



**HRP**

UNDP/UNFPA/WHO/World Bank  
Special Programme of Research, Development  
& Research Training in Human Reproduction

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EXECUTIVE SUMMARY



World Health Organization  
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## INTRODUCTION

The Special Programme of Research, Development and Research Training in Human Reproduction (HRP) represents a global partnership for research in reproductive health. As the main instrument within the United Nations system for such research, the Programme brings together health care providers, policy-makers, scientists, clinicians and consumer and community representatives to identify and address priorities for research aimed at improving global reproductive health.

HRP was established in 1972 by the World Health Organization (WHO). Since 1988 the Programme has been co-sponsored by WHO, the United Nations Development Programme (UNDP), the United Nations Population Fund (UNFPA) and the World Bank. WHO is the Executing Agency. The co-sponsors, together with major financial contributors and other interested parties, make up the Programme's governing body, the Policy and Coordination Committee (PCC), which sets policy, assesses progress, and reviews and approves the Programme budget. Broad strategic advice on the Programme's work is provided by the Scientific and Technical Advisory Group. The Scientific and Ethical Review Group Panel reviews all projects involving human subjects and research in animals and contributes to ethical debate on matters relating to reproductive health. The Toxicology Panel is a complementary review body to the Scientific and Ethical Review Group Panel which provides expertise in the evaluation of pharmacokinetic, metabolic, endocrinological, toxicological, teratogenicity, carcino-genicity and mutagenicity studies of drugs, procedures or devices developed or studied by the Programme or referred to it for advice. In addition, the Programme has several scientific committees that advise on detailed research strategies.

In 1998, following the change in administration within WHO, all WHO divisions and programmes were reorganized into nine Clusters. The former Division of Reproductive Health (Technical Support) was merged with HRP to create the new Department of Reproductive Health and Research (RHR). RHR has been placed in the Health Systems and Community Health Cluster, and discussions have begun within WHO on the future work of the Programmes in the context of the work and objectives of the Cluster.

### Expansion of the Programme's research mandate

In 1998, at its 11th meeting, the PCC approved an expanded research agenda for the Programme and agreed that, in addition to fertility regulation, it should include high-priority research in: unsafe abortion, maternal health, reproductive tract infections (including cervical cancer) and planning and programme in reproductive health. The PCC also agreed that the expanded agenda should incorporate, as appropriate, aspects of adolescent health, harmful reproductive health practices and violence against women.

## WOMEN'S PERSPECTIVES AND GENDER ISSUES

The Women's Desk continued to convene the Gender Advisory Panel (GAP) and to ensure its recommendations were followed up. Practical tools for helping to ensure that gender considerations are taken into account in all the Programme's work are being developed, and the Programme is coordinating the Training Initiative in Gender and Reproductive Health. This course, in a regionally adapted form, will be run in five different centres during 1999.

Results from a study in Turkey on the acceptability, service delivery requirements and use-effectiveness of the diaphragm indicate there is a proportion of clients in both private and public services who are interested in the method. Women who are attracted to this method perceive it as

being safe and virtually free from side-effects. The study suggests that traditional prejudices about the diaphragm being appropriate only for highly educated women over age 35 should be put aside and service providers should help women who would like to use this method to use it correctly.

The Women's Desk continues to work on the "dual protection" approach—the use of one or more methods to protect against both pregnancy and sexually transmitted diseases. The information pack on the female condom was published and distributed in French and Spanish.

Two research projects studying the current practices to obtain informed consent in contraceptive research were completed in Brazil and Chile. The findings highlight that there are differences in what is understood by research subjects and investigators about the research process and the information given. There is also a lack of clarity among the two groups about their rights and obligations. The initiative to conduct research into informed consent procedures will be expanded to other regions, focusing on research projects supported by the Programme.

As a follow-up to the "dialogue" meeting between women's health advocates, scientists and policy-makers in the WHO Eastern Mediterranean region in 1997, the Programme is examining ways of looking at the impact of changes in laws and policies on reproductive health. The dialogue meetings will be continued in 1999 with meetings on long-acting injectables and the potential for their abuse, and ways of implementing a reproductive rights approach in research and services.

In all of these activities, the Women's Desk continues to work closely with women's NGOs to improve information exchange with them regionally and internationally.

## PLANNING AND PROGRAMMING FOR REPRODUCTIVE HEALTH

The Strategic Component on Technology Introduction and Transfer, conducts research to assist governments in broadening technology and service options for fertility regulation and other components of reproductive health, based on the needs of potential users and the capability of health care services. This research uses a three-stage strategy to introduce new or under-utilized technologies into reproductive health programmes.

Stage I of the process consists of an assessment of users' needs and perspectives, available technologies and the capabilities of the service delivery system, all framed within a broader context of reproductive health, and the sociocultural, political and resource settings. The principal focus of the assessments undertaken through 1996 has been on introduction of contraceptives. In 1997 and 1998, the strategic approach was adapted, and the assessment methodology was used to focus also on other aspects of reproductive health, including abortion. The process was also used to evaluate the Quality of Care Experiment in China. A reproductive health assessment is scheduled to take place in the Lao People's Democratic Republic in early 1999 and an assessment of abortion issues in Romania is planned. A field guide for conducting Stage I assessments, designed for use by decision-makers, is under development.

Stage II involves operations research to design and test optimal models for introducing new or underused technologies, while improving the overall quality of services. Stage II introductory research projects are ongoing in Bolivia, Myanmar, South Africa and Zambia. The studies in Brazil and Viet Nam were completed in 1998.

The study in Brazil had focused on the expansion of contraceptive options within the context of improving the quality of reproductive health services in a resource-poor municipal service delivery system. In addition to increasing access to contraceptives for women, vasectomy services had

been added for men and an adolescent centre had been established to provide reproductive health services for youth.

In Viet Nam, a study to develop a national strategy for the introduction of depot-medroxyprogesterone acetate (DMPA) while at the same time strengthening family planning and reproductive health service delivery has been in progress since mid-1996. The results from this study are being used to develop a "toolkit" including training curricula, IEC materials, and other tools to strengthen the managerial adaptations needed to support the broader national expansion of the introduction of DMPA, as well as improvement in the quality of care of family planning and other reproductive health services.

The Stage II project in South Africa is strengthening training for providers in family planning and expanding contraceptive options available to community members. The project developed IEC materials and provider training curricula for the provision of a broad range of family planning methods, including male and female condoms and emergency contraception. In Zambia, the ongoing Stage II activities include the introduction of DMPA and emergency contraception, again in the context of improving the quality of care for all the available contraceptive methods.

In Bolivia, the Stage II study is supporting expanded contraceptive options through improvements in the quality of family planning services and introduction of injectable contraceptives. In Myanmar, a project is focusing on the development of a township-level model for improving the quality of care of family planning and other reproductive health services.

Stage III assessment aims is to ensure that research results become relevant for policy and programme development. It involves the use of the findings and lessons learned in Stage II for replication or "scaling up". In Brazil, the Stage III project took the lessons learnt in one municipality and attempted to replicate these activities in three additional municipalities. A Stage III assessment will commence shortly in Viet Nam.

An evaluation of the strategic three-stage approach was undertaken in 1998. The objectives were to: (1) assess the strategy in terms of its impact, utility in improving quality of care in service delivery, and feasibility in terms of the time, costs and human resources required; (2) refine the design and implementation of the strategy to enhance its utility, feasibility and impact and its application to other reproductive health products; and (3) provide guidance for future activities of the Programme in the area of Introduction and Transfer of Technology. Implementation of the recommendations emerging from the evaluation has begun.

The Programme continues to play a major role in the Consortium on Emergency Contraception, providing information on emergency contraceptive pills and, in particular, making the progestogen-only pill, Postinor-2, more widely available. The Programme has undertaken baseline research in Indonesia and Sri Lanka prior to product introduction, and will support evaluation of these introductory activities in 1999.

The Programme continues to be active in a female condom working group within the new Department of Reproductive Health and Research and UNAIDS. During 1998 this working group: undertook the development and dissemination of information; continued to identify research needs and initiate research projects; and assisted in making the product available. Also, the Programme continues to support studies on the feasibility and safety of potential reuse of the female condom and on the development of strategies for its introduction.

A guide to contraceptive procurement for national programme managers is being developed. Work is also under way on aspects of product management that are essential for ensuring appropri-

ate quality of contraceptive products within the overall concept of quality of care. In 1998, the Programme supported activities to determine the extent of, and reasons for, quality problems with contraceptive products in Bangladesh.

The Strategic Component on Social Science Research is also active in the area of Planning and Programming through the development of reproductive health programme indicators for monitoring and evaluation. In 1998, three major documents reporting on this work were published and widely distributed and five country case studies on the topic were edited for publication.

### CROSS-CUTTING ISSUES IN SOCIAL SCIENCE RESEARCH

During 1998, the research, undertaken by the Programme in this area focused on two interrelated cross-cutting issues in reproductive health: the twin risks of unwanted pregnancy and prevention of HIV infection and other sexually transmitted diseases (STDs), and men's roles in reproductive health, including their perspectives on risk behaviours and contraception.

The first phase of the multicountry study on "Family Planning and Sexual Behaviour in the Era of HIV/STDs" was completed. A workshop was held in Entebbe, Uganda, to review the findings and to revise the questionnaire for the second phase of the study. Results from the first phase were also discussed with the communities participating in the study in Kenya.

Several studies on men's roles in reproductive health were also completed. These have shed light on men's behaviours and perspectives in the areas of sexual risk and contraception in different developing country sites.

### SEXUAL DEVELOPMENT, MATURATION AND GROWTH

In 1998 several research projects were under way on sexual development, maturation, and growth. Under earlier research initiatives on sexual behaviour, the role of men, and the context of abortion, the Programme had supported studies that had focused specifically on adolescents. Some of these projects were completed in 1998. Others, including two multicentre studies in China, are still in progress. These studies, along with others completed in earlier years, have provided a strong rationale for a concerted research effort on the needs and perspectives of young people.

During the year, the Programme developed and launched a new research initiative on "Adolescent Sexual and Reproductive Health". A regional workshop to strengthen research proposals from Asia was held in Thailand. This will be followed by similar workshops in Kenya and Brazil in early 1999.

National seminars to disseminate results and to discuss policy implications were held in China, Colombia, and Peru. A paper was presented at the International Conference on Reproductive Health, held in March 1998 in Mumbai, India, summarizing results on unwanted pregnancy and induced abortion among adolescents in developing countries. Another paper, highlighting the importance of social science research in the protection of sexual and reproductive choice of adolescents, was presented at a Reproductive Rights Workshop, held at the 12th World Congress on Medical Law, held in Siofok, Hungary.

The Programme also coordinated a multicountry project on improving reproductive health services for adolescents in Benin, Burkina Faso, Cameroon, Cote d'Ivoire, Guinea, Madagascar,

and Senegal. In addition to coordinating this research, the Programme is supporting research capacity strengthening in the countries involved, but funds for research are being raised locally.

## RESEARCH ON FERTILITY REGULATION

### Users' perspectives

During 1998, the Programme supported research on users' perspectives on methods of fertility regulation and services in a number of countries. New studies were launched in China, South Africa, and Thailand to examine the acceptability of condoms. Providers' perspectives with regard to fertility regulating methods were examined in Argentina and Myanmar and a study was completed on the postpartum use of contraceptives in China. A paper on users' perspectives was also presented at the International Conference on Reproductive Health, held in March 1998 in Mumbai, India.

A new research initiative to examine the impact of quality of reproductive health care on contraceptive choice, continuation of use, and contraceptive failure and unwanted pregnancy was under development. This initiative will also explore the perspectives of users regarding the definition of "quality of care".

One study completed in 1998 examined the association between women's experience and perception of changes in their pattern of menstrual bleeding and use of the injectable DMPA and Norplant among Thai women. Indeed, continuation rates for both DMPA and Norplant are high in Thailand. However, the use of both methods leads to major menstrual bleeding disturbances, with DMPA inducing increasing amenorrhoea with prolonged use and Norplant inducing more irregular and prolonged bleeding. The study found that for Thai women amenorrhoea was more unacceptable than prolonged bleeding; hence, DMPA was more likely to be discontinued than Norplant. The study highlighted the importance of cultural and social dimensions of side-effects which play an important role in the adoption and continued use of contraceptive methods.

Another study completed in 1998 in Mexico investigated the factors which influence men's use of vasectomy. The factors favourable to adoption of vasectomy in Mexico were noted to include: (i) having three or more children; (ii) prior experience of using withdrawal; (iii) predominant use of traditional methods; and (iv) a high level of communication with the partner on sexuality and contraception. Men who had no intention of having a vasectomy reported that it was either not easily accessible or that they were opposed to the idea of practising family planning. Interestingly, vasectomy was seen, in general, to be socially acceptable, having no impact on virility and as a procedure with few health risks.

### Development of improved and new methods of fertility regulation

The Programme is involved in the development of both improved versions of existing methods (in order to make them safer, more effective and more acceptable) as well as of new technologies and interventions that will fulfil an expressed but as yet unmet need. The current research and development portfolio has evolved from: (i) a process of continuous review of needs, opportunities and progress that is carried out by the Secretariat and by the Research Groups responsible for individual product leads; and (ii) priorities set following in-depth assessments of the overall research programme carried out every two years by the Programme's Scientific Review Committee for Technology Development and Assessment.

*Estrogen-free daily pill (mifepristone)*

The study to investigate the contraceptive efficacy of a daily dose of 0.5 mg of mifepristone was stopped because of an unacceptable number of pregnancies among the subjects. The results are being analysed for publication in 1999. No further efficacy studies involving the daily administration of mifepristone are planned.

*A three-monthly injectable (levonorgestrel butanoate)*

Studies carried out to develop an improved formulation of the levonorgestrel butanoate (LNG-B) suspension and to evaluate its stability have resulted in a preparation which can be readily formulated and easily filled into the desired container. The preparation appears to be both chemically and physically stable for two years. The formulation studies undertaken in 1998 will continue during 1999. Issues to be investigated include continued stability testing and the effect of various solvents used in the synthesis of LNG-B on the yield and resistance of the LNG-B crystals to gamma-irradiation.

In earlier studies it had been found that sterilization by gamma irradiation induced up to 4% of impurities. Investigations undertaken during 1998 found that the level of degradation increased with increasing doses of radiation, but the level of impurity was less than 1%, even after exposure to the highest dose of radiation. The apparent inconsistency of these findings with previous results is being reviewed and alternative sterilization processes are being investigated.

Once a clinically acceptable formulation is developed, pharmacokinetic and local tolerance (muscle irritancy) studies will be carried out in animals. If the outcome of these studies is successful, approval to restart clinical testing will be sought.

*A six/twelve-monthly injectable (hCG immunocontraceptive)*

Research carried out during 1997 and 1998 led to the selection of a composition and formulation of the advanced prototype hCG immunocontraceptive which is capable of eliciting a putatively protective level of immunity to hCG but which does not produce the unacceptable local reactions at the injection site that were seen with the prototype version. Studies were carried out in 1998 to define the conditions and requirements for the manufacture, formulation and subsequent analysis of this selected preparation. A batch of the selected preparation was prepared and analysed according to Good Manufacturing Practices (GMP) and pre-Phase I toxicity studies to evaluate the local tolerance (muscle irritancy) and subacute toxicity of the preparation in rabbits were initiated. Studies were ongoing to develop an optimized hCG immunocontraceptive containing totally synthetic immunogens, that do not need a diphtheria toxoid carrier, and improved delivery systems that will permit the desired duration of protection to be achieved following a single injection.

The results of the local tolerance and subacute toxicity studies carried out with the selected preparation and formulation of the advanced prototype hCG immunocontraceptive will be available during the first quarter of 1999. Assuming a satisfactory outcome to these studies, a submission will be made to the regulatory authorities to initiate a Phase I clinical trial with this preparation later in the year.

Further research will be carried out during 1999 to develop an optimized hCG immunocontraceptive preparation. These studies will involve the continued comparative assessment of selected synthetic or bioengineered B-cell and T-cell constructs and improved delivery systems to identify a preparation that will produce the desired specificity, level and duration of putatively effective immunity following a single injection.

## *Emergency contraception*

### Mifepristone

A randomized trial involving 1717 women was carried out in six countries to compare the efficacy and side-effects of single doses of 600 mg, 50 mg and 10 mg of mifepristone given within 120 hours (5 days) of unprotected coitus. Pregnancy risks were found to be similar in all three treatment groups. A comparison of the numbers of expected and occurred pregnancies (136 vs. 20) showed that the treatment prevented 85% of pregnancies. The delay in onset of next menses was significantly related to the dose of mifepristone (36%, 23% and 18% of women experiencing delayed menses, in the 600 mg, 50 mg and 10 mg treatment groups, respectively).

### Levonorgestrel vs. Yuzpe regimen

Results of a randomized, double-blind study comparing levonorgestrel (given as two 0.75 mg tablets 12 hours apart) with the Yuzpe regimen for emergency contraception were published in 1998. The maximum delay between intercourse and the start of treatment was 72 hours. A total of 21 centres in 14 countries participated in the study, in which 1998 women were enrolled. Treatment started within 24 hours of unprotected coitus in nearly 50% of the women in each group and within 48 hours in more than 80%. The pregnancy rate was 3.2% among women assigned to the Yuzpe regimen, and 1.1% among those assigned to the levonorgestrel treatment. An important finding of the study was a consistent linear relationship between the efficacy and the time from coitus to treatment. The breakdown of the prevention rates for levonorgestrel at different exposure-to-treatment time intervals was as follows: 95% up to 24 hours; 85% for 25-48 hours; and 58% for 49-72 hours. The corresponding figures for the Yuzpe regimen were 77% up to 24 hours, 36% for 25-48 hours, and 31% for 49-72 hours. As expected, nausea (23% vs. 51%), vomiting (5.6% vs. 18.8%), dizziness and fatigue were significantly less frequent among women in the levonorgestrel group ( $p < 0.01$ ). The time to resumption of menses was similar for women in both groups. For both groups combined, menses returned within three days of the anticipated onset of the next menses for most women (57%), had an early onset for 15% of the women, and was delayed by more than seven days for 13% of the women. This study has already had a major impact on emergency contraception services. Drug regulatory authorities in several countries have expressed interest in registering the levonorgestrel-only method and guidelines for providers are being updated.

### Comparison of mifepristone and levonorgestrel

A multinational randomized double-blind study is under way to compare the efficacy and side-effects of 10 mg of mifepristone and two treatments of levonorgestrel (i.e. two doses of 0.75 mg of levonorgestrel administered at 12-hour interval, or as one single dose of 1.5 mg) for emergency contraception up to 120 hours after unprotected intercourse. The study is being carried out in 15 centres and the target is to recruit a total of 4200 women. The clinical phase is expected to be completed by the first half of the year 2000.

### Other ongoing or planned studies

A study is under way in China to observe the continuation rate and late side-effects, if any, of the use of the intrauterine device (IUD) for emergency contraception. The Programme was also planning to evaluate the efficacy and side-effects of the use of gestrinone in emergency contraception.

*Non-surgical abortion regimen (mifepristone plus misoprostol)*

Findings of a trial comparing the efficacy and side-effects of 200 mg versus 600 mg of mifepristone followed, 48 hours later, by an oral dose of 0.4 mg of misoprostol were submitted for publication in 1998. This study found no difference between the two groups in terms of efficacy of treatment. However, the likelihood of complete abortion was inversely related to gestational age so that the use of 0.4 mg of oral misoprostol among women with menstrual delay of more than 21 days is too low to justify its use in the regimen in such pregnancies. More importantly, the continuing live pregnancy rate increased significantly, with menstrual delay being as high as 9% when the delay was between four and five weeks.

The study to investigate uterine contractility and the pharmacokinetics and pharmacodynamics of 0.2 mg and 0.4 mg doses of misoprostol administered either orally or vaginally was completed and the results submitted for publication. This study suggested that the vaginal route of administration was likely to be more effective than the oral route for terminating more advanced, first trimester pregnancies.

Findings were published from a study that examined the possible side-effects of repeated administration of oral misoprostol (0.4 mg twice daily) after pretreatment with mifepristone. About half of the 20 women in the study reported some degree of diarrhoea after the two-week treatment period, but nobody stopped the treatment for this reason. The incidence of other side-effects was low and all women had complete abortions.

A multinational study to compare the efficacy of three different regimens of misoprostol after pretreatment with mifepristone was launched in 1998. This study will involve a total of 2250 women in 15 centres.

*Control and management of post-abortion bleeding*

A study was initiated to investigate whether the practice of starting the oral contraceptive pill soon after abortion is useful for controlling the duration of post-procedure bleeding. The study suggested, however, that oral pills might increase the amount of bleeding after medical abortion and women may need to be advised not to use oral pills until the bleeding decreases.

*A three-monthly injectable (levonorgestrel butanoate plus testosterone buciclate) for men*

Further studies were carried out to identify a formulation of the highest testosterone buciclate (TB) concentration suitable for preclinical studies and clinical trials. As a result of these studies a composition and formulation of the required 400 mg/ml suspension was identified, which appears to be stable for at least one year. Stability studies are under way with this formulation, as are studies to determine the optimal synthesis and sterilization processes for TB.

Testosterone undecanoate (TU) is a testosterone ester which, in its injectable formulation, has a pharmacokinetic profile that falls between the 2-3 weeks' duration of activity provided by testosterone enantate (TE), and the three months expected of TB. TU offers the promise of a one-monthly or two-monthly injectable product for use alone or in combination with a progestogen. A multicentre study to assess the contraceptive efficacy of TU was started during 1998 in six centres in China.

Recent studies have confirmed that cyproterone acetate (CPA) given orally, daily, in combination with TE given by injection weekly, has an antispermatogenic effect in normal men. The Programme is planning to carry out a multicentre study to evaluate the effects on spermatogenesis of

a treatment regimen consisting of a daily oral dose of 20 mg CPA in combination with injections of 1000 mg of TU given every eight weeks.

It has been suggested that the low level of spermatogenesis that persists in some men taking part in clinical trials of androgen alone and progestogen plus androgen combinations as male contraceptives, may be due to a persisting, low level of production of dihydrotestosterone (DHT). Partial funding was provided to a project to investigate if the administration of a 5 $\alpha$ -reductase inhibitor, finasteride, which prevents the conversion of testosterone to DHT, would result in a complete suppression of spermatogenesis in those men who did not achieve azoospermia following the administration of exogenous testosterone. The data obtained in this project failed to show any additional effect of finasteride on the testosterone-induced suppression of spermatogenesis.

#### Acceptability and behavioural studies

An acceptability and behavioural assessment study is being carried out in conjunction with the six-centre TU contraceptive efficacy study in China (see above). Both qualitative and quantitative approaches are being used to collect information on contraceptive use acceptability, family size preferences, decision-making regarding contraceptive use and perceptions on male contraceptive injections. The results of the in-depth analyses are expected in 1999. In addition, a study is being carried out in the United Kingdom to collect, develop, adapt and validate a range of psychometric tools, not previously available or applied, to quantify testosterone-associated changes in behaviour (especially aggression) in healthy adult men. Two questionnaires for use by men and their partners have been developed.

#### *Non-surgical vas occlusion (silicone plugs)*

No research was supported on the silicone plug approach to vas occlusion during 1998, but a small consultation was convened in April 1998 to review, with the investigators and manufacturers of the method, the results obtained in the various animal and clinical studies that have been carried out in this area. In view of the very different results obtained in the Dutch and Indonesian clinical trials, it was concluded that further animal studies were needed before a decision could be made about further clinical testing.

#### *Contraceptive vaginal ring*

Because of concerns about low efficacy of the ring releasing 20  $\mu$ g/24 hours of levonorgestrel, particularly in heavier women, the plan is to develop, as a final product, a higher-dose redesigned vaginal ring releasing 35  $\mu$ g/24 hours of levonorgestrel. In 1998, negotiations were initiated with The Contraceptive Research and Development Program (CONRAD), Arlington, VA, USA, and potential industrial partners for the production of a batch suitable for clinical testing.

#### *Natural family planning*

In 1998, the Programme collaborated with the Institute for Reproductive Health (IRH), Georgetown University, Washington, DC, USA, in the design of a prospective multicentre study of the efficacy and effectiveness of a 9-19 day standard rule method. IRH initiated a pilot study in Bolivia, and it is expected that the target of accumulating 200 cycles of method use in this trial will be reached in the spring of 1999. Following this, the study will be initiated in several Latin American centres and in the Philippines supported by IRH, and in two sub-Saharan African centres supported by the Programme.

### *Lactational infertility*

Owing to the lack of funds, no new initiatives were started during the last four years. The only project ongoing in 1998 was an investigation of the relationship between physical activity and lactational amenorrhoea. This study has been completed and the results are being analysed.

### *Goal-oriented basic research*

#### Endometrial bleeding

The Programme continues to study the mechanisms of normal menstruation and how these are affected by the use of progestogens. Data from recent studies conducted by the Programme and others suggest that menstruation is an inflammatory response to the withdrawal of progesterone, in which cells of the immune system invade the endometrium and/or are activated and release regulatory molecules which increase the production and activation of matrix metalloproteinases (MMPs) but not of their inhibitors (tissue inhibitors of metalloproteinases, TIMPs). This imbalance leads to the destruction of the endometrial connective tissue and degeneration of the functionalis layer with exposure of open blood vessels and endometrial glands. In this new scheme, tissue destruction becomes the primary event initiating menstruation.

Unlike menstruation, progestogen-induced endometrial bleeding is unpredictable and occurs from small superficial veins and capillaries. A study was undertaken to compare the endometria of users of Norplant at the onset of a vaginal bleeding episode and during non-bleeding times. The analysis of biopsies obtained from 23 volunteers in this study showed that abnormal endometrial bleeding was associated with focal stromal breakdown, expression of interstitial collagenase (pre-MMP-1) in some foci of stromal breakdown, and activation of pre-MMP-1.

In another separate study, the immunolocalization of MMP-9 and migratory cells in the endometrium was compared in Norplant users and in normal controls. MMP-9 positive cells were identified as neutrophils, eosinophils, CD3<sup>+</sup> T cells and macrophages and MMP-9 immunostaining was also observed in areas of tissue lysis close to these cells.

Two studies were launched to assess the effects of different treatments on progestogen-induced prolonged bleeding. One, a double-blind, placebo-controlled trial was being conducted in Chile to test the efficacy of mifepristone in improving the vaginal bleeding pattern of Norplant users. The other study was a double-blind, randomized, placebo-controlled clinical trial to test the effect of vitamin E as an antioxidant, and of low-dose aspirin as an anti-inflammatory agent, alone and in combination, on Norplant-induced prolonged bleeding.

#### Male reproductive physiology

Androgens are essential for any hormonal regimen for male contraception. However, a large mass of steroid needs to be injected to have a long-acting depot effect. A study was under way to investigate the effects of a high potency non 17-alkylated androgen on mouse testis, prostate and liver in order to determine if the same level of desired suppression and replacement can be achieved with a lower mass of drug.

Studies were continuing to investigate the mechanism by which triptolide, a compound isolated from the roots of the plant *Tripterygium wilfordii*, causes infertility in male rats. The results obtained suggest that triptolide has two distinct functions on mature and maturing germ cells. The first action manifests earlier and impairs mainly epididymal sperm that show a marked reduction in number and motility. The second action occurs later and appears to impair spermatogenesis.

The Programme continues to study the mechanisms of spermatogenesis. A three-year project was completed which had been investigating the physiological significance in spermiogenesis of a truncated form of the proto oncogene *c-kit* specifically expressed in mouse spermatids. Future studies will involve the production of knockout mice, in which the gene coding for the *tr-kit* promoter has been deleted, to see if these mice exhibit normal spermatogenesis and if the spermatozoa they produce are capable of fertilization and egg activation.

### **Safety and efficacy of existing methods of fertility regulation**

The last main publication based on data from the WHO Collaborative Study of Cardiovascular Disease and Steroid Hormone Contraception was published in 1998. This was a paper on cardiovascular risks and use of progestogen-only pills, progestogen-only injectables and combined injectables. Another related publication in 1998 was the report of the WHO Scientific Group on Cardiovascular Disease and Steroid Hormone Contraception. A key conclusion of the study group was that the incidence and mortality rates of all cardiovascular diseases (stroke, acute myocardial infarction and venous thromboembolic disease) in women of reproductive age are very low. The background papers prepared for the meeting of the Scientific Group were also published.

The multicentre study of bone mass and hormonal contraceptives was completed. It suggested that progestogen-only contraceptives have a small but unfavourable effect on bone mass. A paper from this study was submitted for publication, and a new research proposal was developed for a longitudinal study of the impact on bone density in young (16-20 year) and older women (45-49 year) of DMPA and norethisterone enantate (NET-EN) injectable contraceptives as well as combined oral contraceptives.

A multicentre study on prostate cancer and vasectomy was completed in 1997. Data from this study were analysed in 1998 and a draft publication prepared.

Analysis of data from the Post-Marketing Surveillance of Norplant has been completed and three papers from the study are being prepared. No significant excess of malignant neoplastic disease or cardiovascular events, such as stroke, myocardial infarction, or venous thromboembolism, were observed in women using Norplant compared to women using non-hormonal methods or to the expected number estimated from population based incidence rates.

The studies of long-term safety and efficacy of the Multiload 375 and the 20 µg levonorgestrel IUDs compared to the TCU380A device were continuing in their 9th and 5th years, respectively. Collection of vaginal biopsies for the study of the effect of hormonal contraceptives on vaginal epithelium was completed and evaluation of the samples is ongoing. The study on relationships between prostate cancer and vasectomy in New Zealand is under way, as are the evaluation of safety of use of hormonal contraceptives for women with systemic lupus erythematosus and the Chinese multicentre study of safety of mifepristone induced abortion with regard to subsequent wanted pregnancy.

The research instruments and logistics of the multicentre studies comparing the effects of different contraceptives used by HIV-1 seropositive women on the clinical course of HIV-1 infection and cervical/vaginal shedding of HIV-1, are being tested in a pilot phase of the study.

An initiative to evaluate the effect of enhancing family planning service providers' medical and counselling knowledge and skills, respectively, on safety, efficacy and continuation of family planning methods is in planning. Finally, a study of the contraceptive efficacy of the female condom was being prepared, while the studies of contraceptive efficacy of latex and non-latex condoms are on hold for the time being.

## MATERNAL HEALTH

The main goal of this new Strategic Component is to reduce maternal morbidity and mortality by helping countries to develop acceptable and affordable evidence-based health programmes.

As requested by the Scientific and Technical Advisory Group in 1998, a technical consultation in maternal health was convened during 1998. This group was requested to identify medium- and long-term strategic maternal research areas and recommend priority themes, and, where possible, priority rankings, according to the comparative advantage of the Programme.

The implementation of the Maternal Health Research Strategic Component will be achieved by (i) conducting systematic reviews of the literature, (ii) reviewing methodological issues related to maternal health research, (iii) evaluating promising interventions using the most rigorous methodology and, when feasible, (iv) conducting follow-up studies of the populations included in pregnancy-related research as well as monitoring the implementation of research results. Some of these mechanisms are already being implemented.

A large multicentre randomized controlled trial is under way Argentina, Cuba, Saudi Arabia, and Thailand to evaluate the impact of a new antenatal care programme on the health of mothers and newborns. This new programme limits the antenatal tests, clinical procedures and follow-up actions to those scientifically demonstrated to be effective in improving maternal and newborn outcomes. The selected antenatal care activities are distributed over four visits during the course of pregnancy. A total of 24 703 women presenting for antenatal care at clinics were recruited by April 1998. More than 90% of the data have been obtained. The final data analyses of the three components of the study (clinical evaluation, women/provider satisfaction and economical evaluation) will be conducted during 1999. An extensive dissemination effort is being planned, including presentations at meetings and symposia, and medical and non-medical publications.

A multicentre, double-blind, randomized controlled trial was launched by the Programme in 1997 to evaluate the effectiveness of a 600- $\mu$ g oral dose of misoprostol in reducing severe post-partum blood loss and the need for additional treatment in the third stage of pregnancy when compared with an intramuscular (IM) or intravenous (IV) 10-IU dose of oxytocin. By the end of 1998, approximately 6000 women had completed the study and preliminary data were presented to the Data Safety Monitoring Committee of the trial, which recommended the study to continue without any modification to the original protocol. It is expected that by October 1999 all women will have completed the study. Results are expected to be available before the end of 1999.

## NATIONAL REPRODUCTIVE HEALTH RESEARCH

“National Reproductive Health Research” refers to research of national or global relevance being conducted in the network of centres in developing countries that collaborate with the Programme. In 1998 there were 24 institutions in developing countries receiving support for capacity building: five in Africa and the WHO East Mediterranean region; one in Latin America and the Caribbean; and 18 in the WHO South-East Asia and Western Pacific regions. There were also seven countries in Eastern Europe and Central Asia participating in research projects developed by a Scientific Working Group (SWG) from the region.

Regional Advisory Panels (one each for Africa and the WHO East Mediterranean region, the Americas and WHO South-East Asia and Western Pacific regions) established in 1997 by the Policy and Coordination Committee, provide guidance to the research and capacity building activities of the Programme.

A review of the 54 designated WHO Collaborating Centres for Research in Human Reproduction was completed and a few changes in the number and distribution were initiated. This process is expected to be completed in 1999.

#### *WHO African and the Eastern Mediterranean region*

Collaboration with the Programme occurred in 24 countries of the African and Eastern Mediterranean regions during 1998. Five institutions in these countries received Long-term Institutional Development (LID) Grants and three received a Resource Maintenance Grant, while 17 others got grants for library support and the purchase of consumable laboratory supplies.

During the year, regional research initiatives on two of the three priority research areas identified in the previous year continued to be developed. These were on Female Genital Mutilation (FGM) and reproductive health services for adolescents in French-speaking Africa. The United Nations Foundation Inc. approved funding for a project entitled "Promoting best practice for FGM prevention in six sub-Saharan African countries". The main goal of the project is to derive and disseminate best practice for the prevention and elimination of FGM, drawing on the results of evaluation and research on FGM and of programmes to combat it in six sub-Saharan countries (Burkina Faso, Cameroon, Gambia, Ghana, Kenya and Nigeria).

An operations research project on improving reproductive health services for adolescents was initiated in seven French-speaking sub-Saharan countries (Benin, Burkina Faso, Cameroon, Côte d'Ivoire, Guinea, Madagascar and Senegal). Pilot studies were completed in all countries and baseline surveys were initiated in some countries to define the profile of the adolescent users of health services and the quality of the services offered.

Other inter-country activities included a number of research methodology training courses, workshops on identification of reproductive health priorities and strengthening of mechanisms for dissemination of information. In addition, the Strategic Component of Social Science Research on Reproductive Health initiated a multicountry study on Family Planning and Sexual Behaviour in the era of HIV/STDs in six countries of the region.

At the country level, research was supported under the respective LID Grants and by some of the Programme's Strategic Components. Efforts continue to be made to increase the activities of all the Programme's Strategic Components in Africa. Special efforts are also being made to strengthen the Programme's collaboration with reproductive health research centres in the WHO Eastern Mediterranean region and in French-speaking Africa.

#### *The Americas*

During 1998, centres in the Americas were involved in five regional research initiatives. Three centres from Brazil, Chile and Mexico were conducting the multicentre research project "Acceptability of emergency contraception in Latin America", funded by the Mellon Foundation. Institutions in Argentina, Bolivia, Cuba and Peru were implementing the multicentre social science research study on "Reality and beliefs in the sexual and reproductive decision-making process: men's perceptions and behaviour". Centres in Argentina, Brazil, Cuba, Guatemala and Mexico had completed preliminary work to undertake a multicentre study that will address the problem of the increasing rate of Caesarean sections in Latin America, funded with a grant from the European Community. Women's perceptions on the quality of antenatal care were being evaluated in a multicentre trial initiated in Argentina and Cuba as well as two centres in other regions (Saudi Arabia and Thailand). Three centres in Argentina, Colombia and Venezuela were preparing to take part in a multicentre trial coordinated by Oxford University, Oxford, England, that will evaluate

5 countries  
in Latin  
America

the use of magnesium sulphate for the treatment of pre-eclampsia (Magpie Trial). Lastly, four centres in Argentina, Chile and Mexico involved in basic reproductive biology research had established a regional network to study the mechanisms of action of hormonal methods used for emergency contraception.

In addition to these regional research initiatives, the centres were involved in projects which were addressing national priorities. During 1997, from the overall number of 173 studies, 15 projects (9%) were implemented with support from capacity building grants (LID, Resource Maintenance and Re-entry Grants) and 79 projects were carried out with support from national sources (46%). The participation of the regional centres in the global research effort was exemplified by the 16 projects (9%) supported by other Strategic Programme Components and the 63 studies (36%) being funded by international agencies other than WHO.

During 1998 intra-regional research training continued to be an important component of institutional strengthening activities. Six research training grants were awarded in the areas of reproductive epidemiology, reproductive medicine and in the social sciences; furthermore, three young scientists from regional institutions were selected in a worldwide competitive process and took part in the first Frontiers in Reproduction training programme in advanced reproductive biology organized by the US National Institutes of Health in June 1998.

A survey of the composition and *modus operandi* of Ethical Review Committees (ERC) in 25 institutions was conducted in 1998. Results showed, among other things, that 88% of the centres had ERCs, that 56% of their members were men and 63% were medical doctors; only 46% of ERCs utilized formal guidelines for their operation and 32% produced regular progress reports. These results highlight the need to improve ethical review mechanisms in the collaborating institutions.

#### *WHO South-East Asia and Western Pacific regions*

At its meeting in 1998, the Regional Advisory Panel for Asia and the Pacific endorsed the following new regional strategies: (i) concentrate efforts on collaboration with selected institutions and countries and place greater emphasis on impact; (ii) draft a new research capacity building strategy and adjust financial support accordingly; (iii) devote major efforts to encouraging intra-regional cooperation, especially regional research initiatives and regional networking mechanisms; and (iv) seek partnerships and generate additional support for strengthening research capacities.

The Asia and Pacific Symposium on "Intraregional cooperation in reproductive health research" was held in Shanghai, China, on 12-13 October 1998. Twenty-four directors or representatives of research institutes from thirteen countries in the region, which have been collaborating with the Programme for many years, attended this Symposium.

An innovative, new strategy for research capacity building was recommended at the Symposium with the following key activities: (i) research-based support for research capacity building; (ii) project-specific research training; (iii) regional joint research programmes; (iv) intraregional, research and intra-country networking activities; (v) improving assistance and support among WHO Collaborating Centres for Research in Human Reproduction; and (iv) an electronic mail network for the Asia and the Western Pacific region.

Symposium participants endorsed the regional research priorities and voted for five top priorities as follows: (i) RTI/STDs, cervical cancer, HIV/AIDS; (ii) fertility regulation; (iii) adolescent reproductive health; (iv) unsafe abortion and safe motherhood; and (v) infertility.

### *Eastern Europe*

The East-West European Initiative for Research on Reproductive Health was launched on 15-19 October 1990 when over 50 scientists from European WHO Collaborating Centres for Research in Human Reproduction met in Szeged, Hungary, to identify priorities for collaborative research and research training, prepare outlines for collaborative research projects and identify potential sources of funding. The Group noted that there was "a need to mobilize more resources for research in human reproductive health, particularly in the area of fertility regulation, in those European countries where there are major unmet needs".

The strategy adopted by the Programme was based on the assumption that there already existed in the region adequate infrastructure for research. Therefore the design and conduct of research could be promoted without prior investment in infrastructure. Research training was to be limited to no more than 20% of available resources. It was expected that additional resources could be obtained from other agencies. However, this has proved difficult thus far.

### **CLINICAL TRIALS AND INFORMATICS SUPPORT**

During 1998, 71 single- and multicentre projects were supported, of which 20 were in the planning stage, 10 were in the data collection phase, 28 in the final analysis stage and 13 were completed. A total of 30 000 data forms were processed and entered into the Programme's database during the year. The unit of Clinical Trials and Informatics support coordinated efforts within the Programme to review existing Standard Operating Procedures and to develop new ones in order to start a formal implementation of WHO Good Clinical Practice (GCP) guidelines in all of its research activities.

Strengthening of biostatistical and data processing capabilities of collaborating institutions continued. Staff of the unit supervised on-site centres performing data management of their own studies. They also gave lectures at the Postgraduate Course for Training in Reproductive Medicine and Reproductive Biology at the Collaborating Centre in Geneva, Switzerland, conducted workshops and gave on-site training on data management and GCP compliance in Beijing, China, Geneva, Switzerland and Khon Kaen, Thailand.

In 1999, support to the 58 current studies and any new studies will continue. Implementation of WHO Good Clinical Practice throughout the Programme's research activities will continue. A regional workshop on advanced methods in statistical analysis and computer management of reproductive health research data will be conducted for scientists from collaborating centres in the Eastern Mediterranean Region.

### **STANDARDIZATION AND QUALITY CONTROL OF LABORATORY PROCEDURES**

During 1998, the supply of well-characterized reagents for the immunoassay of reproductive hormones to laboratories collaborating with the Programme continued. The reagents were produced at the WHO Collaborating Centre for Research and Reference Services in the Immunoassay of Hormones in Human Reproduction, London, United Kingdom, (hereafter referred to as "London Centre"). The standardized assay systems had been well validated and were being used for the analysis of samples collected in the course of multicentre research projects and other studies supported by the Programme, including research conducted in the context of institution strengthening activities. In addition to providing reagents, the Programme monitored the perform-

ance of laboratories collaborating with it by means of an external quality assessment (EQA) scheme.

In 1998, a total of 39 laboratories in 26 countries (21 of them developing, three developed and two countries in transition) received matched radioimmunoassay (RIA) and enzyme immunoassays (EIA) reagents sufficient for 368 700 assay tubes and 35 laboratories participated in the EQA scheme. In addition to these reagents the Programme continued to provide training and technical support needed to establish schemes for the development and production of standardized immunoassay systems at the national or regional level.

In spite of unquestionable success and usefulness of the Matched Reagents Programme (MRP) the steadily decreasing need for hormonal measurements induced the meeting of the Scientific and Technical Advisory Group (STAG) in 1995 to recommend that a review of possible alternatives to the present system of reagents production and distribution should be carried out in which cost/benefit considerations would be taken into account. That review was performed and four possible alternative models were considered by the Laboratory Methods Group at its meeting in December 1997. The STAG recommended in February 1998 that the present operations of the London Centre should continue although at a reduced level, but that the Programme should keep a watching brief on the viability of these operations.

The recent severe financial constraints the Programme is experiencing, in association with apparently decreasing needs for reagents for 1999, have resulted in the conclusion that the Matched Reagent Programme should be phased out during 1999. The future provision of reagents would be based on those available commercially. The EQA, if needed on an ad-hoc basis, could also be obtained at a cost from established EQA organizers.

### MAPPING BEST REPRODUCTIVE HEALTH PRACTICES

Systematic reviews of evidence derived from randomized controlled trials are accepted as the gold standard in summarizing all available information regarding health care interventions. The Programme and collaborating institutions around the world have initiated a programme to map the best reproductive health practices through four activities: (i) synthesis of evidence through preparation of systematic reviews of the effectiveness of health care interventions, (ii) capacity building in the preparation of systematic reviews, (iii) dissemination of evidence based reproductive health care information, and (iv) promotion of rigorous evaluation of medical and non-medical forms of care recommended by the Programme. It is expected that the selection of effective practices and their incorporation into services identified through this programme will allow developing countries to maximize their resources and channel them to the needed areas in the most rational and effective way. Improvement in health status of the populations, especially of the under-resourced, is the ultimate goal to be reached, partly as a result of this new initiative.

### COMMUNICATION AND DISSEMINATION OF INFORMATION

During 1998 the Programme continued to produce its usual serial publications, including the quarterly newsletter *Progress in human reproduction research*, *Annual technical report 1997* and *Biennial Report 1996-1997*. The Biennial Report 1996-1997, which not only focused on the work of the Programme during the biennium but also on the new expanded research mandate of the Programme, was published as a formal WHO publication and was distributed widely. Two other key publications in 1998 were *The WHO reproductive health library* (RHL) and the book *Abortion in the developing world*. RHL was distributed widely in developing countries employing a strategic dissemination plan. Judging from the demand for RHL, it would be safe to say that

this electronic journal is proving to be one of the most successful Programme documents of recent years. Work was started on the production of RHL, No. 2. *Abortion in the developing world* was published on behalf of WHO by Vistar Publications (a division of Sage Publications), New Delhi, India (with distribution rights for the Indian subcontinent), and Zed Books, London, England (with distribution rights for the rest of the world).

Scientific writing workshops and communication workshops for researchers were also conducted in 1998. These workshops aim to help centres collaborating with HRP in the strengthening of their capacity to disseminate research findings to scientists, policy-makers and the general public. During 1998, one scientific writing workshop was held in Mumbai, India, at the Institute for Research in Reproduction. Fifteen scientists from the Institute participated in this workshop. A communication workshop, with 15 participants, was conducted at the Shanghai Institute of Planned Parenthood Research, Shanghai, China. A third workshop was conducted in Benin. The aim of this workshop was to strengthen the capacity of the centres in French-speaking African countries to manage their information resources and improve exchange of information with scientists in the centres as well as with constituencies outside the centres.

Two press releases were issued in 1998, one on the launching of RHL and another on levonorgestrel as a method of emergency contraception. The press release on the launching of RHL helped considerably in creating awareness about RHL.

The Internet web site of HRP, *HRP Online*, was maintained and updated in 1998. HRP Online received independent appreciation for providing useful material on reproductive health.

In 1999 HRP will continue to produce and disseminate relevant documents and other information materials. Workshops on scientific writing and communication are also planned.

