

CONTRACEPTIVE TESTING UNIT

**INDIAN CANCER RESEARCH CENTRE
BOMBAY**

**DIRECTORATE GENERAL OF HEALTH SERVICES
MINISTRY OF HEALTH, GOVERNMENT OF INDIA
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CONTENTS

	<i>Page</i>
Introduction	1
I. Testing of Oral and Local Contraceptives	2
II. The Development of Effective Oral and Local Contraceptives	15
III. The Physiology of Reproduction	17
IV. Other Activities	21
V. Expenditure	22
VI. Publications	22
VII. Staff of the Unit	24
Appendices	25

THE CONTRACEPTIVE TESTING UNIT

INDIAN CANCER RESEARCH CENTRE

INTRODUCTION

The Family Planning Research and Programme Committee of the Government of India recommended to the Government in 1954 that a centre for research in family planning should be established. At such a centre research in the physiology of reproduction would also be carried out in order to lead to a better understanding of the problems of fertility and its control. Earlier in December 1952, a special centre had been established by the Government of India, Ministry of Health, in collaboration with the Sir Dorabji Tata Trust, Bombay, for research on cancer in all its aspects. The Centre had already set up departments of Pathology, Experimental Biology, Biophysics, Biochemistry and Human Variation and Statistics, and was therefore ideally suited for the location of the proposed Unit. The Centre itself was also interested in the basic problem of reproduction and growth with a view to understanding the nature of malignant growth. The Centre, therefore, offered the laboratory facilities necessary for the Unit. The activities of the Unit have expanded considerably during the last three years and have been carried out at the Centre and also at two clinics of the Family Planning Association of India in the industrial areas of Bombay. In September 1956, the Unit established its own Family Planning Clinic in the Naigaum area for field trials of contraceptives.

The Unit consists of four sections :

- (a) Chemistry Section,
- (b) Biochemistry Section,
- (c) Biology Section,
- (d) Medical Section.

Three main lines of research are being pursued by the Unit :

- I. The testing of oral and local contraceptives before they could be released to the public.
- II. The development of effective oral and local contraceptives.
- III. Biological studies on the physiology of human reproduction with particular reference to the conditions existing in India.

I. TESTING OF ORAL AND LOCAL CONTRACEPTIVES

In order to determine the acceptability, effectiveness and harmlessness of contraceptives before they could be released to the public, they are subjected to several tests.

All the contraceptives sent for testing by the Director General of Health Services are received under a code number. Each contraceptive must be accompanied by the following information: (a) the type of contraceptive, i.e., oral or local (foam tablet, jelly, paste or rubber), (b) the dates of manufacture and expiry, (c) the chemical composition and the dosage, and (d) in the case of rubber contraceptives, the formula of the dusting powder.

Oral Contraceptives

The oral contraceptives received for testing may be of two types viz., synthetic products and indigenous plant materials. Biological tests are carried out on male and female mice which are fed the substance to be tested. The animals are allowed to mate and the effect on the sex cycle, the normal reproduction, the size of the reproductive organs and the general condition of the animals is observed and recorded. If the females become pregnant, their condition during pregnancy and the condition of the young at birth are noted. The effect of the oral contraceptive on the mating behaviour of the male is also observed.

PROCEDURE OF TESTING

(1) Pilot Experiment

Object: This experiment should show any effect the drug has on the sex cycle, normal reproduction, and the general condition of the female throughout pregnancy. If the experiment shows evidence of abnormal physiology or histology of the reproductive organs then the standard experiments are carried out.

Procedure: Eight female mice are fed the drug for ten consecutive days and the vaginal smears are recorded daily. On the eleventh day the females are kept for mating and the feeding is continued. It is essential that ovulation is confirmed in the experimental animals. This is done by (a) the vaginal smear reading and (b) the presence of the vaginal plug in the breeders. (Mice generally go into estrus when ovulation takes place. They mate only when in estrus.) The animals are kept for the length of a normal pregnancy. If they deliver, the condition of the litter is observed. If they do not deliver, they are sacrificed and the ovaries, uterine horns and vagina are fixed for histology.

(2) Standard Experiments for Testing Synthetic Preparations

Dose : The dose to be administered should be ten times the dose prescribed by the manufacturer (Appendix I). This has a two-fold purpose—(a) it will be possible to see if the action that the drug is accredited with is specific—(b) it will also reveal any toxic effects that the drug may have. (An oral contraceptive is considered effective in mice, at a given dose, only if in any of the four experiments there was evidence of changes in the physiology or histology of the ovaries, uterus, vagina and testes suggestive of an inhibition of the normal reproductive function). The oral contraceptive in solution is fed to the animals by means of a syringe and rubber tubing. If the substance is not soluble, it is mixed with the diet and fed to the animals.

1. *Object* : This experiment should show any effect the drug has on the sex cycle and the reproductive organs of a normal female mouse.

Procedure : Eight female mice are fed the drug six times, once every fifth day. Vaginal smears are taken daily, observed and recorded. At the end of this period the animals are sacrificed and the ovaries, uterine horns and vagina fixed for histology.

2. *Object* : This experiment should show any effect the drug has on normal reproduction, particularly the period for successful mating, the growth of fetuses, the condition of the young at birth and also the general condition of the female through and after pregnancy.

Procedure : Eight female mice are fed the drug six times, once every fifth day and then kept for mating. They are all kept for the length of a normal pregnancy. If they deliver, the condition of the litter is observed. If they do not deliver, they are sacrificed and the ovaries, uterine horns and vagina are fixed for histology.

3. *Object* : This experiment should show any effect the drug has on normal reproduction, particularly the period for successful mating, the growth of fetuses, the condition of the young at birth and also the general condition of the female through and after pregnancy.

Procedure : Eight female mice are fed the drug six times once every fifth day. After the fourth feeding the females are kept for mating and feeding is continued. They are kept for the length of a normal pregnancy. If they deliver, the condition of the litter is observed. If they do not deliver, they are sacrificed and the ovaries, uterine horns and vagina are fixed for histology.

4. *Object* : This experiment should show if the drug has any effect on the mating behaviour of the male while the animals are under treatment. It would also show the effect it had on the female and the young.

Procedure : Eight male mice are fed the drug four times once every fifth day. After the fourth feeding they are immediately kept for mating. Ten days after they are kept for mating, the males are sacrificed and the testes fixed for histology. The females are all kept for the length of a normal pregnancy. If they deliver, the condition of the litter is observed. If they do not deliver they are sacrificed and the ovaries, uterine horns and vagina are fixed for histology.

5. *Object* : By mating the male after the drug is withdrawn, the experiment should show if the drug has a temporary or a lasting effect on the male and the sperm.

Procedure : Eight male mice are fed the drug four times once every fifth day. Twenty days after the last feeding they are kept for mating and sacrificed ten days thereafter. The female mice are all kept for the length of a normal pregnancy. If they deliver, the condition of the litter is observed. If they do not deliver they are sacrificed and the ovaries, uterine horns and vagina are fixed for histology.

(3) Standard Experiment for the Testing of Indigenous Plant Materials

Object : The experiment should show if the preparation has any effect on the sex cycle and normal reproduction in the female, particularly on the growth of fetuses, the condition of the young at birth and also the condition of the female through pregnancy. It should also show if the preparation has any effect on the mating behaviour of the male.

Procedure : Sixteen female and sixteen male mice are fed the preparation either in a solution or mixed in the diet for 30 consecutive days. The vaginal smears of the females are recorded daily. Eight females are kept for mating with eight untreated males and the other eight females with eight of the treated males. The remaining eight treated males are mated with eight untreated females. All the females are kept for the length of a normal pregnancy. If they deliver, the condition of the litter is observed. If they do not deliver, they are sacrificed and the ovaries, uterine horns and vagina are fixed for histology. The males are sacrificed ten days after mating and the testes fixed for histology.

Criteria : If a substance satisfies the following four conditions it is studied further :

(a) The substance should not have any toxic effect on the animals in 10 times the normal dose. Toxic effects are decided by the percentage of deaths, abortions and any after-effects.

(b) In 10 times the dose, the substance should prevent conception *i.e.*, the development of embryos.

(c) The average time for successful mating should be more than 10 days.

(d) In the case of pure products, the substance should be chemically stable.

Since the establishment of the Contraceptive Testing Unit, twenty three oral contraceptives have been tested. So far, none of these preparations has been found to have any effect on the fertility of mice.

Recently a new procedure for testing oral contraceptives has been added to the other tests, *viz.*, the subcutaneous injection of the drug in the female mouse. The dose used is 10 times the dose calculated according to body weight.

The results of the experiments are recorded in a special form (Appendix II)

Local Contraceptives

1. **Laboratory Tests :** Laboratory investigations which include tests for spermicidal activity and for physical and storage properties are first carried out. The contraceptives received are mainly of two types : A. Chemical and B. Mechanical.

A. **Chemical Contraceptives** are subjected to (a) physical tests, (b) spermicidal tests, (c) storage tests and (d) tests for carcinogenicity and toxicity.

(a) *Physical tests :* The physical test of a foam tablet is carried out by studying the duration, quality and amount of foam with saline and semen and that of the jelly or cream is studied with the help of a mobilometer.

Foam test in vitro : foaming in saline—A tablet is introduced into a test tube (1" diam.) containing 6 cc. of saline and the foaming is observed :

- (i) The foaming should start immediately.
- (ii) The foam should be dense and not formed of loose bubbles.
- (iii) The foam should reach the height of at least 5 cms.
- (iv) The foam should be maintained for at least 10 minutes before it begins to collapse.
- (v) The disintegration of the tablet should be within 2-3 minutes.

Foaming in semen—The tablet is added to 2.5 cc of semen and the foaming is observed.:

- (i) The foaming should start almost immediately.
- (ii) The foam column should be at least 3-4 cms. high within 10 minutes.
- (iii) The foam should be made up of small dense bubbles.
- (iv) It should not collapse completely within 40 minutes.

(b) *Spermicidal tests*: The spermicidal tests are compared with those carried out on jellies or tablets with known, reproducible spermicidal properties. The human semen specimen used for testing must meet certain specifications.

- (i) It is essential to use fresh semen *i.e.*, less than 3 hours old.
- (ii) It is important to allow sufficient time for complete liquifaction to occur before using the semen for testing.
- (iii) It should have a count of 50 million or more per ml.
- (iv) 50% or more of the spermatozoa should show good motility. The motility should be active and progressive.
- (v) Phthalate time (*i.e.*, mixing of equal volumes of semen and 2.8% K-hydrogen-phthalate solution and observing for immobilization of spermatozoa) should not be less than 15 minutes.

Davidson's modification of Baker's test is used for estimating the total spermicidal power of the chemical contraceptives.

Procedure: (a) One tablet or 2 gms of jelly or cream is dissolved in 8 cc. of saline and the supernatant filtered to prepare an S/2 solution.

(b) 0.1 cc. of filtrate is mixed with 0.1 cc of semen in a Kahn tube.

(c) A drop of the mixture is observed under the microscope at the end of 5 minutes after mixing and the activity of the spermatozoa is

noted— if very active it is classed as “III”; moderately active “II”; sluggishly active “0”; not active “I”.

(d) If the activity is “0”, 0.2 cc. of Krebs Ringer phosphate buffer solution 7.4 pH is added and mixed.

(e) After five minutes of mixing a drop of the mixture is observed under the microscope to see if the spermatozoa revive their activity—and accordingly it is graded “III”, “II”, “I”, “0”.

(f) 0.1 cc of the semen is mixed with 0.1 cc. of saline and one drop of the mixture observed under the microscope—the activity should be “III”.

(g) In this way it is possible to find out the maximum dilution of the tablet (S/2, S/4, etc.) which is able to immobilise all the sperms within five minutes.

A contact test which is designed in this laboratory is used for the tablets. This method gives an idea of the spermicidal efficiency of the tablet when the semen comes in contact with it.

Procedure : A one centimeter high semen column is sucked into a glass tube and brought in contact with the tablet. The glass tube is removed after 75 seconds of contact, and the semen squirted on the slide and observed under the microscope for the activity of the sperms. All the sperms should die within 75 seconds.

(c) *Storage Tests* :

(1) *Foam Tablets* : Unsealed tubes* of foam tablets are stored for three months at 90% humidity or above and the tablets tested for their foaming and spermicidal properties.

(2) *Jellies and creams* : The tubes are stored at different temperatures for three months and at the end of this period the jelly or cream is tested for its physical and spermicidal properties. The temperature and the duration of the storage are being standardized.

(d) *Tests for carcinogenicity and toxicity* :

The testing for carcinogenicity and toxicity of different active ingredients incorporated in the local contraceptives is carried out by three standard methods

*In the case of vials the wax seal is removed but the stopper is kept in position. In the case of the foil packets the foil is left intact. This is the condition in which women are most likely to store the tablets in their homes.

(1) **Subcutaneous Injection**—Two-month-old Swiss virgin female mice are given a single subcutaneous injection of 2 mgm. of the active ingredient in propylene glycol. The animals are kept under observation for toxic effects.

(2) **Cutaneous Application**—To study the carcinogenic effect of the active ingredient on the skin, 2-month-old Swiss virgins are given bi-weekly applications of 1% solution of the active ingredient in acetone. The hair on the back of the animal is clipped and the solution painted on the back with a camel hair brush. The animals are observed till death and at autopsy, histological study of the treated skin is undertaken.

(3) **Cervix Painting** :—To study the carcinogenic action of the active ingredients on the cervix, 2-month-old Swiss virgins are given intravaginal applications of 1% solution of the active ingredient in acetone, twice a week. The animals are held with their heads lowered and a drop of solution placed on the cervix with a fine-tipped pipette. The solution is allowed to evaporate before the animal is released. Vaginal smears are studied at monthly intervals and the animals observed till death. Histopathology of the ovaries, uterus, cervix and vagina are studied at autopsy.

Experiments are in progress to test the toxicity and carcinogenicity of known spermicidal and foaming agents.

The "String Technique" for testing the carcinogenic effect of active ingredients on the cervix is being standardised in the laboratory.

If further tests for the toxicity of oral or local contraceptives are necessary the material will be sent to the Central Drug Research Institute, Lucknow; Pharmacology Department, Lucknow University, Lucknow; and Central Drug Laboratory, Calcutta.

B. Mechanical Contraceptives : The Mechanical Contraceptives received for testing include condoms, diaphragms and cervical caps. The testing of the first two types is done according to the Draft British Standards of October 1956.

Condoms : **Material**—The condom should be manufactured from natural rubber latex and it should be transparent or translucent prior to the application of dusting powder. The rubber mixings and dusting

powder should not include in their composition any ingredient which is known to be injurious or toxic to the user.

The following tests are done :—

Leakage test : The ring end of the condom is fixed firmly to a glass tube by means of a rubber band and the glass tube is clamped in position exactly one foot above the flat surface on which the lower end of the condom is to rest. 300 ml. of water are carefully poured into the condom. The condom is removed from the glass tube, and carefully lowered to the top of the table where it rests on a filter paper. The upper end of the condom is tightly held with the fingers so that the water may not escape outside. The condom is then gently rolled from side to side on the filter paper to blot off all the water droplets which may have been spilled on its outer surface. The condom is suspended freely, open end upwards, and, while subjected to the hydrostatic pressure exerted by the water it contains, no water should appear on the outer surface of the condom. 98% of the series of samples tested for leakage should be satisfactory.

Visual imperfections : When examined under normal vision in good light after slight inflation, the condom should not show visual imperfections, such as holes, weak spots, etc., as are likely to affect its service ability.

Dimensions : The minimum overall length should be $6\frac{1}{2}$ " and the maximum weight of the condom 240 gms. gross.

Diaphragms : Material—Rubber diaphragms should be manufactured from filled or non-filled natural rubber. The rubber mixings and any dusting powder applied to the diaphragm or cap should not include in their composition any ingredient which is known to be injurious or toxic.

The following tests are done :—

Leakage test : The rubber diaphragm should be free from flaws or holes such as are likely to affect its serviceability and none should be apparent when the diaphragm, inflated to a pressure of approximately 2 lb/sq. in. is immersed in water.

Ageing test : The rubber diaphragm should not tear and should not exhibit any perceptible change in the hardness of the rubber, when stretched over a smooth mandrel three times its height after ageing it at 70°C for a period of 72 hours.

Dimensions : The actual size of the diaphragm should conform to the marked size within a tolerance of ± 1 mm.

The results of the tests are recorded in a special form (Appendix III).

II. Clinical testing of local contraceptives is carried out after they have been investigated in the laboratory.

The clinical testing is done at the Women's Welfare Clinic at Naigaum on women volunteers who come for birth control advice and for investigation of infertility. Recently, testing has also been commenced at the Family Planning Training and Research Centre by the woman doctors of the Contraceptive Testing Unit.

It is most important that a contraceptive should be perfectly harmless to the user. It must not only be efficient and non-irritant but it should also be non-carcinogenic and should not give rise to other pathological conditions. A thorough and periodic gynaecological examination is therefore necessary in order to detect asymptomatic cancer of the uterine cervix, or other pathological conditions of the pelvic organs and to detect the harmful effects, if any, arising from the long-term use of contraceptives.

The menstrual, obstetric and coital histories of each woman are recorded.

Procedure in gynaecological examination :

1. The speculum is inserted with the woman in the usual lithotomy position.
2. The colposcope is adjusted.
3. The mucosa of the vagina is inspected.
4. The vaginal and cervical secretions are observed and the pH recorded.
5. The preparation of slides is carried out. The smears are placed in a mixture of equal parts of ether and 95% ethyl alcohol. They are later stained by the modified Papanicolaou method described by Pastakia (Indian Journal of Medical Sciences 9 : 579-585, 1955).

A vaginal smear is taken for the purpose—(a) of studying exfoliated cells in order to evaluate hormonal activity for studies in reproductive physiology; (b) to detect *Trichomonas* and *Monilia* by a hanging drop preparation.

Cervical smears are taken—(a) to study exfoliated cells for the purpose of detecting early cancer; (b) to detect the presence of gonococcus or other pathogenic micro-organisms as revealed by Gram's stain.

Cervical mucus from the endocervix is collected for biochemical studies and for the "fern test", a procedure for evaluating the functional activity of the ovary for studies in reproductive physiology.

6. The colposcope is further adjusted for the observation of the following : The mucosa of the cervix—(a) as it is; (b) after the application of three per cent acetic acid for delineating the details; (c) with a change of magnification in the colposcope, and the use of colour filters, as might seem desirable; (d) after application of aqueous iodine (Schiller test) to visualize areas free from glycogen.

7. The colposcope is once again adjusted, and the vulva is inspected.

8. A bimanual gynaecological examination is done.

9. Rectal examination is performed.

The findings are recorded in a special form (Appendix IV).

The following tests are carried out with the local contraceptives ;

(1) **Foam test in vagina :** This test indicates the foaming ability of the foam tablet *in vivo*. One moistened foam tablet is placed in the posterior fornix and rubbed on the posterior vaginal wall. 4 ml. of tap water are introduced into the vagina. The following observations are made: the time taken for the foam to be produced; the type of foam; the duration of the foam; the occurrence of symptoms of irritation.—(1) The foam should be produced within one minute; (2) it should be sufficient in amount, *i. e.*, it should fill the posterior fornix and cover the cervix; (3) it should be dense and should consist of small bubbles; (4) there should be no odour; (5) the foam should be maintained for at least 10 minutes; (6) the woman should not complain of burning or itching. Total : 5 cases. Results : 100% satisfactory (5/5).

(2) **Spread test in vagina :** This test indicates the ability of the jelly to form a protective layer on the cervix. One applicator-full of jelly is introduced into the vagina and the adhesiveness of the jelly to the mucosa is noted. (1) The jelly should adhere well to the mucosa of cervix and vagina and should not fall into the posterior fornix owing to its being too viscous or too watery. (2) There should be no odour. (3) The woman should not complain of burning or itching. Total : 5 cases. Results: 100% satisfactory (5/5).

(3) **24-hour Cap Test for foam tablets and jellies :** A complete gynaecological examination including colposcopy, Schiller test and exfoliative cytology is done on the woman.

A plastic cervical cap containing one foam tablet or a 2" ribbon of jelly is placed on the cervix and the time of application is noted. 24 hours later the cap is removed, and a smear is made from the contents. The full gynaecological examination is repeated and any changes are noted.

Requirements

- (1) The cervix should preferably be clean. If there is a small ectopy present, there should be no bleeding points.
- (2) The presence of pregnancy and any pelvic pathology including vaginitis must be excluded.
- (3) There should be no trichomonal or gonococcal infection.
- (4) The exfoliative cytology must be normal (Papanicolaou's stain).
- (5) Menstruation should have stopped and there should be neither macroscopic nor microscopic bleeding from the os.
- (6) The test should not be done at the time of the expected menstrual period.

Criteria for a satisfactory cap test

- (1) There should be no macroscopic bleeding.
- (2) There should be no irritation of the cervical mucosa as evidenced by cervicitis or tissue damage.
- (3) There should be no red blood cells in the smear.
- (4) There should be no abnormal changes in the smear. Total : 5 cases or 10 cases. Results : 80% satisfactory (4/5 ; 8/10)

The results of the laboratory and clinical testing of local contraceptives are recorded in a special form (Appendix V).

(4) **Clinical Trial :**

After a contraceptive foam tablet or jelly has proved to be effective and harmless on the basis of the laboratory and clinical tests described above, its acceptability and harmlessness after long-term use are studied.

Acceptability : 100 or 50 couples should use the tablets or jelly atleast once each. There should be no complaints such as burning or itching in either the husband or wife of at least 75% of the couples (i. e., 75/100 ; 38/50).

Harmlessness : (A) 20 women should use at least 6 tablets or 1 tube of jelly. In at least 90% of these women, colposcopic examination should show no significant changes *e. g.*, the appearance of cervicitis, vaginitis, leukoplakia or abnormal transformation zone, where previously none of these conditions was present.

(B) A long-term trial for harmlessness is also done *i. e.*, the same women who are regularly using the contraceptive are examined by colposcopy every 6 months and by exfoliative cytology every year for at least 3 years.

In at least 90% of these women, colposcopic examination should show no significant changes *e. g.*, the appearance of cervicitis, vaginitis, leukoplakia or abnormal transformation zone.

In at least 90% of these women, exfoliative cytology should not show the appearance of atypical or abnormal smears which cannot be explained *e.g.*, by the occurrence of an intervening trichomonal or gonococcal infection.

(5) Field Trial :

After the clinical tests and trials of the local contraceptives have proved satisfactory, the contraceptive which is being investigated is distributed to the couples willing to use it. The contraceptives tested are those received from the D.G.H.S. as well as the foam tablets developed in the Contraceptive Testing Unit

The work is conducted in four stages.

1. Survey and Introduction to Family Planning.
2. Distribution of Contraceptives.
3. Follow-up of those using contraceptives.
4. Evaluation of Results.

SURVEY AND INTRODUCTION

The women interviewed are between the ages of 15 and 35 years and have had at least one previous child.

The following data are collected on special schedules (Appendix VI) from the couples interviewed.

- (a) Data regarding the education, occupation, living conditions, diet, income and attitude to family planning.
- (b) Data on the physiology of reproduction, including information on the ages at menarche, marriage, consummation of marriage

and first delivery, and the obstetric menstrual and marital histories.

To ensure the accuracy of the information collected in the schedules, these are checked by the doctors in charge.

During the survey, the social workers carry out mass propaganda in the form of group meetings, lectures and film shows on family planning.

DISTRIBUTION OF CONTRACEPTIVES

Those couples willing to use contraceptives are offered the appliances which are being investigated.

The women are advised to attend the clinic for a routine gynaecological examination and special examinations including colposcopy and exfoliative cytology. However, if the women are unwilling to be examined they are given the chemical contraceptive by the social worker or nurse.

FOLLOW-UP

The social workers carry out a systematic monthly follow-up of all the couples using the contraceptives and fill in follow-up cards for the wife and husband (Appendix VII a & b).

Information is obtained regarding the use of the method, risks taken, regularity of the menstrual periods, complaints as to the use of the method and the occurrence of pregnancies and their possible cause. The women using contraceptives are advised to return for a colposcopic examination every 3 months and once a year the exfoliative cytology is repeated.—

The couples using contraceptives are followed up for a minimum period of three years each in order that the effect of the method in lowering the birth-rate may be measured.

EVALUATION

The data available regarding the socio-economic conditions and reproductive physiology are evaluated and the pregnancy rate per 100 years of exposure is calculated according to the Pearl formula

$$R = \frac{\text{Total No. of conceptions} \times 1200}{\text{Total months of exposure}}$$

CLASSIFICATION OF APPROVED CONTRACEPTIVES

The local contraceptives which satisfy the criteria for laboratory and clinical tests are placed in one of the following three categories:

Category I : Pastes, jellies and foam tablets which have satisfactory physical properties, which reach the required level of spermicidal efficiency in laboratory tests and which have been found to be harmless after the 24-hour cap test in 5 women.

Category II : Foam tablets which satisfy keeping qualities for unsealed tubes at 90% humidity and above for 3 months.

The criteria for storage of jellies are still being standardized.

Category III : Pastes, jellies and foam tablets which satisfy the criteria for harmlessness in the 24-hour cap test and which have been found acceptable, reliable and harmless by prolonged use at Family Planning Clinics.

II. THE DEVELOPMENT OF EFFECTIVE ORAL AND LOCAL CONTRACEPTIVES

The Contraceptive Testing Unit is engaged in the development of (a) a suitable Oral Contraceptive, and (b) a suitable Local Contraceptive

(a) ORAL CONTRACEPTIVES :

Research in the development of oral contraceptives is being carried out along two lines: (i) Scrutiny of indigenous plant materials. (ii) Synthetic preparation of organic substances with probable antifertility properties.

(i) *Plant Materials*: Considerable attention is being paid all over the world to the development of a substance which when administered orally has been known to control fertility whose effects are harmless and reversible. In the absence of a clear approach of attack, one of the accepted ways is to systematically scrutinise plant materials which have been known in the Indian and other systems of Medicine and in the ancient folklores of different countries to have antifertility properties. About a dozen of such plants are indigenous to India. The Unit has undertaken systematic work on the scrutiny of some of the plants. The powdered substance is given to experimental animals in their diet. If the material is crude, the extracts with different organic solvents are obtained and fed to animals in their diet. Care is taken to feed the substance as far as possible in the form in which it is known to be prescribed for human beings. Hibiscus flowers, Limitax, and Virbhuti

were tested and found to be unsatisfactory. Betel nuts cured in the banana trunk and seeds of *Carica Papaya* offer results of interest although the experiments are incomplete. The ultimate object of scrutinising these plants is to isolate the active principle, study its chemistry and mode of action.

(ii) *Synthetic Products* : It has been claimed that *m*-xylohydroquinone, the active principle isolated from the oil of *Pisum Sativum* affects fertility (Sanyal). It was thought of interest to study the specificity of the methyl groups. The introduction of the groups of the higher homologous series in the 2, 2 and 6 positions of the hydroquinone nucleus, did not increase the antifertility activity. Hence it was thought that the antifertility property may increase by raising the redox potential of the hydroquinone derivative by the introduction of suitable groups. A few analogues of *m*-xylohydroquinone have been prepared, tested on experimental animals, and yielded results of interest. If the substance is soluble in water or propylene glycol, it is administered by subcutaneous injection. If it is insoluble it is given in the diet.

The following are the criteria by which an Oral Contraceptive is adjudged:

1. It should be safe *i.e.*, it should have minimal toxicity and irritation; it should be non-cumulative, non-abortifacient, and should have minimal side-effects.
2. It should be effective in well controlled animal and clinical tests.
3. It should be rapidly active *i.e.*, it should have a short induction time.
4. It should be rapidly reversible at will with no long-term effects.
5. It should have a simple mode of action *i.e.*, it should not act by disrupting complex balanced systems.

(b) LOCAL CONTRACEPTIVES

With a view to developing a formula for suitable, cheap foam tablets, attempts were made to incorporate sodium chloride as the active ingredient in the tablet. Clinical trials were not found satisfactory. It was therefore decided to incorporate a stronger spermicidal agent. A formula has been evolved incorporating Chloramine-T as the active spermicidal agent. Soap nuts are indigenous and cheap, and therefore their aqueous extract has been used as a foaming agent. Toxicity tests with soap nut extract have not revealed adverse effects in mice.

The foam tablets prepared according to the formula fulfil all the criteria laid down by the Contraceptive Testing Unit. Clinical trials appear to be satisfactory.

III. THE PHYSIOLOGY OF REPRODUCTION

The Unit is engaged in the study of the reproductive physiology in women and men at various periods of their reproductive life.

In women, the problems being investigated are :

1. The establishment of the pattern and variability of the menstrual cycle in a group of Indian women ; the correlation between the diet and the reproductive ability ; the determination of the period of inability to conceive following delivery.

2. The study of the cervical and vaginal mucosae during various periods of reproductive life by speculum examination and colposcopy and the study of cervical, vaginal and endometrial cytology and histology of the endometrium.

3. Immunological and biochemical studies of cervical mucus.

Up to now those chosen for this research are volunteers from the women attending the family planning clinic. These women come for birth control advice as well as for the investigation of infertility.

1. The menstrual, obstetric and coital histories of each woman are recorded and gynaecological and special examinations are done.

Some interesting data have been obtained.

The average age of consummation of marriage in the low-income group was found to be 15 years, whereas in the high-income group it was 20.5 years.

Comparing the spacing between the first and second pregnancies in the same two groups, the average was found to be 26 months in the low-income group while in the high-income group it was 20 months.

The study of the onset of menstruation after delivery showed that the average period of onset of menstruation after delivery was $11\frac{1}{2}$ months whereas in a series of women from a higher income group, the time of onset of menstruation following delivery was found to be $4\frac{1}{2}$ months.

2. A study of the cervical and vaginal smears taken from women at different stages of the lactation period and stained by Papanicolaou's method showed 3 types of smears (a) atrophic, (b) intermediate and (c) mature.

A comparison of the cervical and vaginal smears showed that the vaginal epithelium seemed to be in advance of the cervical epithelium indicating that the cervical mucosa reacts less sensitively to hormone stimulation than the vaginal epithelium. It is intended to correlate these findings with the histological studies of the endometrium and with estimations of pregnandiol in urine from lactating women.

(a) *Immunological work with cervical mucus*

3. This work was commenced in order to find how many proteins and other antigenic substances are present in cervical mucus and whether these are secreted by the cervical mucosa or if some of them are filtered products of blood. The method used is that of Ouetterlong's gel Diffusion Test (*Acta Path. et. Microbiol. Scandinav.* 26: 507, 1949.)

In this test an antigen and antibody are placed in small cups embedded in a gel medium. Both these diffuse towards each other through the gel medium and if the antibody used is specific to the antigen, precipitin lines are formed. The number of lines formed gives the information as to how many antigens are present in the substance under investigation.

Procedure : For carrying out the above type of work the specific antibody must be first produced. This is done by immunizing rabbits with the antigens under investigation. An optimum amount of the antigen (about 0.2—0.3 cc.) is injected into rabbits subcutaneously every week. Depending on the strength of the antigen used, after about 6—8 weeks, antibodies are formed in the blood of the rabbit. The rabbit is bled from the ear vein when the antibody titre is fairly high. At one time about 10—15 cc. of blood can be removed. This is allowed to clot and the clear serum is then separated from the clot by centrifuging. In these studies an antiserum was obtained from rabbits under immunization with cervical mucus. This antiserum was placed in the central cup of an agar plate. Equidistant from the central cup were placed two cups, one of which was filled with cervical mucus and the other with human blood plasma. After 15 days antigen-antibody lines began to develop. By means of this immunological test it has been found that cervical mucus contains

minimum of four proteins of which three are common to blood. That is, three proteins in cervical mucus are filtered products of blood. After carrying on a series of experiments, it has been found that one of these three is a gamma globulin. It is always the gamma globulin which contains the antibodies.

Further immunological studies with cervical mucus are being done.

(b) *Biochemical work with cervical mucus*

A study was carried out to find out whether or not oestrogens are present in cervical mucus and whether there are any fluctuations in the quantity of oestrogen according to the time of the cycle.

Since very small quantities of mucus are available at one time a very sensitive method had to be used which could detect micro quantities of oestrogen. The method used was that of Heftman (Science, 3 : 571, 1950).

The principle of this method is that a colour complex of the oestrogen is prepared and extracted. It is subjected to the ascending method of paper chromatography. Intense violet spots appear which are characteristic for each oestrogen derivative.

Individual mucus samples were repeatedly extracted with ether made peroxide-free. The ether was dried and the residue was dissolved in 0.1 cc. of absolute ethanol, and Heftman's method of paper chromatography was carried out. The colour spots obtained with cervical mucus extracts were reddish violet. It was difficult to say whether these were obtained due to the presence of oestrogens in the mucus or to the presence of non-specific substances. Hence a bioassay was done.

The bioassay with pooled mucus samples was carried out as one or two samples of mucus would not be enough for an assay. The method followed was that of Rubin and Dorfman (Endocrinology 49 : 429, 1951), which depends upon the increase in uterine weight of the oestrogen-injected mice. For this test young albino mice 21 days old were used. For the experiment carried out it was necessary to have groups of animals each containing not less than 12—15 mice.

With these experiments it was not possible to demonstrate the presence of oestrogens in cervical mucus.

In men the problems being investigated are :

1. The physical and morphological study of semen.

2. The immunological and biochemical studies of semen.
3. Hormonal studies of semen.

1. The study of different types of semen is carried out.

The volume of the semen is measured by pouring the liquified semen into a graduated centrifuge tube.

The viscosity is also noted by studying the thread formed while pouring and it is recorded as watery, normal or viscous.

The motility is recorded by observing a fresh drop under the microscope and it is graded as sluggish, moderately active or very active. The total sperm count is done by bulk dilution 1 to 10 or 1 to 20 according to the concentration of the spermatozoa. The dilution is done with 1% phenol saturated with bicarbonate. Similar dilution is done with Krebs Ringer Phosphate buffer pH 7.4 with 1% glucose and only the dead sperms are counted, in a Neubauer's chamber. Thus the percentage motility is calculated.

The morphology of semen is also studied by staining the semen smears by Papanicolaou's method.

2. (a) *Immunological work with semen :*

The antigenic properties of semen were first investigated, using Ouceterlony's Gel Diffusion technique. Work carried out so far has shown that semen is antigenic *i.e.*, if it is injected into an animal system like that of the rabbit, antibodies are formed.

These studies have further shown that semen has 17 antigenic substances of which at least 6 are common to blood, and sperms have some antigens not common to blood.

Stavitsky's haemagglutination technique (J. Imm. 72 : 360, 1954) has also been used to find out antibodies which occur in very small quantities. In this test, sheep red blood cells specially processed by an elaborate procedure, are coated with minute quantities of a desired antigen. When to such treated and antigen-coated blood cells minute quantities of specific antibodies are added, haemagglutination results. This is a much more sensitive test than the gel diffusion method.

(b) *Biochemical work with semen :*

Semen samples with varying counts and motility are being used to find out certain enzyme systems.

The enzyme studied was succinic dehydrogenase which is an important oxidizing enzyme and is closely linked with the respiration and metabolism of all living cells. Kun and Abood's method (Science 109 : 144, 1949) is used to find the succinic dehydrogenase content of the semen samples. This method does not involve the use of costly apparatus and so this was chosen though there are other methods also for estimating this enzyme.

Work is in progress in order to gather more information about this enzyme in semen.

In order to know whether there is any biochemical change in the seminal plasma of different types of semen, the estimations of total nitrogen, total phosphorus and total proteins, fructose and citric acid are being done. For the estimation of total nitrogen the digestion was done with sulphuric acid digestion mixture and the colour development done by nesslerization. Perchloric acid digestion and the colour development by hydroquinone and molybdate was done for estimating the total phosphorus. For estimating proteins, suitable dilutions of the seminal plasma were made and the colour developed directly with phenol reagent.

The total nitrogen and total phosphorus content in azoospermic, oligospermic and low motility types of semen are observed to be higher than they are in normospermia.

The estimation of fructose and citric acid were carried out according to the methods of T. Mann (Lancet 254 : 446, 1958) and Densted (J. Biol. Chem. 175 : 849, 1948) respectively.

3. *Hormonal estimations :*

Experiments are being carried out to detect gonadotrophins in human semen by chemical methods. Aluminium hydroxide is used for adsorbing gonadotrophins (Mulbury and Goodman J. Clin. End. Met. 14 : 66, 1954). Preliminary bioassay has indicated the presence of gonadotrophins in semen.

IV. OTHER ACTIVITIES

Since August 1957, the Unit has been co-operating in the courses held at the Family Planning Training and Research Centre, Bombay and at the Demographic Training and Research Centre, Chembur, Bombay. Lectures and demonstrations relating to the physiology of reproduction and research in contraceptives are given by the workers of the Unit.

A film strip on the Physiology of Reproduction is being prepared by the Unit.

V. EXPENDITURE

Amounts sanctioned to Contraceptive Testing Unit.

1954-55	Rs. 35,325
1955-56	Rs. 43,457
1956-57	Rs. 30,000
1957-58	Rs. 51,900
1958-59	Rs. 25,950

(First instalment)

Total	1,86,632
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VI. PUBLICATIONS

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2. The Effect of Metaxylohydroquinone on mice and rats. B.K.
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3. The Work of the Contraceptive Testing Unit of the Government
of India. M. Kamat (Read at the 3rd All India Conference on
Family Planning, Calcutta, 1957) Med. Dig. (Bombay),
25 : 117, 1957.
4. The Vaginal Smear : its application in diagnosis and research.
H. Peters*, H. Pastakia*, S. Israel and K. Rijsinghani* with
the technical assistance of Mr. M.N. Mehta.—Indian J. Med.
Sci., 11 : 383, 1957.
5. A Clinical Method of Contraceptive Testing. S. Israel
H. Peters* and M. Kamat. J. Indian Med. Assn. 29 : 360, 1957.
6. The Lactation Period in Indian women. H. Peters*, S. Israel
and S. Purshottam. (Read at the Scientific Seminar on Family
Planning Bombay, 1955, Fertil. & Steril. 9 : 134, 1958.
7. Colposcopy in gynaecological Practice. M. Kamat (Read at
the Indian Science Congress, Madras, 1958)
8. Practical Methods of Family Planning. S. Israel Swasth Hind
Family Planning Number 2 : 22, 1958.
9. The Cellular Detection of Adenocarcinoma.—H. Peters*,
K. Sundaram*, S. Israel Acta Un.int. Cancr.—14 : 380, 1958.

10. Colposcopy in a Family Planning Clinic. M. Kamat. J. Indian Med. Assn. 31 : 127, 1958.
11. Cytology in a Family Planning Clinic. S. Israel. J. Ass. med. Wom. India. (Read at the Golden Jubilee of the Association of Medical Women in India, Bombay, 1957).
12. A New Method of Testing Spermicidal Action of Foam Tablets. M.S. Joshi & M. Kamat. J. Indian. Med. Assn. 31 : 246, 1958.
13. The Acceptability and Effectiveness of two Birth Control Methods : An evaluation of 352 cases. S. Israel & M. Kamat. —J. Family Welfare. 5 : 3, 1958.
14. Immunological work with human semen. S. Rao & K.K. Sadri. (Read at the Conference of the Ind. Assn. of Pathologists, 1957)—(in press).
15. Laboratory Testing of Chemical Contraceptives. M. S. Joshi. —(Sent for publication).
16. The Onset of Menstruation in Indian Women. S. Israel.—(Sent for publication).
17. Antigenic composition of Buffalo Semen. S. S. Rao & K.K. Sadri. (In preparation).
18. Diet and Fertility in India. M. Kamat.—(In preparation).
19. A preliminary note on the Succinic dehydrogenase activity of Human Semen. Shanta S. Rao, A.R. Sheth and A.M. Phadke** (Under publication in The Indian J. Med. Sci).

**Family Welfare Bureau.

*Members of other Units.

VII. STAFF OF THE CONTRACEPTIVE TESTING UNIT

Director :

Dr. V.R. Khanolkar, B.Sc., M.D. (Lond.), F.N.I., Director, Indian Cancer Research Centre.

Staff :

Dr. (Mrs.) M. Kamat, B.Sc., M.D., D.G., D.T.M. (Lisbon)—Research, Medical Officer.

Dr. (Mrs.) S. S. Rao, M.Sc. (Toronto), Ph.D., Asstt. Research Officer.

Mr. M.R. Paranjpe, M.Sc. (Tech.), Sr. Res. Asstt.
(At present on study leave in the U.S.A.)

Mr. M.S. Joshi, M.Sc., Sr. Res. Asstt.

Dr. R.M. Naik, M.Sc., Ph. D., Sr. Res. Asstt.

Miss S. Hakim, M.Sc., Sr. Res. Asstt.
(At present on study leave in the U.S.A.)

Miss K.K. Sadri, B.Sc., B.Sc. (Tech.), Res. Asstt.

Miss K. Ranadive, B.A., Social Worker.

Miss S.K. Shahani, B.Sc., Res. Student.

Mr. A.R. Sheth, M.Sc., (Raptakos Scholar).

Mr. M.J. Viegas, B.Sc., Lab. Asstt.

Miss T.A. Shetye, B.Sc., Lab. Asstt.

Miss N. Korde, Jr. Lab. Asstt.

Mr. S. V. Jayakar, Jr. Lab. Asst.

Mr. M.R. Joshi, Lab. Attendant.

Field Trials of Contraceptives (I.C.M.R.)

Dr. S. Israel, M.D., Medical Officer.

Mrs. K. Shanbag, B.Sc., Social Worker.

Mr. K.J. Gujerati, M.A., S.T.C., Social Worker.

Mrs. R. Prabhu, B.P.N.A., Nurse.

BIOLOGICAL TESTING OF ORAL CONTRACEPTIVES

Procedure—

Test animal : Swiss strain male and female mice, 3-month old.

Dose : Prescribed dose/day/40 kg. body wt. (Human).

Calculated dose/day/30 gm. body wt. (Mouse).

10 X the calculated dose to be administered to mice.

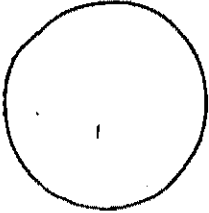
Experiment number	Object of Experiment		Number of animals used	Whether kept for mating	Number of days of administration of drug	
					Before mating	After mating
Pilot	Test for Toxicity		8 females	Yes	10	10
I	Effects on sex cycle		8 females	No	6 times, once every fifth day.	Nil
IIa	Effect on	administration of drug before mating	8 females	Yes	6 times, once every fifth day.	Nil
IIb	Conception	administration of drug after mating	8 females	Yes	4 times, once every fifth day.	Twice, once every fifth day.
III	Effect on mating	Immediate	8 males	Yes	4 times, once every fifth day.	Nil
	behaviour	Lasting	8 males.	Yes	4 times, once every fifth day.	Nil

APPENDIX II

1. (a) Name of contraceptive
 - (b) Test animal used
 - (c) Solvent
 - (d) Method of administration
 - (e) Total dose administered
 - (f) Total period of administration
2. Estrus cycle after feeding
 - (a) Normal
 - (b) Long estrus
 - (c) Long diestrus
 - (d) Irregular
3. Mating response
 - (a) Induced
 - (b) Normal
 - (i) immediate
 - (ii) delayed
4. Length of pregnancy
 - (a) Normal
 - (b) Short
 - (c) Prolonged
5. Number in the litter
6. Condition of the litter
 - (a) On 10th day after mating
 - (b) At term
 - (i) healthy
 - (ii) anaemic
 - (iii) any abnormalities
7. Condition of the mother
 - (a) normal
 - (b) sickly
8. Toxic effects
9. Histology
10. Remarks

APPENDIX IV
GYNAECOLOGIC EXAMINATION

Case No. : Research No. : Date :
L. M. P. : L. S. I. : L. D. : Lactation :
Per Speculum : Macroscopic examination of secretions :

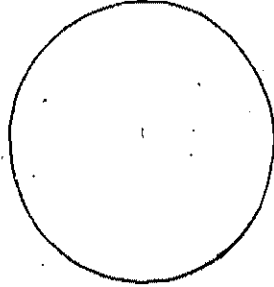
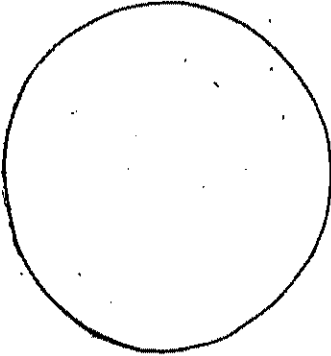


Cx. : pH :

Vag. : pH :

Colposcopy :

Schiller test :



Date :

Exfoliative cytology :

Gram's Stain :

Wet vaginal smear :

Biopsy :

Bimanual examination :

Vulva :

Perineum :

Introitus :

Vagina :

Cervix :

Uterine body :

Adnexa-left :

Right :

Breasts :

Weight :

Height :

Other Examination :

Contraceptive advice :

Remarks :

APPENDIX V
CONTRACEPTIVE TESTING UNIT
FORM—I

(For Chemical Contraceptives)

I. Description :

1. Code No. of Contraceptive :— (No. Received) :— Type :—
2. Ingredients :— Remarks :— Received
From :—
D. G. H. S.
3. Packing :— Remarks :—
4. Date of manufacture :— Date of expiry :—
5. Received for testing on :—

II. Physical properties :—

1. Colour :—
2. Shape & weight of tablet :—
3. Consistency of Jelly or Cream :— Remarks :—
4. pH :—
5. Foaming ability at 37° C. Remarks :—
In saline :—
In semen :—
6. Others :—

III. Storage :

Condition of storage :—	Duration of storage :—	Change in physical properties :—	Change in spermicidal properties :—
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IV. Spermicidal properties :

Method of Testing :	Date :	Sperm :	Motility :	Result :	Remarks
---------------------	--------	---------	------------	----------	---------

—	—	—	count	—	— : —
—	—	:	(mill/cc) :	(%) :	— : —

1.—

2.—

3.—

4.—

5.—

6.—

V. Clinical Testing :—

1. Foam test *in vivo* :

2. Spread test :

3. 24-hour cap test : No. of cases : Symptoms : Significant changes :
Clinical : Cytological

4. Others :

VI. Clinical trial :—

Total cases :

Tablet/Jelly Regularly used :

No complaints :

Complaints :

VII. Remarks :—

Tested by :—

APPENDIX VI

INDIAN CANCER RESEARCH CENTRE CONTRACEPTIVE TESTING UNIT

Serial No.: Date : Case No. : Date : Research No. : Date
 Date closed : Reason for closing :
 Referred by: (1) Self (2) Our own propaganda (3) Post partum
 clinic or hospital (4) Private doctors or nurses (5) Other social
 workers (6) Relatives or friends including old patients (7) Other.
 Name of wife ; Name of husband:
 Address :

Socio-economic status :

	Age	Religion	Caste	Place of birth	Mother tongue
Husband					
Wife					

	Education	Occupation	Income	Health
Husband				
Wife				

No. of dependants—Over 15 years : 15 years and under :

No. of earning members :

Joint income :

Expenditure on Food Rent Education Clothing
 per month : per month : per month : per month :

Type of house : No. of rooms :

Toilet facilities : (1) Own washing place and toilet :

(2) Share washing place and toilet { With other mem-
 bers of family :-
 (3) Own washing place No toilet : { With others :

(4) Share washing place { With other members of
 family :
 No toilet. { With others :

(5) No washing place or toilet :

Sleeping arrangements : (1) Sleep in one room with children :

(2) Sleep in one room with others :

(3) Have own bedroom :

Pregnancy History :

Age of marriage :

Age at consummation :

Age at first delivery :

Serial No.	Month and Yr. of delivery	Months of						Lactation	Result			Remarks
		Amenorrhoea			Abstinence				Sex	Present age	Age at death	
		Preg.	Post partum	Others	During preg.	Post partum	Others					
0												
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												

Other details :

1. Parity : 2. No. of living children 3. No. of living boys
 4. No. of living girls 5. No. of abortions 6. No. of still births

Menstrual History :

Age at menarche :—

Past menstrual cycle :—

Last menstrual period :—

Present menstrual cycle :—

Sexual Intercourse :

Usual frequency for the past one year :—

Difficulties :—

Last date :—

Attitude to Family Planning—Wife

1. Do you desire to have any more children ? Yes : No :
 (a) If so, why ? (b) If not, why not ?
2. Have you ever thought of planning your family ? Yes : No :
3. Do you know of any method of contraception ?
 (a) Nil (b) Abstinence (c) Rhythm (d) Withdrawal
 (e) Foam tablets (f) Jelly (g) Diaphragm (h) Condom
 (i) Other.
4. How did you come to know of it ?
5. Have you ever used any contraceptive method ?
6. If so, which ?
 (a) Abstinence (b) Rhythm (c) Withdrawal (d) Foam tablets
 (e) Jelly (f) Diaphragm (g) Condom (h) Other.
7. After which delivery ?
8. For how long ?
9. Regularly or irregularly ?
10. Successfully or unsuccessfully ?
11. Why did it fail ?
12. Why did you stop using it ?

Advice by Social Worker :

13. Response to offer : (a) Eager (b) Indifferent (c) Against
 (d) Reject for time being.
 14. Reason for acceptance : (a) Economic (b) Health of mother
 (c) Organic disease of mother (d) Limitation (e) Spacing
 (f) Other.
 15. Reason for rejection : (a) Religious (b) Wants more children
 (c) Wants more sons (d) Prefers oral contraceptives or injections
 (e) Other.
 16. Method chosen : : Diaphragm and Jelly ; Tablets ; Other.
 17. Reason for choice : Safe ; Easy ; Convenient ; Other.
- Remarks :

Attitude to Family Planning—Husband

1. Do you desire to have any more children ? Yes : No :
 (a) If so, why ? (b) If not, why not ?
2. Have you ever thought of planning your family ? Yes : No :

3. Do you know of any method of contraception ?

- (a) Nil (b) Abstinence (c) Rhythm (d) Withdrawal
 (e) Foam tablets (f) Jelly (g) Diaphragm (h) Condom
 (i) Other.

4. How did you come to know of it ?

5. Have you ever used any contraceptive method ?

6. If so, which ?

- (a) Abstinence (b) Rhythm (c) Withdrawal (d) Foam tablets
 (e) Jelly (f) Diaphragm (g) Condom (h) Other.

7. After which delivery ?

8. For how long ?

9. Regularly or irregularly ?

10. Successfully or unsuccessfully ?

11. Why did it fail ?

12. Why did you stop using it ?

Advice by Social Worker :

13. Response to offer : (a) Eager (b) Indifferent (c) Against
 (d) Reject for time being.

14. Reason for acceptance : (a) Economic (b) Health of mother
 (c) Organic disease of mother (d) Limitation (e) Spacing
 (f) Other.

15. Reason for rejection : (a) Religious (b) Wants more children
 (c) Wants more sons (d) Prefers oral contraceptives or
 injections (e) Other.

16. Method chosen : Diaphragm & Jelly ; Tablets ; Other.

17. Reason for choice : Safe ; Easy ; Convenient ; Other.

Remarks :

Signature of S. W.

APPENDIX VII A
FOLLOW-UP

Wife's Name : Case No. : Contraceptive given :
 Date :
 Address : Date :

Date of visit, Initials	H or C	I/C with		Tablets		Menstruation		Preg. Yes or No	Lact. Yes or No	Method rejected or discontinued, Reasons and Remarks.
		Other method.	No method.	In hand.	Issued.	Onset.	Duration,			

APPENDIX VII B
FOLLOW-UP

Husband's Name : Case No. :
 Contraceptive given :
 Address : Date : Date :

Date & Initials	H. or C.	I/C with		Method rejected or discontinued, Reasons & Remarks.
		Other method	No method	

INSTRUCTIONS TO BE FOLLOWED WHILE DESPATCHING CONTRACEPTIVES FOR TESTING

Each product must be accompanied by :—

1. Name of contraceptive :
2. Name and address of manufacturer :
3. Name and address of importing agent :
4. Type of contraceptive (foam tablet, jelly, paste, rubber, etc) :—
5. Quantitative formula from which the contraceptive is prepared and the dosage :—
6. Standards for test including methods of Chemical assay adopted by the manufacturer. :
7. Wholesale rate of contraceptive :—
8. Date of manufacture :—
9. Date of expiry :—
10. Name of countries where already in use (with date of such use in each case) :—
11. Date when the product was first made available in India :—
12. Information regarding its approval by other Government or recognised organisation of other countries like their Family Planning Association :—
13. Official Publication (with true copies of approving the product) :—

Two copies of specimens of all advertising and descriptive matter instructions, leaflets, labels etc., concerning the contraceptive.
14. The following quantities of free samples for initial testing foam tablets, 22 tubes of 10 tablets each, jellies/paste/gel 23 tubes about 2 ounces.
15. Rubber contraceptives 18.
16. Oral contraceptives—total dose for one month for 3 patients.
17. In case of chemical contraceptive one gramme of each of the active chemical ingredients.
18. Further samples will be required for clinical trials if the contraceptive is found satisfactory in laboratory tests.
19. Contraceptives sent for testing should be in sealed containers.

PROVISIONAL LIST OF CONTRACEPTIVES AS ON 7.3.58.

(This list supersedes all previous lists issued.)

Category I

Pastes, Jellies and Suppositories including foam tablets which in the opinion of the Contraceptive Testing Unit have been found to have satisfactory physical properties, to reach the required level of spermicidal efficiency in laboratory test and to satisfy the criteria for harmlessness in the short-term harmlessness test (24 hour cap test). Recommended for use.

Name	Manufacturer/Importer	Spermicidal Agent
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JELLIES & PASTES.

Preceptin.	Ortho Products, Raritan, N. J., U. S. A. (Ortho Pharmaceuticals, Imperial Chemical Industries (India) Private Ltd., P.B. 310, Bombay-1)	P-Diisobutyl phenoxy polyethoxy ethanel ricineleic acid.
Cooper Creme.	Whittaker Laboratories INC. 898 Washington Street, Peekskill, New York. (Dr. Jai Singh's Son & Co., Private Ltd.) 18/4Asaf Ali Road, P.O. Box 457, New Delhi.	Trioxymethylene 0.04%, Sodium Oleate 0.67%
Volpar Paste.	British Drug Houses, London (British Drug Houses (India) Private Ltd., Imperial Chemical House, Bombay-1.)	Phenylmercuric Acetate.

FOAM TABLETS.

Contab (Formula IV)@	Smith Stainstreet & Co., Ltd., 18, Convent Street, Calcutta.	Chloramine-T.
Durafcen @	Durex Products INC. 684 Broadway, New York, 12. N. Y. (M/S. Biddle, Sawyer & Co., India (Private) Ltd., 25 Dalal Street, Fort Bombay.)	3½% P-Triisopropylphenoxy-polyethoxyethanel 0.1% p-propylhydroxy benzoate.

Name	Manufacturer/Importer	Spermicidal Agent
Planitab.	Hind Chemical Ltd., Sircar Road, P.B. 227. Kanpur.	Pyridine mercuric chloride.
Sampoon.%@	Nipon Eisai Co., Ltd., 88 Jakenha yache, Bunkye, Ku, Tokyo, Japan (Shah & Jani C/O Andre Labo- ratories Aidun Building, 1st Dhobitalao Lane, Bombay-2.)	Phenylmercuric acetate.
Volpar.*	British Drug Houses, London, (British Drug Houses (India) Private Ltd., Imperial Chemical House, Bombay-1.)	Phenylmercuric acetate.

%As the foam produced with one tablet seems to be insufficient, hence 2 tablets instead of one are advised.

*Storage quality reported to be unsatisfactory for the present.

@ These foam tablets can be used in places having a high humidity.

Category II.

Foam tablets which satisfy keeping qualities for unsealed tubes at 89% humidity for 3 months.

Durafoam	Durex Products INC. 684 Broadway, New York 12, N.Y. (M/S. Biddle Sawyer & Co., India (P.) Ltd., 25 Dalal Street, Fort, BOMBAY.	3½% P-Tiisoprop lphenoxy-polyetho- xyethanel 0.1% p-propylhyproxy- benzoate.
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Contab (For- Smith Stainstreet & Co. Ltd., Chloramine-T.
mula IV) tab- 18 Convent Street, Calcutta.

lets.

Mycone.	Allied Laboratories Ltd. 140 Park Lane, London W.1 (Dr.Jai Singh's Son & Co. Private Ltd. 18/4 Asaf Ali Road, P. O. Box 457, New Delhi.)	Phenylmercuric acetate.
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Sampoon.	Nipon Eisai Co., Ltd., 88 Jaken- hyache, Bunkye Ku, Tokyo, Japan (Shah & Jani C/o Andre Labo- ratories, Aidun Building, 1st Dhobi- talao Lane, Bombay-2).	Phenylmercuric acetate.
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Category III.

Pastes, jellies and suppositories, including foam tablets which in the opinion of the Contraceptive Testing Unit reach the required level of spermicidal tests and which have been found reliable and harmless by prolonged use at the family planning centres approved for this purpose.

No contraceptive has yet been placed by the Contraceptive Testing Unit in this Category.

Pastes, jellies and suppositories which in the opinion of the Family Planning Association, London, reach a satisfactory level of spermicidal efficiency by laboratory tests and which have been found reliable and harmless by prolonged use at Family Planning Association Clinics and/or laboratory tests have been approved provisionally for use and include the following :—

Name	Manufacturer/Importer	Spermicidal Agent
PASTES & JELLIES.		
Volpar Paste. b.c.	British Drug Houses, London. (British Drug Houses (India) Private Ltd., Imperial Chemical House, Bombay-1.)	Phenylmercurio acetate.
G. P. Ointment. b.	Gilmont Products Ltd., Tileyear Road, York Way, London No. 7.	Hexylresorcinol.
**G. P. Jelly No. 479. a.	- do -	- do -
Dura-creme. b.	London Rubber Co., Ltd., Hall Lane, Chingford, London, E. 4. (M/s. L.D. Seymour & Co., Ltd., Mereweather Road, Apollo Bunder, Bombay.)	Hexylresorcinol.
Ortho Creme. b. c.	Ortho Pharmaceutical Ltd., Lane End, High Wycombe, Bucks, England. (M/s. Imperial Chemical Industries (India) Private Ltd., P. B. 310, Bombay-1.)	Ricinoleic Acid and Sodium Lauryl Sulphate.
Orthogynol Jelly. a. c.	- do -	Ricinoleic acid and p-diisobutylphenoxypolyethoxyethanol.

**Known in some Family Planning Association Clinics as "H.R. Jelly."

Name	Manufacturer/Importer	Spermicidal Agent.
Prentif Spermicidal Compound.	Prentif Ltd., Long's Court, St. Martin's Street, London W.C. 2. (M. Valab & Co., Botwala Chambers, 4 Sir P. M. Road, Fort, Bombay-1.)	Hexylresorcinol.

SUPPOSITORIES.

Gynomim. e.	Coats & Cooper Ltd., Fyramid Works, West Drayton, Middlesex, England.	Sodium p-toluene-sulphonchloroamide.
Volpar Gels. d.	British Drug Houses Ltd., Graham Street, City Road, London N. 1. (British Drug Houses (India) Private Ltd., Imperial Chemical House, Bombay-1.),	Phenylmercuric acetate
G.P. Solubles. d.	Gilmont Products Ltd., Tileyard Road, York Way, London No. 7.	Hexylresorcinol.
Prentif Gels. d.	Prentif Ltd., Long's Court, St. Martin's Street, London, W.C. 2. (M. Valab & Co., Botwala Chambers, 4 Sir P. M. Road, Fort, Bombay-1.)	- do -

(a) Products which are also lubricants.

(b) Products in form of paste or cream.

(c) Sold with applicator.

(d) Non-greasy gels.

(e) Foaming tablets can be used in tropics and are less sticky than suppositories with a glycerin-gelatin base.

Notes.

1. The Contraceptives containing hydroquinone and quinoline and its derivatives should not be used as they are not considered harmless at present.
2. Clinics should report immediately to this Directorate if any untoward effects are noticed.
3. G.P. Solubles are not suitable for use in tropical climate as they do not withstand temperatures higher than 98.4°.

4. "DURAFOAM Tablets are quite stable at temperatures of 40° centigrade for long periods of time—for two years or more. It is, therefore, suggested that they may be stored at temperatures below 40° centigrade. They will withstand for a number of months temperatures much higher so that in the period when they are distributed to a patient whose home in the hot season may be appreciably warmer they will nevertheless remain stable; however, as the temperature goes up, especially above 50° centigrade, there is some danger of a gradual reduction in foaming power. The spermicidal ingredient, however, is not affected by 50° temperature or higher temperatures."

Pastes, jellies and suppositories including foam tablets which, in the opinion of the F.P.A., London, reach the required level of spermicidal efficiency by laboratory tests. No tests for harmlessness have been done by the Contraceptive Testing Unit, Bombay, on these contraceptives. They will be recommended for use after cap tests at the Contraceptive Testing Unit are found satisfactory.

PASTES & JELLIES.

Name	Manufacturer/Importer	Spermicidal Agent
Antemin. b.	Coats & Cooper Ltd., Pyramid Works, West Drayton, Middlesex, England.	Trioxymethylene and Sodium Dioctyl sulphesuccinate.
Contraceptalene. a.	Lamberts (Dalston) Ltd., 200/2 Queensbridge Road, Dalston, London, E. 8.	Lactic Acid Boric Acid.
Rendell Creme. b.c.	W. J. Rendell Ltd., Ickleford Manor, Hitchin Herts, England. (M/s. Framjee & Son, Nanjee Buildings, Horniman Circle, Fort G.P.O. Box No. 542, Bombay.)	Hexylresorcinol.
Penotrane. b.c.	Ward Blenkinsopp & Co., Ltd., 37, Queen's Square, London, W. C. 1. (M/S. Ward Blenkinsopp & Co. (India) Ltd., 1/110, Haines Road, Bombay-18.)	Phenylmercuric dinaphthylmethane disulphonic acid.

Name	Manufacturer/Importer	Spermicidal Agent
SUPPOSITORIES		
Bymeston. e.	Lamberts (Dalston) Ltd., 2002, Queen's Bridge Road, Dalston, London, E.8.	Chloramine-T.
Bircon. e.	Hall London Rubber Co., Ltd., Hall Lane, Chingford, London, E. 4.	Chloramine-T.
Rendell Gels. d.	W.J. Rendell Ltd., Ickleford Manor, Hitchin Herts, England. (M/s. Framjee & Son, Nanjee Building, Horniman Circle, Fort, G.P.O. Box 542, Bombay.)	Hexylresorcinol.
Rendell Foam. e.	W.J. Rendell Ltd., Ickleford Manor, Hitchin Herts, England. M/s. Franjee & Son, Nanjee Building Horniman Circle, Fort, G. P. O. Box 542, Bombay.)	Zinc Phenol Sulphonate.
Mycon. e.	Allied Laboratories Ltd., 140 Park Lane, London, W. 1. (Dr. Jai Singh's Son & Co., (Private), Ltd., 18/4 Asaf Ali Road, P. O. Box No. 457, New Delhi.	Phenylmercurio acetate.
NON-SPERMICIDAL LUBRICANTS		
K. Y. Jelly.	Johnson & Johnson Ltd, Bath Road, Slough, Bucks, England. (M/s Imperial Chemical Industries (India) Private Ltd., P. O. Box 9099, Calcutta.	
Durol.	London Rubber Co., Ltd., Hall Lane, Chingford, London, E. 4. (M/s. L. D. Seymour & Co., Ltd., Mereweather Road, Appollo Bunder, Bombay.)	
Prentif Surgical.	Prentif Ltd., Long's Court, St. Martin's Street, London, W. C. 2. (M. Valab & Co., Botawala Chambers, 4 Sir P. M. Road, Fort, Bombay-1.)	

- (a) Products which are also lubricants.
- (b) Products in form of paste or cream.
- (c) Sold with applicator.
- (d) Non-greasy gels.
- (e) Foaming tablets can be used in tropics and are less sticky than suppositories with a glycerin-gelatin base.

RUBBER AND PLASTIC APPLIANCES

Name	Manufacturer	Importer
OCCLUSIVE CAPS/DIAPHRAGMS		
1. Cavical ("Racial")	Constructive Birth Society 108, Whitfield St., London W. 1.	
2. Vimule Caps.	A. Lambert & Co., 16, Dalston Lane, London, E. 8.	
3. Dutch Dumas type (5 sizes) Cervical.	Lamberts (Dalston) Ltd., 200/2, Queensbridge Road, London, E. 8.	M/s. British Drug Houses (India) Private Ltd., Imperial Chemical House, Bombay.
4. Dutch Caps (Durex) flat or spiral spring.	London Rubber Co., Hall Lane, Chingford, London, E. 4.	-do-
5. Cervical Caps (Check pessaries Durex)	-do-	M/s. L. D. Seymour & Co; Ltd., Mereweather Road, Appollo Bunder, Bombay.
6. Vaginal Diaphragma, latex, spiral spring. (Dutch cap type.)	Ortho Pharmaceutical Ltd., Lane End, High Wycombe, Bucks, England.	M/s. Imperial Chemical Industries (India) Private Ltd., P. B. 310, Bombay-1.

Name	Manufacturer	Importer
7. Plastic caps: Dumas type (5 sizes)	Lamberts (Dalston) Ltd., 200/2, Queensbridge Road, Dalston, London, E. 8.	M/s. British Drug Houses (India) Private Ltd., Imperial Chemical House, Bombay.
8. Vaginal Diaphragms, latex spiral spring (Dutch cap type) "Prencaps" (Dumas type) Cervical Caps. "Cercap", cavity rim; Seamless Dome.	Prentif Ltd., Long's Court, St. Martin's Street, London, W. C. 2.	M. Valab & Co., Botwala Chambers, 4 Sir P. M. Road, Fort, Bombay-1.
9. Durex.	Durex Products, 684 Broadway, New York 12. N.Y., U.S.A.	M/s. V. Sharma & Co., Behind State Bank, Chandni Chowk, Delhi-6.
10. Koromex	Holland Randoz Corp., New York, U.S.A.	Herbans Ltd., Prospect Chambers, Hornby Road, Bombay-1.
11. Kemi	Kemi Products Corp., N.J., U.S.A.	Bombay Surgical Co., Charni Road, Bombay-4.
12. Check Pessaries	Rubber Industries (India) Ltd., 243 Abdul Rehman Street, Bombay-3.	
13. Cooper	Whittaker Laboratories INC. 848 Washington Street, Peekskill, New York.	Dr. Jai Singh's Son & Co., Private Ltd., 18/4 Asaf Ali Road, P. O. Box. 457, New Delhi.

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