

- 45 Gupta H M, Talwar G P and Salunke, D M, *Proteins*, 1993, 16, 48-56
- 46 Fraser H M, Dewart, P J, Smith, S K, Cowen, G M, Sandow, J and McNeill, A S, *J Clin Endocrinol Metab*, 1989, 69(5), 996-1002
- 47 Jayashankar, R, Chaudhari, M, Om, Singh, Alam, A and Talwar, G P, *Prostate*, 1989, 14, 3-11
- 48 Giri, D K, Chaudhuri, M, Jayashankar, R, Neelaram, G., Javaraman, S and Talwar, G P, *Exp Mol Pathol*, 1990, 52, 54-62
- 49 Giri, D K, Javaraman, S, Neelaram, G S, Jayashankar, R and Talwar, G P, *Exp Mol Pathol*, 1991, 54, 255-264
- 50 Giri, D K, Wadhwa, S N, Upadhyay, S N and Talwar, G P, *Prostate*, 1993, 23, 329-336
- 51 Moudgal, N R, Ravindranath, N, Murthy, G. S, Dighe, R R., Aravindan, G R and Martin, F, *J. Reprod Fertil*, 1992, 96, 91-102
- 52 Talwar, G P, Naz, R K, Das, C. and Das, R. P, *Proc. Natl Acad Sci USA*, 1979, 76, 5882-5885
- 53 Naz, R. K and Talwar, G P, *Int J Androl.*, 1981, 74, 251-257
- 54 Talwar, G P and Naz, R K, *Arch Androl.*, 1981, 7, 177-185.
- 55 Upadhyay, S N, Dhawan, S and Talwar, G P, *J. Androl*, 1993, 14, 275-281

ACKNOWLEDGEMENTS Various projects whose results are discussed in this review are supported by grants from the Department of Biotechnology, Govt of India, the International Development Research Centre (IDRC) of Canada, the Rockefeller Foundation and the South-to-South Cooperation in Reproductive Health. The work has benefited by cooperative interaction with the International Committee on Contraception Research of the Population Council

New leads in contraception and innovations in existing contraceptive methods

Horacio B. Croxatto

Instituto Chileno de Medicina Reproductiva, José Ramon Gutiérrez 295, Depto 3, Correo 22, Casilla 96, Santiago, Chile

ONE quarter of the world population are women in the ages of 15 to 49 years and approximately 70% of these are coupled to men in an established relationship, most commonly marriage. It is estimated that 40-50% of these 800 million couples control their family size using modern contraceptive methods.

Current methods can be broadly classified into: behavioural, hormonal, intrauterine devices, barriers to sperm and sterilization. The percentage of contracepting couples using each method is shown in Table 1.

Female sterilization which reflects the decision of the woman to have no more children for the rest of her life remains at the top of the list with 26% of all contraceptors choosing this method. Considering that the reproductive life span of the woman extends from the ages 15 to 49 years, that the age at marriage is close to 20 years and that the size of the family is decreasing and progressively approaching replacement level, it is understandable that for a significant proportion of women a definitive non-hormonal method is preferred after completing the desired family size.

Efforts to increase the variety of methods, their availability and the quality of their service delivery continue to be fundamental to expand contraceptive use to the level required for stabilizing the human population at the earliest possible time during the next century. As the rate of population growth is beginning to decline

other motivations for contraceptive usage are getting increased recognition and contraceptive development begins to focus more and more on the needs of individuals and couples. Thus, a new generation of methods that can increase the choices and meet the diversity of needs that suit the gender, the different ages, the life styles and so on is much needed. Development of a larger variety of contraceptive methods is expected to lead to safer, more convenient and more affordable methods.

Regardless of population issues, the existing trend towards smaller family size is likely to be irreversible and implies that the use of contraceptive methods will be a common and widespread feature of human life from now on. Given this expectation, family planning should become an obligatory subject in general education and

Table 1. Worldwide prevalence of use of various contraceptive methods

	%
Female sterilization	26
Intrauterine devices	20
Behavioural	15
Oral contraceptives	14
Male sterilization	10
Condoms	10
Others	5

standards of quality for service delivery of contraceptive methods and allied health care provision should be developed for worldwide implementation.

Until recently most contraceptive products resulted from opportunistic developments based on serendipity rather than from strategic planning that started from basic science. However, future contraceptive development should use new technology, both to identify molecules or processes which are specific of reproductive entities and to find ways to intercept their functioning. The strategic planning should consider also the reproductive health issues as well as the user and service perspectives.

The most recently introduced method for women called NORPLANT^R, is a multiunit device that releases levonorgestrel for several years once it is implanted under the skin (Figure 1) and offers greater than 95% protection for five years. The excellent acceptability of this long-term method of hormonal contraception, with over one million users worldwide since its introduction in 1983, has prompted the development of other implantable single unit devices using other progestins as well as a simplified version of NORPLANT^R, called NORPLANT-2 (ref. 1).

Two other hormonal methods for women just being introduced are the monthly injectable preparations called Cyclofem and Mesigyna which contain a progestin and an estrogen. Data from phase III clinical studies encompassing over 40000 woman-months of use with each of these products indicate they have a high contraceptive efficacy with pregnancy rates at 12 months in the vicinity of 0.2–0.4 per cent².

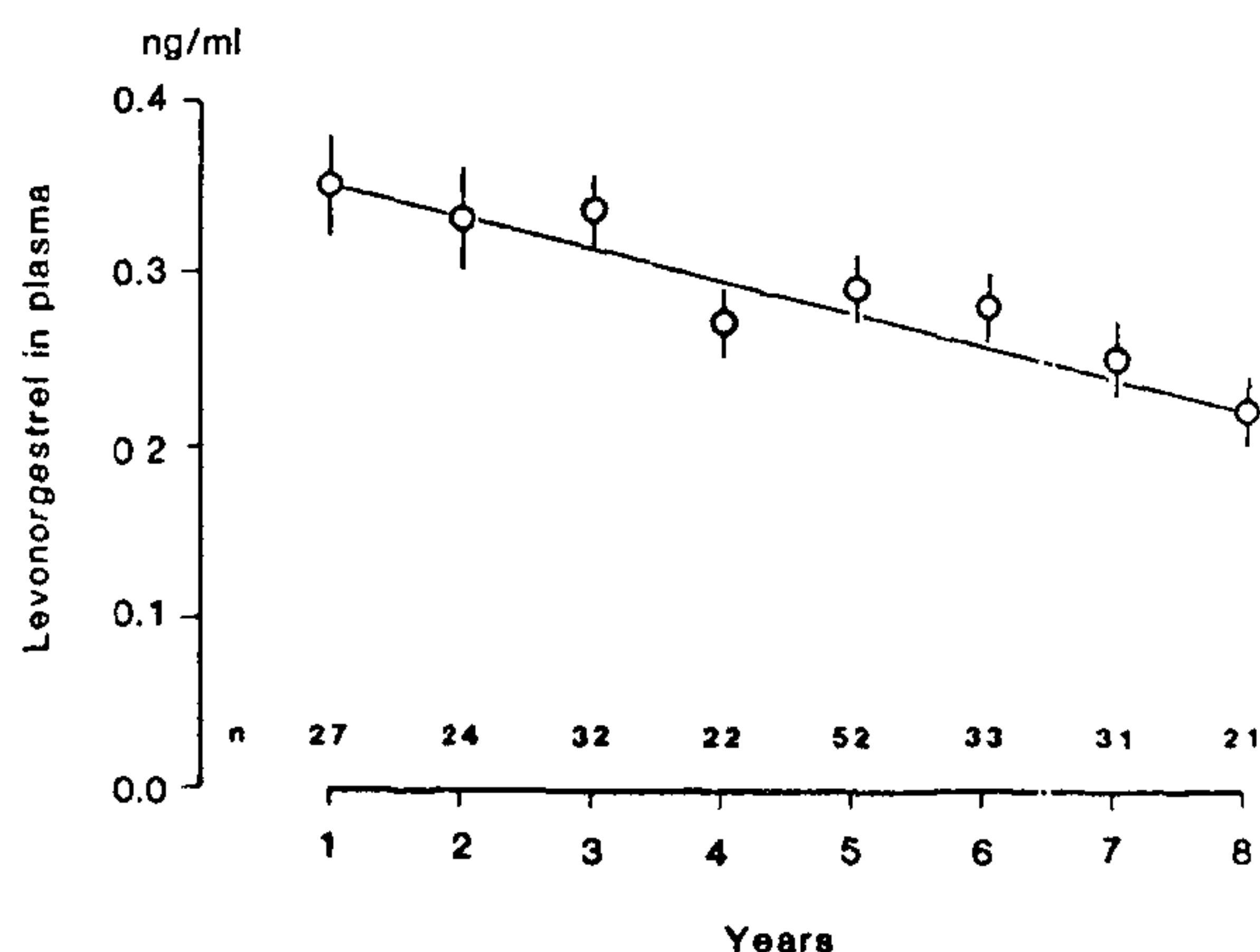


Figure 1. Levonorgestrel plasma levels over a time span of eight years in women who received a single administration of NORPLANT subdermal implants. In field use, satisfied users have the implant removed at five years and replaced for a new set if they wish to continue using this method. This figure illustrates the ability of this system to achieve long-term, sustained release of the active substance without precedent in the history of therapeutic systems other than the release of copper from intrauterine devices (from Croxatto¹).

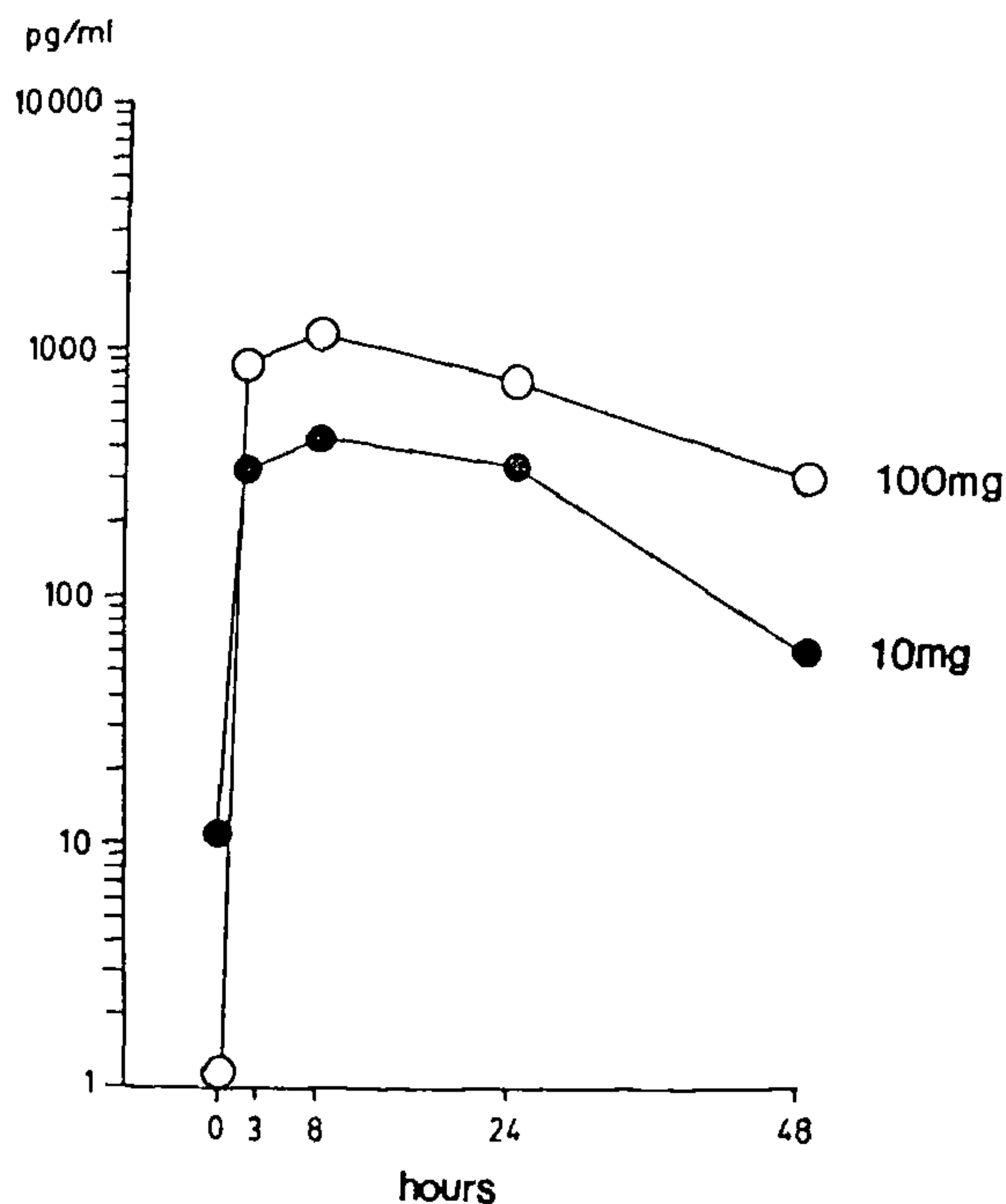


Figure 2. Nestorone serum levels in two volunteers after spreading acetylated lanolin containing 100 or 10 mg of steroid over 100 cm² on the submandibular skin. Serum levels of the steroid remain far above the concentration required to inhibit ovulation in women and illustrate the feasibility of using percutaneous absorption of steroids for contraceptive use (from Croxatto and Zepeda⁴).

Among the hormonal methods which are under development one delivers progesterone, the natural progestin, from a vaginal ring and it is specifically designed to be used by postpartum women during the period of lactation. This treatment prolongs the duration of amenorrhea and carries no risk for the child³.

Another potential method in an early phase of development uses a synthetic progestin, called Nestorone, which is absorbed through the epidermis and can be administered applying a cream or lotion on the skin (Figure 2). Continuous daily administration of this formulation inhibits ovulation⁴. Because it is an estrogen-free method that bypasses the gastrointestinal tract, it is under user control and its application is more pleasant than introducing and removing devices from the body, getting injections or even taking a pill, it offers specially attractive features for a segment of users.

Antiprogestins which have been found to inhibit follicular and endometrial maturation, at daily doses several hundred-fold lower than the current dose used to terminate pregnancy, are being tested in several different schemes for contraceptive application^{5,7}. Among them are: a) The continuous daily administration of a minidose that will make the endometrium mimical to implantation of the embryo, without disturbing the

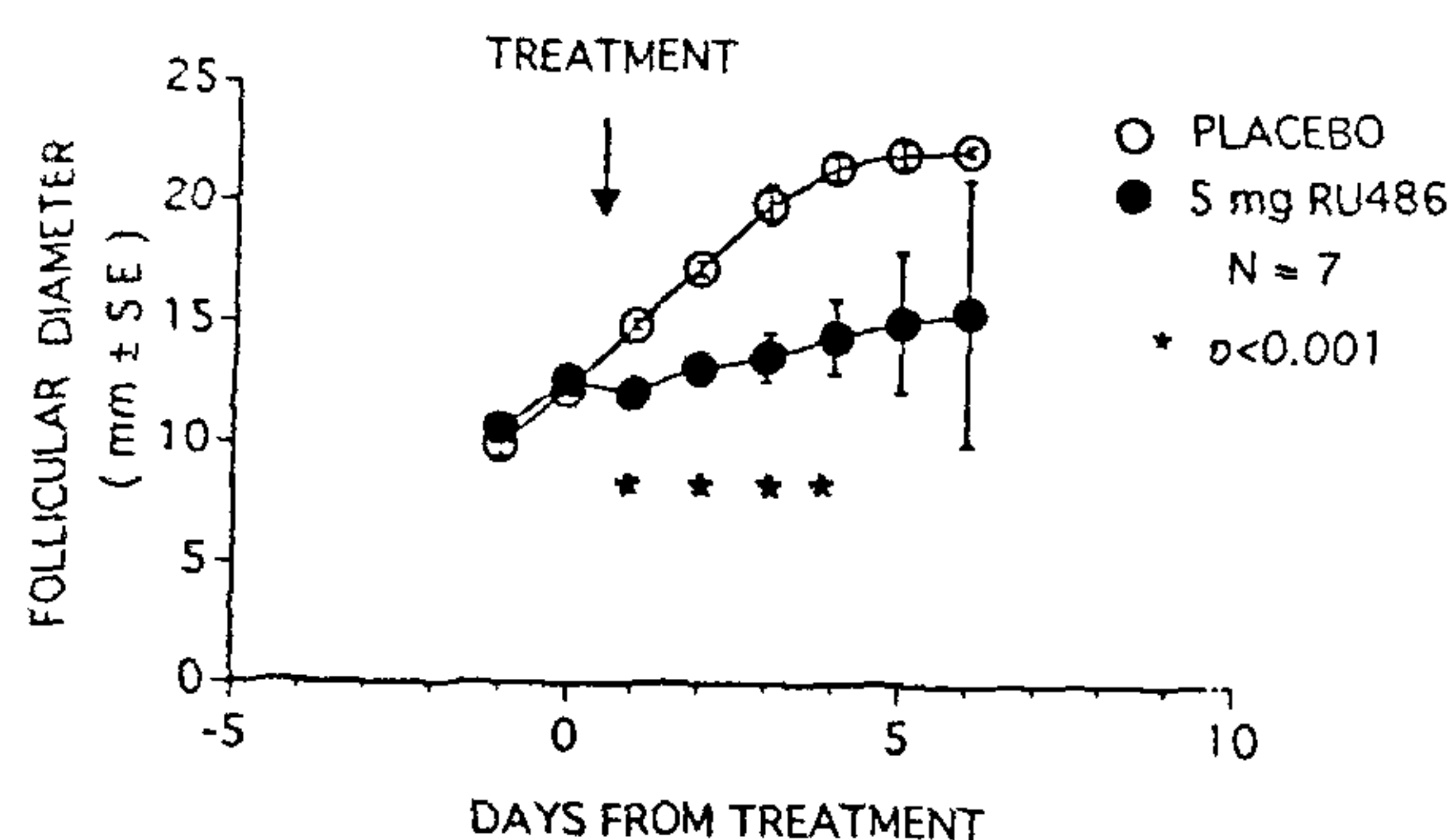


Figure 3. Growth of the dominant follicle in women treated at the arrow with 5 mg of the antiprogestin RU486 or placebo. Note that the dominant follicles cease to grow under the effect of RU486 and this effect can be used to prevent or postpone ovulation (from Croxatto and Salvatierra, unpublished)

ovarian cycle. b) An antiprogestin-progestin sequential regimen that will inhibit ovulation. This method has the potential to decrease the number of menstrual periods per year by one half to one quarter, depending on how long the antiprogestin treatment is maintained before switching to the progestin. c) A weekly pill containing a higher dose than in the above schemes that will disrupt follicular and endometrial maturation. d) A once a month pill compounded with a prostaglandin to be taken near the end of the cycle to work as a menses regulator or inducer. e) A postcoital pill for emergency contraception.

A promising breakthrough in female sterilization procedures is the possibility of medical sterilization using intrauterine administration of quinacrine. The introduction of slow-release quinacrine pellets in the uterine cavity leads to permanent obliteration of the utero-tubal junction. Since this is an outpatient procedure comparable to an IUD insertion it should offer great programmatic advantages over surgical sterilization⁸. Although the final form of this method still needs to be worked out and some toxicological concerns also require to be addressed, its potential benefits are worth the effort.

Hormonal methods under development for male use, based on inhibition of spermatogenesis, are now more likely to succeed. The choice of methods to suppress GnRH secretion or action has expanded from steroids through potent GnRH-analogues that shut down gonadotropin secretion up to immunoneutralization by vaccina-

tion against GnRH. The associated reduction in testosterone production, the main drawback of these approaches, can now be overcome in a more acceptable manner by the availability of long-acting testosterone analogues that require less frequent administration.

Vaccination against molecules which play an essential role and are specific to the reproductive process is another approach that has received much attention for its potential use in male and female contraception. Vaccination against human chorionic gonadotropin (hCG), the only contraceptive vaccine tested so far in humans, has reached phase II clinical trials in India and Sweden. Although there are multiple possibilities for this approach, turning the idea of contraceptive vaccines into practical methods depends very heavily on technical improvements in biomolecular engineering and more profound understanding of the factors governing the immune response and its wide interindividual variation⁹.

A concerted effort of international organizations, donors, research groups, industry, governments, NGOs which represent users and health care personnel perspectives, and educators is required now to assure the personal reproductive health of the people of tomorrow.

The generation of a wider range of contraceptive methods to suit individual needs, improvements in the quality of service delivery and users education, concern and appropriate legislative steps by governments to reduce risk-factors affecting reproductive health are among the most obvious multidisciplinary macroprojects that need to be boosted.

- 1 Croxatto, H. B., *Ann Med*, 1993, 25, 155-160
- 2 Newton, J. R., d'Arcangues, C. and Hall, P. E., *Obstet Gynecol*, 1994, 14, Suppl 1.
- 3 Diaz, S. and Croxatto, H. B., *Curr. Opin Obstet Gynecol*, 1993, 5, 815-822
- 4 Croxatto, H. B. and Zepeda, A., in *Contraception Newer Pharmacological Agents, Devices and Delivery Systems* (eds Sitruk-Ware, R. and Bardin, C. W.), Marcel Dekker, New York, 1992, pp 101-115.
- 5 Croxatto, H. B. and Salvatierra, A. M., *Parthenon*, 1992, 2, 245-252
- 6 Baird, D. T., in *Clinical Applications of Mifepristone (RU 486) and Other Antiprogestins* (eds Donaldson, M. S., Dorflinger, L., Brown, S. S. and Benet, L. Z.), National Academy Press, Washington, DC, 1993, pp 148-163
- 7 Spitz, I. M., Croxatto, H. B., Lähteenmäki, P., Heikinheimo, O. and Bardin, C. W., *Hum Reprod*, 1994, 9, suppl. 1, 69-76.
- 8 Hieu, D. T., Tan, T. T., Tan, D. N., Nguyet, P. T., Than, P. and Vinh, D. Q., *Lancet*, 1993, 342, 213
- 9 Alexander, N. J., *Vaccine Research and Developments* (eds. Koff, W. C. and Six, H. R.), Marcel Dekker, New York, 1992, vol 1, pp 117-141.