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SUPPORT

OTHER FUNDS AND PROGRAMMES

UNITED NATIONS FUND FOR POPULATION ACTIVITIES

Report of the Executive Director on support to contraceptive research and development

Summary

This report is being submitted to the Governing Council in response to paragraph 9 of its decision 81/7, Part I, in order to provide the Council with information on the needs in the field of contraceptive research and development, the current status of contraceptive technology, present funding of contraceptive research and development, and the opportunities for future UNFPA support to this field.

It is intended that the present report be read in conjunction with DP/1982/36, in which policy issues relating to UNFPA support of contraceptive technology are addressed.

82-10592

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I. BACKGROUND

1. By decision 78/33, the Governing Council, inter alia, stated that it shared the view of the UNFPA Executive Director "that research on contraceptive technology is crucial to the attainment of the Fund's objectives..." By decision 79/28, the Council, inter alia, agreed "that UNFPA should continue to support the WHO Special Programme of Research, Development and Research Training in Human Reproduction and that in the period 1979-1982, it gradually increase its contribution to attain a level of $2 million in 1982, and that the Governing Council should review the question of continued UNFPA support for this programme at its regular session in 1982". At its twenty-eighth session, the Governing Council by decision 81/7 requested the Executive Director to: undertake a comprehensive review of needs and opportunities in the field of contraceptive research and development which would address, inter alia, (i) the question of identifying these activities as a category separate from other intercountry activities, (ii) the question of what set percentage of the Fund's intercountry activities, if any, should be earmarked for research programmes designed to develop and improve various kinds of contraceptives including natural family planning methods, and (iii) the question of continued Fund support (including the annual level of such support) for the World Health Organization Special Programme of Research, Development and Research Training in Human Reproduction and other research programmes within the proposal presented, as earlier requested by the Governing Council at its twenty-sixth session. The decision of the Governing Council also requested UNFPA to explore with the World Bank and other interested agencies (World Health Organization, International Planned Parenthood Federation, and private foundations) how the World Bank proposal for the establishment of a joint board for health research could affect the contraceptive research field.

2. To obtain the technical advice necessary to respond to the request of the Governing Council at its twenty-eighth session, UNFPA employed a consultant to prepare a brief non-technical paper on the status of contraceptive development research. This paper was then circulated to more than seventy scientists and family planning programme managers around the world for their comments and criticisms. Some thirty-five responses were received and have been reviewed and, as appropriate, incorporated into the final paper, titled "Report on Contraceptive Technology." To provide further advice to UNFPA in responding to the Governing Council's request, the Executive Director appointed an Advisory Group on Contraceptive Development Research to review the draft "Report on Contraceptive Technology", and the comments upon it and to consider the questions (i), (ii) and (iii) of decision 81/7.

3. The Advisory Group was composed of:

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Karolinska Institute
Stockholm 60, Sweden

Dr. Lidija Andolsek
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Dr. V. Ramalingaswami, Director-General of the Indian Council of Medical Research, accepted the invitation to join the Advisory Group for its second meeting but at the last moment was unable to attend. The Advisory Group met on 6-7 January 1982 in New York and again on 4-5 March 1982. Their "Report" and the consultant's "Report on Contraceptive Technology" have been used by UNFPA in preparation of this paper.

II. NEED FOR NEW OR IMPROVED CONTRACEPTIVE TECHNOLOGIES

4. UNFPA has been directed by decision 81/7 of the Governing Council, inter alia, to give highest priority to supporting family planning programmes including research into existing and new contraceptive methods and development of improved means of contraception, including natural family planning methods. The need for new and improved technologies has been emphasized recently in a number of conferences. The International Conference on Family Planning in the 1980's, which was jointly sponsored by IPPF, the Population Council and UNFPA and attended by family planning programme managers from many developing countries, (26 - 30 April 1981) stated in the Jakarta Statement that "Improved means of fertility regulation are urgently needed. The safety, acceptability and effectiveness of methods must be enhanced. Support for research to improve existing methods and to develop and test new technologies must be substantially increased". The Substantial New Programme of Action for the 1980's for the Least Developed Countries, adopted by the United Nations Conference on the Least Developed Countries, held in Paris from 1-14 September 1981, urged, among other policy measures, that "within the framework of national demographic policies, countries will take appropriate measures for family planning and population control. Emphasis must be given to biomedical and social science research into safer, more efficient and more widely acceptable techniques of family planning". 1/

5. The review of the needs in the field undertaken by UNFPA has confirmed these statements. Each scientist and each programme manager UNFPA consulted has emphasized the need for better fertility regulating methods. The World Health Organization estimates that out of a world total of one billion couples of reproductive age, approximately 300 million are at present using modern methods of contraception. Of 600 million couples living in developing countries, only 100 million are using modern contraceptive methods. 2/

1/ See A/CONF. 104/22, paragraphs 38-39.
2/ WHO, Tenth Annual Report on HRP, p.8.

6. The World Population Plan of Action, in paragraph 14f, draws attention to the fundamental rights of couples and individuals to decide freely and responsibly the number and spacing of their children and to have the means to do so. Broadening the choice of safe, effective and acceptable methods cannot help but contribute significantly towards meeting this need. The increasing momentum of demographic change emphasizes the need for prompt responses to the demand for better contraceptive technology.

7. It would be unrealistic to foresee the development and introduction of entirely new contraceptive technology within the next ten years, but the investment of public funds in contraceptive research and development over the past decade has begun to produce results. The copper-bearing intrauterine devices have been widely tested and are now available for introduction though their use is not yet widespread. A new steroid-releasing implant system which offers five years of protection following its placement is now in field trial in five countries. Other significant new technology is undergoing clinical assessment under the sponsorship of the World Health Organization and other international agencies and as the new technology becomes available it must be adapted and introduced into programmes by training personnel in its use and by designing information and educational materials to inform potential acceptors of its advantages and disadvantages. Eventually, national systems to procure and distribute the new technology must also be put into place. The introduction of improved technology into programmes represents a critical step in the research and development process, but increasing attention must also be directed to post-introduction surveillance studies. The detection of rare adverse side effects can only come from observations of large numbers of users over an extended period. Systems to monitor contraceptive safety can be improved.

III.

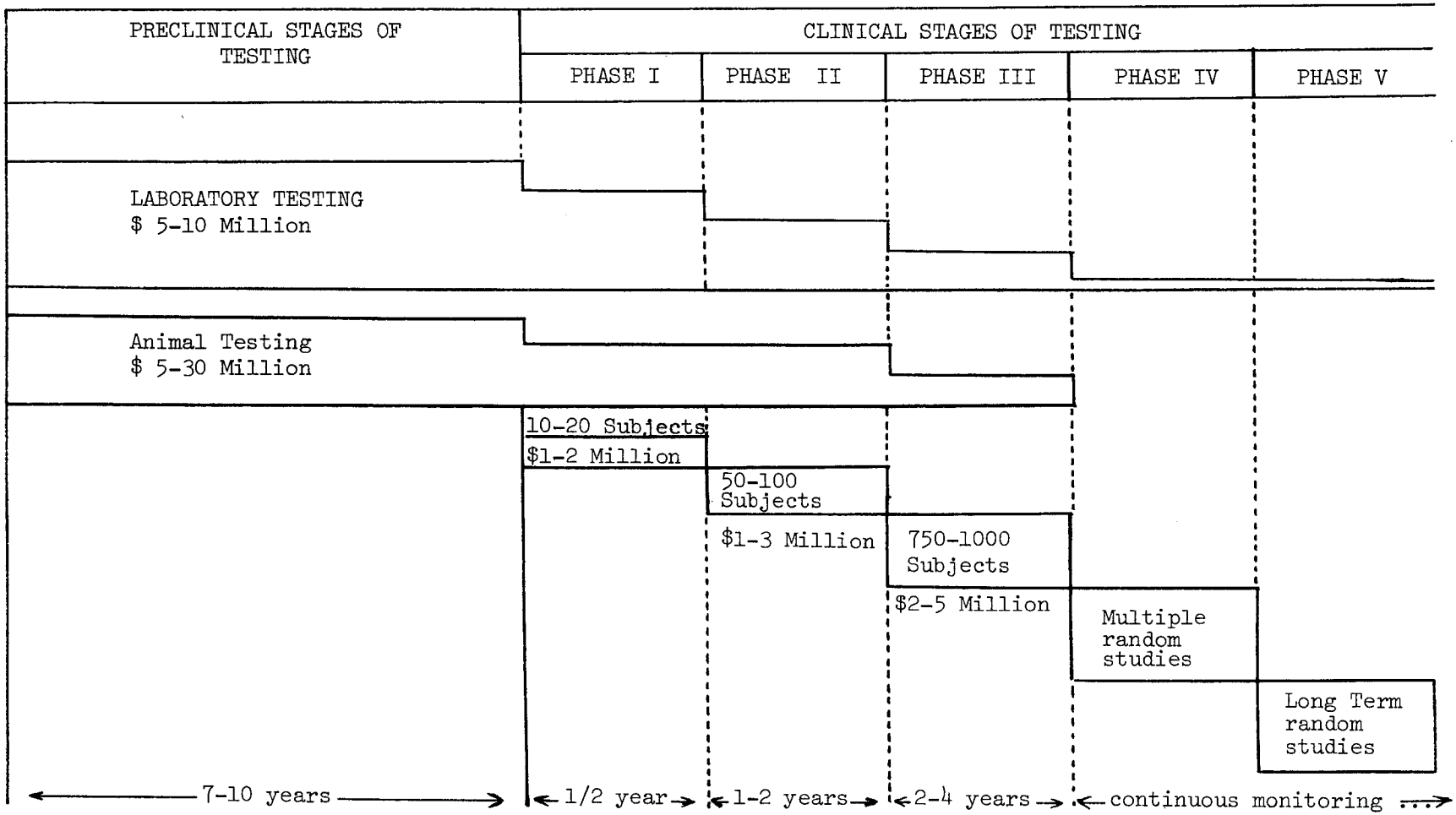
A. Time required for research and development

8. The development and successful introduction of a new contraceptive method takes many years. Table A shows the process involved in contraceptive development starting after a finding from basic research in reproductive biology has been judged to have clinical potential. Laboratory and animal testing is begun, including biochemical assays and tests for the potential induction of adverse effects such as malignancy. Tests in animals are designed to discover any toxic effects of the drug on the animal and/or the foetus, and to prove the drug's usefulness as a contraceptive. Only when the product has been shown to be safe and effective with animals is human testing begun.

9. Traditionally, testing in humans has been carried out in three phases. Phase I testing involves a small number of subjects (usually 10-20) who are studied intensively for about six months, looking for any adverse effects and evaluating efficacy. If there are no contraindications, Phase II is begun in which 50-100 subjects are studied for one to two years but not so intensively as in Phase I. Again, if there are no problems, Phase III is undertaken, observing up to 1000 subjects for an extended period of time, two to four years. Data required for drug registration necessary to meet the regulatory requirements of countries is usually in hand by the end of Phase III. Toxicological and other data may be collected thereafter, but the contraceptive method is approved for widespread use

TABLE A

PHASES OF CLINICAL TESTING IN DEVELOPMENT OF A NEW CONTRACEPTIVE DRUG



at that point, subject only to adverse findings which may result in the withdrawal of the approval. The concept of post-marketing surveillance during Phases IV and V of contraceptive development is gaining support. This involves multiple tests of randomly selected individuals who have had prolonged exposure to the method to observe adverse side effects which may occur only rarely or after a prolonged period of use. Epidemiological research is continued.

10. In parallel with the biomedical aspects of contraceptive development, the process of preparing for the eventual introduction and adaptation of the method into a national programme is essential. Psychosocial research to determine the acceptability of the new method and the subgroups within the population for which it is most suitable should begin in Phase II. During Phase III operational research concerning aspects of service delivery and the development of training and educational plans and strategies need to be undertaken in preparation for widespread introductions. This may also involve small-scale field trials, as well as studies to determine the possibility of local manufacture or other means of ensuring an adequate supply of the new contraceptive. During Phase IV, after the validity of the new method has been established, further development and implementation of education and training programmes, service delivery and the like is undertaken to encourage widespread use. Large-scale acceptability studies are also necessary to ensure acceptance, utilization and continuation of the method. A key issue thatneeds attention is how best to adapt and use the new method in the context of the other methods already in use in the programme. Thus, while the annual expenditures in biomedical aspects of the programme of contraceptive development are decreasing, costs involved in the introduction and adaptation of the method may be increasing.

B. Location of contraceptive research and development

11. Most of the basic research which resulted in the currently used contraceptives was done in developed countries. As funds gradually were provided in these countries for research in human reproduction, qualified investigators were available to move into this field of research using well-equipped laboratories which were already established. All three of these elements were generally lacking in most developing countries.

12. For the same reason, Phase I and II human testing was originally done primarily in developed countries. Extensive laboratory evaluations were usually required for this phase, involving the use of expensive and complicated scientifiec equipment. On the other hand, once the Phase III field trial stage had been reached, studies were set up in many areas, in both developed and developing countries.

13. In recent years, the pattern just described has begun to change. As the number of well-trained researchers in developing countries has increased and as laboratory capabilities have grown concomitantly, there has been a slow expansion of developing country research in the earlier phases of development. However, the number of highly sophisticated centres still remains relatively small and thus much of the preliminary work will, of necessity, have to be carried out in developed countries, at least in the immediate future.

14. By way of contrast, skills in conducting clinical trials have increased much more rapidly in developing countries. Therefore, a growing percentage of these studies can be and are expected to be done in developing countries. In fact, it is essential that this be the case, so that national authorities may assess the risks and benefits of contraceptive methods in their own countries.

15. As a result of the growth of developing country research capability, studies are now under way in a number of centres, as can be seen in Table B. While this table is not meant to be comprehensive, it shows the large potential that already exists in developing countries for further contraceptive studies, particularly in the area of clinical trials. The information in Table B comes from the United States Agency for International Development, the Association for Voluntary Sterilization, the International Fertility Research Programme, the United States National Institute of Child Health and Human Development, the Population Council, the Program for Applied Research on Fertility Regulation, the Program for the Introduction and Adaptation of Contraceptive Technology, the Population Information Program of The Johns Hopkins University and the World Health Organization.

IV. REVIEW OF THE STATUS OF CURRENT AND FUTURE CONTRACEPTIVE TECHNOLOGY

A. Introduction

16. Ever since primitive peoples first connected the act of sexual intercourse with the subsequent arrival of a baby, they have attempted to find ways to control the number, the timing, and the sex of their offspring. Medical history records innumerable techniques that have been used over the centuries, some amusing, many exotic, and a few actually lethal. In the modern era, people continue to try to control pregnancy. In fact, some of the techniques in use today are actually only scientific improvements on the same general types of methods that have been employed over many centuries.

17. With rapidly increasing concern, both personal and societal, about the effects of uncontrolled population growth the impetus to develop safe and effective means of fertility regulation increased. Originally it was felt that it would be possible to find methods that were "ideal"- totally safe, totally effective, widely acceptable, easily reversible, simple to administer, inexpensive, easy to transport,with a long shelf life in a variety of climates, adaptable to multiple types of health care programmes, and with no temporal relationship to coitus. Unfortunately, with continued research it became clear it would be most unlikely to develop a so-called ideal method in the foreseeable future. Recognition of this fact led to the emergence of a wide variety of different techniques, each with advantages and disadvantages.

B. Present contraceptive technology

18. Oral preparations: When the oral contraceptives were developed more than a quarter of a century ago, many people believed that the "ideal contraceptive" had finally been found. Continued studies over the years, however, have revealed that, although oral contraceptives are highly effective and safe for the majority of women, they have adverse side effects for some women. Since 150 million women around the world have taken or are taking the pill,it is one of the most widely used

Table B

Contraceptive Research by Region/Country

METHODS	REGIONS					
	North America	The Caribbean Central and South America	Europe	Africa	Asia	Oceania
Implants and Injectables	USA	Brazil Chile Colombia Cuba Dominican Republic El Salvador	Denmark Finland Italy Luxembourg Netherlands Sweden United Kingdom Yugoslavia	Egypt Nigeria Zimbabwe	India Korea,Rep.of Pakistan Philippines Singapore	Australia
IUDs	Canada USA	Brazil Chile Colombia Cuba El Salvador Mexico	Belgium Finland Netherlands Hungary Sweden United Kingdom USSR Germany,Fed.Rep. of Yugoslavia	Egypt Tunisia Zimbabwe	China Israel India Japan Korea,Rep.of Pakistan Philippines Singapore Thailand Viet Nam	Australia New Zealand
Male Hormonal Methods	USA		Austria			
Prostaglandins	USA	Cuba	Belgium Hungary Norway Sweden United Kingdom USSR	Zimbabwe	China Hong Kong India Japan Singapore	
Vaccines	USA	Brazil Chile	Finland Sweden		India	
Abortifacients	USA	Cuba	Hungary Sweden United Kingdom Yugoslavia		India Korea,Rep.of Singapore	
Gossypol	USA	Brazil	Austria Finland		China	
Postcoital Methods	USA	Chile Cuba	Austria Belgium France Hungary Norway Sweden United Kingdom USSR	Zimbabwe	China Hong Kong India Japan Singapore	
Male Sterilization	USA	Brazil Colombia			China India Korea, Rep. of Pakistan	
Ovulation Detection	USA	Chile	France Hungary	Egypt Nigeria	India Israel Korea, Rep. of Thailand	
LRF Analogs	USA	Chile	Austria France			
Vaginal Rings	USA	Colombia Cuba Mexico	Belgium Finland Sweden United Kingdom USSR Yugoslavia		India Korea, Rep. of Thailand	
Female Sterilization	Canada USA	Chile Colombia Cuba Mexico Nigeria	Sweden United Kingdom Germany,Fed.Rep.of	Egypt Morocco	Bangladesh China India Korea, Rep.of Philippines Singapore Thailand	Australia
Barrier Methods	USA	Brazil Chile Dominican Republic Mexico	Denmark Finland Sweden		India	
Female Hormonal Methods	Canada USA	Chile Colombia Cuba El Salvador Mexico	Hungary Sweden United Kingdom USSR Yugoslavia	Egypt Nigeria Tunisia Zimbabwe	Hong Kong India Pakistan Philippines Singapore Thailand	

and studied medications in human history and large amounts of data have been amassed. It appears that the most serious side effects related to use of the oral contraceptives are those involving the cardio-vascular system, specifically thrombo-embolism, stroke, and myocardial infarction. However, the risk of developing these diseases has declined as the dosage of hormones in the pill has been decreased. In addition, specific factors have not been found which are directly related to the degree of risk such as increasing age and heavy smoking.

19. Much less attention has been given to the beneficial aspects of the pill. It is now recognized that women taking oral contraceptives are statistically less likely to develop benign breast disease, benign ovarian cysts, ovarian and probably endometrial malignancies, iron-deficiency anaemias, certain thyroid diseases, rheumatoid arthritis, and duodenal ulcers. Of great importance today in the face of a world-wide epidemic of sexually-transmitted diseases is the fact that the pill also offers at least partial protection against pelvic inflammatory disease. Furthermore, in many societies where maternal mortality is high, evidence suggests that the pill is safer than an undesired or unplanned pregnancy.

20. Intrauterine devices (IUDs): IUDs became generally available several years after the oral contraceptives had achieved world-wide usage. The first IUDs to be evaluated were the non-medicated devices, made out of plastic and/or metal. Two conclusions soon became clear. First, the larger the device, the lower the pregnancy and expulsion rates but the higher the pain and bleeding rates. Second, and conversely, the smaller the device, the higher the pregnancy and expulsion rates but the lower the pain and bleeding rates.

21. The next step in IUD development stemmed from these observations. It was found that a small, atraumatic T-shaped plastic platform coupled with a metal such as copper, or a hormone such as progesterone, had fewer side effects but effectiveness rates equal to those of the non-medicated devices.

22. None of the currently available intrauterine devices is as effective as the pill when taken properly and all IUDs have adverse side effects such as cramping, bleeding, perforation and expulsion. On the positive side, the IUD continues to be widely used because it has a number of very specific advantages. Acceptance requires only a single act of motivation and continuation rates with intrauterine devices actually exceed those of oral contraceptives. Morever, IUDs act locally in the female reproductive tract and thus do not have a major impact on a number of body systems. Finally, the devices can be inserted by paraprofessionals and require, in most instances, minimal follow-up care, important considerations in areas with limited health care infrastructures.

23. Barrier methods: The condom continues to be one of the most widely employed forms of contraception used by men today, despite the fact that it must be used with every act of intercourse. It has been found that the effectiveness rates of condoms, used properly, are extremely high.

24. In the past, condoms have had a somewhat negative image, being associated with prostitution and veneral disease prevention. Therefore, to change this image and make the use of condoms more readily accepted, condoms are now being made in colours, are ribbed for the production of erotic stimulation, and are being manufactured

of thinner materials in order not to inferfere with sensation.

25. Prior to the development of the pill and the IUD, the only contraceptive agents for female use with a relatively high level of effectiveness were the vaginal spermicides, used alone or with a diaphragm. Their popularity declined rapidly following the introduction of the non-coitally-related methods but more recently, in response to the growing concerns about the side effects of these newer birth control techniques, there has been a return to barrier methods because of their safety. It is now more generally appreciated that a diaphragm and a spermicidal agent, coupled with the use of the condom, have an efficacy rate equal to that of the oral contraceptives.

26. Natural family planning: There are a number of techniques of natural family planning (NFP) which depend on the identification of the fertile and infertile portions of the menstrual cycle by observing a number of signs and symptoms, with abstinence being practiced during the fertile stage. One of the earliest techniques of NFP was the calendar method, based upon the fact that there is a constant relationship between the time of ovulation and the onset of the next menses. The temperature method of NFP is based upon the observation that the basal body temperature rises at the time of ovulation, sexual intercourse being restricted to the post-ovulatory phase of the cycle. Most recently the sympto-thermal methods of NFP have been developed, based upon the detection of certain physical changes which are used to pinpoint more exactly the fertile period, such as changes in the cervical mucus.

27. An obvious advantage of NFP is the avoidance of the use of drugs and devices which may produce adverse side effects or in situations where religious or socio-cultural beliefs do not approve their use. However, the long-term acceptability of these methods has always been low except for certain highly motivated couples because of the necessary periods of abstinence, and use effectiveness rates are generally low compared with other methods.

28. Sterilization: Male sterilization has achieved great popularity in recent years. Because of the extra-abdominal position of the vas, sterilization of the male is technically easier and safer than sterilization of the female. Significant morbidity and rare mortalities have been almost entirely due to infection resulting from a break in sterile technique.

29. Sperm antibodies have been found in the blood of a high percentage of men after vasectomy. In addition, studies have shown an increase in atherogenic changes in vasectomized monkeys. There is still much debate as to the relevance of these findings to the human male, but the impact of this information has had a considerable negative effect on the utilization of male sterilization.

30. Many different techniques have been devised in recent years to produce temporary or permanent sterilization of the human female. The original methods were predominantly surgical in nature, a variety of techniques being used to occlude and/or remove a portion of both fallopian tubes. These required physicians skilled in abdominal surgery and also the availability of hospital and anesthetic facilities.

31. Following the development of the laparoscope, it was possible to visualize and manipulate the tubes through a very small abdominal incision. The entire procedure was usually of short duration and the complications resulting from anesthesia and major surgery were decreased. However, even these methods were found to be too demanding for use in areas with limited medical capabilities. Consequently, when the minilap procedure was developed, which requires minimal surgical training and resources, it was widely accepted.

32. Pregnancy termination: Although considered by many people not to be a form of family planning, pregnancy termination continues to be viewed as such by many women all over the world and despite major advances in contraceptive technology, the voluntary termination of pregnancy continues to be one of the world's most frequently used forms of family planning. Different techniques are employed depending on the duration of the pregnancy, each of these techniques having specific advantages and disadvantages. It has been repeatedly argued that pregnancies should not have to be terminated, given our advances in contraceptive technology. However, these procedures continue to be carried out in great numbers, both legally and illegally.

C. Future contraceptive technology

Short-term (3-5 years)

33. Oral hormonal preparations: Despite the perceived need for an oral hormonal contraceptive for men, and despite a considerable amount of research in this area, no contraceptive pill for men will be available in the short-term.

34. The oral hormonal contraceptives for females will probably not undergo major changes in the foreseeable future. However, two new approaches may make the oral contraceptives of the future equally effective but somewhat safer and easier to administer. First, new hormonal agents are now being evaluated which appear to have fewer side-effects than those currently being used. The second approach is related to finding better ways to administer the currently available hormones in preparations which may be given once a week or once a month, such as the tri-phasic and the mini-estrogen pill.

35. Injectables and implants: A number of hormonal agents are being evaluated as injectables and/or implants for males, the more promising regimes appearing to be implants. However, failure to produce total and permanent cessation of sperm production continues to be a problem.

36. Because of the generally perceived need for injectable methods for women, work is now being done on a variety of hormones. They have also been incorporated into silastic implants in the forms of capsules or rods. The major advantages of the injectable route are the ease of administration, the elimination of the need for highly trained personnel and the generally favourable acceptance of this type of methodology by women.. In fact, numerous country programmes have rated the injectable highest among all currently available techniques for these reasons.

37. The implant technique for women has also been found to be highly effective and quite well accepted. Implants require only a single act of motivation to obtain

long-term contraception; they can be inserted by paramedical personnel; they are generally inexpensive to make; when re-inserted at appropriate intervals they have the potential for many years of use; to date they have shown no serious adverse side-effects; and finally, they are reversible, either by removal or degradation.

38. Vaginal rings: Another approach to the periodic administration of contraceptive steroidal agents has been the development of various types of vaginal rings made out of biocompatible polymers such as silastic and loaded with a steroid. The ring is inserted after menses; three weeks later it is removed and menses begin. As in the case of other steroidal agents, the major problem encountered during the development of the rings was abnormal bleeding patterns, but this problem has been largely overcome.

39. Intrauterine devices: The IUDs of the future will probably be of the medicated type. One of the problems with the earlier copper devices was the gradual fragmentation of the copper wire which limited their duration of use. However, the addition of a small silver core, placed in the centre of the copper wire, seems to have resolved this particular problem. A major problem with the current progesterone-bearing devices is the need for removal and replacement at one-year intervals. However, there is experimental evidence that this time frame may be extended in the near future.

40. Inasmuch as there continues to be concern about the role of the tail of an IUD in the induction of intrauterine infection, consideration is once again being given to the tailless IUDs. There are two practical problems which must be solved, first, finding an accurate, safe, atraumatic, non-invasive and inexpensive way to identify the location of the IUD and, second, developing safe and easy methods of removal.

41. Finally, work is now being carried out attempting to find devices suitable for post-abortal and post-partum usage. It is very important, particularly in developing countries, to be able to offer an acceptable form of contraception to women following abortion or delivery while they are still under the care of health professionals and are often highly motivated to prevent a pregnancy in the immediate future.

42. Barrier methods: Research has recently been undertaken on water-soluble condoms, and the early data on these devices appear promising. If perfected, they could have major advantages in terms of developing countries since they would be easy to carry, easy to use, and would require no medical supervision.

43. New barrier methods for women currently being studied are combinations of physical barriers such as sponges made of collagen and polyurethane plus the use of various spermicidal agents. Work has also been carried out on the use of spermicides in new vehicles including several types of suppositories and dissolving diaphragms. There has also been considerable interest in reviving research on the cervical cap. However, it is doubtful that the cap will prove to have a significantly higher rate of effectiveness than the diaphragm and spermicide and it will be more difficult to insert and remove.

44. Ovulation detection: Innumerable attempts have been made to find easier and more accurate ways by which to pinpoint the precise time of ovulation in order to practice periodic abstinence, using chemical tests and electronic instruments, without conspicuous success. Because of the importance of the NFP method, however, research is being continued in this area.

45. Sterilization: Techniques for female sterilization have been considerably simplified in recent years. A prime objective of current research is to develop techniques which would be applicable to developing countries, especially techniques which can be performed by paraprofessionals. Two major approaches have been used - the intrauterine injection of materials such as methyl-2-cyanoacrylate and the insertion of IUDs containing quinacrine.

46. In the case of the male, more work must be done to determine whether or not occlusion of the vas, with or without the development of sperm antibodies, produces deleterious effects on the cardio-vascular system. Only appropriately designed and executed studies can answer the questions that have been raised, and allow individuals to make informed decisions about these procedures.

Medium term (5-10 years)

47. Oral preparations: Chinese scientists have recently reported that a pigment found in the cotton plant known as gossypol, when administered orally to males, produces azoospermia in almost all subjects. If the preparations currently being evaluated in the laboratories are found to have an acceptable level of safety and efficacy, it would be very worthwhile to continue to explore this new avenue of approach to male contraception.

48. A long-sought goal has been the development of a product for females which could be taken once a month, either at the time of anticipated menses or at the time of a missed period in order to produce an early termination of pregnancy. A number of protaglandins have been studied for this purpose; however, their toxicity when taken by mouth has thus far proven to be a major deterrent.

49. Great interest has recently been aroused in the LRF analogs. A number of antagonists have been studied in animals and early work is being carried out in the human female, using intranasal administration and subcutaneous injections. The mode of action of these agents is the blockage of LH and therefore of ovulation.

50. Reversible sterilization: In recent years it has been repeatedly stated that, if male and female sterilization could be made both reliably and completely reversible, the use of sterilization as a family planning technique would increase greatly. Therefore, attempts have been made to block the vas with a variety of techniques including plugs, valves which can be turned off and on, and surgical techniques with minimal trauma which permitted reanstomosis to be accomplished with a high degree of effectiveness. However, despite the ability to restore anatomically the continuity of the vas and to have sperm appear in the ejaculate, the actual return of fertility is at a much lower level.

51. Considerable research has also been done in the female, trying to find totally reliable, safe, and effective reversible forms of sterilization.

Numerous attempts have been made to do this , primarily by the introduction of foreign bodies into the ampulla of the tube, the area of the tubal ostis, or at the fibrial end of the tube. What remains to be determined is the frequency of reversibility following the removal of these devices.

Long-term (more than 10 years)

52. Ovulation, ovum and sperm transport: Considerable animal work has been carried out trying to elucidate the hormonal mechanism(s) by which the process of follicular development and ovulation takes place. It appears that such a substance has now been identified. The possibility exists that this type of agent could be developed in order to block ovulation in the human female.

53. Very early work has also been done on identifying those factors which are involved in the transport of the ovum to the tube. Similarly, studies have been carried out attempting to find chemical agents that would block the orderly development of sperm and their transport through the vas and the epididymis.

54. Vaccines: To date, vaccines have been found to be most complex and, therefore, the adaptation of this particular area of research to contraceptive development appears to be quite remote. In the light of present knowledge, it seems reasonable to assume that it should be possible to vaccinate a human being against some portion of that individual's reproductive tract, alternately, against the reproductive tract of the opposite sex or possibly against some component of a developing embryo or its supporting placenta. It has also been suggested that vaccines could be developed against various portions of the sperm and the ovum. However, these are remote possibilities and much work needs to be done before safe and effective agents of this type could be expected to become available.

V. FUNDING FOR CONTRACEPTIVE DEVELOPMENT

A. Sources and trends

55. Reproductive and contraceptive research did not benefit from the rapid expansion of funding for biomedical research by the governments of developed countries in the two decades following World War II, largely because of the traditional taboos against the study of sex and reproduction and the moral and religious controversies over government involvement in fertility regulation. The oral contraceptive was developed with the support of private philanthropy and some sectors of the pharmaceutical industry, but without any government funding. During the mid-1960's, increasing concern about the problems caused by rapid population growth spurred increased support for research to find better contraceptive methods. In 1967, an Office of Population was established within the United States Agency for International Development and while most of its funds have been expended for family planning service programmes, about 3.5 per cent of its budget each year (from $7 million to $9 million) has gone to research in contraceptive development. The Center for Population Research was established as part of the United States National Institute of Child Health and Human Development in 1968 and is now the largest programme for reproductive and contraceptive research in the world. Other developed countries, Canada, France, Sweden, the Federal Republic of Germany and the United Kingdom, also began to fund reproductive and contraceptive research in the late 1960's.

56. During the 1970's five new scientific organizations were created that focused on the contraceptive needs of developing countries: the Special Programme of Research, Development and Research Training in Human Reproduction of the WHO (HRP); the International Fertility Research Program (IFRP); the International Committee for Contraception Research (ICCR), organized by the Population Council; the Program for Applied Research on Fertility Regulation (PARFR); the Program for the Introduction and Adaptation of Contraceptive Technology (PIACT). All of these are operating today. Smaller efforts, most of them supported by international assistance agencies, were undertaken in some developing countries; the largest of these was in India by the Indian Council for Medical Research.

57. Worldwide expenditures for all aspects of reproductive research rose rapidly, from an estimated $31 million in 1965 to $117 million in 1973. Although this total worldwide research budget has continued to climb as measured in current dollars (to an estimated $155 million in 1979), expenditures corrected for inflation peaked in 1973. By 1979, constant-dollar expenditures were below the 1971 levels. Although all aspects of funding for reproductive and contraceptive research have declined when measured in constant dollars, expenditures for contraceptive development have fallen most sharply, as may be seen in Table C. 3/

58. In response to UNFPA's request, WHO prepared an estimate of expenditures annually by agency and by main area and method for 1977-1981 for contraceptive development. The WHO/HRP estimates that expenditures have remained almost level from 1977 through 1981 at about $16 million per annum.

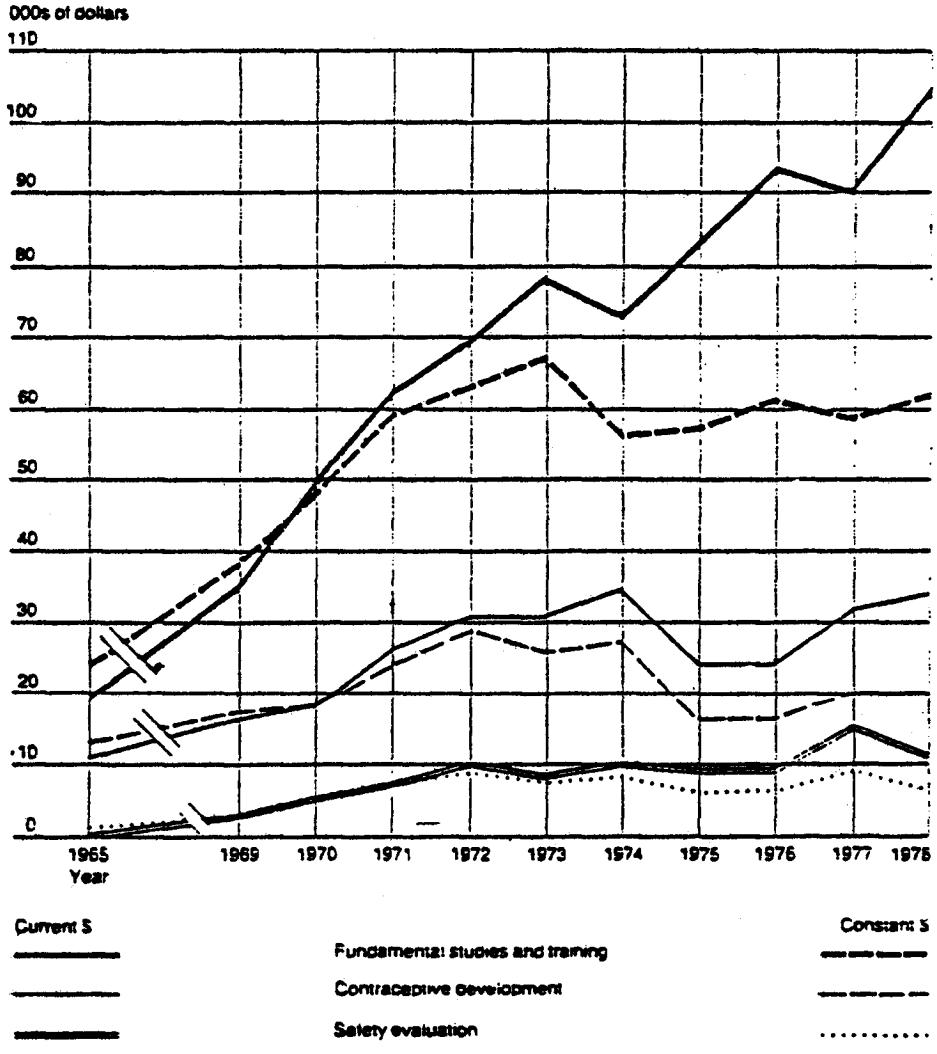
59. The main sources of funding for international research and development that are directed toward needs of developing countries are the developed countries that now voluntarily contribute to UNFPA and to the WHO Special Programme of Research, Development and Research Training in Human Reproduction (HRP). The trend of support from the usual donors is downward. Investment in this research by the private sector in developed countries has greatly diminished.

60. The largest single organization carrying out research in population is the Center for Population Research of the National Institutes of Health (NIH) of the United States, but of its estimated budget for 1981 of $82.9 million only about $8.3 million was devoted to contraceptive development. About $41.3 million went to fundamental biomedical research with the remainder applied to the evaluation of current contraceptives, social sciences, population research centres and training and direct operations management. Most of NIH's support goes to universities in the United States.

3/ International Family Planning Perspectives, "Prospects for Improved Contraception", Atkinson, et al., Vol. 6, No. 2, June 1980, pp 45-48

TABLE C.

Worldwide expenditures for fundamental reproductive studies and training of scientists, contraceptive development and evaluation of contraceptive safety, 1965–1978 (in 000s of current and constant [1970] U.S. dollars)



Source: Atkinson et al., 1980

61. The United States Agency for International Development (USAID) has contributed to research in methods of fertility regulation in recent years by funding six organizations including the WHO/HRP, in varying amounts. USAID provided $8.3 million in 1979, $7.8 million in 1980, and $9.7 million in 1981. The 1981 funding included a one-time contribution to WHO/HRP of $3 million. Estimated funding to the field from USAID in 1982 will amount to about $6.5 million, for three organizations, the IFRP, PARFR and the ICCR.

62. From 1978 through 1980, Sweden contributed from 43 per cent to 45 per cent of all contributions to the WHO/HRP, and in 1981, approximately 36 per cent. Voluntary contributions to the WHO/HRP have not kept up with inflation and have declined in the past year. Contributions and number of donors to the HRP for the past four years are shown in Table D.

Table D
Contributions to WHO/HRP, Number of Government donors and UNFPA contribution

Year	Total contributions	Government donors	UNFPA contribution
1978	$ 14 381 328	6	$ 950 000
1979	15 990 504	10	1 000 000
1980	16 156 569	9	1 500 000
1981*	14 631 579	13	1 500 000

* Includes one-time contribution from United States of $3 million.

Source: WHO/HRP Annual Reports, 7th-10th.

B. Projection of needs

63. It is difficult to project future needs for development of contraceptives with any accuracy given the uncertainties of the development process. The HRP has gathered information from the principal organizations in the field and has recently estimated the total expenditure by public sector agencies from 1982 to the completion of Phase IV testing in twelve general areas of research at $200 million. See Table E. This estimate does not include costs of adaptation in individual countries, nor the cost of surveillance or post-marketing surveys. These costs of introduction might require $100,000 per country per year for a span of two to five years for each method.

64. The Advisory Group to UNFPA believed that this estimate was too modest and at best uncertain. They preferred to give examples of specific needs and pointed out that to complete development through Phase IV of the Norplant implant is

ESTIMATED TOTAL EXPENDITURE BY PUBLIC SECTOR AGENCY, 1982 TO COMPLETION OF PHASE IV

(expressed in US $ 000)

	1982	1983	1984	1985	1986	1987	Additional cost to complete Phase IV	Additional costs 1982 to end of Phase IV	Total cost per general area	% of total
Oral Contraceptives										
- New formulations	690	690	410	360	360	360	-	2,870	5,940	2.97
- Slow release	200	740	690	360	360	360	360	3,070		
Vaginal Rings										
- Combination	300	1,090	690	680	440	440	-	3,640		
- Progestogen only - 3 month	540	540	530	290	290	-	-	2,190	8,320	4.16
- Progestogen only - 1 year	75	235	110	290	290	290	1,200	2,490		
Steroid IUDs										
- High dose	400	580	480	480	480	300	900	3,620		
- Low dose	430	230	180	480	300	300	900	2,820		
- Diamidine IUD	150	510	410	470	470	470	2,920	5,400	17,120	8.55
- EACA IUD	150	570	470	470	590	590	2,440	5,280		
Injectable										
- Combination monthly	160	570	710	690	690	690	3,600	7,110		
- Existing monthly	160	740	740	930	690	640	-	3,900		
- Ester 3-monthly	100	510	650	640	640	640	2,920	6,100		
- Ester 6-monthly	25	300	460	360	490	490	4,240	6,365	33,055	16.51
- Microcapsule 6-monthly	210	650	640	640	440	290	1,920	4,790		
- Microcapsule 3-monthly	50	50	100	460	510	640	2,980	4,790		
Implants										
- Alzamer	370	524	520	870	940	840	3,360	7,424		
- Capraner	520	920	1,260	1,090	1,280	890	840	6,800	16,634	8.31
- Norplant	890	1,130	290	50	50	-	-	2,410		
Anti-Fert./Anti-Implantation Agents										
- Progesterone blocking agent	300	500	400	460	530	370	2,640	5,200		
- LHRH antagonist	270	520	590	590	540	340	480	3,330		
- Agordrin	100	350	350	460	410	370	2,960	5,000		
- Plant product	200	200	350	450	400	410	3,890	5,900	32,020	16.00
- ECC derivative	200	200	350	500	450	470	4,350	6,520		
- Post coital - levenorgestrel	120	120	360	480	480	240	-	1,800		
- Post coital - STS 557	460	460	470	320	560	680	1,320	4,270		

TABLE E (continued)

ESTIMATED TOTAL EXPENDITURE BY PUBLIC SECTOR AGENCY, 1982 TO COMPLETION OF PHASE IV (continued)

	1982	1983	1984	1985	1986	1987	Additional cost to complete Phase IV	Additional costs 1982 to end of Phase IV	Total cost per general area	% of total
Abortitacients										
- Prostaglandins - vaginal	240	240	240	-	-	-	-	720		
- Prostaglandins - intramuscular	240	240	240	240	-	-	-	960	7,970	3.98
- Prostaglandins - oral	690	880	530	290	-	-	-	2,390		
- Plant product	350	560	840	690	690	290	480	3,900		
Vaccines										
- BhCG subunit	250	800	750	730	730	690	4,530	8,480		
- BhCG peptide	400	430	580	690	690	640	3,200	6,630		
- Plancen	400	400	400	250	250	250	6,230	8,180	45,480	22.72
- Zona pellucida	400	400	400	250	250	250	6,230	8,180		
- Sperm pellucida	400	250	250	700	750	550	5,430	8,330		
- Passive immunization	200	400	700	980	880	790	1,730	5,680		
Barrier										
- Plant spermicide	200	400	450	350	460	360	1,060	3,280	6,340	3.17
- Other	100	350	400	410	430	650	720	3,060		
Female sterilization										
- MCA	440	340	580	290	480	240	240	2,610	4,780	2.38
- Fimbrial hoods	160	110	170	170	360	240	960	2,170		
SUB-TOTAL	11,540	18,729	18,740	18,910	18,650	16,060	75,030	177,659	177,659	88.75
Male drugs										
- Androgen-gestagen combination	250	320	320	890	890	890	2,520	6,080		
- Inhibia	200	200	400	460	630	470	1,930	4,290	19,610	9.80
- Gossypol	100	350	450	470	420	420	3,700	5,910		
- LHRH antagonist	270	520	590	590	540	340	480	3,330		
Male sterilization										
- Reversible	100	100	150	310	310	370	1,560	2,900	2,900	1.45
SUB TOTAL	920	1,490	1,910	2,720	2,790	2,490	10,190	22,510	22,510	11.25
TOTALS	12,460	20,219	20,650	21,630	21,440	18,550	85,220	200,169	200,169	100.00

Source: WHO/HRP: 28/12/81

estimated by HRP to require $2.4 million in the period 1982-1986. Similarly, comparable costs for development of vaginal rings during the period 1982-1987 is estimated by HRP at $8.32 million. To the costs of each of these methods must be added the estimated $200,000 to $500,000 for each developing country for adaptation and introduction of the method.

VI. OPPORTUNITIES FOR UNFPA SUPPORT FOR CONTRACEPTIVE RESEARCH AND DEVELOPMENT

A. Opportunities for research

65. UNFPA's review has concluded that while reasonably adequate contraceptive technology exists, no one knowledgable in the field is fully satisfied with the effectiveness, reliability, applicability or availability of contraception techniques in developing countries. The growing number of couples of child bearing age emphasizes the need for new or improved contraceptives and better means of making the availability of contraceptives known to persons in developing countries who wish to use them. Improved contraceptive technology for both men and women would be welcomed in many developing countries.

66. In making decisions on funding these research opportunities UNFPA should observe certain criteria including the following: acceptable cost: UNFPA should sponsor research on contraceptive methods which can be delivered at acceptable cost in developing countries. The potential for economies of scale and reductions in prices over time coincidental with improvements in contraceptive technology must be kept in mind and weighed against initial heavy costs of development. Acceptability to clients and health care providers: The wide variations which exist in the personal, cultural, religious and economic practices of individuals must be taken into account by UNFPA in deciding on research priorities. No matter how safe and effective, if a contraceptive method is not acceptable to a significant proportion of clients, the community and/or health care providers, it will be of limited value. Require minimal health care facilities and services for use: Family planning should be incorporated as an essential element in primary health care programmes, utilizing non-medical and paramedical personnel whenever appropriate. Emphasis, therefore, should be given to the development of new or improved contraceptive methods which do not require the continued involvement of highly trained personnel and which have a low frequency of involvement between users and health care providers. Low frequency of required application: Although efforts to increase motivation to utilize family planning methods should be encouraged, frequent use or use related to sexual activity may be inconvenient and requires a conscious decision on the part of the users resulting in diminished acceptability over time.

67. Several technologies now under development meet these criteria. They include improved oral products; injectables and implants; improved IUDs; male and female sterilization; post-coital agents; natural family planning methods; vaginal rings and barrier methods. Male methods, LHRH analogues and vaccines, while potentially important, will require much more time to develop to the point of field application. It is not possible to assign precise priority ranking to these areas, given the intrinsic uncertainties of research and development programmes but the

review by UNFPA found that these methods mentioned above correspond closely to those currently receiving priority attention from organizations active in the field.

B. UNFPA funds available

68. In the period 1976-1981 UNFPA allocated $6.15 million to the WHO/HRP and in accordance with Governing Council decision 79/28 UNFPA will provide $2 million to HRP in 1982. UNFPA has provided substantial support to the Program for the Introduction and Adaptation of Contraceptive Technology (PIACT) in the last few years and will provide approximately $400,000 in 1982. It has provided modest amounts to other organizations in the field of contraceptive development, usually travel funds for participants from developing countries to attend technical conferences.

69. The Advisory Group has recommended that a fixed percentage of UNFPA's total programme resources be allocated each year to contraceptive research and development so that the recipient organizations could be assured of continuity in their funding and could make long-term plans more easily. The Advisory Group further recommended that 5 per cent of UNFPA total programmable resources go to contraceptive development and research. This would have amounted to approximately $5.55 million in 1982 and would more than double the amounts now allocated to this field by the Fund. UNFPA has considered its existing obligations and the probable resources available in future years and has concluded that approximately 5 per cent of total programmable resources could be allocated to contraceptive development research from 1984 onwards without jeopardizing existing allocations. Earmarking 5 per cent of programmable resources for these intercountry purposes would affect other future intercountry allocations, however, if all such activities must fall within the present 25 per cent limitation. UNFPA would have the flexibility necessary to cope with the demand for funds for intercountry activities if the Governing Council, having decided that 5 per cent of programmable resources should be earmarked for contraceptive research and development, would give the Executive Director authority to allocate up to 27 or 28 per cent of programmable resources to intercountry activities, if necessary. If the Governing Council decides that UNFPA should increase its allocations to contraceptive research and development as recommended, it will be necessary for UNFPA to employ one senior technical officer funded by project funds to assist with these activities.

C. Funding from UNFPA for WHO/HRP

70. The activities of the HRP extend beyond contraceptive research and development. As stated in its Tenth Annual Report the HRP addresses itself to: research on the provision of family planning care, including the service and psychosocial aspects, and the safety and efficacy of current methods of fertility regulation; development of better methods of fertility regulation; research on the diagnosis and treatment of infertility; strengthening of manpower and facilities in developing countries in the above areas of research; and dissemination of information on research in family planning to policy makers, programme administrators, service providers, scientists and the public. In 1981, 80 countries were involved in the Programme, of which 54 were developing countries.

71. The Advisory Group commended the substantial progress which the HRP has made in the first decade of its work but it noted with concern that funding for the HRP has declined during the last few years and that less than half of its resources

are expended on contraceptive research and development. The Advisory Group concluded that UNFPA should commit itself to providing long-term financial support to HRP at an increased level of at least 3 per cent of its programmable resources each year. At the 1982 level of resources this would amount to approximately $3.3 million in comparison to the $2 million to be provided to HRP by UNFPA in 1982.

72. The Advisory Group was of the opinion that a mechanism ensuring a more active participation by donors and recipients in financial and policy decisions would help to ensure continued and increased commitment of donors to the HRP and they feared that without such a mechanism a continued decline in the level of funding for the HRP would be likely. The Group suggested that an organizational structure for contraceptive research in the United Nations system similar to that of the UNDP/World Bank/WHO Special Programme on Research and Training in Tropical Diseases (TDR) could help achieve the co-ordination and collaboration necessary for the whole field of contraceptive research and development. In the TDR structure there is a Joint Co-ordinating Board of which twelve members are selected by the donors, twelve by WHO Regional Committees and three by the Joint Co-ordinating Board plus WHO, UNDP and the World Bank. The equivalent mechanism in the HRP is the Annual Meeting of Agencies Interested in the HRP to which participants are invited by the Director-General of WHO. Both the TDR Joint Co-ordinating Board and the Annual Meeting of Agencies Interested in the HRP review progress of the special programmes and their expenditures, plans, budgets and future financing. The Tropical Diseases Research Programme also has a Standing Committee of the Joint Co-ordinating Board composed of UNDP, the World Bank and WHO. This Committee meets at least twice a year. There is no corresponding body in the HRP organization. Independent scientific and technical advice is provided to the TDR by a Scientific and Technical Advisory Committee appointed by the Joint Co-ordinating Board and reporting to it. Similar scientific and technical committees appointed by WHO advise the HRP. The Advisory Group stated that these adjustments in the HRP structure were so important that the commitment of UNFPA to long-term increased funding support to HRP should be made contingent upon their being accomplished.

73. The Director-General of WHO has reviewed the Report of the Advisory Group and does not agree that any change in the structure of the WHO/HRP is necessary or desirable, stating that with one possible exception no donor has expressed dissatisfaction with the present administrative structure of the Programme. Depending upon the decisions of the Governing Council, the Director-General of WHO wishes to obtain the views of the policy-making mechanisms of the WHO/HRP, such as its Advisory Group and its Group of Donors and other Interested Agencies, and subsequently of the governing bodies of WHO.

74. An increase in UNFPA funding to HRP to 3 per cent per annum of programmable resources would give an increase of 65 per cent over UNFPA's 1982 contribution and is an increment of about $1.3 million. The total UNFPA contribution would still be less than the 1981 contribution of at least one of the donor governments. Thirteen governments contributed to the HRP in 1981. Eight of these governments are members of the Governing Council as are two governments that were contributors to the HRP in 1978 or 1979.

D. Funding other research and development institutions

75. The Advisory Group recommended that at least 2 per cent of UNFPA's programmable resources be allocated for contraceptive research and development to organizations in

the field other than the WHO/HRP, and recommended specific criteria for funding research projects of these organizations as follows:

76. The work has a clear chance of successful application at field level, within a reasonable period of time (usually 5-10 years); the technology involved meets the needs, including the financial needs, of less developed countries and is likely to be suitable and acceptable for their use; UNFPA support for the project can be expected to expedite development and/or delivery of new or improved technology, or provide information on the safety, efficacy, acceptability, introduction and adaptation of current, improved or new methods; the project should so far as possible contribute to the development of research capabilities in less developed countries; if a product is involved, there must be a reasonable assurance that a sustained supply of it would be available at affordable prices.

77. Four organizations active in the field internationally and whose work might qualify for future UNFPA funding, are the ICCR, the IFRP, PARFR and PIACT, as described below.

78. The International Committee on Contraception Research (ICCR) was established by the Population Council in 1971 to focus on biochemical and pharmacological studies, product formulation work and clinical trials of promising new contraceptive methods, through an international network of co-operating institutions. Its budget for 1981 was $2.7 million.

79. The International Fertility Research Program (IFRP), founded in 1971, concentrates on prototype development and Phase III and IV international trials of new contraceptive methods. IFRP's budget for 1981 was about $6 million, of which $4 million was for contraceptive research and evaluation.

80. The Program for Applied Research on Fertility Regulation (PARFR), established in 1969, puts major emphasis on laboratory and Phase I and II trials. Its budget for 1981 was $1.6 million.

81. The Program for the Introduction and Adaptation of Contraceptive Technology (PIACT) was set up in 1976 to bridge the gap between contraceptive development and introduction in developing countries. PIACT works through national affiliates, and in collaboration with contraceptive development agencies. It generally concentrates on quality control, packaging, production facilities and training, informational materials, product servicing and repair facilities and product distribution needs associated with the introduction of new technologies. Its operating budget in 1981 was about $2 million.

82. Other research and development organizations in the public sector whose projects meet the above criteria would also be eligible for UNFPA funding.

E. Research and development in country programmes

83. Contraceptive research and development at the country level, carried out as part of governments' family planning programmes, can also be funded by UNFPA in addition to the intercountry activities described above. Requests for funds to

meet a government's needs in clinical testing and evaluation, acceptability studies, operational research or for improvement or establishment of regulatory standards of safety and efficacy of contraceptives could be encouraged and UNFPA could place greater emphasis on these activities in over-all assessments with governments of their needs.