabriel Dialy
Medical Effects of Contraception	: Dr.R.R.Chaudhury	: Dr.Heinz Berendes

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SECRETARIAT

Secretary : Dr.R.N.Saxena, Deputy Director-General,ICMR(Indian side)
Dr.P.Corfman, Director, HCD/CHD (US Side)

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*To be jointly prepared by participants from India and US as grouped above

PROTOCOLS FOR IMMEDIATE INITIATION

1. Reagent bank
2. Hybridoma workshop
3. Collaborative drug testing
4. Inhibin standards and assays
5. Indo-US Collaborative workshop on Semen Analysis
6. Exchange Programme to Foster Research on Medical Effects
7. Inhibin in testicular function

REPORT OF REAGENT BANK TASK FORCE

PROJECT TITLE: ESTABLISHMENT OF A REAGENT BANK

Discussions held during the Indo-US Workshop in Reproduction and Contraception Research identified the need to establish a hormone Reagent Bank under the auspices of the ICMR. Provision of a variety of hormones relevent to reproductive studies should optimize research operations. The National Institute of Child Health and Human Development currently distributes through the National Pituitary Agency (NPA) a number of hormonal preparations. This facility is accessible to scientists from all over the world and many Indian scientists have received preparations through the NPA. However, the current distribution system is time consuming and transit delays result, at times, in loss of bioactivity of perishable reagents. The group proposed the setting up of a NPA Reagent Bank for use of investigators in India under the ICMR.

The NICHD will provide ICMR a reasonable stock of the following reagents:-

1. HCG - Purified (11,000 IU/mg)
2. HCG - Semipurified (5,000 IU/mg)
3. HCG α Subunit
4. HCG - β Subunit
5. Antisera to the above and HCG - β fragments as well as to fragments.
6. LH α
7. LH - β

   Ovine
8. LHRH and antiserum
9. PMSG
10. Nonhuman primate pregnancy test kits
11. RIA reagents for monkey LH and FSH

Reagents generated by the Indian Scientists such as Anti - OFSH, Anti OLH, anti-Inhibin, anti 45 CTP of β HCG, anti β hCG will be supplied to NICHD for evaluation and distribution to other interested investigators.

The ICMR will set up an appropriate storage and distribution system for these reagents. The perishable nature of some of these material requires that they be stored under deep refrigeration preferably at - 70°C or below.

BUDGET REAGENT BANK

Capital outlay

1	Deep Freeze	Rs. 10,000
1	Refrigerator	Rs. 10,000
	Emergency generator	Rs. 85,000
		Rs.1,05,000
1	Revco ultra Deep Freeze	Rs. 40,000

Running Expenses

one Technician	Rs. 9,000
Dessicator & Dessicating material	Rs. 2,000
Forwarding costs package/ Postal charges	Rs. 5,000
Record & Stationery	Rs. 2,000
	Rs. 18,000

The Reagents will be rechecked for specification by competent local laboratories periodically to ensure the preservation of stated activity during storage.

REPORT OF HYBRIDOMA TASK FORCE

PROJECT TITLE : ICMR - NIH SPONSORED WORKSHOP ON HYBRIDOMAS

In recent years, an important development is the technique permitting the hybridization of somatic cells in a manner that the genetic capability of making distinct proteins is retained. This technique opens up new possibilities for basic and applied studies, namely systems for study of regulatory mechanism for expression of genetic information and for development of cell lines making useful products. These approaches can be of particular interest to reproductive research. Antibodies of defined specificity and affinity can be generated adding a new dimension for having immunological reagents for radio-immunoassays of hormones, pregnancy detection kits and researches aimed at control of fertility by immunological approaches. A number of investigators in Universities and research institutions in India would welcome a laboratory based work conference in this area.

PROPOSITION :

To organize a workshop, under the auspices of NIH & ICMR on Hybridomas. The workshop can be held at the ICMR-WHO Research & Training Centre in Immunology at the All India Institute of Medical Sciences, New Delhi. The workshop will be of 3 weeks duration, scheduled in November, 1980.

12-16 midcareer investigators selected by ICMR from medical colleges, universities and National Research Institutes in the country will take part in the Workshop. In addition, opportunity may be provided to about 50 observers for auditing the lectures and demonstrations.

The Course will consist of (i) Lectures, discussion sessions covering the background and theoretical concepts; and (ii) laboratory work.

The Faculty will be composed of two Consultants from USA. They will be backed by local counterparts for covering the related topics. Two technicians from laboratories experienced in maintaining hybridomas will also be required.

NIH will meet the travel expenses and honorarium of the Scientists/technicians coming from U.S.A. ICMR together with other local Agencies will look after the local expenses.

Suggestions on possible Faculty Members from U.S.A. are :

1. Mr. Max D. Cooper
   Tumor Institute
   University of Alabama
   Birmingham

2. Dr. L.A. Herzenberg
   Department of Genetics
   Stanford University
   California

3. Dr. U. Hammerling
   Sloan Kettering Research Institute
   New York

4. Dr. M.D. Scharff
   Albert Einstein College of Medicine
   New York

Local Convenor : Dr. G.P. Talwar
All India Institute of Medical Sciences
New Delhi

The detailed programme of the Course will be chalked out in February and finalized by June, 1980.

BUDGET HYBRIDOMA WORKSHOP

I. NIH RESPONSIBILITY

Travel to and from of 2 US Scientists

2 US Technicians

Per Diem for Technician 30 days

Per Diem for Scientists 20 days

Material costs for Reagents not available in India
(Subject to consultation with faculty) to be determined.

II. ICMR RESPONSIBILITY

-	Participants in country travel cost	- Rs.10,000
-	Stay expenses for 16 for 15 days	- Rs.36,000
-	Workshop running expenses Reagents Glassware, Plastics ware, Honorarium to faculty, overtime to technical staff, contingencies	- Rs.30,000
		- Rs.76,000

PROJECT III

REPORT OF COLLABORATIVE DRUG TESTING TASK FORCE

PROJECT TITLE: COLLABORATIVE DRUG TESTING

Aims and Objectives

People in India have for the past many decades used traditional medicines and the Ayurvedic System of medicine describes the extensive use of many plant products for the treatment of various diseases. Systematic investigation of plant products to obtain biologically active materials started over three decades ago and investigators in India now have considerable experience in testing plants for antifertility activity. Over 2500 plants collected from various parts of the country in different seasons have been tested in various laboratories for antifertility activity. Out of these about twenty plants have shown promise as a potentical contraceptive agents.

This collaborative study would take advantage of the large experience and information available and attempt to focus on early development of a local/systemic contraceptive of indigenous origin. Some of the institutions engaged in this activity are the Central Drug Research Institute, Lucknow, the Postgraduate Instt. of Medical Education & Research, Chandigarh, the Institute for Research in Reproduction, Bombay, the Indian Institute of Experimental Medicine, Calcutta, the Regional Research Laboratory, Jammu, the Institute of Medical Sciences, BHU, Varanasi and Medical College, Trivandrum. The ICMR has established a Task Force on antifertility plants to ensure that a coordinated and integerated approach aimed at early development of contraceptive agents and

METHODOLOGY

The programme of work to be carr[illegible] involves two approaches since it has been observed [illegible] ifertility activity increases on extraction and subsequent [illegible]nation in some plants whereas in others it decreases. [illegible]equires that two different strategies need to be adopt[illegible] he former, extraction and isolation needs to be carried out [illegible] as possible. In the latter, clinical evaluation after [illegible]te toxicology studies should be initiated under cu[illegible] itored conditions. Both of these approaches would be fo[illegible] he steps of the collaborative effort are as follows:

1) Identification of selected [illegible]ducts by the Indian Scientists to be s[illegible] for confirmation of activity identified by [illegible]

2) Confirmation of the biolo[illegible] vity by the CDB, CPR, NICHD

3) Further Drug Development st[illegible] (a) Chemical
(b) Toxicological
(c) Clinical

It is understood that no clini[illegible]ation would be undertaken unless the product has bee[illegible] for use in human both by the Toxicology Review Panel a[illegible] Committee of the Indian Council of Medical Research.

DETAILS TO BE PROVIDED TO THE NICHD

Full details of the plant pro[illegible]on that would be sent to the USA would be provided. [illegible]es the experiments carried out, species of [illegible], chromotographic fractions etc. Adequate qu[illegible] product/

fraction would be supplied and corresponding samples would also be kept in the concerned Indian Laboratory.

The USA Scientists would provide to the ICMR all results obtained in the screening of the products. The usual confidentiality clause would be observed by both sides to protect the interest of the concerned Scientists.

PHASING OF THE PROGRAMME

It is expected that ten products/fractions exhibiting promising activity would be sent for screening to the USA every year for three years. It is also envisaged that toxicological study would be carried out on 5-6 products/fractions.

It is hoped that Phase I clinical trial could be carried out on 4-6 products/fractions in the second and third year of this collaborative programme.

The usual protocol for toxicological studies as followed at the Central Drug Research Institute, Lucknow will be used. The two protocols developed at the Postgraduate Institute of Medical Education & Research, Chandigarh for (a) Contraceptive clinical evaluation (b) Early MTP Programme will be followed. The protocols are available and can be made available if necessary The present document is only an outline of understanding arrived at this workshop. It is recognised that a complete proposal detailing all the procedures involving chemistry, and biology will be provided in the official proposal document.

BUDGET

1.	Collection, Identification of plants Isolation and characterization of active constituents (in India - 2 Centres)	Rs. 9.00 lacs
2.	Acute, Sub-acute toxicological studies to be done in at least two centres in India	Rs.4.00 lacs
3.	Clinical evaluation - Phase I and Phase II studies	Rs.5.00 lacs
4.	Contingencies	Rs.2.00 lacs

Total - Rs.20.00 lacs per year

Duration of project - Three years

Total funds required for the duration of the project Rs.60.00 lacs

This collaborative venture would not only assist in the immediate development of contraceptive agents/devices but would contribute substantially to the development of this important area which has been identified as a national priority for the future years.

REPORT OF INHIBIN TASK FORCE

PROJECT TITLE: INHIBIN STANDARDS AND ASSAYS

As members of the INDO-US Workshop have pointed out, there is an urgent need for an international standard for inhibin and international agreement on a sensitive, specific, reproducible and practical bioassay. To these ends we propose the following:

Current Goals

1. Partially purified inhibin preparations from different sources (male human and ovine, Dr.Sheth; male bovine and female ovine, Dr.Duraiswami; female porcine, Dr.Moore; male ovine, Dr.Moudgal) be exchanged by the participants fortesting on each investigators bioassay.

2. On the basis of the experience gained from 1, a reference preparation as well as one or two bioassays will be chosen and proposed for universal international acceptance and exchange.

3. Exchange of purification procedures between laboratories will aim to reproduce individual purification results.

4. Immunological cross-reactivity of preparations of different sources will be examined with a view to RIA application.

5. Dr.Moudgal will test material from each investigator in model system being used in his laboratory primate.

ong Range Goals

. Utilize inhibin RIA for examination of human reproductive atus.

7. Purified material will bd utilized to determine the physiological role of FSH and inhibin in developing and adult males and females.

8. Once a good degree of purification has been agreed on, material will be tested in the male and female for possible contraceptive applicability in a) rats initially; b) sub-human primates (Dr.Moudgal has kindly indicated a willingness to provide sub-human primates for examination # of effectiveness).

9. We propose a workshop to take place in 2 years to review progress towards these goals.

Budget for 3 years

1. Research Fellows

Two for two Indian Centres	Rs. 50,000.00
One for one US center	$ 37,500.00

2. Raw materials

Indin side	Rs. 20,000.00
US side	$ 2,000.00

3. Animal facilities

Indian side	Rs. 8,000.00
US side	$ 5,000.00

4. Chemicals & Reagents

Indian Side	Rs. 1,18,400.00
US side	$ 25,000.00

5. Travel cost

Indian side	Rs. 48,000.00
US side	$ 2,500.00

REPORT OF MALE REPRODUCTION TASK FORCE

PROJECT TITLE : IRMO-US COLLABORATIVE WORKSHOP ON SEMEN ANALYSIS

OBJECTIVES:

1. Review of standardization of available methods of semen analysis.

2. Definition of criteria for evaluation of efficacy of male contraceptive agents

3. Documentation of the recommendation as a common protocol to be used in drug trials for male fertility regulating agents in the two countries

AGENDA ITEMS:

1. Spermatozoa:

1.1 Number

1.2 Motility

1.3 Morphology

1.4 Biochemical and Biophysical characteristics

1.5 Functional evaluation

i. Cervical mucus penetration

ii. In-vitro tests for fertilizing ability

2. Seminal Plasma:

2.1 Physical

2.2 Biochemical

2.3 Immunological

3. Preferred criteria for the evaluation of effects of male [illegible]tility regulating agents and qualitative alter[illegible]n semen.

4. Documentation of a common protocol based on above

OPERATIONAL FRAMEWORK:

There would be plenary session as well as the meetings of working sub-groups on the specific items listed in the Agenda. Background documents, thus prepared, will be jointly deliberated upon in the plenary session to evolve common and mutually acceptable recommendations.

IDENTIFICATION OF PARTICIPANTS

It is recommended that optimal group size for this Workshop would be 15 to 20 participants. Suggested list of participants is enclosed. The final identification of the participants would be made on the basis of the recommendations of the Coordinating Agencies for Indo-US Collaboration in consultation with the two convenors specifically nominated for this workshop (Dr.Phillip Troen(USA) and Dr. J.S. Bajaj (India).

VENUE OF THE WORKSHOP:

New Delhi (INDIA)

PROVISIONAL DATES FOR THE WORKSHOP:

October 1980

DURATION WORKSHOP

4 days

FINANCIAL REQUIREMENTS

Travel (International) to be supported by US funds	Rs.140,000
Travel (Local) to be supported through ICMR	Rs. 8,000
Per-diem (For US Participants)	Rs. 30,600
Per-diem (For Indian Participants)	
Secretarial Assistance*	Rs. 8,000
Local Workshop Arrangements*	Rs.195,200

*These funds will be provided through the ICMR

PROJECT VI

REPORT OF MEDICAL EFFECTS TASK FORCE

PROJECT TITLE: EXCHANGE PROGRAMME TO FOSTER RESEARCH ON MEDICAL EFFECTS

INTRODUCTION

Although there are only a few trained epidemiologists in India, the vast family planning effort which this community has generated has resulted in the development of many projects aimed at the evaluation of family planning services, acceptability and contraceptive safety. These projects are conducted by medical scientists, public health workers, social scientists, demographers and other groups who are relatively isolated from contact with similar investigations done in the United States, especially the CDC and the NIH.

We propose a two part exchange programe in the field of family planning evaluation and contraceptive safety.

The first part would provide for a few (upto four) US investigators of family planning evaluation and contraceptive safety to spend from one to three months in India. During their stay they would give lectures on relevant topics of contraceptive safety, discuss in workshops the specific investigations in which they are involved and provide advice and consultation to Indian scientists working in this field.

US participants in this programme would be selected based upon their epidemiological expertise in the field and their involvement i[illegible]ng studies on contraceptive safety.

The second part of the programme would provide for several selected Indian scientists to come to the US for advanced training and practical experience in epidemiology related to family planning.

OBJECTIVES

To provide opportunities to Indian Scientists who are working in the field of family planning evaluation and contraceptive safety to become acquainted with the relevant researches in these fields conducted by the CDC and by the NIH. Furthermore, to increase their epidemiological and investigative skills by working with investigators of the CDC as the NIH involve in studies of contraceptive safety.

SPECIFIC ASPECTS OF PROGRAME

Indian Scientists would be selected to spend from 3 months to upto 2 years in the Family Planning Division of the CDC or the Epidemiology and Biometry Research Programe and the Center for Population Research of the NICHD. They would be involved during their stay in the planning, initiation and conduct of studies of contraceptive safety. Opportunities for analysis of data would be provided including the preparation of Scientific reports and manuscripts for publication. The Indian Scientists would be encouraged to bring along data which they may want to analyse and specific ideas for projects which they may want to initiate after returning to India and for which they may want US advice.

Preceptors : Dr Ory, CDC
Dr Berendes, NIH

FUNDING:

US Scientists going to India will be funded by PL-480 funds. Travel to the US by Indian Scientists will be provided for by PL-480 funds. CDC & NIH can provide funds for stipend and living expenses for Indian Scientists while they are living in the U.S.

REPORT OF INFERTILITY TASK FORCE

PROJECT TITLE: ROLE OF INHIBIN IN TESTICULAR IN FUNCTION*

Joint project on inhibin in Testicular function.

It is proposed to initiate a joint Indo-US study on the role of inhibin in testicular function with emphasis on male infertility.

1. In the first phase, Dr. Sheth will send the necessary reagents for inhibin RIA developed at I.R.R. Bombay alongwith methodology to Dr. P. Troen at Pitsburgh to standardise the methods.

2. Once this inhibin RIA is established, then further collaborative projects may be drawn.

PROTOCOLS FOR FURTHER DEVELOPMENT AND REVIEW

1. Drug Delivery Systems : Statement of Intent
2. Development of an Intranasal Spraying Device
3. Study of Pituitary Gonadal Axis Following LH-RH Administration
4. Study of Pituitary Gonadal Axis Following Intranasal Medroxyprogesterone
5. Fertility Regulation in the Adult Male Primate by Actively Immunization with FSH Beta Subunit
6. Vasectomy-Tubectomy Follow-up
7. Lipid and Coagulation Profiles in OC users
8. Health and Nutritional State following Steroid Administration
9. Human Uterine Steroid Receptors
10. LH-RH Statement of Intent
11. Implantation
12. Private Resource Exchange : Statement of Intent

BEST AVAILABLE DOCUMENT

DRUG DELIVERY SYSTEMS TASK FORCE REPORT : Statement of interest.

The group felt that support should be provided through this INDO-USA collaborative venture for development of devices which would ensure controlled release of drugs for long periods of time. Experts on membranes & polymer chemistry are available in USA. It is hoped that these investigators can be persuaded to share the technology with Indian scientists through the joining auspices of the NIH and ICMR.

In the first phase information will be obtained by N.I.H personnel as to the feasibility of delivering prostaglandin synthetase inhibitors and an anti-fibrinolytic agent by using existing membrane or polymers. It is recognised that the cost of developing new IUDs to release only 2 selected inhibitors of PG synthetase (i.e. Mefanamic acid and naproxen) and 1 selected anti-fibrinolytic agent (i.e. etamsylate) would be prohibitively expensive. It was suggested that alternative modes of delivery might be considered for initial studies of the efficacy of these compounds i.e. if these substances can be delivered from microcapsules of the type develop by the Southern Research Institute, Birmingham, Alabama then such capsules could be delivered to the uteri of monkeys by laparoscopy at the time of IUD insertion and again at selected intervals. Measurements of blood lost could be made by the methods developed by Shaw in Los Angeles in intact cycling monkeys or in overiectomized model subjected to estrogen withdrawal regimen.

Such microcapsules could be initially tested in small laboratory rodents. Only when the most appropriate compounds have been selected can development of an IUD releasing this compound be envisaged.

This type of activity would require funds in excess of US $ 500,000 for development of one device which would be evaluated in primates and following the appropriate toxicological studies, in women in India.

The specific and detailed toxicological studies that need to be carried out with an IUD containing a drug would need an input of Rs. one lakh per year to the Indian side.

REPORT OF DRUG DELIVERY TASK FORCE

PROJECT TITLE: Development of Intranasal Spraying Device to improve the Bioavailability of Contraceptive Steroids.

2. Introduction: Administering contraceptive steroids by the intranasal route is a concept which is totally of Indian origin. This concept was first enunciated in 1974 and it aims to reduce the overall dose of contraceptive steroid and thus reduce not only the cost of contraceptive but also reduce the overall drug-load on the body. It also offers the possibility of using naturally occurring hormones, as opposed to synthetic steroids for contraceptive purposes.

Extensive studies have been carried out in this area both in India and in various other collaborating centres and the method has shown promise. However, further extensive studies need to be carried out to develop an approach spraying device which will deliver a known amount of steroid as well as to determine whether administering contraceptives over prolonged periods by the intranasal route will cause any adverse effect in the nasal mucosa or associated brain tissue. These studies are a prerequsite before entering a large-scale clinical trial.

In view of the promise shown by this approach the Indian Council of Medical Research has constituted a National Task Force comprising senior investigators from various institutions in India.

This Proposal envisages to augment the function of this Task Force to take this novel Indian concept to its logical conclusion.

The work envisaged in the Proposal will be carried out in India by investigators identified by the ICMR. US collaboration in technical know-how would be made available as and when required to further this Task. Dr. Szbkati Gabriel Bial from the US side has agreed to act as the US co-ordinator during the initial stages.*

3. Objectives:

a) To improve the contraceptive efficacy of hormonal contraceptives by intranasal administration

b) To try and reduce adverse side-effects of hormonal contraceptives

c) To determine the pharmacokinetics of steroids and other compounds in csf and blood in monkeys following intranasal administration of contraceptive steroids and using the spraying device set to deliver diverse particle sizes

d) To study the ultrastructural effects of nasal sprays on the olfactory mucosa by quantitative Scanning Electron Microscopy as well as x-ray dispersal analysis with Transmission Electron Microscopy.

4. Procedure:

a) The compounds to be tested will be sprayed intranasally using various solvent systems as established in our laboratories. Blood and csf samples will be drawn at various intervals of time to determine the various pharmacokinetic parameters related to the bioavailability of the compounds in the blood. The analytical techniques to be used in this study will be clearly established for sensitivity, precision and reliability. The studies will be carried out in monkeys.

b) The second aspect of these studies will be related the study of any deleterious effects on the nasal mucosa following chronic administration of the drugs. Such studies will be carried out in the EM facilities available in our laboratories.

5. Summary of Research Project (150 words)

The concentration of steroids in the blood and cerebrospinal fluid and consequently their bioavailability to target

* A detailed Toxicological Protocol may be generated by the ICMR as an adjunct to this proposal with an amended budget.

organs is much higher following intranasal administration as compared with systemic administration. This pattern of transfer is dependent on the size of the particle delivered by the spraying device and it has been shown to be due to the slow, but ready, transfer of steroids from the nasal mucosa into the humoral compartments of the body.

The spraying characteristics of the device, facilitating such a pattern of transfer, have been determined at the AIIMS and a laboratory prototype in which the size of the sprayed particle can be varied at will has been developed. It is proposed to use this device for determining the optimal size of the sprayed particle which will ensure the maximal bioavailability of steroids to target tissues and also carrying out long-term toxicity studies for carrying out future trials in human subjects.

6. Present Knowledge

As far as we are aware studies in this area have been extensively carried out only in our laboratories and therefore this review pertains mostly to our studies.

Spraying steroids into the nostrils results in their being concentrated to a greater extent in the body fluids in blood and csf as compared with their systemic administration (Anand Kumar et al., Current Science 43: 435, 1974). This preferential transfer of steroids into the humoral compartments has been shown to be dependent on the way in which steroids are administered into the nostril. The spraying

Technique used in our laboratories has been previously described (Gopinath et al., Current Therapeutic Research, 1 23: 596, 1973). These studies have shown that the spraying device used in our studies deposits the maximal amount of the compound in the olfactory region of the nasal mucosa from where the sprayed substances are transported transneuronally into the brain and csf by the olfactory rods as well as transcellularly by the supporting cells into the subepithelial capillaries.

The method of calibrating the spraying device and the spraying characteristics have also been described (Anand Kumar et al., in: Recent Advances in Reproduction and Regulation of Fertility, Ed., G.P. Talwar, Elsevier/North Holland Biomidical Press, 1979). Our spraying device delivers a particle size of about 7um.

The contraceptive efficacy of steroids administered by the intranasal route has been tested in the rhesus monkey. These studies (Anand Kumar et al., Nature, 270: 532, 1979 ibid) have shown that microdoses of progestrone administered intranasally during the periovulatory period of the menstrual cycle can cause anovulation in a significant percentage of treated monkeys. More recent data using a combination of estrogens and progestrone have shown that the contraceptive efficacy of steroidal nasal sprays can be improved.

Other data from our laboratories indicate that microdoses of progestins or estradiol can impair the spermatogenesis as well as the endocrine function of the testes in

male rhesus monkeys.

Short-term toxicity studies using our device in rhesus monkeys have been carried out at Hintingdon Research Centre where about 100 times the expected dose/kg body weight was given daily to rhesus monkeys over a period of 28 days. These studies did not reveal any deliterious effects on the nasal mucosa.

As a consequence of these studies a limited endocrine study was carried out in human subjects who partipated in a multicentre trial. No adverse effects were observed in any of the women. Indeed the acceptability of this method of steroid administration was found to be quite high.

It must be pointed out that the steroids administered with this spraying device is almost exclusively deposited in the olfactory mucosa which is anatomically located in the superiod nasal concha. In the instance of common cold, it is the respiratory mucosa lining the inferior and middle concha which is inflamed. Therefore there is no impediments for steroids to reach their desired target when sprayed intranasally.

Thus, these studies carried out so far have encouraged us to pursue the intranasal approach to fertility regulation to its logical conclusion.

More recent studies carried out in this direction which are under publication have shown that the concentration of steroids in the nasal and ear compartments following intranasal administration is much greater than intravenous

injections. However, when steroids are slowly infused then their bioavailability in the humoral compartments is greatly enhanced. These findings led us to conclude that the higher bioavailability of steroids in the humoral fluids is because of their slow transfer into the body fluids from the richly vascularized nasal mucosa.

7. Preliminary work: Summarized above.

8. Reprints : Attached (to be)

9. Detailed Research Plan:

1) Choice of sprayed particles size: Using the device developed at this Institute it is proposed to choose 4 particle sizes viz., 1-5um, 5-10um, 10-20um and 20-30um.

2) Calibration of device: This will be carried out as described previously (Anand Kumar et al., 1979 ibid).

3) Choice of compounds: In the first instance the choice of compounds tobe tested will be restricted to estradiol, progesterone, 17 hydroxyprogesterone and norethisterone because these are the compounds which have been almost exclusively found to have great potential in terms of safety and efficacy in our animal studies.

4) Test animals: Adult male and female rhesus monkeys will be used. A total number of 25 animals of each sex will be used. The steroids will be administered by intranasal spray using 4 different spraying characteristics and the animals will be analysed in a cross-over study. The number of animals has been chosen to provide sufficient data to facilitate statistical analysis of variance. The animals used for testing the naturally occurring

steroids will be ovariectomised before use in order to discriminate between endogenous and the exogenous steroids.

Estimation of hormones in body fluids : These will be estimated by specific radioimmunoassay procedures with inbuilt quality controls.

Long term effects of nasal sprays on nasal mucosa and associated regions of the brain. 10 adult monkeys of each sex will be sprayed daily with the steroids at a dose level of about 100 times greater than the physiological levels for a period of 6 months. The spraying characteristics will be such that the maximum bioavailability of steroids occurred in the body fluids.

At the end of the treatment the animals will be sacrificed and the entire nasal mucosa and associated rhinenphalon regions of the brain and the adenohypophysis will studied by optical, transmission and scanning electron microscopy. Techniques for such studies have been standardized our laboratories.

The detailed ultrastructural effects will be studied qualitatively as well as quantitatively by Energy Dispersal Analysis (EDA) and microscopic quantitation (Quantimat) method permitted statistical analysis of data.

10. <u>Facilities available at the All-India Institute of Medical Sciences:</u>

a) A well-equipped Private Research Facility (Preprint about the facility enclosed).

b) Optical, transmission and Electron Microscopic facility excepting the SEM and quantitation available.

c) Expertise in operating techniques for isotopic radioimmunoassay of steroids.

d) A specially equipped radioimmunoassay laboratory for assaying steroids.

BEST AVAILABLE DOCUMENT

BUDGET (Tentative)

(In Rupees)

		I YEAR	II YEAR	TOTAL
1.	Research & Technical Staff	75,000	75,000	1,50,000
2.	Supplies (Chemicals and glassware)	25,000	25,000	50,000
3.	Animal costs (100 monkeys)	10,000	-	10,000
4.	Maintenance cost for 100 animals	30,000	30,000	60,000
5.	Costs of radioimmunoassay @ Rs.3/- per assay tube-estimated assay 10,000 tubes.	30,000	30,000	60,000
6.	Equipment (accessories for electron microscopic facility)			
a)	Quantimet for quantitating ultrastructural changes in brain and olfactory mucosa to enable statistical analysis of data	2,00,000	-	2,00,000
b)	Energy dispersal analyser for detecting precise chemical changes in the constituent of cells and tissues by ultrastructure	4,00,000	-	4,00,000
7.	Contingencies	15,000	15,000	30,000
		7,85,000	1,75,000	9,60,000

PROJECT : 3

REPORT OF MALE REPRODUCTION TASK FORCE

PROJECT TITLE : A STUDY OF PITUITARY GONADAL AXIS FOLLOWING THE ADMINISTRATION OF LH-RH ANALOGUE D TRYP^{6} LHRH - ETHYL AMIDE.

[illegible]

LH-RH analogues are being actively investigated during the recent few years as a possible male methods of fertility control. They have been shown to cause inhibition of the testicular function both at the spermatogenic and steroidogenic levels in the experimental animals. While the compound D-SER(TBU)^{6}-LH-RH ethylamide given at supra-physiological dosage may bring about a direct inhibition of the pituitary gonadotropins secretion and a decrease in gonadotropin testicular receptor level in male rats, the other compound D-ALA^{6}, DES-Gly-NH$_2^{10}$-LH-RH ethylamide has not been shown to suppress the pituitary gonadotropins when administered chronically. In fact FSH and LH levels are shown to increase following its administration. It is, therefore, obvious that the exact mechanism of action of the LH-RH analogues large remains obscure in the suppression of testicular functions.

OBJECTIVES

The present study aims at investigating the effect of LH-RH analogue D TRYP^{6} LH RH-Ethylamide, on the testicular functions and the possible mechanism of action of this compound.

EXPERIMENTAL DESIGN:

30 normal healthy male subjects (age range 25.45 years) who would have completed their families will be included in the study. They will be fully informed about the nature and scope of the study. It will be ensured that these subjects will be free from any endocrinal metabolic, nutritional, hepatic, renal or any other chronic disease likely to affect the study. Alcoholics, drug abusers and all those taking drugs on long term basis will be excluded from the study. The experimental design of the study includes a control phase of eight weeks duration, a treatment phase of 12 weeks duration and a finally a recovery phase of 12 weeks or as long as complete recovery is achieved. During the treatment phase, the subjects will be randomly allocated to three

different groups. Group I will receive vehicle only (Placebo) Group II will receive LH-RH analogue D TRP^6 LHRH-Ethylamide, dose 50 ug per day given intramuscularly, Group III will receive the analogue in the same dose and frequency of administration and also testosterone given in th dosage of 100 mg every two weeks. All these Groups will have equal number of subjects (ten subjects)

Throughout the period of study, the seminal fluid examination will be done regularly at two weeks interval while the blood samples w be taken regularly after every 4 weeks for the normonal assay as well as for the toxicological studies. On the day of blood sampling, four samples will be collected at 20 minutes interval(time 0,20 min,40min. 60 min). All these blood samples will be collected between 9 A.M. and 10.A.M., preceding the intramuscular administration of the compound.

In three subjects from each group, blood sampling schedule will additionally include samples collected 20 min,40min,60 min,180 min, 360 min following the intramuscular administration of the compound.

In three subjects from Group II, an HCG stimulation test will be carried out during the control period and following termination of the treatment period.

LABORATORY METHODS

The semen will be collected by masturbation following a four days period of abstinence. Following the collection of the sample in the laboratory, the studies on the volume, viscosity, pH and sperm count will be done immediately while spermmotility will be investigated at one hour following the coll ctions of the seminal fluid, Semen smear wi be stained for the study of sperm morphology.

Standard methods will be used for hormone assays and all the samples from any one volunteer will be assayed together at the completion of the treatment period. Aliquotes of venous as well as seminal plasma will be kept frozen for any additional studies.

The following parameters will be studied:

1. Plasma testosterone
2. Oestradiol
3. FSH
4. LH
5. Cortisol
6. T_3 T_4

SEMEN ANALYSIS:

1. Volume
2. Viscosity
3. Sperm count
4. Sperm motility
5. Sperm morphology

PRE-CLINICAL TOXICITY STUDIES:

These studies have been done in the U.S.A. and the [illegible] released to a selected number of investigators for first [illegible].

ETHICAL ASPECTS:

The permission for this trial will be obtained from the local Ethics Review Committee. The subjects will be informed about the background and nature of the investigation. They will be compensated for their travel expense, lost income, personal inconvenience etc. Each subject will sign a Consent Form (Form enclosed).

CLINICAL SCREENING:

The following volunteers will be selected from amongst healthy adult men over the age of 21 (legal age of consent for human experimentation). A complete clinical history, general physical and systemic examination will be carried out with a view to excluding the following from the study:

- Persons with significant anaemia or nutritional deficiency or clinical debilitating illness.
- Chronic diseases
- Persons on chronic drug therapy (e.g. [illegible], [illegible], tranquillisers, [illegible], [illegible] etc.)
- Illicit drug users [illegible]

BEST AVAILABLE DOCUMENT

i. Evidence of acute or chronic liver disease manifested by any of the following:-

a) Clinical evidence of hepatomegaly, splenomegaly, jaundice, pruritus, or other signs of chronic liver disease such as spider angiomata, palmar erythema or ascites.

b) Abnormal routine tests of liver function (SGOT, SGPT, total serum bilirubin. Alkaline phosphatase, total serum albumin and globulin).

Any adverse drug reactions, if observed during the control or the treatment periods, will be recorded. Treatment will be discontinued in the event of a serious drug toxicity. Clinical examination will be conducted during the control period and at monthly intervals during the treatment period. Any abnormality detected will be followed during the phase of recovery. Psychosomal assessment (proforma enclosed) will be carried out twice during the pre and post treatment period.

TOXICOLOGICAL SCREENING:

The following parameters will be included in the routine toxicological screening:

i. Blood
Haemoglobin
TLC
DLC
SGOT
SGPT
Serum bilirubin
Serum albumin
Serum globulin
Glucose
Urea

ii. Urine

Complete physical, chemical and microscopic examination.

The toxicological screening will be done during the initial screening phase as well as regularly after every 4 weeks during the period of the study. All subjects having significant abnormality in the initial screening phase will be excluded from the study. If an abnormality appears during the treatment period, the subjects will be followed up for sufficient length of time till the reversal of the observed abnormality.

B U D G E T

Funds requested (Total duration of study: 15 months)

A.	Personnel	
1.	Research Associate (Stoukes)	$ 4000
2.	Senior Research Officer (M.D., Senior Resident Level)	$ 2000
3.	Technical Assistant	$ 1500
4.	Laboratory Assistant	$ 1000
B.	Equipment & Supplies	
	Chemicals and Reagents, Radio-isotope Glassware Miscellaneous	$ 10,000
C.	Patient cost (travel cost, reimbursement of lost income, etc.)	$ 1,000
D.	Other expenditure	
	Stationery, office maintenance, office equipment, secretarial assistance, travel within India for scientific meetings, books, or monographs, scientific periodicals or reprints.	$ 500
E.	Institutional overhead expenditure	$ 3000
	TOTAL :	$ 22,000 *

* To be paid in Indian Rs

BEST AVAILABLE DOCUMENT

REFERENCES

1. Auclair, C., Kelly, P.A., Labrie, F., Coy, D.H. and Schally, A.V.: Inhibition of testicular LH/hCG receptor level by treatment with a potent LH-RH agonist or hCG. Biochem Biophys Res Commun 76: 855, 1977.

2. Pelletier, G., Cusan, L., Auclair, C., Kelly, P.A., Desy, L. and Labrie, F.: Inhibition of spermatogenesis in the rat by treatment with (D-Ala^6, DES-GLY.NH 10) LH-RH ethylamide. Endocrinology 103: 641-643, 1978.

3. Sandow, J., V Rechenberg, W. and Jergabele, G.: Endocrine ~~D-Ser(TBU)xxxxxxxxx~~ effects of chronic treatment with the LH-RH analogue D-Ser (TBU) ethylamide. Acta Endocrinol (Suppl.)(Kbh) 208 : 25, 1977.

4. Sandow, J., V. Rechenberg, W., Jeanbele, G and Stoll, W.: Pituitary gonadotropin inhibition by a highly active analog of leutinizing hormone-releasing hormone. Fertility and Sterility, 30, 2: 208-209, 1978.

Proforma for the assessment of psychosexual effects during the study:

It would be done by two methods:

i) Self assessment/administered questionnaire, using for scoring three point Likert's scale and visual analogue scale (Aitken, 1969)

ii) Structured interviews

These would be done before the drug trial, as far as possible with the couple, jointly and separately, and at monthly intervals along with other medical assessments. In subsequent assessment in the self administered questionnaire the reference point of time would be changed to 'since the drug was started'. The structured interviews would be conducted by the same person (Senior Psychiatrist-Collaborator) so as to eliminate/or keep the bias constant.

SCHEDULE

Identification data :

Name	Age	Religion
Local address		
Literacy level	Occupation	Income
Family type	Joint/Nuclear	Family income
Wife's age	Literacy	Occupation/income
No. of children	M F	Age gap Sex
Duration of married life.		

... Contd.

BEST AVAILABLE DOCUMENT

Given below are some statements or questions followed by a line. We would like you to indicate by making apoint on the line your own feeling regarding the question.

Example:

My sleep these days is

Very good ——————————————— Average ——————————————— Very bad

The two extremes are the end points and the point made by pencil (shown in asteriks) indicates your own assessment of your sleep.

Now answer the following questions:

1. My appetite these days is

Very good o ——————————————— Very poor

2. Since last one year my sexual (coital activity) has been

Very good o ——————————————— Very poor

3. My bowel movements generally are

Very satisfactory o ——————————————— Very unsatisfactory

4. My sleep these days has been

Very good o ——————————————— Very poor

5. Since last one year my penile erection has been

Very good o ——————————————— Very poor

6. Our married life over the last one year has been

Excellent o ——————————————— Poor

....contd.

7. My sexual desire over the last one year has been

o——————————————————————————o
Excellent — One at all

8. My work adjustment over the last one year has been

o——————————————————————————o
Excellent — Very poor

9. To me over the last one year my partner/spouse has been

o——————————————————————————o
Most desirable — None at all

10. In my opinion over last one year my wife/husband was satisfied in sexual relations

o——————————————————————————o
Maximally — not at all

11. In my opinion our family relations over the last one year have been

o——————————————————————————o
Very good — Poor

12. In my opionion my partner's sexual desire is

o——————————————————————————o
Very strong — None

13. I have erection over the last one year

o——————————————————————————o
Easily spontaneously — None at all

14. Have you had any extramarital affair during your married life Yes/No.

Contd.....

15. Does it continue now

Yes/No

16. Do you find other women sexually attractive now

Yes/Don't know/No

17. Have your derived sexual satisfaction by other means also (e.g. Masturbation, homosexual activity, stroies, movies, books) please specify.

18. In your opinion, is your own sexual performance

a) Good/don't know/bad

b) Any reason ?

Present state of health:

19. How is your present state of physical health

Good/don't know/bad

20. How do you feel mentally

Good/don't know/bad

21. How is your married life now
very good/good/satisfactory/indifferent/bad

22. How is your job adjustment

Very good/good/satisfactory/indifferent/bad

23. How are your relationships with other people, relatives
Very good/good/satisfactory/indifferent/bad

24. What is your attitude to this drug treatment

Positive/indifferent/negative

Contd.....

25. What has been the effect of this drug treatment on your health

Good/no change/bad

26. What has been the effect of this drug treatment on your mental health

Good/no change/bad

27. Would you recommend it to others

Yes/ Don't know/no.

Note: A similar proforma in Hindi will also be made available to facilitate interaction with those subjects whose knowledge of English language is either nil or fragmentary.

REPORT OF MALE REPRODUCTION TASK FORCE

PROJECT TITLE: A STUDY OF PITUITARY-GONADAL AXIS FOLLOWING ADMINISTRATION OF NORMAL HUMAN MALE SUBJECTS

Introduction: Intranasal administration of contraceptive steroids is a new approach developed by the scientists at the All-India Institute of Medical Sciences. Although this was initially intended for fertility regulation in the female, it soon became apparent that an equally profitable therapeutic approach could be developed for the male. Recent data have shown that following the daily intranasal administration of 17B-oestradiol, norethisterone and progesterone for a period of 60 days causes an impairment of testicular function both in terms of spermatogenesis and circulating levels of testosterone. In view of these findings it is now proposed to use norethisterone (NET) in human male volunteers and study its effect on pituitary-gonadal axis.

Objectives: The studies will be aimed at assessing pituitary gonadal function following intranasal administration of NET in human male and to find out if a steroidal contraceptive can be further developed for use in the male.

Experimental Design: Eight male healthy volunteers will be studied.

Following two weeks control period during which vehicle only will be sprayed intranasally daily for a period of ten days. Blood samples will be obtained on each day of intranasal spray (vehicle or vehicle plus NET). Basal blood sample will be obtained at a prefixed time (between 9 - 9.30 AM). Four

additional blood samples will be dr. immediately at the termination of intranasal spray, and at 20 minutes intervals for a period of one hour. Semen specimens will be obtained at the beginning of the study (Day 0) and thereafter every week till the end of week 4. The experimental design is shown below:

CONTROL			NET			
v	v	v	v	daily		
Day 0, 1	week 1		week II	week III	Day 24	week

*Semen specimen
v: vehicle only
•: Toxicology screening.

The following parameters will be studied:

1. Plasma testosterone
2. Dihydrotestosterone
3. Androstenedione
4. Oestradiol
5. 17α-hydroxyprogesterone
6. FSH
7. LH
8. Prolactin
9. Cortisol

SEMEN ANALYSIS:

1. Volume
2. Viscosity
3. Sperm counts
4. Sperm motility
5. Sperm morphology
6. Seminal plasma analysis for testosterone, dihydrotestosterone, androstenedione, oestradiol, and fructose.

PRE-CLINICAL ANIMAL TOXICOLOGY:

NET was administered at the dose level of 36ug/kg/day in two groups (3 animals of each sex) of *Macaca mulatta* for a period of 28 days. No adverse effects, ascribable to treatment were observed.

ETHICAL ASPECTS

The permission for this trial will be obtained from the local Ethics Review Committee. The subjects will be infomed about the background and nature of the investigation. They will be compensated for their travel expenses, lost income, personal inconvenience etc. Each subject will sign a Consent Form (Form enclosed).

CLINICAL SCREENING

The following volunteers will be selected from amongst healthy adult men over the age of 21 (legal age of consent for human experimentation). A complete clinical history, general physical and systemic examination will be carried out with a view to excluding the following from the study:

1. Persons with significant anaemia or nutritional deficiency or clinical debilitating illness.

2. Chronic alcoholics

3. Persons on chronic drug therapy (e.g. Dilatin, Phenobarbital, tranquilizers, Aldomet, Isoniazid etc).

4. Illicit drug users - addicts

5. Evidence of acute or chronic liver disease manifested by any of the following:

   (a) Clinical evidence of hepatomegaly, splenomegaly, jaundice, pruritus, or other signs of chronic liver disease such as spider angiomata, palmar erythema or ascites.

   (b) Abnormal routine tests of liver function (SGOT, SGPT, total serum bilirubin, alkaline phosphatase, total serum albumin and globulin).

6. Any pathology of the nose or the respiratory tract; anatomical, allergic infectious or inflammatory conditions.

or the treatment periods, will be recorded. Treatment will be discontinued in the event of a serious drug toxicity. Clinical examination will be conducted twice during the treatment period (day five and day ten) and also at the end of week four.

TOXICOLOGICAL SCREENING

The following parameters will be included in the routine toxicological screening:

1. Blood

Haemoglobin
TLC
DLC
SGOT
SGPT
Serum bilirubin
Serum albumin
Serum globulin
Glucose
Urea

2. Urine

Complete physical, chemical and microscopic examination.

The toxicology screening will be done once at the beginning of the control period and repeated on day 24 following the termination of the trial. In case of any significant abnormality in the initial screening the subject will be excluded from study; if an abnormality appears during treatment period, subject will be followed up for sufficient length of time till the reversal of the observed abnormality.

BUDGET FOR ANNUM

	IN RUPEES
STAFF	
1. Senior Research Officer (One)	25,900
2. Laboratory Technicians (Two) (One for toxicological studies and one for semen analysis and RIA)	21,000
Supplies including patent costs	50,000
Total	Rs. 97,900

Project Title: Fertility Regulation in the adult male primate by Active immunisation with FSH - B subunit.*

Duration of the Project 3 years.

Total Financial assistance Approx Rs. 4,05,000/- required for 3 years.

INTRODUCTION / RATIONALE.

Of the two pituitary gonodotropins ICSH(LH) and FSH, the former is clearly known to be needed for production of androgen by the leydig cells, the androgen in turn being essential for maintainance of all secondary sexual characteristics including libido. While in the adult rodent androgen has also been shown to be able to maintain spermatogenesis when given soon after hypophysectomy in the primate it is unable to do so. Till very recently the need for FSH for maintanance of fertility in the adult was doubted. It has however, been demonstrated by us that chronic deprivation of FSH in the adult male bonnet monkey leads to infertility as ascertained by their inability to inpregnate cycling females. Fertility in these monkeys can be restrituted by withdrawing antibody treatment (1) This demonstration of a critical need for FSH for maintainance of fertility has been confirmed by Nieschlag and coworkers using the rhesus monkey. It should be emphasized that administration of FSH antibody did not influence androgen production and consequently libido.

Immunization against FSH then appears to pro the desired effect in the monkeys - production of a state of in ility without in any way effecting libido. The added advantage of this approach is that this appears to be a totally reversable process, the animals returning to fertility following withdrawl of antibody treatment while the above study using passive immunization provided the much needed basic information establishing a need for FSH to maintain testicular function, the feasibility of this approach can only be ascertained by carrying out carefully controlled activeimmunization studies with the subunit of ovine FSH.

Choice of the immunigen :OVSH has been shown by us earlier (2) to be a good immunigen it producing in the monkey high titer antibodies capable of cross reacting with FSH of a variety of species. By using highly purified immuno affinity column cleaned OVSH B subunit will be used as an immunogen, thus overcoming the problem of obtaining contaminatin antibodies. The experience we have had with OLH B subunit in the monkey/Chimpanzee would suggest that the B subunit of FSH would prove to be a fair and it should be possible to obtain ~~immunumd~~ antibodies of good titer with minimal effort. The OVSH B subunit ~~takmr~~ to be used in this study will be prepared in the laboratory.

Choice of the animal: The Bonnet monkey, from the information available to us appears to be an ideal animal model for such studies. It produces throughout the year almost the same quantity of spermatozoa and the androgen levels are mostly constantand consequently libido remains unaltered.

Experimental protocol (1) A group of 20 adult male bonnet having similar sperm counts and testosterone will be vecraited for this study. Preferably "leader" male monkeys and those known to be fertile (by their past performance in the colony) will be chosen. If considered

essential as we are prepaired to check the fertility of the rest of the males by putting them for mtint with fertile females. The hormonal profile of these animals as well as differential semen analyses will be carried out prior to initiation of treatment. A control group of ten monkeys will be immunized with a non-specific protein like Sheep Serum Albumin following the same protocol as experimentals.

The Experimental group of 10 monkeys will be immunized with FSH B submit given as a alum precipitated protein. No noxious adjuvants will be used. The immunization schedule constitute of 5-10 injections, the first two 15 days apart and the remainder at judicious intervals depending upon the titre of the antibody, the presence of free' monkey FSH and finally theeffect of this on the 'fertility' tatus of the monkey.

Differential semen analysis will be carried out on samples of semen obtained by electro ejaculation - total Nos. viability mitility MP content of washed spermatogoa and fructose concentration of minal plasma will be analysed.

Once some of the above parmeters show a drastic reduction, perimental and controls will be tested for their fertility by assessing eir ability to impregnant cycling females. Each one of the exprimentals ll exposed to a total of 5 females (exposure to one female at a time).

Testicular biopsy samples will be removed at later stage of the periment to assess the effect of FSH lack on testicular function.

The serum samples will be periodically analysed for LH (ICSH) l testosterone.

Renal function tests will be carried our periodically to assess effect immunization has on this important metabolic function. Kidney opsy will also be taken toward the end of the experiment to check for deposition of [illegible]

The total period of immunization and fertility testing would require 18-24 months. To assess the effect of stopping the immunization on return to fertility should take an additional 12 months.

Several of the experimental protocols to be used have already been worked out in our laboratory and we refer you to reference given below:

REFERENCES

1. Murty G.S.R.C. Sheela Rani C.S. Moudgal N.R. and Prasad MRN. Effect ofpassive immunization with a specific anti-serum to FSH on the spermatogenic process and ferility of Adult Male Bonnet Monkeys. J. Reprod. Fert. Suppl. 26 (1979).

2. Sheela Rani C.S. Murty G.S.R.C. and Moudgal N.R. Effect of chronic nutrilization of endogenous FSH on testicular function in the adult male bonnet monkey - assessment using biochemical parmeters.
International J. And 1 , 189, (1978)

3. Rao A.J. and Moudgal N.R
Arch. Biochemistry Biophys. (1971)

Contd.... 5/-

B U D G E T

A. Non-Recurring.

1. Procurement of Monkeys, Quarantine etc. - 25 males and 50 females @ Rs. 100/- per animal Rs. 75,000/-
2. Extension of physical facility to house these monkeys. Rs. 1,00,000
3. Import of equipment Radio and biochemical Rs. 50,000/-

B. Recurring Expenditure

Personnel	Rs. 50,000
Monkey Feed	Rs. 80,000
Laboratory supplies and contingencies.	Rs. 50,000
Total of B per year	Rs. 1,80,000

Grand total of the project (A+B)= Rs. 4,05,000/-

REPORT OF MEDICAL EFFECTS TASK FORCE:

PROJECT TITLE: VASECTOMY/TUBECTOMY FOLLOW-UP STUDY

Justification/Background

The long term effects of vasectomy & tubal ligation are not known and they should be. This is true both in the U.S. and India.

With respect to vasectomy: Animal work suggests that over the long term vasectomized men compared to non-vasectomized men may be at increased risk of cardiovascular disease. In addition the immediate risk of morbidity and mortality from the operation itself needs to be measured and evaluated.

With respect to tubal ligation: The immediate risk of morbidity and mortality associated with this procedure should be measured and evaluated. The long term death rate in women having had a tubal ligation may be lower than the rate in non-sterilized women because the latter are continually at risk to be pregnant and hence at risk of mortality from pregnancy related conditions. Such a fact would be useful in promoting sterilization.

OBJECTIVES:

1. Compare the subsequent risk of death in men vasectomized about 10 years ago with a comparable group who were not vasectomized.

2. As a second phase (if warranted by results in 1) do the above specific for cause of death.

a) Examine patterns of immediate (without 1 month) mortality. Evaluate patterns and suggest ways to reduce immediate mortality.

b) Evaluate whether cardiovascular disease is more common in vasectomized compared to non-vasectomized men over the long term.

3. Compare the subsequent rate of death in women having undergone tubal ligation about 10 years ago with the rate in women not having the procedure.

4. As a second phase (if warranted by results in 3) do this for specific cause of death.

OVERALL DESIGN:

- A retrospective cohort study of railroad workers and their spouses is planned. Apparently good records have been kept on such people since about 1965.
- Starting at about 1965 identify the first 5000 of these men who have had vasectomies and 5000 women who have had tubal ligations in several regions of the country. (we want to enroll 1000 sterilized men and women per year, 1965-1969.)
- The control groups will consist of systematic samples of 5000 each of non-sterilized men and women. (Hopefully the sterilized groups and control groups will be similarly distributed by year of birth, year of entry into the rail road workers system and socio-economic status. If not, adjustment for differences must be made during the analysis.)

Review the railway records (medic. and other) of 20,000 subjects (5000 X 4) and record demographic and reproductive histories. In addition record all medical events after the sterilization. In particular determine whether the person is alive or dead. If dead, Record cause of death. All above will be recorded on a standardized form. (Attached) If alive/dead status unknown-try and trace the person and find out status.

The study will take 1 year to complete, including analysis.

ETHICAL CONSIDERATIONS:

Since this is a record review study there are no "Human subjects" considerations except for follow up to determine if subjects are alive or dead.

SAMPLE SIZE CONSIDERATION

In the U.S. the death rate in reproductive age (20-44) among women and men is about 1/1000 per year. Assuming at least as great a rate in Indian men and women each group of 5000 people will suffer 50 deaths in a 10 year follow-up study. This no. of deaths will be adequate to meet the stated objectives.

PLANS FOR ANALYSIS:

The goal is to compare mortality (+ in a second phase morbidity) rates in sterilized and non-sterilized groups. If comparison groups vary (by age, occupation etc.) standarize rates to adjust for these differences. A life table analysis would be ideal; person-years approach would be satisfactory

BUDGET - 1 YEAR - PHASE 1

	PERSONNEL	TIME		COST PER MONTH
1.	Epidemiologist (Principal Investigator)			
1	Statistician	1.0		1000
1	Record Abstract Supervisor	1.0		1000
10	Abstractors	1.0	@ 600 x 10 =	6000
1	Data clerk/Coder	1.0		600
				8600
Total for 1 year				106,600
	TRAVEL			10,000
	OTHERS			5000
FORMS (20,000) Printing				20000
Computer Time				
Supplies				
Phone				5000
Mailing Costs				
Total 1 year				145,600

ANTICIPATED PROBLEMS

(1) Gaining cooperation of Railway System.

(2) If Railway System does not keep centralized records, follow-up will involve much travel and/or correspondence.

(3) Determining cause of death and no. and cause of hospitalizations will probably involve substantial work. This could be second year's work if results warrant continued evaluation.

(Last known) P

Current Address ----------

Year of Birth _____

Year first joined Railway _____

For woman: Was sterilization postpartum Yes
No
Unknown

No of living children At time of sterilization _____
How many of these are boys_____
Age of youngest child _____

For Man being sterilized:

Occupation at time of sterilization _____

Salary at time of sterilization _____

For woman being sterilized:

Husband's occupation at time of her sterilization ___
" salary " " " " ___

RELIGION:
Hindu
Muslim
Sikh
Christian
Other

Is the person dead - Yes
No

If No:

In what year was the person last known to be alive_____
(Need logic to decide if we need to trace)

If Yes:

What is cause of death_____

For Phase 2

Dates of Hospitalization _____

SUBSEQUENT TO STERILIZATION	REASON FOR HOSPITALIZATION
1. _____	_____
2. _____	_____
3. _____	_____

REPORT OF MEDICAL EFFECTS ... FORCE

PROJECT TITLE: TO STUDY CHANGES IN LIPID AND CO-AGULATION PROFILES IN O.C. USERS

A. Rationale

Available data from the developed countries indicate that the risk of cardiovascular disease is a major health hazard in OC users. The changes in lipid and lipoprotei profile, platelet and coagulation factors brought about by OC use are thought to be the important factors responsible for the increased CVD risk. There is no epidemiological data on CVD risk in OC users and for logistic reasons, it will be difficult to collect epi emiological data on CVD risk pill users in India at the moment. There had been speculations that CVD risk in OC users in India may be lower because

a) There is a clinical impression that thromboembolic risk in Indian women in lower.

b) Trigycerides and cholesterol levels in India women are lower than those found in Western women.

c) Very few Indian OC users smoke or drink.

There is a paucity of data on changes in lipid and congulat on factors in normal women or OC users in India. Some of the available data in normal women and women with cardiovascular diseases indicate that though both these groups have lower levels of triglycerides and cholesterol than their western counter parts, the magnitude of differences between the two groups are similar to that seen in the Western Group. This may mean that it is not the absolute

lipid levels but the magnitude of the di. nce and factors responsible for the alterations that determine the CVD risk.

A study of lipid lipoprotein and coagulation profile, of normal women, women with CVD and OC users are similar to that seen in women with CVD then it is a possibility that Indian OC may not be at a lower risk as far as CVD is concerned. The fact that there are regional differences in reversal of the biochemical parameters including triglycerides and cholesterol makes it mandatory that the study should be multicentric.

B. Objectives

To study lipid, lipoprotein And coagulation factors profile of healthy women not using any form of contraception, OC users and women suffering from CVD, to find out whether use of OC is associated with alteration in these parameters similar to that seen in those CVD.

C Study design

The study will be done in 3 centres. It will be hospital based cross sectional one. Three age groups will be studied 20-29, 30-39 and 40-49 years only women who are not lactating will be taken up for the study because some of the available data indicates the lactational status may influence lipid profile. In each age group an attempt will be made to obtain 50 normal women (not using any contraceptives), OC users (who had used OC for at least six months) and women currently suffering from CVD (Venous thrombo embolism, hypertension and myocardial infarction). There may be

problems in getting adequate numbers in women which CVD below 30 years and OC users in the over 40 group. Women who had taken OC within the last 6 months will be excluded from both the normal and the CVD groups.

Demographic and reproductive profile will be obtained in a precoded protocol. Specific information will also be collected on the smoking, drinking habits and nutritional anthropometric (Ht. wt. arm circumference) measurements will be obtained in all women. The following parameters will be estimated, a) Hb, Albumin, Total proteins, b) Triglycerides, cholesterol, LDL, VLDL and HDL cholesterol, c) Platelet count, platlet aggregation, d) Coagulation factors(to be selected).

D. Case selection Women with CVD & those using OCs will be taken as cases. Control will be matched by parity and socio-economic status. Uniform criteria will be used to select cases of CVD. Methods of evaluating biochemical parameters will be standardised. There will be an internal and external quality control between the laboratories to ensure uniformity in estimation of biochemical parameters.

Period of study : 12 months at 3 Indian Centres

E. Ethical aspect

The women participating in this study incur no risk or inconvenience. In fact they may receive a complete health check up and may benefit from the health care provided.

F DATA ANALYSIS

All data will be analysed in IRMS Delhi using computer facilities. Comparison will be made not only between the 3 groups in the same centres but also between centres. Possible effect of nutritional status, smoking and drinking habit on biochemical profile will also be evaluated.

G. BUDGET

for each Centre		Salary
Research Associate	1	Rs.1000/-
Research Asstt.	2	Rs. 700/- each
Research Asstt.	1 (clinic)	Rs. 700/-
Personnel 3100 x 12 mths =		Rs. 37,200/-
Chemicals		Rs. 20,000/-
Contingencies		Rs. 5,000/-
	Total Rs.	62,200/-
Total for 3 centres	Rs.	1,86,600/-
Analysis	Rs.	10,000/-
Statistical Asstt.		8,400/-
	Total:	2,05,000/-

PROTOCOL FOR THE STUDY OF LIPID AND COAGULATION PROFIL
IN OCUSERS

Proforma

1-4
Project card No.
5
Centre -

Patient identification data

Name of the woman

Husband name

Study number 6 - 8

Study Group 9

1) Normal control

2) Oc user

3) CVD

Age 10 - 11

Religion 12

1. Hindu 2. Muslim 3. Sikh
4. Christian 5. Others

Marital status 13

1. Single 2. Married 3. Divorced/Separated
4. Widow

Education (Husband) 14

1) Illiterate 2. Primary 3. Secondary school
4) Technical Training
5) Graduate 6. Post graduate

Education (wife 15
(code as before)

Occupation specify 16 - 17
(Husband)

Occupation Specify 18 - 19
(wife)

Total family income/mth

Total family members 20 - 21

'r capita income/month 22 - 24

Do you smoke Yes No

If Yes

1) 1 - 4 1 day 2. 5-10 1 day 3) / 10 / 1 day

Do you drink alcholic drinks

If yes No

If yes how often do you drink

1) Daily 2) twice a week

3) Once a week 4) once in fortnight

5) once a month 6) Occasionally

How much of liquor do you drink

1) very small amount

2) Moderate

3) Heavily drinks

Total number of pregnancies 25 - 26

Live births 27 - 28

Dead born 29

Abortions (spontaneously) 30

abortion (induced) 31

Out come of last pregnancy 32

1) Live birth 2) intrauterine death

3) intra partum death 4) Spontaneous

abortion 5) Induced abortion 6) ectopic pregnancy

7) Never pregnant

Interval since last pregnancy (in months 33 - 35

Have you used any contraceptives in the last six months 1) Yes 2) No 36

If yes specify 37

1) combination pill 2) I.U.D. 3) tubectomy

4) Conventional methods

Duration of contraceptives use (in months) 38 - 39

If using combination pill specify composition and dosage 40 - 41

If suffering from CVD specify

type and severity of the disease

Thrombo embolism 42

1) Superficial venous thrombosis

2) deep vv thrombosis

3) " " with minor pulmonary infartion

4) " " with moderate pulmonary infartion

5) Cerebral venous thrombosis

6) cerebro vascula accident

Myocardial infarction 43

1) Angina pectoris 2. Mild inland MEx

3) Moderate infarction hypertension

4) Mild 2) Moderate 3. severe

Physical examination

Height 45 - 48

Weight 49 - 51

Aim circumference 52 - 54

Skin fold thickness 55 - 57

Blood pressure systolic 58 - 60

Diastolic 61 - 63

Laboratory investigations

Haemoglobin

Total proteins

Serum Albumin

Triglycerides

Cholesterol

HDL
VLDL } fractions
IVDL

Platetet

Coagulation factors.

Project Title: HEALTH AND NUTRITIONAL STATUS IN RELATION TO CONTRACEPTIVE USAGE.

RATIONALE:

Exploration of health hazards associated with contraceptive use with a view to minimise these risks is one of most important areas of research work in any country. It is essential to obtain data on the health and reproductive profile and pattern of contraceptive use in order to draw a plan of research priorities and channalize the available funds to appropriate areas of investigations.

In India there are well documented regional differences in health and nutritional status and contraceptive acceptance. Some differences are noted even in the type of contraceptive use. There is no hard data available on the factors responsible for these differences, though there had been speculations that availability of the health and contraceptive care services as well as ability of the community to use these facilities may play a vital role. Even within a region there are district and rural urban differences not only on the acceptance of contraceptives but also in the type of contraception used for example in rural areas. Surgical sterilisatin is the most common form of contraception and I.U.D. users are relatively few, while in urban areas tubectomy, vasectomy, IUD pill and condoms are all being used. There is an impression that rural women do not resort to any method for spacing of pregnancies mainly because prolonged successful lactation which is universal ensures an interpregnancy interval of nearly 4 months. These impressions however, need be confirmed by obtaining actual data. If confirmed, the pattern of contraceptive care to be made available in rural areas may be considerably modified with an emphasis on terminal methods rather than ones for spacing.

ome of the data available from small regional studies indicate that ontraceptive acceptors have a better health and nutritional status mpared to thenon acceptors belonging to the same socioeconomic and ducational class. The fact that contraceptive advice seekers resemble the ontraceptive users in these parameters seem to indicate that these ifferences between acceptors and non-acceptors are not due to the regnancy protection effect of the contraceptive.

The pattern of contracepive use in different groups may also ive some concrete basis for drawing up priority areas where research fforts should be concentrated. It was an unexpected finding in the rials conducted by - ICMR that pill users were usually in their twenties. ven pill users seldom continued to use the pill for periods longer than to 3 years.But IUD wearers often upto 10-12 years. If this is the neral pattern obviously one need not undertake detailed studies side effects of prolonged use of in older women but but it comes very important to find out whether long term use ofIUD is sociated with ay side effects.

OBJECTIVES

To obtain insight into the possible health hazards associated ith different contraceptive measures that need further indeph vestigation. To draw up the list of priority research activities it essential to obtain data on a) the reproductive and health prifile d contraceptive profile in urban and ural areas in different regions the country.

Characteristics of the acceptors and non-acceptors of ontraceptive measures.

Incidentally data obtained from the study may provide some formation on areas of health care delivery system that needs strengthening in order to provide better contraceptive care.

STUDY DESIGN

The study will be a community based survey in urban and rural areas. Three regions where health care and contraceptive acceptance differ widely will be chosen:-

Kerala or Maharashtra may be taken as the region where health care and contraceptive acceptance are found to be the best in the country. UP, Orrissa, Bihar which form the other extreme, may form the second region. Andhra may be taken as the lying somewhere in between these two extremes, and form the thrid region.

There will be an urban and rural component in each area. A primary health centre and an urban localitywith a population of about 1,00,000 will be chosen, and will be taken up for study in each of the 6 areas. It is expected that 18,000 women in reproductive age will be surveyed in each of the areas.

The following aspects will be studied:-

1) Demographic profile including smoking, tobacco chewing, drinking
2) Reproductive profile-obstetric and lactational data, interpregnanc interval.
3) Contraceptive acceptnce and duration of use. Among women not usin any form of contraception data regarding their knowledge regarding contraceptive measures. Their attitude towards the small family norms and the reasons why they do not practice contraception will be obtained. Among Contrecepptive users again data on the former two aspects andthe reason why they accepted the particular form of contraception will be obtained. In both the groups their idea about the ideal family size will be collected.

Data will be colected also on the available health care facilities in the area andtheextent to which these women make use of the available facilities.

Physical examination including:

a) nutritional anthropometric measurements
c Height, Weight, Arm Circumference)

b) Systemic examination to detect clinical obvious
and blood pressure recording

c) Haemogtobin estimation for assessing haematological status
will be done in all these women.

It was estimated that each of the study teams can survey about 20 women every day and 3 teams working for a period of 1 years will be able to cover the all the women in the reproductive age group.

Period of study:

Data collection 12 months.

Collected data will be processed simultaneously for analysis. For final analysis and report wriging a further period of 3 more months may be required.

Ethical aspects.

Women participating in the study incur no risk or inconvenience. They may infact benefit from the health check up and care provided.

Analysis

All data from different centres will be sent after coding to IRMS Delhi. IRMS Delhi will be responsible for getting the data analysed. Analysis of data will be done to ascertain

a) the health and nutritional profile of women in different regions.

b) Knowledge and attitudes of women in different regions towards contraception.

c) Pattern of contraceptive use, side effects, problems in usages and use effectivity seen in different communities.

d) Intra and inter regional differences in women accepting contraceptive methods and non acceptors.

e) Identify areas where health and contraceptive care delivery system need strengthening.

f) Identify thehealth hazards associated with the use of different methods of contraception which need, indepth investigation with a view to minimise morbidity associated with different contraceptives.

BUDGET FOR EACH CENTRES:

3. team consisting of

1 Medical officer	Rs.	1000
1 Research Asstt.	Rs.	700
1 ANM	Rs.	500
1 Driver	Rs.	500
		2700 x 3
		8100 X 12
Personnel	Rs.	97,200
Transportation Petrol	Rs.	30,000
Drugs, Chemicals contigencies	Rs.	10,000
	Rs.	1,37,200
for 3 centres	Rs.	4,11,600
Protocols printing postage etc.	Rs.	20,000
Transfering data to IBM cards	Rs.	20,000
Punching verification etc.Analysis	Rs.	40,000
~~XXXXXXXXX~~	Rs.	4,91,600

INTERVIEW OF ALL CURRENTLY MARRIED WOMEN

NAME _____ Religion/Caste _____ EDUCATION Wife ____ Husband _____

OCCUPATION WIFE _____ Husband INCOME _____

AGE _____ Yrs. Age at Menarche _____ Yrs.

	1st	2nd	3rd
Age at marriage			
Age at consumption of marriage			
Duration of marriage			
Reasons for dissolution (if dissolved)			

Pregnant/Not pregnant, LMP_____ IF PPA_____ Date of termination of pregnancy
Date

Pregnancy Roster

(1) Order	(2) Outcome	(3) Month/Yr. of termination	(4) Interval between terminations	(5) If interval 24 mths or more Reasons.	(6) Sex if L/S

(7) Present Age If alive)	(8) If dead Age at death	(8)a Cause of death	(9) If used a contraceptive	(9) a If discontinued Why.

*INVESTIGATOR: get information as abstinece fetal wastage or contraception and make necessary correction in col. 1 and 9.

MEDICAL CHECK UP

Height _____ Cms Weight _____ Kgs

HR _____ Aim Circumference

BP _____

Systemic examination

CVS

RS

Abdomen

CNS

Addictions e.g. Drinking/Tobacco Chewing/smoking etc.

Current illness _____

_____ _____

Project 9.

REPORT OF RECEPTOR ASSAYS TASK FORCE

Project Title: HUMAN UTERINE ESTROGEN RECEPTOR AND PROGESTERONE RECEPTOR : PHYSIOLOGY AND IMPLICATIONS FOR PREVENTION OF IMPLANTATION.

RATIONAL :

Estrogen and Progesterone Receptors provide the means by which E and P exert their effect on endometrium and other target tissues. In many tissues both ER and PR synthesis is increased by estrogen stimulation and is decreased by progesterone stimulation. Quantitative details of these feed back mechanisms and details of the translocation of receptor ligand complexes to the nucleus, however have only been partially characterized in human tissues.

In general, ligands which react with high affinity with a steroid receptor must be either an agonist or an antagonist of the natural receptor ligand. In the case of the estrogen receptor, DES represents a synthetic agonist and Nafoxidine is antagonist.

In the case of the progesterone receptor, numerous synthetic agonists are known, but to date no satisfactour antagonists have been found. Verma and Lauman, however, have found a series of compound including 5 - pregnandione, which act as effective inhibitors of progesterone - receptor association in the human uterus, and yet have not been shown to have significant progestational activity. Conversely, retroprogesterone Duphaston has been known since the 1960's to cause secretory chang in proliberative endometrium, but does not inhibit ovulation or sustain pregnancy in the ovariectomized rabbit. We hypothesize that retroprogesterone will have high affinity for the human uterine PR and that compounds such as 5a - Pregnandione may be capable of converting proliferative to secretory endometrum.

A hydroxylapatite adsorption (HA) assay has recently been developed by Hoffman et al (1980) which provides a sensitive, reliable method of measuring ER and PR, bound and unbound, in the nucleus and cytoplasm. The assay is suitable for determining association and dissociation rates as well as total receptor content and affinity constants.

.....2/-

We propose the following objectives;

1. To establish the hydroxylapatite adsorption assay for ER and PR in Department of Reproductive Biology laboratory, and validate it against established technique using human uterine nuclear and cytoplasmic receptor.
2. To determine by this technique the nuclear and cytoplasmic ER and PR in human endometrium in the various phases of the normal menstrual cycles and in early pregnancy as well as in hyperplastic endometrium.
3. To determine for non-progestins which have apparent high affinity for human cytosol PR, the association and dissociation rate constant for both cytoplasmic and nuclear receptors in human myometrial and endometrial tissue.
4. To determine whether these compounds are translocated to the nucleus and whether they alter production of ER and PR in the uterus of the estrogen stimulated ophorectomized rat.

Non progestins which bind to cytoplasmic PR do not inhibit ovulation, nor do they terminate pregnancy once established. Their influence on endometrium however has not been studied. They may either be capable of retarding endometrial proliferation by inhibiting production of ER or cause premature secretory development by acting as progestins in the endometrium but not the other tissues. Such compounds might provide a method of contraception based on prevention of implantation without inhibiting ovulation, and possibly without producing the extra uterine metabolic changes associated with other forms of steroidal contraceptives.

Ref:

MATERIALS AND METHODS:

Assay Procedure

The hydroxylapatite adsorption Assay has been described. Briefly, cytosol or the 0.6 M KCl nuclear extract is adsorbed to hydroxylapatite and is washed prior to exposure to radioligand. The procedure reduces non specific binding as compared to the usual dextran-charcoal technique and largely removes the problem of proteolysis encountered when the nuclear receptor is

incubated at temperatures as high as 30°C. Thus the RA assay allows exchange of endogenous hormones for radioligands without significant receptor loss. The technique also provides a simple way of measuring dissociation rate constants.

The assay will be established in the laboratory with the modifications and improvements which become necessary and will be validated against the charcoal absorption and sucrose gradient methods currently used in the laboratory. Initially full Scatchard analysis procedures will be used, but the feasibility of using single saturating ligand concentrations will be investigated for use with small samples.

Using uterine, tissue, cytoplasmic and 0.4 M KCL nuclear extracts, the KD for the progesterone-receptor and estrogens- receptor reactions will be determined. Dissociation rate constants will be determined by exchanging endogenous ligand for 3-H- ligand at appropriate temperatures (30°C for ER, and 20°C for PR for 2 hrs) then determining the dissociation rate over time in the presence of excess unlabled ligand. The association rate constant is obtained by the relationship kass=kdi/KD or, in the case of unoccupied cytosol receptors, by determining the initial rate of association.

ER, PR under different clinical conditions:

Once the basic techniques, and the fundamental estradiol and progesterone- receptor interactions are established, endometrial and myometrial samples will be collected from a series of normally cycling premenopausal women undergoing hysterectomy for indicated reasons. Nuclear and cytoplasmic ER and PR will be measured, as well as serum estradiol and progesterone (by standard RIA). Uterine specimens will be collected at days 5-7, 8-10, 1-13, 14-16, 17-19, 20-22, 23-25 and 26-28 periods of the menstrual cycle-10 specimens will collected at each interval of days mentioned above. 20 specimens of early pregnancy- a situation when the uterus is exposed to high quantities of progesterone will be taken for the study. 25 cases of endometrial hyperplasia involving a high level of estrogen will be studied.

Screening of compounds:

Simultaneously with the clinical studies above, A series of compounds, including those which have previously been shown (Verma & Lamma, 1979) to complete with progesterone for

.....8/-

Pregnandione and 1.4 Pregnadienedione. Where tritrated compounds of sufficient activity are available direct scatchard analysis and dissociation studies with nuclear and cytoplasmic receptor will be done. If only unlabled material is available, competition studies using 3H-Progesterone, will be used to determine whether inhibition is strictly competitive and to determine KI and the dissociation rate constants. Compounds which show significant binding to the nuclear progesterone receptor will be further tested in an animal system.

Evaluation of potential compounds in Animals.

The matone castrated female rat will be used. The animal will be given estradiol, approximately 1 ug/day for 5 days to stimulate PR production, a large dose of the compound to be tested, approximately 4 mg/kg will be given. Animals will be sacrificed at 0,1,2,6,12 hours to determine 1) whether nuclear translocation of PR occured, and 2) whether alterations in ER occur, either inhibition or changes in the nuclear/cytoplasmic receptor ratio.

Ethical Aspects

Uterine Tissue will be obtained at operation from patients undergoing hystectomy for medical reasons. No ethical aspects are involved. Blood samples (6 ml) will be obtained prior to operation, involving no risk to the patient.

Co-ordination:

Dr. Hoffman at San Francisco will be the collaborator in this project. He will procure compounds of interest from pharmaceutical companies and research investigators for testing in the human uterine system at the AIIMS. The HA assay is established in his laboratory and this facility will be used to do some of the preliminary screening of compounds and to confirm or support findings of the Delhi laboratory. Each laboratory will serve as a reference sources for the other.

....5/-

1.	Senior Research Officer (Rs.1100-1600)		22,000
2.	Research Officer (Medical) (700-1300)		18,000
3.	Research Officer(700-1300)		14,000
4.	Senior Technical Asstt.		12,000
5.	Lab. Attendant		6,000
			72,000
2.	Radioisotopes	Rs.	£
		3,000	
3.	Rare chemicals, assay supplies	5,000	8,000
4.	Chemical, solvents, glassware	25,000	
5.	Cold Room renovation	20,000	
6.	Air-conditioning of the Laboratory	35,000	
7.	Animals	5,000	
8.	Animal maintenance	10,000	
9.	Secretarial help and stationery	10,000	
10.	Equipments		
		177,000	8,000
A)	Rotor Titanium		4,500
b)	Liquid scientillation counter spare parts		4,000
c)	Maintance of the ultracentrifuge	5,000	
d)	Measuring equipment for RIA		1,000
11)	Co-ordination (One visit per year of the collaborator from India or USA to each other laboratory)		3,000
		182,000	20,5000
12.	Expenses on Radioisotopes and chemicals for use in San Francisco		3,000
		or	
		£ 22,800	23,500
		22,800	23,500
			*469 =46,300

First year	Second year	Third year
46,300	46,300	46,300

REPORT OF LHRH TASK FORCE

Project Title: LHRH Analogs:-

Background

The decapeptide gonadotropin-releasing hormone (Gn-RH/LHRH) has been shown to be the trigger for the release of luteinizing hormone (LH) and follicle stimulating hormone(FSH) and by that virtue plays an important role in the regulation of the reproductive processes in both male and the female, while Gn-RH stimulates the secretion of both the pituitary gonadotropins, an alternate mechanism for control of FSH is not excluded. The primary structure of the decapeptide has been elucidated and a number of analogs have been synthesized having a considerably increased biological half-life and potency. One of the expected therapeutic use of these preparations was to induce gametogenesis in hypogonadal infertile cases. However, a number of reports have appeared showing the paradoxical effects of these analogs to suppress oestrus, to delay the onset of puberty when administered chronically and to effect luteolysis. Further, LHRH and its analogs have been shown to inhibit FSH induced increase in estrogen and progesterone production in vitro by rat ovarian granulosa cells. When injected postcoitally into rats either before the onset of implantation or following implantation, LHRH and its analogs were found to interfere in pregnancy.

A number of reports in the literature are contradictory to each other which may in part be due to the differences in doses and time of administration of the effector agent. The basic biology of LH-RH may not be limited to the initial concept of its role as a chemical mediator between hyporthalamus and pituitary. Hyporhalamus is not the only site of its production and there are evidences for the presence of immunoreactive LH-RH in other parts of the brain and in placenta. It has also been shown recently that pituitary is not the only target organ of its action and direct action of LH-RH on gonada has been demonstrated. Suggestive evidence has also been presented on its role in the regulation of gonadotropin receptor populations on both Leydig cells and granulosa cells. Its normal

Physiological secretory pattern in pulsatile and the impact of administration of preparati with long biological half-life needs to be evaluated carefully. Conversely the impact of t itralization of the biologically active hormone, over-prolonged time period by antibodie require to be studied in sub.human primates and in animals with periodic oestrus such as the dogs.

Aims and Objectives

The general aim of the present project is to gain, further understanding on the biological action of LH-RH and to evaluate the consequences of using the peptide with long biological half-life on (a) gametogenesis (in males and females), (b) pattern of sex steroids secretion, (c) function of the corpus luteum and (d) side effects, if any on other metabolic and organ functions. The focus of studies in the female will be to evolve if possible consistently workable luteolytic regimens with minimal side effects. In the male, the aim will be evaluate the consequences of chronic LH-RH loading and or anti-LH-RH immunization on spermatogenesis and testosterone production.

Operational Plan

The studies will be carried out on the following analogs which will be made available by the National Institutes of Child Health and Development (NICHD), and by other sources (Dr.Wayne Hardin of Population Council, New York).

The effects will be evaluated primarily in primates (rhesus monkeys and baboons). These investigations will be carried out in a minimum of 6 rhesus monkeys and 3 baboons. Basal studies will be carried out in stabilized animals of both sexes to determine the steroid hormone levels and other metabolic and organ functions (Liver function, Kidney, thyroid and adrenal functions).

In the female animals the following regimens of administration of LH-RH analogs will be followed.

1. Single injection (IM) of 25 ug of LH-RH given at (a) mid follicular phase, (b) mid cycle and (c) at various time intervals following LH surge. In each case, the length of the menstrual cycle, the effect of LH-RH administration on estrogens and progesterone profiles will be evaluated. In baboons the analogs will be injected on days of (a) maximal

sex-skin turgidity and on various days following its regression. The hormonal profiles will determined for the control and treatment cycles and also the length of the menstrual cycle.

ii) Dose response : depending on the results obtained from the above mentioned investigations the time of injection of LH-RH for optimal luteolytic effect will be discerned. In the next series of experiments the dose of LH-RH will be varied keeping the period of administration constant.

iii) In the event that a single dose does not suffice to produce the luteolytic effect, multiple dose regimens will be tried. The general objective will be to evolve a schedule requiring minimal number of injections to induce insufficiency of luteal functio

The animals will be kept under careful observation. Investigation on metabolic a endocrine functions of the type listed above will be repeated in the treatment cycles and in two cycles following the treatment, together with measurement of estrogen, progesteron levels and cycle length. In the males, studies will be carried out primarily on the effect of induction of neutralizing anti-LH-RH antibodies on testicular size, semen composition (sperm count, volume, motility, acid phosphatase, fructose concentration) and blood testosterone levels.

LH-RH will be conjugated to tetanus toxoid (TT) and/or the rabies vaccine. A number of conjugates will be prepared with linkages at 1,2 or 3 amino acid residues in the decapeptide. Immunization will be carried out with permissible adjuvants such as aluminium phosphate and liposome. The laboratory has already gained preliminary information on effective immunization of dogs and mice with LH-RH-TT conjugates.

In the event of successful significant diminition in sperm count, a group of monkeys will be taken for the phase-II of the study namely, the combined effect of the anti-LH-RH immunization and androgen supplementation, long-lasting testosterone either known previously (testosterone enanthate) or newly developed compounds such as 17 - hyl testosterone enanthate will be used for this purpose at the appropriate doses.

In every case, animals will be followed during treatment and post-treatment cycles for not only the evaluation of the testicular function by the parameters mentioned above but also for the normalcy of other metabolic and organ functions (liver, Kidney,

thyroid, adrenal etc.) The libido of the animals will be tested by mating with females at appropriate stage. The collaborators in USA for these studies with Dr. Wayne Bardin (Population Council, New York) and or Scientists designated by NICHD.

BUDGET

ANIMALS	NUMBER	COST
Rhesus monkeys	12	4,000
Baboons	6	40,000
Maintenance for 1 year (Food, Medicine etc.)	-	20,000
Baboons	"	20,000
Monkeys	"	25,000
Personnel		
Senior Research Officer for Steroid Estimations	1	21,600
Technical Officer (Organ function test clinical chemistry)	1	10,800
Technical Assistant	1	9,000
		Rs.1,50,400
Chemicals/Miscellaneous		50,000
	Total	Rs.1,00,400

REPORT OF IMPLANTATION TASK FORCE

Project Title: IMPLANTATION.

The process of implantation by the blastocyst in the uterus is a critical step in he reproductive process. However, despite much intensive study, understanding of this rocess has remained obscure. Empirical approaches to the problem have generally been ruitless. Despite screening of many thousands of compounds by drug firms in many ountries, no useful lead compounds have been discovered. This failure may have been i ie in particular to the fact that screening has been done in mice or rats, with hind ight we now know that mice are unsuitable because many substances can cause failure of iplantation in this species through indirect mechanisms thus giving rise to many false sitive results. While this not true from the rat, this species has other special isadvantages. Firstly, it is necessary to take daily vaginal smears to determine the age of the cycle for mating purposes ; this is a very time consuming activity. Secondly, id more importantly, this species like the mouse, requires estrogen for induction of iplantation and as far as present evidence is concerned, this appears not to be true r the primate. Because of this requirement for estrogen for implantation, the rat is cularly sensitive to the actions of antiestrogenic compounds and to the actions of cess amounts of estrogens. Hence the majority of compounds that have been discovered be effective inhibitors of implantation in rats have fallen into estrogens and antiestrogens into these two categories- Aymorteroids, ORF 3353, Stilbestrol, Tamoxifen, emiphene, rafoxidine, etc. None of these compounds have been found to be effective hibitors of implantation in women, even though they may have contraceptive efficacy other mechanisms, e.g. actions on ovulation, ovum transport, or luteal function. her compounds that might have been found effective such as cytotoxic agents or nadotrophin inhibitors have generally proved toxic. It is possible that GnRH analogues, given prior to implantation, might be effective but this is not known. Alternatively, hibin (folliculostative) might also be effective by means of an action on luteal action.

BEST AVAILABLE DOCUMENT

This premise strengthens one conviction that a new approach to the problem of implantation should be undertaken. As a first step preliminary screening should be undertaken in hamsters, a species not requiring estrogen for implantation and not susceptible to the actions of estrogens or anti-estrogens. If rats are still to be used for primary screening, then cinfination of activity in hamsters is mandatory before proceeding with further development of a compound. Some tests may be more conveniently done in rabbits because of their size (thus providing more endometrial tissue) and because this species also does not require estrogen for implantation. Thirdly, the need for more basic studies to eliminate the process of implantation becomes paramount. It is only by understanding this process, it will be possible rationally to design drugs to inhibit the process specifically. To this end we suggest here certain lines of investigation which have not been fully explored and which might provide some of the information required.

(a) Role of prostaglandins in implantation).

It is now known that certain PGs are elevated in the endometrium at the time of implantation- specifically PGE_2 and 6-keto-$PGF_{1\alpha}$ (a major metabolite of PGI_2). These PGs are probably involved in the capillary permeability changes seen at the site of blastocyst attachment. Whether they or other PGs are involved in initial attachment of the blastocyst is not known. It has been reported on histochemical evidence that the major enzyme metabolizing PGs-15-hydroxy PG dehydrogenase is present in early stage hamsters embryos but not in blastocysts. If one of the major control mechanisms for the amount of PGs experienced by any particular cell, ~~xxxiv~~ then is by changes in the metabolic enzyme, then this histical evidence would suggest that early stage embryos would not be releasing PGs while blastocysts would. This may be an important factor for initiation of attachment; however, is not yet clear whether it is the blastocyst or the endometrium which is the initiating factor. However there is evidence from two species, the sheep and the rabbit, that the endometrium of the pregnant animal produces less PGF and PGE than that of the pseudopregnant animal, perhaps indicating the importance of the blastocyst as the initiating factor. It is also known that PG synthesis inhibitors either prevent implantation completely or reduce blastocyst growth and inhibit the appearance of endometrial capillary permeability changes

the site of attachment.

All this information indicates that a effort should be made to investigate the ability of various stage embryos and associated endometria to produce and metabolize PGs in normally pregnant animals and of endometrial capacity in preudo-pregnant animals. When such baseline information is obtained then various experimental manipulations can be envisaged such as what happens in delayed implantation in rats or mice, what happens when various steroid regimens that interfere with implantation are used, what happens in homozygous yellow mice where embryonic development fails at the blastocyst stage etc.

Initial studies will be done in the USA in Dr.Harper's laboratory under an NIH grant that is expected to commence early in 1980. A scientist from India, Dr.M.Raj Kumar, is undergoing post-doctoral training in this laboratory and is involved in these investigation On his return to ~~another~~ India, studies can be commenced at a laboratory to be selected. In addition, another Indian scientist, Dr.R.R.Badkhe, Gwalior Medical College, Jabalpur received post-doctoral training in Dr.Harper's laboratory in 1978 and has experience of studies of metabolism of PGs and could commence similar stidies in India, if he was in a situation where research could undertaken. Detailed protocols of the studies that could be done in both countries can be supplied by Dr.Harper, if required.

The budget requirements for Indian scientists can only be determined when it is decided who is to be involved and at which laboratories, since in addition to salaries for senior personnel and technical assistants, funds for radioactive isotopes, solvents, antibodies, media, glassware, chemicals, animals and specialised instrumentation may be required.

It is envisaged that this effort will commence in 1980 in the USA perhaps in late 1980 or 1981 in India and continue for atleast 3 years.

Approximate budget- $60,000

PROJECT: 12

STATEMENT OF INTENT: EXCHANGE OF NON-HUMAN PRIMATE RESOURCES

The group recognized the importance and the need for the use of non-human primates in various aspects of reproductive research.

Both India and the USA have resources for the use of non-human primates. Old World monkeys constitute a part of the natural fauna in India. The USA has set up primate research facilities containing chimpanzees which are much closer to man in certain aspects and these are therefore essential for certain types of crucial, preclinical experimentation. Other types of researches could carried out in the Old World Monkeys. However, the number of the latter species are declining in the wild and therefore there is a need to conserve these and to identify alternate species to experimentation on monkeys.

It was therefore felt that briefing could be made by exchanging information between the USA and India on "Good laboratory Animal Facilities" and also to identify specific areas of research for which the use of either monkeys or apes is inescapable on scientific grounds. This would facilitate a reciprocal exchange of facilities.