acnment 1.

Date _____

ETHICAL REVIEW COMMITTEE, ICDDR,B.

Principal Investigator Dr. Brian Seaton
Co-investigators; Dr,J,F,Phillips and P, Claquin
Trainee Investigator (if any) _____
Application No. 81-022
Supporting Agency (if Non-ICDDR,B) _____
Title of Study Reproductive Endocrinology in Relation to Contraceptive Safety in Bangladesh.
Project status:
(✓) New Study
( ) Continuation with change
( ) No change (do not fill out rest of form)

Circle the appropriate answer to each of the following (If Not Applicable write NA).

1. Source of Population:
   (a) Ill subjects (Yes) No
   (b) Non-ill subjects (Yes) No
   (c) Minors or persons under guardianship Yes (No)
2. Does the study involve:
   (a) Physical risks to the subjects Yes (No)
   (b) Social Risks Yes (No)
   (c) Psychological risks to subjects Yes (No)
   (d) Discomfort to subjects Yes (No)
   (e) Invasion of privacy Yes (No)
   (f) Disclosure of information damaging to subject or others Yes (No)
3. Does the study involve:
   (a) Use of records, (hospital, medical, death, birth or other). (Yes) No
   (b) Use of fetal tissue or abortus Yes (No)
   (c) Use of organs or body fluids (Yes) No
4. Are subjects clearly informed about:
   (a) Nature and purposes of study (Yes) No
   (b) Procedures to be followed including alternatives used (Yes) No
   (c) Physical risks (Yes) No
   (d) Sensitive questions (Yes) No
   (e) Benefits to be derived (Yes) No
   (f) Right to refuse to participate or to withdraw from study (Yes) No
   (g) Confidential handling of data (Yes) No
   (h) Compensation &/or treatment where there are risks or privacy is involved in any particular procedure (Yes) No
5. Will signed consent form be required:
   (a) From subjects Yes No
   (b) From parent or guardian (if subjects are minors) Yes No
6. Will precautions be taken to protect anonymity of subjects (Yes) No
7. Check documents being submitted herewith to Committee:
   ___ Umbrella proposal - Initially submit an overview (all other requirements will be submitted with individual studies).
   ✓ Protocol (Required)
   ✓ Abstract Summary (Required)
   ✓ Statement given or read to subjects on nature of study, risks, types of questions to be asked, and right to refuse to participate or withdraw (Required)
   ✓ Informed consent form for subjects
   ___ Informed consent form for parent or guardian
   ✓ Procedure for maintaining confidentiality
   ✓ Questionnaire or interview schedule *

* If the final instrument is not completed prior to review, the following information should be included in the abstract summary:
1. A description of the areas to be covered in the questionnaire or interview which could be considered either sensitive or which would constitute an invasion of privacy.
2. Examples of the type of specific questions to be asked in the sensitive areas.
3. An indication as to when the questionnaire will be presented to the Cttee. for review.

I agree to obtain approval of the Ethical Review Committee for any changes involving the rights and welfare of subjects before making such change.

Brian Seaton
Principal Investigator

Trainee

81-022
Rec'd 27/5/8

SECTION I - RESEARCH PROTOCOL

1. Title: Reproductive Endocrinology in Relation to Contraceptive Safety in Bangladesh.

2. Principal Investigator: Brian Seaton

3. Co-Investigators: James F. Phillips & Pierre Claquin

4. Starting date: June 1981

5. Completion date: December 1982

6. Total direct cost:

June - December 1981	$153,837
Jan. - December 1982	$ 91,396

Total: $ 245,233

7. Incremental cost:

June - December 1981	$ 48,329
Jan. - December 1982	$ 57,626

Total: $ 105,945

8. Scientific Program Head:

This protocol has been approved by the Community Services Research Working Group, as described in Dr. M.M. Rahaman's attached letter.

*Signature of Scientific Program Head: [signature]

Date: 22/5/81

*This signature implies that the Scientific Program Head takes responsibility for the planning, execution and budget for this particular proposal.

9. Abstract Summary:

The introduction of modern, western, hormonal contraceptives into the less-developed countries, and particularly the poorer rural areas of those countries, raises certain qeustions about the interactions between contracepitve use and chronic ill-health (particularly malnutrition and diarrhoea) and the consequences of those interactions in terms of the effectiveness and safety of contraceptive use.

...../

This protocol provides an integrated program for the study of the clinical and epidemiology aspects of the side-effects of contraceptive use and the comparative endocrinology of contraceptive use by women whose general health status is low (by western standards).

10. Reviews:

a) Ethical Review Committee: _____

b) Research Review Committee: _____

c) Director: _____

d) BMRC: _____

e) Controller/Administrator: _____

International Centre for Diarrhoeal Disease Research, Bangladesh

Memorandum

TO Dr. Stan D'Souza
Program Head, CSRWG

FROM M. Mujibur Rahaman
Program Head, NWG

DATE 21.5.1981

SUBJECT Protocol entitled "Reproductive Endocrinology in Relation to Contraceptive Safety in Bangladesh By Dr. B. Seaton and other

The above protocol was discussed during the absence of both you and Dr. Greenough. As you may notice from the minutes of the meeting that the Working Group gave an approval to the protocol in principle. It was realised that the protocol had been extensively reviewed at earlier meetings including the one where W.H. Mosley was also present. The suggestions made are reportedly incorporated in the protocol.

The group felt that this approval did not include financial commitments as the fund requested was considerable and that this should be decided by the Program Head and the Director.

The possibility of persuing outside financing was also discussed and the P.I. was strongly advised to go ahead to look for a suitable agency.

MMR:ok

c.c: Dr. W.B. Greenough
Dr. B. Seaton
Mr. Shafiqul Islam

Summary of Ethical Issues for Ethical Review Committee

It is rapidly becoming widely accepted that studies on the effectiveness and safety of hormonal contraceptives may not give an accurate indication of the consequences of contraceptive use by women in the less-developed countries where the general health status is much lower. Similarly animal models can provide only limited information which is directly relevant. Hence the need to conduct research directly amongst the population of acceptors and potential acceptors.

Since the ICDDR,B has been at the forefront of developing non-invasive methods for studying reproductive endocrinology the proposed studies do not involve any risks to the patients other than those associated with contraceptive use. No subjects will be requested to accept contraceptives solely for the purpose of the research program; only those subjects who are voluntarily accepting contraceptives for the purpose of regulating their fertility will be studied.

This protocol, together with its sister protocol "The Community Health Services Project, Matlab" provides a comprehensive system of patient monitoring and referral to competent paramedics, physicians and family-planning specialists to ensure that any undesirable side-effects are quickly detected and effectively managed.

All subjects will be identified by a code number. The link between the code-number and the patient identity will be kept separately from the data and will be accessible only to the senior investigators and the field-workers responsible for day-to-day patient care on an individual basis.

Since there is no risk to the subjects, and all subjects will benefit from closer medical attention, a consent form will not usually be required. However, where a study involves a degree of inconvenience to the subject (eg. the necessity to collect samples regularly or to attend a centre for anthropometric measurements) informed consent will be obtained using the attached form. All subjects will be kept fully informed of the nature and purpose of the study and all questions will be answered except in the compliance study where subjects will not be informed that we are monitoring their compliance since this would necessarily prejudice the results of the study. Permission for the witholding of information in this way has been given previously by the ERC (vide the memorandum dated 4-10-79, 15-11-79, 30-11-79 and 6-12-79.

The interviews required will consist if simple clinical and menstrual histories and will not normally take more than 2-5 minutes.

The individual will benefit from closer medical attention and the community will benefit from safer and more effective contraceptive programmes.

Medical histories (including records of hospitalisation, where appropriate) will be required from all subjects. Selected subjects for certain studies will give saliva and usine samples. Occasionally blood samples may be required; where necessary these will be obtained by venepuncture in the usual way by a physician or suitably trained paramedic.

SECTION II: RESEARCH PROTOCOL

A. INTRODUCTION

1) Objectives

This protocol addresses the need to monitor and evaluate safety issues in the "Community Health Services Project, Matlab" (protocol no. 80-042).

The objective of this protocol is to provide both clinical and technical (i.e physiological and endocrinological) evaluations of the consequences of contraceptive use in Bangladeshi women in order to minimise the risks of undesirable side-effects associated with contraceptive use and thereby to improve the safety, acceptability and effectiveness of Family Planning programs.

2) Background

In Bangladesh as in many other less-developed countries, the interrelated problems of high birth-rate, over-population, malnutrition, chronic illness (particularly diarrhoeal diseases) and high morbidity/mortality are widespread causing a great deal of misery and impeding the development of the nation. The casual relationships between the various factors is still a matter of controversy (1), for example--does high birth-rate inevitably lead to high mortality or does high mortality inevitably lead to high birth rate? Examination of demographic trends in other societies produces conflicting theories: for many years it was commonly held that a decline in mortality was an essential prerequisite for a decline in birth-rate (2). However, more recent studies, including data emerging from the Matlab MCH-FP program (3) have shown that there can be a substantial decline in birth-rate which is not only not preceded by a drop in mortality, but is not even accompanied by a drop in mortality.

What is becoming widely accepted is the hypotheses that the various factors need to be tackled simultaneously in an integrated program in order to optimise the effectiveness of the various interventions (4).

Thus, studies on the physiology and endocrinology of the interactions between hormonal contraceptive use and diarrhoeal diseases and malnutrition are very appropriate and relevant within the overall mandate of the ICDDR,B.

Modern contraceptives, whether they be oral contraceptives (OCs), injectable contraceptives such as depo-medroxcy progesterone acetate (DMPA) or intrauterine devices (IUDS) have all been based on an understanding of reproductive physiology and endocrinology derived from research on women in the developed countries, particularly of Europe and the USA. Furthermore, the mode of action of the contraceptives has been optimised to suit the physiological characteristics and socio-cultural norms of those women. For example: a typical western woman has a reproductive life-span of approximately 33 years during which time she would typically have 3 pregnancies of 9 months duration, each followed by a short period of amenorrhoea of approximately 2 months duration. Thus, out of 33 years all but 33 months are spent in regular menstrual cycles. It is therefore hardly surprising that the menstrual cycle has come to be regarded as the "normal" endocrinological state for women with pregnancy occuring as an occasional "interruption" (5). The typical Bangladeshi women, however, has a birth interval of 36 months composed of 9 months gestation, 18 months of lactational amenorrhoea and only 9 months of recurring menstruation, often of irregular cycle length (6). Thus a Bangladeshi women typically spends only 25% of her reproductive life in recurring menstruation in contrast to a western woman who typically spends more than 90% of her reproductive life in menstruation. It is interesting to note that throughout the animal kingdom very few species in their natural environment exhibit extended periods of regularly recurring estrous. In most species the female is either pregnant or in lactational/seasonal anestrous. It can therefore be argued that regularly recurring estrous/menstruation is, in fact an artefact of domestication/ developed-cultures and that in evolutionary terms the primary and normal function of female reproductive endocrinology is the maintenance of pregnancy and lactational amenorrhoea and that it is recurring estrous/menstruation which is the "interruption" of the normal pattern.

This distinction has a significance beyond mere semantics in the context of the introduction of western contraceptives into Bangladesh (and similar environments) since it means that one must seriously consider the endocrinological and related consequences of forcing a transition from the natural reproductive pattern to an artificial one. In addition there are the significant pharmacological implications of using potent drugs at dose-levels intended for western women whose body weight is 30-50% higher and general health status considerably better than that of Bangladeshi women. Finally there are the psychological implications of imposing different socio-cultural norms through alien schemes of medication.

The Issue of Safety

Despite the fact that they are some of the most widely and thoroughly tested drugs available, hormonal contraceptives, both DMPA and OCS, are still the centre of intense controversy about their safety (7,8). Several factors contribute to this controversy, not all of them amenable to scientific study; (a) there are some groups who oppose any forms of contraception on religious or moral grounds; (b) pregnancy is a self inflicted condition and abstinance from intercourse is 100% effective at preventing pregnancy and totally safe (if totally unacceptable in the majority of cases); (c) there is a wide variety of contraceptive methods available which vary considerably in their effectiveness, particularly those which are self-administered (e.g. condoms, foams, OCs); (d) personal preference is a powerful force which can, and often does, completely override rational evaluation; (e) pregnancy is a natural and desirable state essential for the propogation of the species hence, whilst temporary contraception is desired by many, permanent contraception (e.g. by sterilisation which is relatively safe and free from side-effects) is acceptable only to those who are sure that they have completed their desired families.

Since contraceptive safety is a relative concept, the result of balancing the benefit and advantages of contraception against the risks and disadvantages of pregnancy it is inevitable that perceptions of contraceptive safety will be influenced by a diverse range of factors such as (a) socio-cultural views on the role of children as economic providers during parent's old age; (b) availability and quality of ante-and post-natal health-care services; (c) a comprehension of the principles of prophylactic medicine; (d) the effects of chronic ill-health on the pharmacology of contraceptive drugs. It is clear that the contributions of the above factors in the evaluation of the risk/benefit ratio in the Bangladesh context will be substantially different to those in western societies. For example, it has been argued (18) that, in Bangladesh, the virtual absence of effective ante and post-natal care services and consequent high risk of maternal mortality completely dominates the risk/benefit in favour of contraceptive use, particularly against the background of the social risks of uncontrolled population growth. Whilst this view is widely accepted it does not mean that other factors, such as the effect of chronic ill-health on the pharmacology of contraceptive use, are irrelevant and, in particular, it does not mean that contraceptive programs are absolved from the moral and ethical responsibility to investigate and attempt to minimise any adverse effects due to such factors.

The Fundamental Hypothesis

The fundamental hypothesis underlying this protocol is that chronic ill-health (particularly malnutrition and diarrhoeal disease), such as is prevalent amongst contraceptive acceptors of low socio-economic status

in rural Bangladesh, has a significant effect on the pharmacology of hormonal contraceptives which, in turn, has a significant effect on the risk/benefit ratio, or safety, of contraceptive use in such population. Hence, research in all relevant areas (clinical, epidemiological, endocrinological is essential for the development and successful implementation of MCH-FP programme.

Previous Studies

A detailed review of the interrelationships between reproductive endocrinology, ill-health and population has been presented previously in a support document entitled "Reproductive Endocrinology in Bangladesh: The Nutritional and Demographic Context". That review is still valid and is attached as Appendix A as part of this protocol.

There have been very few systematic studies on the effects of malnutrition on contraceptive use. Recent data from research in India (9-11) show that nutritional status, as assessed by anthropometric measurements, influences the pharmokinetics of the systematic steroids used in oral contraceptives. However, even in those studies the average mid-arm skin-fold thickness was 15.2 mm, as compared to 11 mm in a group of poor women in Nandepara (a village on the outskirts of Dacca). In the Indian studies only two women had mid-arm skin-fold thickness of less than 10 mm and in each case their pharmokinetics were dramatically different to the remainder of the group.

The predecessor to this protocol, a protocol entitled "Endocrinological Factors in relation to Reproduction in Bangladesh" (78-008) studied the levels of progesterone, LH, FSH, N-acetyl-B,D-glucosaminidase and glucose throughout the menstrual cycles of women of low socio-economic status in Nandepara. The data from that study have been very encouraging and entirely consistent with the fundamental hypothesis. The studies on salivary glucose and N-acetyl-B,D-glucosaminidase have indicated that, while these substances show some variations during the menstrual cycle, the patterns of variations are not sufficiently consistent to permit a reliable estimation of the time of ovulation as has been previously suggested (11,12).

The hormonal data from the study indicate that approximately 70% of the menstrual cycles had hormonal patterns which were "abnormal" by comparison with the "normal" pattern for western women (e.g. 13,14). At present the data are insufficient to demonstrate a clear casual relationship between chronic ill-health and abnormal endocrinology but they are more than adequate to indicate that the hypothesis is valid and merits further investigation. Of particular interest is the observation that abnormally low progesterone levels frequently occur in the later part of the cycle and are indicative of luteal insufficiency or anovulation. In the former case, conception (i.e. fertilisation of the ovum would occur) but, even if

implantation took place, there would be inadequate priming of the uterus to sustain pregnancy and an early spontaneous abortion would occur. Since the bleeding associated with such an abortion may occur only a short time after the normal period were due it might not be recognised as an abortion but thought to be a delayed and abnormally heavy menstruation.

Previous studies (15,16) have indicated a high incidence of fetal wastage in the second month of pregnancy. However, the pregnancy detection method and the frequency of sampling (1 month) used in that study would not permit identification of pregnancy at a very early stage (i.e. within 7-10 days of conception) and hence would not identify fetal wastage associated with only slightly delayed menstruation).

Studies on this phenomenon are important for several reasons (1) a high incidence of very early fetal wastage could explain the relatively low fecundity of Bangladeshi women; (2) such occurrences have to be taken into account in interpreting menstrual cycle data; (3) if the probability of luteal insufficiency were critically dependent on health-status it could explain seasonal variations in fecundity; (4) such factors would have to be taken into account when evaluating return-to-fertility data following discontinuation of contraceptives; (5) it may explain the usually high incidence of hydatiform role in Bangladeshi women.

There have been few, if any, studies on the effects of chronic ill-health on reproductive endocrinology and the pharmacology of hormonal contraceptives in the developed countries. This is probably due to the fact that such studies would be unethical there since they would necessitate the induction or perpetuation of chronic malnutrition in study subjects. In the less-developed countries few institutions have the technical capability or operational capacity to undertake such research.

An Integrated Approach to Contraceptive Safety in Less-Developed Countries

Contraceptive safety research can be conveniently divided into two broad areas; (1) clinical and epidemiological studies; (2) endocrinological and contraceptive technology studies. Clinical and epidemiological studies seek to identify the conditions and syndromes which occur as side-effects to contraceptive use, to determine their frequency and to assess their morbidity and mortality risk. Endocriological and contraceptive technology studies seek to identify the causal relationships between contraceptive use and its side-effects in order to improve the technologies to mitigate or eliminate the side-effects, or to devise criteria whereby patients who are specially succeptible to side-effects can be simply identified in order that appropriate measures may be taken. Whilst these two areas of research can be, and often are, undertaken separately they are clearly complementary and it is therefore mutually beneficial if both areas are studied jointly in an integrated program. The ICDDR,B has substantial relative advantage to

undertake such research since it is not only located in a less developed country and has expertise in malnutrition and diarrhoeal disease (two of the most common causes of chronic ill-health likely to affect contraceptive use) but it also has the technical capability and operational capacity to undertake research in both the clinical/epidemiological and endocrinological areas.

Central Services and Ancillary Studies

Many of the relevant questions in contraceptive safety can be approached as discrete studies, both in the clinical/epidemiological area and the endocrinological area provided that they are adequately integrated into an overall program. In particular the various discrete studies require a common data base of demographic, clinical, socio-economic and nutritional information on contraceptive users and an appropriate control group, plus a laboratory capacity to perform the relevant endocrinological and biochemical determinations. Furthermore, even in the absence of specific studies in contraceptive safety such services are desirable, if not mandatory, on ethical grounds to provide clinical monitoring and diagnostic services for contraceptive acceptors so that emergent safety issues can be quickly identified and appropriate responses made.

In order to ensure proper integration of the discrete studies, in particular the continuity and standardisation of data collection, data processing and endocrinological diagnostic services, this protocol is structured as providing central services for data collection and processing and endocrinological and biochemical determinations, around which ancillary studies are attached, not as independent entities but as a group of modules which together make an integrated program. These ancillary studies will not necessarily be undertaken simultaneously and other ancillary studies may be integrated into the program as necessary.

The following ancillary studies are proposed as relevant to the overall objectives of the protocol:

1) Incidence of side-effects in contraceptive acceptors. This study will be an on-going evaluation of the epidemiology of side-effects in contraceptive users for both scientific and ethical reasons. Special attention will be given to monitoring the incidence of side-effects in DMPA acceptors. DMPA still has only the status of an experimental drug in Bangladesh and may therefore only be used under the direction of a physician for research purposes. A particularly pertinent review of the safety issues related to DMPA has been made by Rosenfield & Maine and is attached as Appendix B to this protocol. The review particularly indicates that morbidity and mortality risks due to cancer and the risks of induced infertility are exceedingly low, if not zero. Thus, it has to be recognised that the relatively small number of DMPA acceptors within the Matlab MCH-FP (approximately 2,500 acceptors) may be too small to permit any statistically significant conclusions to be made (McDaniel was unable to find any significant evidence

for DMPA-induced endometrial cancer in 86,000 women over 13 years of use]. Nevertheless, DMPA acceptors will be closely monitored for the incidence of side-effects, both major and minor.

2] Incidence of side-effects in non-contraceptive acceptors. This study will effectively provide case-controlled data for the previous study. It is tacitly assumed that the side-effects complained of by contraceptive users are actually related to contraceptive use. In fact there is reason to believe that the same complaints are common in non-acceptors and that, as mentioned previously, contraceptive use may only heighten the acceptors' awareness of them. This study will examine the incidence of such complaints in non-acceptors.

3] Consequences of non-use of contraceptives. The non-use of contraceptives exposes the persons concerned to risk of pregnancy and, hence, to risk of maternal morbidity and mortality. The degree of risk is clearly an important consideration in evaluating the overall risk/benefit ratio of contraceptoye use. This study will evaluate the morbidity and mortality rate of pregnancy.

4] Oral contraceptive compliance. One of the major problems of oral contraceptive use, even in the developed countries, is forgetfullness in taking the pill regularly. Literate women who fully understand the principles of prophylactic medicine are highly motivated to take the oral contraceptive regularly and well-designed markings on the packet can provide a valuable aide-memoire to guard against inadvertant omissions. Illiterate, uneducated women may not only be less highly motivated but may also be unable to utilise aide-memoires on the packet. Such women are expected to have a high rate of ommissions (non-compliance) which may not only increase the risk of method failure but may also increase the incidence of side-effects. This study will examine the level of non-compliance among OC acceptors and investigate correlations with the level of side-effects.

5) Menstrual patterns in different socio-economic groups. It is well-established that rural Bangladeshi women have more irregular cycles than normal European/USA women. However, casual observations of menstrual cycles in expatriate women living in Dacca suggests that they, too, may exhibit greater irregularity than is considered normal. This study will investigate this phenomenon.

6) Early spontaneous abortions. Data from the predecessor protocol indicate that luteal insufficiency following ovulation may result in a relatively high-incidence of very early spontaneous abortions due to an inability of the uterus to sustain the implanted conceptus in the absence of adequate progesterone levels. This would result in delayed menstruation with, perhaps, rather greater than usual blood-flow but, because the delay may be only days, rather than weeks, it would not be recognised that there had

been a fetal loss. The observation [17] that the incidence of hydatiform mode is 10 times higher in this population than in western populations is also consistent with this phenomenum. This study will investigate this phenomenum.

7] The Endocrinology of the Menstrual Cycle. The predecessor protocol investigated the endocrinology and demonstrated that the hormonal patterns were substantially different from the normal patterns observed in western women. This study will further investigate this phenomenum and, in particular, try to establish the correlations, if any, of hormonal patterns with chronic ill-health.

8] Pharmokinetics of DMPA. This study will investigate the effects of chronic ill-health on the pharmokinetics of DMPA.

In all of the above ancillary studies nutritional status, as assessed by anthropometric measurements and chronic illness as assessed by clinical observations (supported by laboratory investigations where appropriate) will be regarded as determinants of reproductive parameters and will be carefully monitored and controlled for in each study.

The Existing Service System

MCH-FP services in Matlab are implemented in an area of 80,000 people. The main hospital complex acts as a referal centre for the whole area. The area is divided into 4 blocks (designated A,B,C & D) of 20,000 people; each block has its own sub-centre for activities which do not require access to full hospital facilities. Each sub-centre is staffed by a Lady Family Planning Visitor (LFPV), a Male Senior Health Assistant (MSHA) and 20 Community Health Workers (CHWs). The abilities and responsibilities of each may be summarised as follows:

a] Community Health Workers

CHWs are young (aged 30 approx.) married women, with children, and have been selected from the community in which they work. The educational level in class VII or above. At the beginning of the program (early 1978) a 6-weeks training programme was given and on-going formal training is still provided every 2 weeks through meetings of all the CHWs at the sub-centre. Informal, ad-hoc training is provided through regular contact with the LFPV and MSHA at other times. Each CHW is responsible for approximately 1000 people. The CHW's duties include: (1) documentation of demographic events in her area, visiting every family 3 times each month; (2) promotion of contraceptive use by providing information, motivation, service-delivery and follow-up 3 times each month; (3) clinical management of diarrhoeal

disease through promotion of oral rehydration therapy; (4) promotion of tetanus toxoid immunisation for pregnant women; (5) promotion of MCH activities. A particularly important role of the CHW is the referal of clients who are suffering from diarrhoeal disease, the side effects of contraceptive use or other minor symptoms. Clients may be referred either to the sub-centre or to the central facility as appropriate to the nature and severity of the complaint.

b) Lady Family Planning Visitor

LFPVs are qualified through the 18 months courses provided by the Government of Bangladesh. In addition they receive on-going, informal, ad-hoc training from senior ICDDR,B staff. LFPVs are responsible for 1) performing menstrual regulation; (2) inserting IUDs; (3) giving advice on the type of contraception best-suited to the client and performing any necessary clinical and amnestic check-ups; (4) treating minor ailments and referring more complex cases to the central hospital facility; (5) the supervision of CHWs in the field; (6) additional advice to clients in the field.

c) Male Senior Health Assistant

The MSHA collaborates with the LFPV in the supervision of the CHWs in the field and the provision of additional advice and assistance to clients.

d) Senior Clinical and Supervisory staff

In order to ensure that, in the event of side-effects occuring acceptors have access to the best medical care which van reasonably be provided in the circumstances the sub-centres are backed-up by a central hospital facility and an experienced MCH-FP physician at the Matlab centre. The usual procedure is for clients to be referred to the central facility by the CHW, LFPV or MSHA but clients may, and frequently do, attend the central facility or their own accord. The MCH-FP physician and senior supervisory staff also visit the villages regularly to provide on-the-spot back-up to the field workers.

The central hospital facilities are well equipped and staffed under the supervision of the MCH-FP physician. In addition to providing surgical facilities for tubectomy and vasectomy the clinic handles gynaecological emergencies, the treatment of severe or unusual side-effects of contraceptive use and provide an advisory service for clients who want more detailed information or privacy than is available at the sub-centre.

It will be seen that the structure represents a very comprehensive scheme for the delivery,monitoring and supervision of MCH-FP services in the area. For convenience the organisational structure for the monitoring of side-effects and referal of complications is summarised in figure 1.

Rationale

Whilst there is ample evidence to indicate that chronic ill-health (malnutrition and other conditions such as diarrhoea, hepatitis, etc.) affects the endocrinology and physiology of reproduction and, consequently, the risks and benefits of contraceptive use there have been no systematic studies of such phenomena,primarily due to the fact that it would be unethical to create or perpetuate chronic ill-

health in western populations where the bulk of such research is undertaken.

The introduction of western contraceptive technology into developing countries such as Bangladesh where chronic ill-health is endemic thus creates safety issues to the interrelation between contraception and ill-health for which research data are either sparse or non-existent. This protocol seeks to generate the relevant data and thereby to contribute to the effectiveness, efficiency and safety of such contraceptive programs.

B. SPECIFIC AIMS

Central Services

1] To provide demographic/epidemiological, clinical and endocrinological services as a basic resource for the evaluation of safety issued in relation to contraceptive use in the MCH-FP program. (In additon to their use for the generation of research data, such services may be utilised by clinicians for the treatment of patients.]

2] To develop improved methods of surveillance and clinical diagnoses appropriate to the requirement to provide optimum safety evaluations in accordance with the needs and objectives of the program.

Ancillary Studies

1] To determine the incidence of side-effects in contraceptive acceptors
2] To determine the incidence of "side-effects" (that is, conditions or syndromes similar to those called side-effects in contraceptive acceptors) in non-contraceptive acceptors.
3] To determine the morbidity and mortality risks of pregnancy.
4] To determine the minimum level of non-compliance in acceptors or oral contraceptives.
5] To determine the effects of socio-economic status on menstrual patterns in Bangladeshi and expatriate women.
6] To determine the incidence of early spontaneous abortions.
7] To study the detailed endocrinology of the menstrual cycle.
8] To study the pharmokinetics of DMPA.

In all of the specific aims, the correlation with nutritional status and the effects of chronic ill-health (eg, diarrhoeal disease, hepatitis,etc.) will be of primary importance.

C. METHODS OF PROCEDURE

A. Central Services:

1] Admission Report. An admission report and clinical history will be documented on all new contraceptive acceptors and control-group

For acute conditions (eg. dizziness) the data will be analysed for repetitive complaints by individuals. The usual statistical procedures (eg. life-table analyses) will be used to estimate the risk of the various side-effects.

2) Incidence of "Side-Effects" in Non-Contraceptive Acceptors. A group of about 2,500 women will be selected for study. The criteria for selection will be women who are eligible for contraception (see MCH-FP protocol) but who are not using hormonal contraceptives, (users of barrier methods, eg. condom, diaphragm, may be included in the study). Pregnant women will be excluded or dropped from the study. Non-menstruating lactating women will be excluded if their youngest child is less than 1 year old, otherwise they may be included.

Data evaluation will be the same as for the previous study.

3) Morbidity and Mortality Risk of Pregnancy. In two blocks (A & C; see MCH-FP protocol for detailed description of the blocks) pregnant women will be identified and examined twice (or more frequently if indicated clinically) for blood-pressure, albumun in the urine and clinical symptoms of anemia and toxamia. Any other pregnancy-related conditions will be documented when observed. The regular twice-weekly visits by the CHW will continue, providing additional opportunities for pregnancy-monitoring. At 2 months post-partum an additional check-up will be made.

Any maternal death occurring during pregnancy or the first 3 months post-partum will be carefully evaluated to determine, as far as is possible, the cause of death and the probability that it was related to the pregnancy. The data will be evaluated to give morbidity and mortality rates during the various stages of pregnancy (1st trimester, 2nd trimester, 3rd trimester and post-partum trimester) with a breakdown by cause if adequate data are obtained.

4) Minimum level of Non-Compliance. All oral-contraceptive acceptors will be studied. Regular visits are made to all households every two weeks as part of the ongoing surveillance scheme. On each visit the field worker will request to see the OC packet and will record the number of pills consumed and the number remaining. The field worker will not question the client about her contraceptive use. Analysis of actual number of pills consumed as compared with expected number will indicate the level of compliance. The compliance data will be linked with the side-effects data (ancillary study 1) to examine for correlations between non-compliance and incidence of side-effects.

5) Menstrual patterns in different socio-economic groups. A large number of

women will be studied (up to 1000 if possible) of all nationalities and conditions. Subjects will be recruited from the Traveller's clinic volunteers, ICDDR,B staff, embassy and aid personnel, etc. A simple menstrual history will be taken and the subjects will keep a menstrua-diary (appendices D-1 and D-2) for the duration of the study (or as long as possible). The data will be analysed for (i) mean interval between menstruation; (ii) duration of menses; (iii) occurrence of irregularities (spotting etc.); (iv) mean interval between menstruation for each subject and standard deviation; (v) distribution of intervals between menstruations (all observations); (vi) distribution of subject mean intervals. Subjects will be crudely stratified into 3 socio-economic groups on the basis of total family income (less than Tk. 750 per month, Tk 750 to Tk 5000 per month and more than Tk. 5000 per month). However, it may be expected to be difficult to get reliable information on family income hence some subjectivity in assigning subjects to socio-economic groups is inevitable.

6) Incidence of early spontaneous abortions. Approximately 500 menstrual cycles will be studied. If early spontaneous abortions occur with a frequency of 2% we should observe 10 such occurrences. If early spontaneous abortions occur with a frequency of less than 2% then they can be regarded as a rare event and the hypothesis that early spontaneous abortions occur frequently in the population is regarded as disproved. If early spontaneous abortions occur with a frequency of greater than 2% then an increasing number will be observed and the estimate of the frequency will improve as the number of observations improves. If the frequency rises above 20% (i.e. 100 occurences in 500 cycles) the study will be terminated when 100 observations have been accumulated.

Approximately 100 apparently normal non-contracepting women will be recruited for the study. The women will be aged between 15 and 35, married and currently living with their husbands and desiring additional children for their family.

Saliva and urine samples will be collected weekly, as far as is possible, at the same time on the same day each week. A menstrual history will be recorded by recall over the previous week. The saliva will be assayed for progesterone (to estimate luteal activity) and the uring for BHCG (to detect conception). A standard latex-agglutination pregnancy test (Prepurex will also be used and subjects will be discontinued from the study when two consecutive latex-agglutination tests are observed.

As subjects drop out of the study, either voluntarily or due to confirmed pregnancy, new subjects will be recruited until the requisite number of menstrual cycles have been observed.

All subjects who discontinue due to pregnancy will be followed-up to record the pregnancy outcome.

7) Endocrinology of the Menstrual Cycle. The previous study indicated considerable variability in the endocrinology of the menstrual cycle. This continuation will endeavour to further characterise the hormonal patterns, particularly LH and FSH levels in order to evaluate the role of the pituitary in the control of the menstrual cycle. The subjects will be a sub-group of the previous study and will be purposefully selected on the basis of mid-arm skin-fold thickness, into 3 groups of 10 subjects (low group masf < 10 mm; medium group 10 mm ≤ masf ≤ 15 mm; high group 15 mm < masf). Note that, whilst there is some debate as to whether masf is the most valid indicator of nutritional status, it is certainly a useful indicator and has the advantage of being very easy to determine under field conditions. Weight for height will also be determined, if practicable, as an alternate indicator.

8) Pharmokinetics of DMPA. 15 subjects who are receiving DMPA for the first time will be purposefully selected, 5 in each of the low, medium and high mid-arm skin-fold thickness groups as described previously. Preference will be given to the selection of subjects who have never previously used hormonal contraceptives but, if these cannot be found within a reasonable period of time, subjects who have not used any hormonal contraceptive within the preceeding 2 years may be selected.

Saliva samples will be collected immediately prior to the first injection; 6 hours after the injection; thereafter daily for the first week; then twice weekly for the remainder of the month; then weekly until the next injection of DMPA when the collection regime will reset. Subjects will be followed over 4 successive injections terminating one month after the 4th injection.

All samples will be assayed for DMPA; weekly samples will be assayed for progesterone.

The pharmokinetics of DMPA will be studied using standard multi-compartmental models using computerised least-squares, non-linear curve-fitting procedures. Rate constants will be correlated with (i) anthropometric data, (ii) incidence of side-effects, (3) sequence of injections.

D. SIGNIFICANCE

This study will promote an understanding of the nature and consequences of interactions between contraceptive use and chronic ill-health (particularly malnutrition and diarrhoeal disease]. The information thus obtained can be used as a basis for improving the effectiveness and acceptability of contraceptive programs in areas where chronic ill-health is prevalent.

E. FACILITIES REQUIRED

1) Office space - the existing facilities for the investigators is adequate. However, additional space in Dacca for the clinical endocrinologist and computer programmer will be required and some in Matlab for the clinical endocrinologist and the Field Research Officers.

2) Laboratory space - the existing bench space will be nearly adequate, an additional 6' of bench space may be required.

3) Hospital resources - none

4) Animal resources - none

5) Logistic support - supported by existing transport facilities.

6) Major irems of equipment - ice-maker, refrigerated centrifuges, vortex mixers/evaporators, -counter, B-counter, GLC, spectrophotometer, AA spectrophotometer,fluorescent spectrophotometer, analytical balance. All are available

F. COLLABORATIVE ARRANGEMENTS

1) Dr Diane Riad-Fahmy, Tenovus Institute, Cardiff, Wales
2) Prof. T.A. Chowdhury, IPGMR , Dacca
3) Dr. Pramaun Vieutamasen, Chulalongkorn Medical School, Bangkok Thailand.
4) Dr. Kosin Amatayakul, Research Institite for Health Sciences, Chiang Mai, Thailand.

Matlab or sub-centre.

FIGURE 1 SCHEME FOR THE DETECTION, TREATMENT AND REFERRAL OF CONTRACPETIVE CASES REPORTING PHYSICAL AILMENTS IN MATLAB

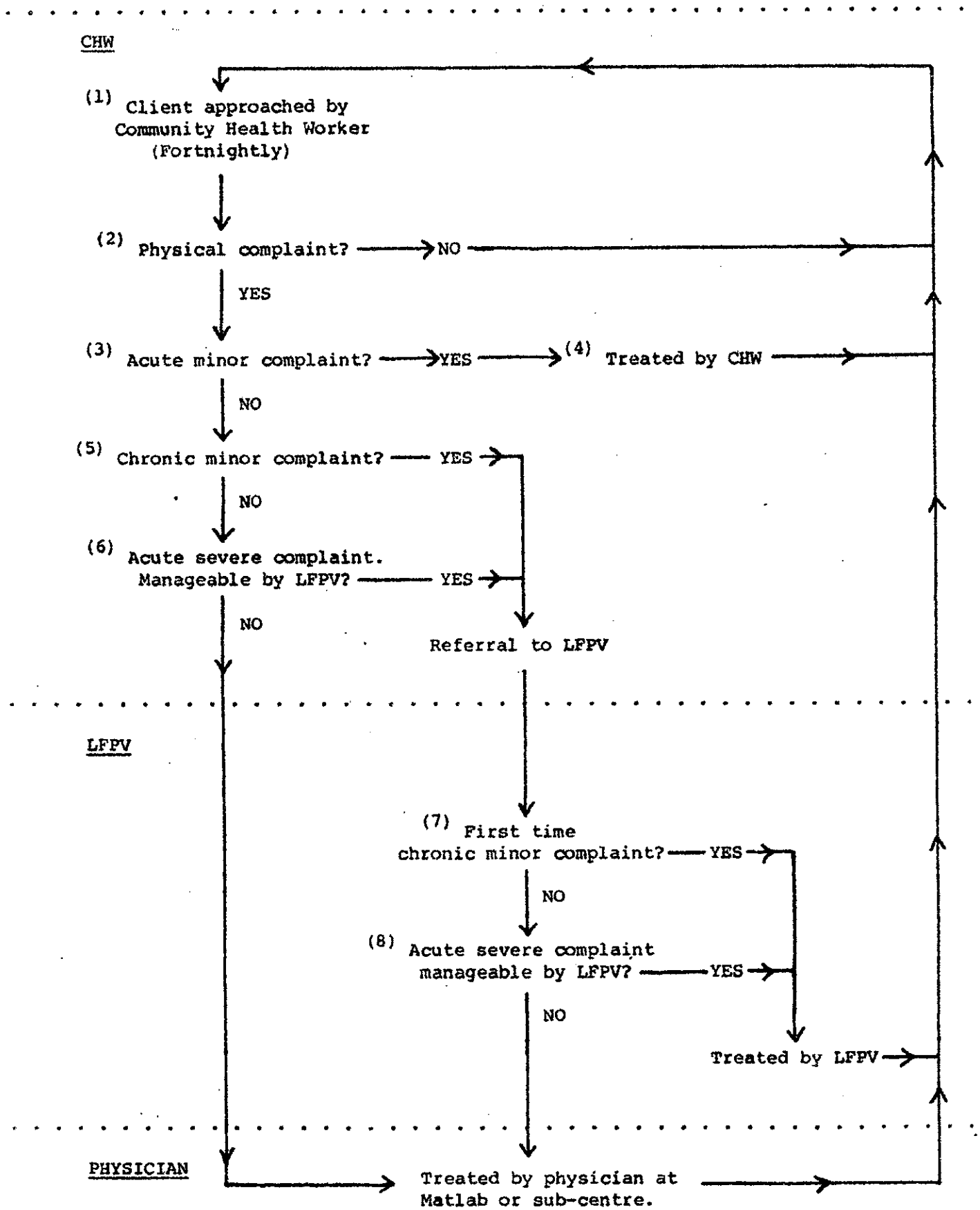

FIGURE 1 DESCRIPTION OF THE SCHEME

1) All women are visited fortnightly by the CHW.

2) All contracepting women are asked if they are experiencing any discomfort. A physical complaint is any ailment which either the CHW or the client has reason to believe might be related to contraceptive use. Whilst the Community Health Services in Matlab cannot deal with all medical problems, particularly those outside the terms of reference of the ICDDR,B, most minor complaints are nevertheless treated by the CHW or referred to LFPVs.

3) An acute minor problem is a complaint which is recent and causes tolerable discomfort. Examples are headache, burning sensation, dizziness, minor pain, menstrual spotting, nausea, anorexia, etc.

4) Acute minor problems are dealt with by the CHW immediately.

5) Persisting minor complaints are refered to the LFPV.

6) Serious complaints are either refered immediately to the LFPV or, if the condition is severe, refered directly to the physician in Matlab without the intervention of the LFPV. CHWs are instructed to refer to the physician immediately any cases of severe or persistent vaginal bleeding, paralysis or post-tubectomy cases with evidence of fever.

7) The LFPV, in turn, makes a clinical assessment to determine whether to refer the case or treat it. Chronic persistent cases such as chronic cough, severe back-ache or intermittant bleeding will be treated by the LFPV on the first presentation but subsequent presentations are refered to the physician.

8) Acute conditions which are manageable by the LFPV (eg. vomiting, lower abdominal pain, bleeding) will be examined and treated if possible but refered in case of doubt, or if the condition is too severe.

Records are maintained of all refered cases and their treatment. All subjects, whether experiencing problems or not, are visited fortnightly. LFPVs visit each village monthly and target their house calls on women who have recently expressed complaints or who have been treated by a physician and require paramedical follow-up. A physician visits each sub-centre fortnightly and sees patients brought to the sub-centre by the CHW at that time.

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Summary of Hormone Assays

1]	Side-effects, acceptors	None
2]	Side-effects, non-acceptors	None
3]	Morbidity/Mortality of pregnancy	None
4]	Oral contraceptive compliance	None
5]	Menstrual patterns	None
6]	Early conceptus wastage	
	500 cycles x 4 samples per cycle x 2 duplicates	4000 (Pr, BHCG)
	500 cycles x 4 samples per cycle	2000 (Preg.test)
7)	Menstrual Endocrinology	
	15 subjects x 4 cycles x 12 samples x 2 duplicates	1440 (Pr, FSH, LH)
8)	Pharmokinetics of DMPA	
	15 subjects x 25 per month x 3½ months x 2 duplicates	2625 DMPA
	15 subjects x 4 per month x 3½ months x 2 duplicates	420 Pr

Totals (including 25% for standards, quality control and wastage)

DMPA	3300
Progesterone	7500
BHCG	5000
FSH	2000
LH	2000
Pregnancy tests	2500

SECTION III - BUDGET

A. DETAILED BUDGET

1) Personnel Services

Name	%	Salary	June to Dec 81	Jan to Dec 82	Yearly Incremental Cost
Dr. Brian Seaton	60	$ 30,000/yr	10,500	19,800	Nil
Dr. James Phillips	10	$ 24,000/yr	1,400	2,640	Nil
Dr. Pierre Claquin	10	$ 39,000/yr	2,275	4,290	Nil
Clinical Endocrinologist	50%	$ 24,000/yr	7,000	13,200	12,000
Senior Research Officer	100%	Tk 5,000/mn	2,333	4,400	Nil
Research Officer (x2)	100%	Tk 3,000/mn	2,800	5,280	2,000
Field Res.Officer(x4)	100%	Tk 2,250/mn	4,200	7,920	7,200
Computer Programmer	100%	Tk 3,000/mn	1,400	2,640	2,400
			31,908	60,170	24,000

Notes: Taka salaries include benefits at 33% of basic pay
10% has been added to the rates for 1982 to allow for inflation.
The clinical endocrinologist is budgeted as a part-time expatriate position as preliminary enquiries indicate that it may be difficult to find a Bangladeshi national for this position.

Taka amounts have been expressed as US$ at the rate of Tk. 15 = US$ 1

2) SUPPLIES AND MATERIALS

	Project Requirement	June to Dec 81	Jan to Dec 82
DMPA reagents	3300@ $0.3/test	445	490
Progesterone reagents	7500@ $ 0.2/test	750	825
BHCG reagents	5000@ $ 1.5/test	3750	4125
FSH reagents	2000@ $ 1.0/test	1000	1100
LH reagents	2000@ $ 1.0/test	1000	1100
Misc reagents		2000	1000
Tubes for -RIA	10000@ $ 50/1000	500	-
Tubes for B-RIA	11000@ $ 90/1000	990	-
Scintillation fluid	50 litres @ $ 20/litre	1000	-
Scintillation vials	12500@ $ 12/100	500	-
Sample collection vials	5000@ $12/100	600	-
Pipettes etc.		1000	1100
Training materials		1500	1000
Stationery and printing		1500	1000
Miscellaneous and contingencies		2000	3000
	Sub-totals	18,535	14,740

3) EQUIPMENT

NE 1612 - counter	26,400
Atomic absorption spectrophotometer	57,200
Low temperature circulator	4,000
	*87,600

*These items have already been provided out of special funds from ODA and JICA.

	Jan to Dec 81	Jan to Dec 82
4) PATIENT HOSPITALISATION	Nil	Nil
5) OUTPATIENT CARE	Nil	Nil
6) CRL TRANSPORT		
Travel to (from Matlab provided under MCH-FP protocol]		
Travel in Dacca		
25 miles/week @ Tk. 3,50/hr = Tk,4550/yr	177	334
5 hrs/week @ Tk, 3,00/hr, = Tk 780	30	57
Sub-totals	207	391
7) TRAVEL AND TRANSPORTATION OF PERSONS		
Attendance at meeting and consultation for PI		
Air travel @ $ 2950 + 15 days @ $ 70	4000	4400
Visiting Consultant		
Air travel @ $ 2950 + 30 days @ $ 35	4000	4400
Visits to/from Bangkok/Chiang Mai		
Air Travel @ $400	400	1200
Per diems @ $40	400	1200
	8800	11200
8) TRANSPORTATION OF SUPPLIES		
Importation of equipment included in (3) above		
Importation of supplies @ 25%	4700	3700
9) RENT COMMUNICATION AND UTILITIES		
@ Tk, 10,000	667	733
10) PRINTING AND REPRODUCTION		
Mimeography 5000 copies/year @ Tk, 0,2	70	77
Xerox 1000 copies/year @ Tk, 0,5	30	33
Sub-total	100	110

11] OTHER CONTRACTUAL SERVICES		
Prof, T,A, Chowdhury, Obst, Gyn, Consultancies (as required, up to Tk, 5000]	320	352
Computer time IBM System 34	Rates not available	
12] CONSTRUCTION, RENOVATION AND ALTERATIONS		
Almirahs, godown for solvents and special supplies	1000	Nil

B. SUMMARY BUDGET

		Jan to Dec 81	Jan to Dec 82
1)	Personnel services	31908	60171
2)	Supplies and materials	18535	14740
3)	Equipment	87600	-
4)	Patient Hospitalisation	-	-
5)	Outpatient care	-	-
6)	CRL Transport	207	391
7)	Travel and Transportation of persons	8800	11200
8)	Transportation of supplies	4700	3700
9)	Rent, communication, utilities	667	733
10)	Printing and Reproduction	100	110
11)	Other contractual services	320	352
12)	Construction, Renovation and alteration	1000	-
	Totals	153,837	91396
	Less cost of capital equipment already provided	66,237	91396
	Less salaries of current personnel	48,329	57626
	Total Project cost (Incremental)	$ 105,945	

Reproductive Endocrinology in Bangladesh: The Nutritional and Demographic Context

Brian Seaton Cholera Research Laboratory February 1978

The commonly held notion that the biology of human reproduction is invariant between different geocultural groups has, in recent years, been increasingly recognized as a misconception. Whilst many of the components of the reproductive process are similar or identical for all women some striking differences exist. This is particularly apparent in the reproductive pattern of typical low socio-economic/nutritional status women in Bangladesh (fig.1) where major differences exist between the relative amounts of time spent in the menstrual, gestational and amenorrheal phases of the reproductive process as compared to women in more developed countries (fig. 2). It is therefore pertinent to review the endocrinology of the various stages of human reproduction with particular reference to the nutritional and demographic context in Bangladesh, in order to discern appropriate strategies for future research in these areas.

Menarche

The onset of reproductive capacity is demarcated by menarche and, in comparison with well-nourished populations, menarche in Bangladesh is significantly delayed (1-4). A similar situation exists in other less developed countries (5,6) and has been shown to be associated with poor nutritional status (7-9). More specifically, the age of menarche has been shown to be correlated with body weight in both developing and developed countries (1,2,10) and has shown a secular trend (3,11). At present the mechanism linking nutritional status and menarche is not known but Frisch has advanced the hypothesis that menarche is closely related to the attainment of a critical body weight which represents at critical fat-lean ratio or fat-body weight percentage (12,13). More recently, Frisch has suggested that critical weight is associated with a particular metabolic rate which influences the hypothalmic production of gonadotrophins (14). In this context it is interesting to note that Angsusingha et al. (15) have found that LH, estrone, estradiol and FSH can be higher in some premenarcheal girls than in postmenarcheal girls of the same age and Hansen et al. (16) have observed periodic fluctuations in ganadotrophin levels several years premenarche.

In a society such as Bangladesh where menarche is the signal for marriage (1), factors which influence the age of menarche also influence the age of marriage and, hence, in the absence of contraceptive practices, the age at which females are likely to become pregnant. However, Chen has observed (17) that the interval between marriage and first birth is about 36 months and is therefore rather longer than the 15-18 months which might otherwise be expected (6-9 months to conception followed by gestation). For example, Chowdhury has shown (18) for a similar population that in parous women the waiting period from the first post-partum menstruation to conception is only 11 months. Although behavioural causes for this long delay to first conception have not

yet been ruled out it is plausible to postulate the cause as a period of sub-fecundability after menarche due to a continuation of the interplay between nutritional and endocrinological factors which result in delayed menarche. In support of this hypothesis there is some clinical evidence that malnutrition in women is associated with irregular menstrual cycles and a higher frequency of anovulatory cycles (19).

In the absence of any changes in behavioural patterns, intervention programs which result in an improvement in the nutritional status of prepubertal and pubertal girls could have a combined effect on the age of menarche and the interval between marriage and conception such that the first birth occurs as much as several years earlier. The converce effect, a delay in menarche (and, presumably, marriage and age of first birth) due to famine conditions between 1971 and 1975, is expected to be observed soon in Bangladesh (20). The impact, in terms of population growth, of a decrease in maternal age at first birth may or may not be large. A far more important consideration is the health problems associated with a rise in maternal mortality and infant morbidity and mortality which would accompany a reduction in maternal age (21). For this reason studies on the nutritional and endocrinological factors which influence menarche and post-menarcheal fecundibility are of importance to health programs in Bangladesh.

Pregnancy

The effects of malnutrition on the course of pregnancy are less obvious than in the other phases of the reproductive process. Whilst there are numerous reports (see ref. 22 for review) on the effects of dietary deficiencies in animals which result in intrauterine death, malformations or growth retardation, none have been proved in man due to the obvious ethical objections to properly controlled experiments. In humans, malnutrition commonly means multiple (and, probably, variable) deficiencies in specific nutrients as well as in total calorie content. Nevertheless, some conclusions about the general effects of malnutrition on pregnancy in man may be made. Studies of the extreme famins in Holland in 1944-45 (23) and in Bangladesh 1974-75 (24) indicate that fetal wastage in established pregnancies is largely unaffected. Antoncv (25) reported an increase in fetal wastage in the 1942 Leningrad famine but it is arguable (26) that both the dietary deficiencies and the emotional stress on that occasion were more severe. Stress is known to have a profound effect on the outcome of pregnancy in animals (27) and this is probably the case in man also. The data on the effects of malnutrition on fertility are more difficult to interpret but Mosley in a recent review (28) concludes that "direct biological factors related to nutrition may play only a very minor role in the fertility of a population." The most clear-cut effect of malnutrition in pregnancy is the well-documented correlation between malnutrition and low birth-weight (29-37). Whether the higher incidence of low birth-weight infants to malnourished mothers is due to retarded fetal growth or to premature delivery (or both) is not yet clear, particularly in less-developed countries where reliable information on the time of conception is difficult to obtain. Whether low birth-weight babies from malnourished mothers are due to growth retardation (small-for-dates) (33) or to prematurity (37,38) the significance of maternal malnutrition

is that low birth-weight is strongly correlated with infant mortality and morbidity (39-42). Thus, while maternal malnutrition may or may not directly effect the course of pregnancy it certainly presents a major problem in terms of the subsequent health of the offspring. In the context of potential geo-cultural differences mentioned in the opening paragraph North (43) reported a lower neonatal mortality in low birth-weight black infants than in white infants of similar birth-weight and concludes that this is due to an intrinsic 'advantage' for survival in the black infants.

Zinc and folic acid deficiencies merit special mention as two of the few specific deficiencies which have been positiviely identified as detrimental to maternal and child health during pregnancy. Zinc deficiency is associated with fetal malformations(44,45) and abnormal gestation lengths (45) and has been implicated in reduced tensilestrenght of tissues and poor wound healing (46) and with pregnancy complications such as lacerated uterus and excessive bleeding at parturition. Zinc deficiency also causes growth retardation and hypoganodism(47) and it has been suggested that teenage girls who became pregnant before completing their own growth may be particularly susceptible to zinc deficiency. Whether or not zinc deficiency is a problem in Bangladesh is, at present, unknown. Studies undertaken at the CRL (48) suggest that zinc is readily available in common Bangladeshi fruits and vegetables but whether or not the diet of pregnant women includes sufficient of these items is not known. The situation is further complicated by the fact that chelating agents (e.g. phytates in rice and wheat) can substantially reduce the availability of trace elements, including zinc (49), so that deficiencies can arise even when the intake is apparently adequate.

The nature of the clinical consequences of zinc deficiency lead one to suppose an interelation between zinc deficiency and endocrinological function: this is, indeed, the case and has been recently reviewed by Henkin (50). Most of the available data relate to effects in the male and suggest that the site of action of zinc is at the pituitary, zinc being necessary for the production and/or release of pituitary hormones (see ref. 50). Reports of comparable studies in the female have not been found: this is clearly an important gap in this area. Limited, and conflicting, reports are available on the effects of exogenous hormones on zinc levels (including the effects of oral contraceptives); the best that can be said at present is that hormones do affect zinc levels (51-53) and that this, too, is an important area for further study.

Folic acid deficiency is associated with megaloblastic anemia and may be accentuated in preganacy due to competition between mother and fetus, to the detriment of both. It is now well established that folic acid metabolism is related to endocrinological status and that oral contraceptives not only depress folic acid (53,54) but that the effect may persist for some time after discontinuing the oral contraceptives (55). This is of particular relevance to the Bangladesh situation where a relatively large proportion of oral contraceptive acceptors subsequently drop out because of undesirable side-effects (56-58) and, because they do not switch to alternative methods, become pregnant again in a short space of time. In such circumstances their intrinsic folic acid deficiency in the ensuing pregnancy may be accentuated as a result of their previous contraceptive use. If such a situation were found to exist it

would be a good example of the way in which modern contraceptive technologies, which were designed for and evaluated in well-nourished women in developed countries, may not only fail to meet the cultural and contraceptive needs of poorly nourished women in less-developed countries but may even aggrivate their health problems.

Post-partum lactation and amenorrhea

The endocrinological, nutritional and demographic significance of post-partum lactational amenorrhea has been extremely well reviewed by Tyson (60) and need only be summarised here.

The interval between the birth of one child and the conception of the next is the major determinant of overall reproductive performance and consists of two phases: (i) a period of lactation-induced amenorrhea in which fecundity is low or zero (61-65) followed by (ii) a period of recurrent menstruation in which fecundity returns to normal. The period of lactational amenorrhea is particularly important to maternal and child health in less-developed countries for a variety of reasons:

(a) maternal milk is the ideal nutrient for the infant in terms of the composition of major nutrients e.g. carbohydrate, protein, fat, lactose, etc. (66), minor nutrients, e.g. trace elements (67) and other non-nutrient constituents of value to the infant, e.g. immunoglobulins which confer resistance to illness (68, 69);

(b) breast-milk is essentially sterile, inexpensive, requires no special preparation and is readily available;

(c) lactational amenorrhea inhibits an early return to pregnancy which might seriously overload the strained resources of a malnourished mother.

Thus, it is crucial that intervention programs be carefully evaluated in terms of their effect on lactational amenorrhea in order to ensure that they do not adversely affect this natural process.

Endocrinologically, lactation is a relatively simple process. Nipple stimulation is transmitted by a neuronal pathway to the pituitary and results in prolaction secretion; prolactin stimulates milk production by the breast and appears to inhibit ovarian activity (70,71) resulting in amenorrhea and infertility. Thus, although the elevated prolactin levels of pregnancy predispose the post-partum mother to lactation, pregnancy is not an essential prerequisit for lactation which may be induced in any woman by nipple stimulation (72), particularly if accompanied by the administration of prolactin-stimulating drugs (72,73). The interrelation between malnutrition and lactation is much more complex (28,60). Demographically, the duration of lactation is highly correlated with maternal socio-economic/nutritional status (74,75) i.e. malnourished women breast-feed longer though Huffman et al. (79) showed that in one small population the duration of lactation was not affected by the nutritional status of the mother; in individuals, improvement in nutritional status results in an increase in milk production, though not necessarily in quality (75). It has been suggested that the answer lies in the central role of nipple stimulation in lactation: poorly nourished women produce less milk and have less food available for supplemental feeding so the infant suckles longer

and more frequently, thereby increasing the stimulation of prolactin and the duration of lactation. In well-nourished, high socio-economic status women the reverse effects occur (encouraged no doubt by social factors, e.g. shyness at breast-feeding in public, pressure of other activities etc.) so that lactation terminates early. Clearly, this is an area in which there is still considerable uncertainty. Nevertheless, the period of lactational amenorrhea is currently a popular target for intervention programs in less developed countries since it presents the opportunity to attack two problems at once, namely infant health care (improved nutrition and resistance to infection) and population control (extension of inter-birth intervals). Yet it is precisely this complex interrelationship between endocrinological, nutritional and behavioural factors which necessitates that great care be taken in the design of such programs to ensure that they really are beneficial to the recipients and this, in turn, requires sound basic research in each of these areas. By way of example, it is enlightening to consider the issues involved in the potential use of thyrotropic releasing hormone (TRH), a known stimulator of prolactin secretion (76), to promote and/or prolong lactation in Bangladeshi women. (i) What is the appropriate dose rate for poorly nourished Bangladeshi women whose body weight may be only half that of the women in whom the initial trials were conducted? (ii) Since TRH also stimulates TSH production (and there is no evidence to suggest that TRH is involved in the physiological mechanism of prolactin production) what is the risk of hyperthyroidism as an undesirable side-effect in Bangladeshi women and is this risk altered by malnutrition? (iii) Has enough basic pharmocological research been undertaken to justify contemplating trials of intervention programs? For example; the drug cyproheptadine has been shown (77) to augment the prolactin response to TRH and to attenuate the TSH response and may therefore make the TRH safer in the context of the previous question. (iv) Are the complications of TRH administration sufficiently well characterised that they can be readily diagnosed in Bangladesh (e.g. by paramedic field-workers) or do they require fully qualfied physicians with supporting modern laboratory facilities (e.g. radioimmunoassays for prolactin, TSH, T_3, T_4, FSH, E_2, etc.) for adequate monitoring of patient response? (v) What are the predominant causes of poor lactation in Bangladeshi women? If factors other than inadequate nipple stimulation and prolactin are involved (e.g. malnutrition) TRH therapy may be irrelevant to the problem. (vi) What are the consequences of stimulating lactation in a malnourished mother, both in terms of the effect on the nutritional status of the mother and in terms of the quality of the milk produced? (vii) What are the bio-social determinants of lactation in Bangladeshi women? Do they really want to suckle longer and cannot or are they compelled to breast-feed for longer periods because of inadequate alternative food supplies for the children?

In the context of these issues it is interesting to note the conclusions of Hall and Kay (78) who investigated the use of TRH in six black South African women:

> "In no case did the milk output rise in the two feeds following TRH administration. In five of the six women the post-TRH feed actually produced less milk than the feed immediately before TRH.
>
> These results suggest that ... other factors must be responsible for lactation failure. ... our results suggest that the evaluation of such agents [as TRH] must be based on actual measurements rather than subjective impressions ...".

The above issues have been discussed as typical of the problems of designing sound intervention programs, particularly where the long-term administration of hormones or other drugs is involved. That is not to say that the problems are insurmountable nor that the questions are unanswrable. What is clear, however, is that (i) inspired guesses are no substitute for sound research, particularly in the case of complex, multifactorial problems; (ii) multifactorial problems require an intergrated, multifactordal research program; (iii) much of the research carried out on well-nourished women in developed countries is irrelevant to the situation of poorly-nourished women in Bangladesh and other less-developed countries; (iv) trials of intervention programs utilizing modern technology require on-the-spot appropriate technological support facilities to monitor the effects of the intervention, particularly with respect to undesirable side-effects.

Recurring Menstruation

Like the period of lactational amenorrhea, the period of recurring menstruation is of particular importance since its duration affects the interbirth interval and, hence, the rate of population growth. In developed countries the majority of women practice some form of birth control and, therefore, experience long periods (i.e., many years in some cases) of recurrent menstruation characterised by regularly recurring menstrual bleeding. By contrast, very few women in Bangladesh practice birth control and hence the duration of recurring menstruation is much less, being typically about nine months (61). The pattern of recurring menstruation of Bangladeshi women is also rather different from that in women in developed countries. Chiazze et al. (59) studied 30,655 cycles in 2,316 American and Canadian women and found the cycle length to be 29.1 ±7.5 days (mean ±S.D.). The standard deviation is, perhaps, surprisingly high and is due to the fact that the distribution curve is appreciably skewed with approximately 10% of the cycles being larger than 35 days in duration. When the data are stratified by age-group the broad distribution of cycle lengths is particularly noticable among the younger age-groups (fig.3). It is tempting to speculate that these long inter-menstruation intervals may be due to diminished or impaired interactions in the pituitary-gonad axis, perhaps resulting in anovulatory cycles. Unfortunately, comparable data for rural Bangladeshi women are not yet available but preliminary results from the 'Determinants of Natural Fertility' study being undertaken at the CRL (79) indicate that intermenstrual intervals are both long and variable in all age-groups. Furthermore, whilst seasonal variations in birthrates occur in almost all societies (80,81), the effect is particularly noticable in Bangladesh where some 50% of births occur in a three to four month period (17). Coupled with this is a distinct seasonality in the end of lactational amenorrhea and return to menstruation.

These marked differences in the patterns of recurring menstruation between women in developed countries and women in Bangladesh point to significant differences between the endocrinology and physiology of menstruation in these two groups. A proper understanding of the basis of these differences is of crucial importance in the context of fertility control programs in Bangladesh which utilise exogenous hormones (oral or injectable contraceptives) to modify the endocrinology of recurring menstruation. Such contraceptives were originally designed for and evaluated on women in developed countries whose culture, nutrition and endocrinological status may be quite different. That this is a real problem can be seen from the nature of side-effects found to occur in

Bangladeshi women and which are different from those in women in developed countries (Table 1).

Table 1. Common Side-Effects of Oral Contraceptives

Bangladesh (57)	Developed Countries (82)
Dizziness	Nausea
Weakness	Vomitting
Burning sensation	Abdominal cramps
Menstrual problems	Weight changes
Breast-feeding problems	Breast tenderness
	Irregular menstruation
	Headaches

In developed countries, oral contraceptives are generally only available from medical practitioners who, in prinicple at least, thoroughly examine new acceptors to determine the most appropriate contraceptive and then follow up to monitor for side-effects. Nelson (83) observes "There is no pill that is acceptable to all women ... Patient acceptability of oral contraceptives is complicated by many variables... Drug tollerance of the individual is often unpredictable. Side-effects can only be partially anticipated by a review of the patient's past history and physical examination." By contrast, in Bangladesh, because of the low numbers of doctors relative to patients, oral contraceptives are frequently made available through untrained or partially trained personnel with little or no preliminary examination or follow-up. As a result, adverse side-effects due to inappropriate contraceptives or frank misuse are common; for example some women are under the misaprehension that oral contraceptives are for use after conception (i.e., as an abortifacient) and have been known to take large doses for this reason.

It may well be true that the problems of overpopulation is so severe in Bangladesh that the risk of contraceptive misuse is a lesser problem. This argument, however, does not diminish the obligation to take all practicable steps to evaluate the endocrinological impact of hormonal contraceptives on the population as a whole if not on individuals.

The major issues involved can be summarised as follows:

1) What is the appropriate dose-rate for Bangladeshi women? Bangladeshi women are typically only two-thirds the weight of women in developed countries. However, the answer may not be as simple as reducing the dose by one-third since the relative proportions of body compartments (e.g., bone, musele, fat, etc.) are quite different and may affect the distribution and metabolism of the contraceptives. An important question, particularly in connection with long-acting injectable contraceptives is what is the effect of malnutrition on the metabolism and clearance of exogenous hormones?

2) What are the effects of contraceptive abuse? The regular taking of medication is an alien cultural practice in Bangladesh. Hence, apart

from misunderstandings about the purpose of contraceptives mentioned earlier, oral contraceptives are often taken very eratically. An understang of the endocrinological and clinical consequences of irregular contraceptive use is of critical importance to the interpretation and management of side-effects in Bangladeshi women. An obvious advantage of long-acting injectable contraceptives is that such abuses are much less likely to occur.

3) What are the metabolic and nutritional consequences of contraceptive use? Apart from their effects on the reproductive system, hormonal contraceptives have diverse effects on metabolism (84-88); carbohydrate metabolism lipid metabolism and protein metabolism have all been shown to be affected. Such effects appear to be of little consequence to well-nourished women who have sufficient "reserve capacity" to cope, but we have no knowledge of their significance in the poorly-nourished Bangladeshi woman. The effect of oral contraceptives on folic acid metabolism mentioned on page 3 is a good example of this problem.

4) What are the health consequences of contraceptive use? Because of the vast differences in health status between developed and less-developed countries, attention tends to focus on such problems as thromboembolism (89) and cancer (90), which are of very minor significance in countries like Bangladesh. In such a situation it is easy to overlook the fact that hypertension and liver disease (both of which are contraindications for oral contraceptives (85,91)) are common complaints in Bangladesh and the latter, if sub-clinical, is likely to go unrecognised.

5) What are the effects of hormonal contraceptives on lactation and lactational amenorrhea? It is well established (92,93) that hormonal contraceptives of the combined estrogen-progestogen variety diminish milk production though relatively few mothers gave this as a reason for abondoning the contraceptive (57). In addition, exogenous hormones may be transferred to the infant via the milk. This gives rise to two subsidary issues: (a) what is the effect of contraceptive-induced diminution of milk production on the nutritional status of an already poorly-nourished infant? ; (b) what are the effects of exogonous hormones transfered through the milk, on the infant? An additional, and particularly important question is whether the acceptance of hormonal contraceptives induces an earlier return to menstruation than would otherwise have occurred? There is evidence to suggest that this may be so. If the mother then discontinues contraceptive use because of undesirable side-effects she is left with neither the protection of the oral contraceptive nor of lactational amenorrhea. Furthermore, a recent preliminary evaluation of data from the CRL - Contraceptive Distribution Program by Osteria (94) suggests that there may be a 'rebound' effect from oral contraceptives among Bangladeshi women such that their fecundity is increased (relative to non-users) after discontinuation of the contraceptive. If further investigation substabtiates these phenomena their combined effect (abolislition of lactational amenorrhea, early discontinuation, rebound fertility) will be to shorten, <u>not</u> lengthen, the inter-birth interval.

All of these issues illustrate ways in which the imposition of modern technology on less-developed countries, without first understanding essential basic research to evaluate their potential effects, can be to the detriment rather than to the benefit of the recipients.

Conclusions

Reproductive biology is a complex, multi-factorial subject. Nowhere is this more true than in Bangladesh, where, in additional to the physiological and endocrinological factors which affect reproductive performance in all humans, factors such as malnutrition, disease and behavioural patterns have a marked effect. Thus, whilst much excellent research has already been done on the demographic aspects of reproduction, progress is being hampered by the lack of facilities and expertise to identify and evaluate the role of endocrinological factors in the overall pattern. As a result, many women are finding that modern contraceptive technology is quite inappropriate to their situation and this is reflected in high drop-out rates and low levels of new acceptors.

Sophisticated endocrinological research facilities will not solve all of these problems overnight, nor will they alone make contraception more acceptable to the 65% of the population who have no desire to limit their families at present. Nevertheless, the establishement of such facilities can make a valuable contribution towards improving the effectiveness, acceptability and safety of modern contraceptive technology for those who do wish to limit their families and their satisfaction is the key to more widespread acceptance of family planning technology in the future.

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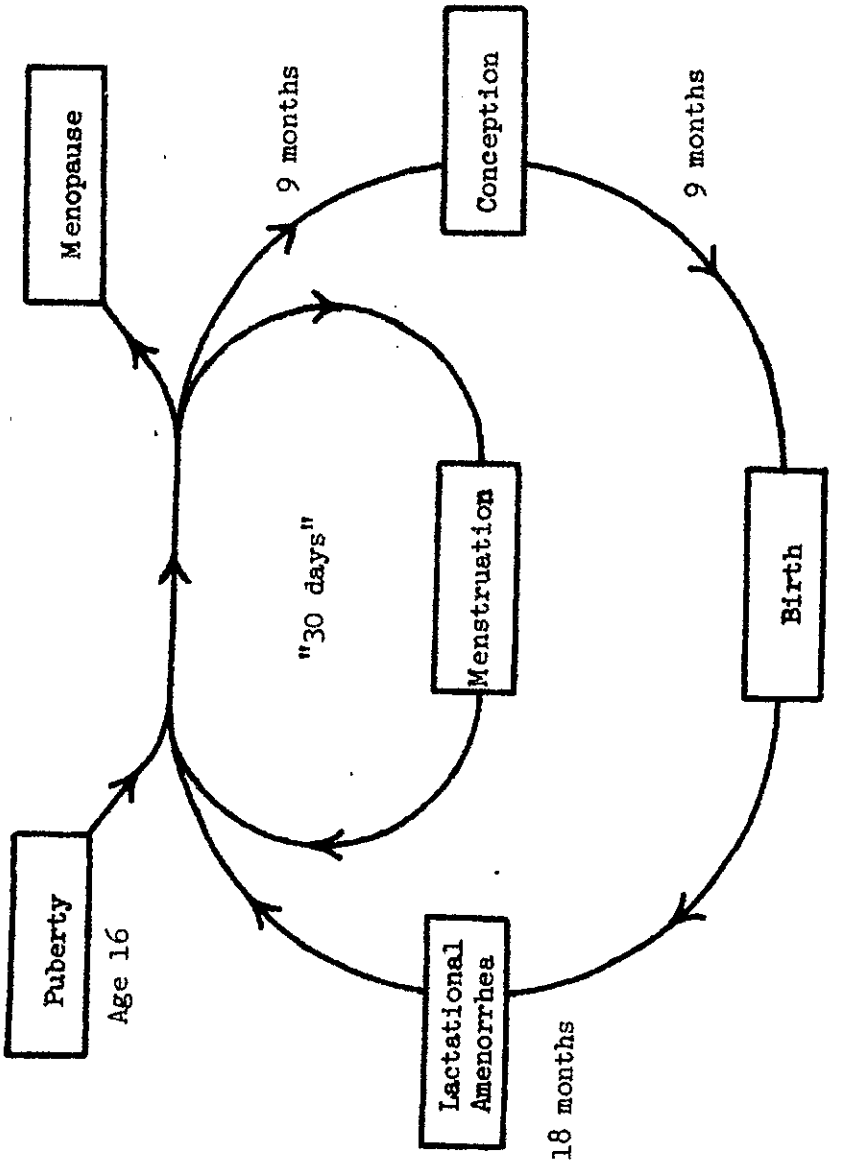
FIGURE 1 Diagramatic Representation of the Reproductive Cycle in Bangladeshi Women



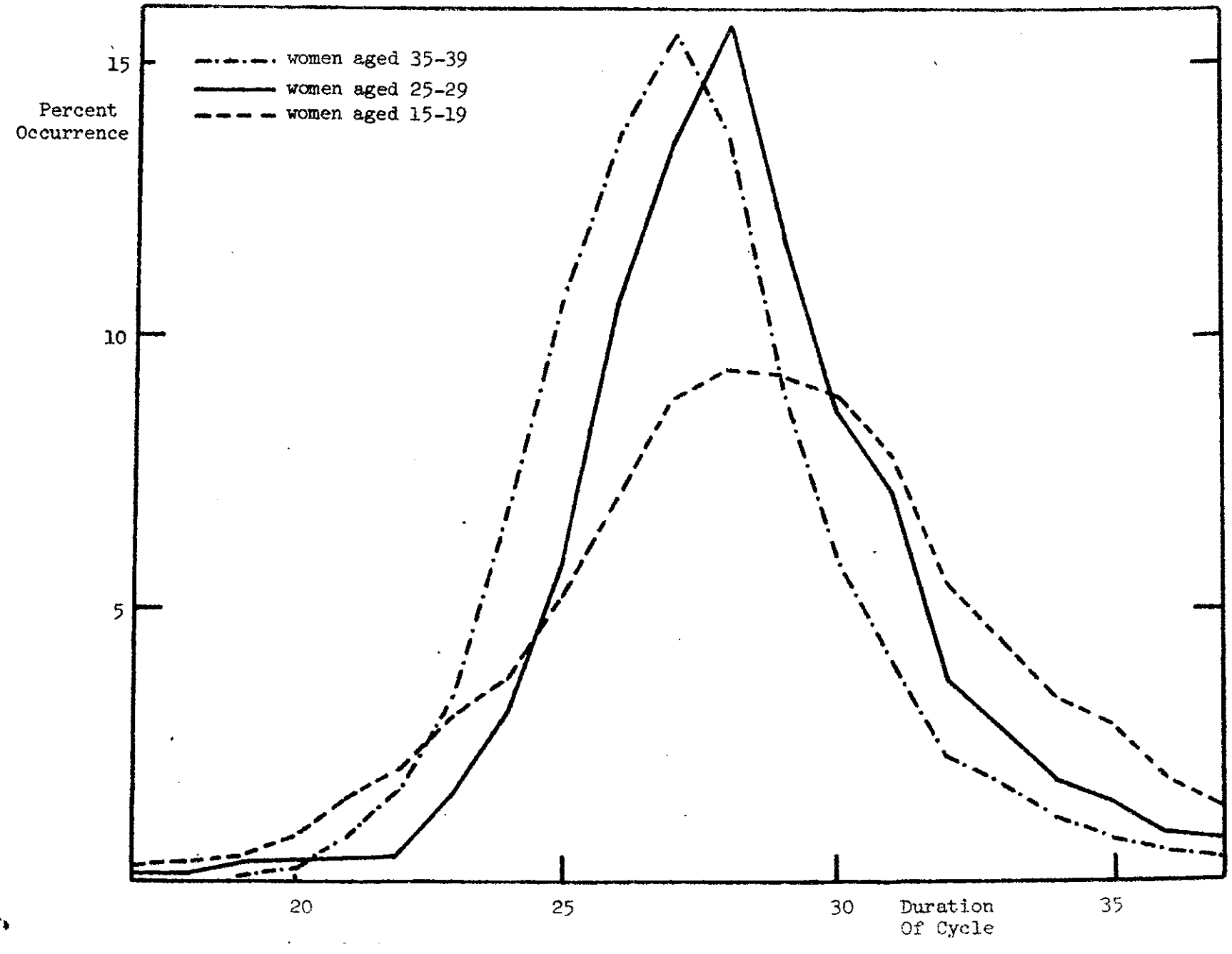


FIGURE 3 Distribution of the Duration of the Menstrual Cycle.

Appendix - B

DEPOT MEDROXYPROGESTERONE ACETATE AND HEALTH: WHAT DO THE DATA TELL US?

Allan Rosenfield,
Deborah Maine

Injectable depot medroxyprogesterone acetate (DMPA), popularly known as Depo-Provera, is the most controversial contraceptive in use today. There are many reasons for this, a number of which reflect the timing of DMPA's arrival on the scene. One of these is the growing awareness of the complexity of the effects of chemicals on human beings. Several decades ago it seemed that there would be relatively easy answers to some of humankind's problems. Medical science in particular appeared to promise great (and relatively safe) advances. In those decades, however, we have discovered many troubling things. The progress of development of improved contraceptives has been slower than expected. Even more troubling is the fact that all the effective contraceptives available pose serious health risks of one sort or another, risks which were not, and, in some cases, could not have been foreseen.

For example, the intensive study of oral contraceptives, which has taken place in the 20 years since they were first marketed, has shown many things. Some of the anticipated adverse effects (such as increased risk of breast cancer) appear not to be a problem, and unanticipated beneficial effects have been found (such as decreased risk of benign breast disease and possibly ovarian and endometrial cancer as well) (4, 32, 36, 37, 39).

On the other hand, the real health risks of oral contraceptives (such as cardiovascular disease and liver tumors) were not anticipated, and there was no way to know of these risks, despite preliminary studies on various test animals, until hundreds of thousands of women had used the pill and their experience could be studied (3, 7, 21, 38). This is a very troubling truth, one which many people do not understand or cannot accept. This does not mean that we should be casual about the potential dangers of drugs. What it means is that we must learn as much as we can beforehand, and then weigh the need for the drug against our best understanding of its possible health effects.

In 1978 the U.S. Food and Drug Administration denied DMPA approval for use as a contraceptive (8). This chapter we will examine the reasons given for this action, and the scientific data on which they rest. However, it is important to note at the outset that if the pill were under consideration by the FDA today, its chances for approval would be poor. And, given everything we know, would that be good? Would than, in fact, better the health of women around the world? The answers to these questions vary, depending on the group of women in question, their access to and ability to use other methods. But in all cases, what is needed is thorough evaluation of the existing knowledge.

What do we really know about DMPA? Only after this question is answered can any country or individual make a reasoned decision about the suitability of DMPA use.

BENEFITS OF DMPA

Before we examine the complex issues of the safety of DMPA, it is worth reviewing the benefits of this method of contraception, the attributes which make it worth the effort of continued controversey and evaluation. In brief, they are the following: DMPA has a higher use effectiveness than any other reversible method and it is the only available injectable contraceptive which is effective for three months (21, 41). Further, its effectiveness continues, even if the user is a few weeks late in obtaining a repeat injection (24). It is an especially desirable method for women who prefer injections over other approaches to contraception. DMPA is not used in relation to coitus, it requires infrequent administration, it is provided outside the home, and it requires no supplies to be left around the home, thus giving the user a high degree of privacy. Further, it can be administered by any person who normally gives injections in a health care system and it does not necessarily require a clinical setting for administration. Because it is administered periodically by injection and has few potentially harmful metabolic side effects (31), DMPA may be the preferred method for women who desire effective contraception but who have special medical or psychosocial needs which contraindicate the use of other methods, and for whom sterilization is not legal or desired.

Unlike oral contraceptives, DMPA does not suppress lactation, and therefore has been considered advantageous for postpartum women (19). This could be a major benefit in the developing world, where successful and prolonged breast-feeding is of critical importance to child health. However, there is inadequate information available on possible effects on the nursing infant of the DMPA in the breast milk. This important subject is currently under study.

In populations where iron deficiency anemias are common, the development of oligomenorrhea and secondary amenorrhea during use of DMPA may help alleviate this problem.

There appear to be no abosolúte contraindications to DMPA use, other than pregnancy. There have been no reports of deaths attributable to DMPA, despite its use for gynecologic and contraceptive purposes in the United States and other countries. While this lack of reports of fatal complications does not eliminate the need for careful epidemiological studies of DMPA safety, it is worth noting that long before the life-threatening side effects of the pill and IUD were well documented, there were case repors which pointed out the hazards of these methods.

Clearly, the benefits of DMPA would make it a valuable addition to many family planning programs. However, over the years there have been many reports commenting on its risks as well as its benefits. Evaluation

of the extensive medical literature is a complex task, but one which is absolutely essential for clinicians for their practices and even more for planners considering incorporation of this method into national programs.

Several evaluations of the scientific data on the safety of DMPA have taken place in the past few years. In 1978 the FDA completed a decade of deliberations by announcing that it would not approve DMPA for use as a contraceptive in the United States (8). Subsequently, the World Health Organization's Toxicology Review Panel conducted its own review, and found no reason to withdraw DMPA from use (42). Finally, in 1980 and Ad Hoc Consultative Panel, chaired by the senior author of this chapter, after an 18-month period of review, presented its findings and recommendations to the U.S. Agency for International Development (USAID), which it had been asked to advise on the safety of DMPA for use in international family planning programs (1*). The Ad Hoc Panel recommended that AID make DMPA available to national family planning programs, upon request, in the same way that it does other methods of contraception, after ascertaining that the requesting government has had access to all the current information on the drug. This recommendation was based on careful consideration of the medical and ethical issues involved by Panel Members with expertise in the fields of obstetrics and gynecology, animal physiology and toxicology, epidemiology, pathology, law, and health policy. In this chapter, we will summarize the review of available data which led the Ad Hoc Panel to its final recommendation.

Initially, DMPA was used for treatment of two conditions, one benign (endometriosis) and one malignant (endometrial carcinoma). In both instances, very high dosages of the drug were used (often starting at 100 mg per week, with slightly lower maintainenace dosages, as compared to 150 mg once every 3 months, the contraceptive dosage). Treatment of these high dosages was maintained in some instances for several years with no acute toxic effects reported (14). However, it must be added that no systemic studies have been published which specifically reported on long-term follow-up of these women.

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* USAID's policy has been not to provide programs with any drugs not approved for use in the United States. However, after the FDA denial of approval of DMPA, USAID decided to reconsider this policy, in light of the growing number of requests from the governments of developing countries for the Agency to provide DMPA at reduced cost, as it does other contraceptives.

DMPA APPROVAL DENIED

DMPA at present is approved for contraceptive use in 76 developed and developing countries (6). However, the decision by FDA to deny approval for this use in the United States caused great concern among health authorities around the world. After continued review, however, the FDA announced its decision in March, 1978, to deny approval of the Upjohn application for the following five reasons: 1) safety questions, raised by studies in dogs showing an increased incidence of mammary tumors associated with the drug; 2) the availability of a number of safer alternative methods of contraception in the United States, and the lack of clear evidence that significant patient population in need of the drug exists in the United States; 3) the possibility that bleeding disturbances caused by the drug may necessitate administration of estrogen, imposing an added risk factor and decreasing the benefits of a progestogen-only contraceptive; 4) the possibility that exposure of fetuses to DMPA, if the drug fails and pregnancy occurs, poses a risk of congenital malformation, a risk potentially enhanced by the prolonged action of the drug; and 5) serious reservations about the ability of the postmarketing study for breast and cervical carcinoma proposed by the Upjohn Company, to yield meaningful data.

AD HOC PANEL APPEAL

This decision was appealed by the Upjohn Company and the FDA announced in July, 1979, that this appeal will be heard by the FDA-appointed Board of Inquiry (10).

The Ad Hoc Panel reviewed the literature on DMPA studies involving beagle dogs, and found that it was not reasonable to infer any danger to women from the data. The major reason for this is that there is now a wealth of information which indicates that beagles react strongly and negatively to progestogens (including progesterone) in ways which women do not. DMPA stimulates the endometrium of beagles to such an extent that a large proportion develop mucometra and/or pyometra, often resulting in death. Consequently, in order to study the effects of DMPA on beagle breast tissue, it was necessary to hysterectomize the dogs first, to prevent their dying of pyometra. When this was done, mammary nodules developed in almost all dogs given DMPA who survived the first few years of the experiment, and some of these nodules became malignant.

There are substantial differences in the effect of DMPA on women. First of all, while DMPA overstimulates the endometrium of beagles, in women it produces an initial stimulatory effect, followed by continuous suppression of endometrial growth (25). Other differences in beagle dog response were noted. Many of the dogs demonstrated significant acromegalic changes, a complication not seen in women. Of particular importance are significant differences in progesterone receptors in the beagle as compared to the human, which probably account for the different responses.

Secondly, a variety of studies have shown no increase in breast disease among women who have taken DMPA, although more data are necessary before we can say that there is no effect (13,22,43). Furthermore, several reports released in the last few years support these studies: data from 11 years of prospective study of women using oral contraceptives in Britain were specially analyzed to see if women using pills containing progestogens closely related to DMPA (which had also been implicated in beagle studies) caused any increase in breast cancer (36). No increase was found. A 10-year study of postmenopausal women using estrogens and MPA in pill form showed that these women had significantly lower rates of breast cancer than women using estrogen alone (26).

In addition to work on beagle dogs, studies have also been done on rodents and monkeys. The WHO Toxicology Panel reviewed these in depth. Included were studies in both mice and rats, using doses up to 200 times the recommended human contraceptive dose. The results indicated no change in mortality rates and there was a similar incidence of neoplasms in both treated and untreated animals. No mammary cancer was observed. Studies on monkeys also showed no demonstrable differences between control groups and monkeys treated with low, middle, or high doses of DMPA, in the development of mammary nodules, except for one study in which mammary nodules were noted in some of the animals receiving the middle but not the high dose (35). These nodules were benign.

As a result of these and other data showing profound and numerous differences in reactions to DMPA, both the WHO Toxicilogy Review Panel and the Ad Hoc Panel concluded that is was not possible to conclude from the beagle studies that DMPA poses any increased risk of breast cancer to women. The Committee on Safety of Medicines of the United Kingdom concluded that "because of differences between the beagle bitch and the human female in the sensitivity to and the metabolism of progestogens, positive carcinogenicity studies in the beagle bitch can no longer be considered as indicative of significant hazard to women" and it stopped requiring beagle dog studies of contraceptive steroids (5).

The Ad Hoc Panel reviewed the available data on teratogenic effects of sex hormones and found that several studies suggest that prenatal exposure appears to pose some increased risk, probably about twofold (12, 15, 17, 18, 28). However, there is very little information on the effects of progestogens alone, since most of the studies have been done on women who have taken combined oral contraceptives. The panel concluded that the data do not suggest that DMPA poses more of a threat of fetal malformation than do other hormonal contraceptives. Furthermore, the Panel pointed out that "Since effective contraception prevents both normal and abnormal pregnancies, it can be shown that even if a two-fold increase in congenital defects were associated with prenatal exposure to DMPA, widespread use of the drug would result in a net decrease in the number of anomalies. Because of this, only a very small number of fetuses

would be exposed to the two-fold increased risk associated with maternal use of the drug." Nevertheless, even this small risk (in terms of numbers of children affected) is of concern, since some women may begin DMPA use with an unrecognized pregnancy, or conceive before DMPA had completely cleared from their system. Continued study of this question is necessary.

There is no evidence to support the FDA assertion that DMPA users will be given estrogen to control bleeding disturbances. It is true that DMPA disrupts the menstrual cycle. During the first 6-12 months of use, spotting, staining and irregular bleeding are common. Later, 40% to 60% of users become amenorrheic. However, heavy bleeding or bleeding severe enough to require treatment is very rare (11, 16). The FDA allegation is probably based on the fact that during the 1960s, estrogens in low doses were sometimes used to treat menstrual disturbances caused by DMPA (31), but the results of this practice were equivocal, and it is no longer recommended. Cyclical estrogen adm-nistration to bring on monthly bleeding is also not recommended. Therefore, DMPA is not suitable for women who will not tolerate spotting or amenorrhea. For other women, thorough and supportive patient counseling is the best method of dealing with concerns about irregular bleeding and amenorrhea.

As for the FDA contention that useful studies are not being planned to give better answers to the questions about DMPA safety, this is not the case. Several agencies, including the WHO and the International Fertility Research Program (IFRP) have already planned safety studies. These will make use of data from family planning programs where substantial numbers of women have used DMPA for many years. The manufacturer of DMPA, Upjohn Pharmaceuticals, has also begun new studies of a variety of issues. The Ad Hoc Panel stressed the importance of careful studies of the effects of DMPA, but concluded that, given the commitment of international health agencies to this task, this does not pose a barrier to current use of this method.

It is necessary to keep in mind that the most useful studies of oral contraceptives were done after widespread use of the pill had been underway for may years.

Finally, while the Ad Hoc Panel had not been asked by AID to evaluate the FDA claim that there was no need for DMPA in the United States, the Panel did not agree with this assertion.

In addition to the issues raised by the FDA, there were several others which the Ad Hoc Panel thought needed careful consideration. One of these is the issue of resumption of fertility among DMPA users. There appears to be some delay in the return of fertility after discontinuation of DMPA use. However, this seems to be a temporary effect, and should not be considered evidence of permanent impairment.

The following table compares a series of 756 DMPA users with 437 oral contraceptive users in Thailand (29). The women in both groups had discontinued use in order to become pregnant. The mean time for establishment of pregnancy after the discontinuation was 5.1 months for DMPA users, as compared to 2.5 months for pill users. The table demonstrates that there is a delay in return of fertility, with substantial differences at 6 and 12 months. By 24 months, however, there was no significant difference.

TABLE 1. Return of fertility following discontinuation of DMPA vs OC

	Prior DMPA Users	Prior OC Users
Number	756	437
Mean Age	24.5	22.3
Mean Gravidity	1.5	0.7
Proven Pregnancy		
6 months*	53%	75%
12 months	75%	85%
24 months	92%	94%
Mean months	5.5	2.5

(Source: Pardthaisong T, 1978) (30)

* Months after stopping contraception; contraception was considered stopped after last cycle of OC was taken, or 3 months after last injection.

Another analysis of data for this population in Thailand found that the proportions of women who had become pregnant were almost identical at 12, 18, and 24 months among women who had discontinued DMPA and those who had an IUD removed in order to conceive (30).

Because of these data and other studies with similar findings, the Panel concluded that, "While there is a delay in the return of fertility, the vast majority of women desiring a pregnancy were able to conceive within a two-year period of time. Thus, concerns about irreversibility, or chemical sterilization, do not appear to be substantiated (33)."

ENDOMETRIAL CANCER

A second issue not addressed by the FDA is that of endometrial cancer. In December 1978, after the FDA had announced it would not approve DMPA for contraceptive use in the United States, and after the Ad Hoc Panel had concluded its meetings, it was learned that the FDA-required, 10-year studies of DMPA in rhesus monkeys had been concluded. The autopsy findings contained surprising information: two of the 10 monkeys receiving 50 times the human dose for the duration of the study had developed endometrial cancer, while none of the 20 monkeys receiving other doses of DMPA or of the seven control monkeys showed any signs of endometrial disease (34).

The Chairperson of the Ad Hoc Panel, after consultation with Panel members, arranged for a special toxicology committee to consider this information and the reports of consultant toxicologists (to The Upjohn Company) who reviewed the microscopic specimens of all the test monkeys. A group of experts was recruited for this meeting from a variety of relevant fields, including obstetrics and gynecology, gynecologic pathology, veterinary pathology, and reproductive physiology. Committee members had experience in cancer epidemiology, international public health programs, and one was a lawyer with experience in ethics.

In its deliberations, the Committee stressed the difficulty of interpreting the information, because so little is known about endometrial disease in monkeys: few institutions keep monkeys for such prolonged periods of time (10 years in the Upjohn study). There is no information on the baseine incidence of endometrial cancer in monkeys. However, it does appear to be uncommon. For example, the San Diego zoo performs autopsies on all animals. Of 46 female macaque monkeys examined, none had endometrial abnormalities (2). However, the zoo's Director of Research, Dr. Kurt Benirschke, who gave the Committee this information, cautioned that there is great variation among the many species of macaques, and there were less than a dozen rhesus monkeys (the species of macaque used in the DMPA test) in their sample. The Armed Forces Institute of Pathology does not have any cases of uterine cancer in its collection of primate neoplasia. On the other hand, Committee members said that they knew of two cases of uterine abnormality in monkeys, neither of which had undergone hormone administration (one case occurred in a control monkey in a copper IUD study).

It was suggested by the Committee that the monkeys' endometrial cancer could have arisen by any of three routes: through hormonal action of the DMPA; through some nonhormonal, toxic action of the DMPA; and independently of the DMPA, by chance.

If the hormonal action of the DMPA caused the cancers, then they were unusual in several ways: 1) They were associated with the superficial layers of the endometrium, whereas in women, cancer usually arises from deeper layers of the endometrium. 2) Endometrial cancer in women is usually associated with hyperplasia, such as that caused by estrogen. There was no evidence of hyperplasia among the DMPA treated monkeys. 3) The endometria of the monkeys treated with DMPA were atrophied, a condition which has been thought to decrease the risk of carcinoma developing. In short, the theory that the hormonal action of DMPA caused the endometrial cancer in the test monkey does not agree with what is known of the natural history of endometrial cancern in women.

Additional evidence against the hormonal action of DMPA having caused the endometrial cancer is found in a variety of clinical and epidemiologic studies. Excess estrogen is known to increase a woman's risk of developing endometrial cancer. There is evidence that progestogens neutralize this effect. For example, while use of estrogens by postmenopausal women increases the rate at which they develop endometrial cancer, use of a combination of estrogen and a progestogen does not increase the rate of this disease (9). Similarly, while use of sequential oral contraceptives (which emphasize estrogenic action) may increase the risk of this disease among young women, use of oral contraceptives (which contain estrogen and progestogen in each pill) does not have this effect. In fact, there is new evidence from a case-control study which suggests that women who use combined oral contraceptives may have less risk of endometrial cancer than do women who do not take oral contraceptives - in other words, these preliminary data suggest that progestogens may even protect against endometrial cancer (23). Finally, DMPA and other progestogens have been used clinically to slow the growth of advanced endometrial cancer in women. While none of these findings rule out the possibility that DMPA may have caused cancer found in the monkeys, they do call into question the meaning of that finding.

It is also possible that the massive doses of DMPA may have affected the monkeys in the 50x group through some nonhormonal action - i.e., as a toxin. The Committee members thought that this seemed unlikely, because there was no evidence of a dose response: there was no higher mortality rate among the monkeys receiving DMPA than among the control monkeys, nor any increase in mortality with increasing dosage. Neither was a cancer found in sites other than in the uterus.

Finally, the possibility that the two cases of endometrial cancer in the 50x group arose by chance cannot be ruled out. Statistical analysis showed that the probability that the results of the monkey test could have occurred by chance was at least one chance in three.

In addition, exploration with a variety of statistical techniques showed that these data lack both significance and power, even if margins of error much larger than usual are allowed.

In addition to trying to interpret the monkey data and assess their applicability to humans, the Committee considered the experience of women who have used this method of contraception. In response to the endometrial cancer finding at the conclusion of the monkey trial, Drs. Edwin McDaniel and Malcolm Potts have attempted to determine whether there was an increase in endometrial cancer among women in Chiang Mai and Lumpoon provinces in Thailand, where DMPA has been used by more than 86,000 women since it was introduced in 1965 (23).

McDaniel and Potts report that a search of the records of all seven hospitals operating in these areas produced evidence of 39 cases of proven or presumptive endometrial cancer in 1974-1978. During these years, although there was a steadily increasing patient load for diseases of all kinds, there was no clear increase in the number of cases of endometrial cancer seen each year.

Of the 27 women with proven endometrial cancer, 16 came from Chiang Mai or Lumpoon province, where they could have received DMPA. Of these 16, four were too old to have received DMPA (63-84 years old at diagnosis), one had never been married, and two could not be located at the time of the report. Of the remaining nine women, none had ever used DMPA. Because the numbers are so small, the time too short, and the conditions of the study far from satisfactory, these findings cannot be construed as proof that DMPA does not cause endometrial cancer. Nevertheless, the lack of a substantial increase in endometrial cancer - in an area where hundreds of women are known to have used DMPA continuously for 10-13 years and many thousands for shorter periods - "... is a reassuring preliminary observation."

The Committee members emphasized the need for further and more intensive investigation of this issue. Several studies are already planned by the World Health Organization and the International Fertility Research Program.

Weighing the data against the considerable benefits of DMPA, the Committee was unanimous in supporting the original recommendation of the Ad Hoc Panel that DMPA should be made available to developing countries, upon request, as a part of its assistance program, provided that careful study of the possible health effects of DMPA continues. Thus, the Committee was in agreement with the WHO Toxicology Review Panel which, in October 1979, issued its final appriasal of the DMPA monkey study. After reviewing all the data that Panel concluded "that the adenocarcinomas in these two monkeys were the result of massive overdosage. The panel felt that the current and planned WHO studies of the health effects of DMPA should continue, and that there is no reason to recommend discontinuation of the use of DMPA in national family planning programs" (40).

CONCLUSION

We have reviewed the medical evidence on the health effects of DMPA, and the evaluations of this evidence by the FDA, the WHO, and an Ad Hoc Concultative Panel to USAID. The reasons given by the FDA for denying approval of DMPA do not appear to be supported by the data available. Both the WHO and the Ad Hoc Panel have concluded that, at this time, there is no reason to withdraw DMPA from use. Furthermore, the Ad Hoc Panel recommended to USAID that it make this method of contraception available to those developing world governments which request it. These are not simple conclusions. They represent complex risk/benefit analyses in which questions of the effects of DMPA are weighed against its unique advantages, the known risks and disadvantages of the other efficient methods of contraception, the much greater risks of pregnancy and childbearing, and the growing demand for effective, convenient contraception throughout the world.

In the end, each country must do its own risk/benefit analysis. What we have tried to do in this chapter is present the scientific evidence to date, to facilitate that analysis. There are many questions about DMPA which have yet to be answered. However, we believe that health officials can, in good conscience, make DMPA available, provided that sincere efforts are made to help women make an informed choice of methods, and to learn more about the effects of DMPA use.

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INTERNATIONAL FERTILITY RESEARCH PROGRAM

SYSTEMIC CONTRACEPTIVE STUDY
ADMISSION RECORD

APPENDIX C-1

PATIENT IDENTIFICATION: 1. Hospital or clinic no. _____ 2. Admission date _____ *day month year*

3. Patient's name _____ 4. Husband's name _____

5. Address _____ Telephone _____

6. Relative/friend's name _____

7. Address _____ Telephone _____

STUDY IDENTIFICATION

8. Center name _____ and number: [1-3]

9. Study name _____ and number: [4-6]

10. Patient order number: [7-10]

PATIENT CHARACTERISTICS

11. Residence: 1) urban 2) rural [11]

12. Age: *(completed years)* [12-13]

13. Gainfully employed: 0) no 1) yes [14]

14. Race: 1) Caucasoid 2) Mongoloid 3) Negroid 8) other _____ [15]

15. Religion: 0) none 1) Buddhist 2) Catholic 3) Hindu, caste _____ 4) Jewish 5) Muslim 6) Orthodox 7) Protestant 8) other _____ [16]

16. Marital status: 1) never married 2) currently married 3) formerly married 8) other _____ [17]

17. Patient's education: *(school year completed)* [18-19]

18. Husband's education: *(school year completed)* [20-21]

19. Total live births: [22-23]

20. Children now living: number of males *(8 or more = 8)* [24] number of females [25]

21. Age of youngest child: *(completed years; 8 or more = 8)* [26]

22. Number of additional children wanted: [27]

23. Total number of abortions: [28-29]

24. Number of spontaneous abortions: *(8 or more = 8)* [30]

25. Total stillbirths: *(8 or more = 8)* [31]

26. Contraceptive method mainly used before this prescription: 0) none 1) IUD 2) orals 3) female sterilization 4) male sterilization 5) condom 6) withdrawal/rhythm 7) foam/diaphragm/jelly 8) other _____ [32]

SPECIAL STUDIES

27. _____ [33-34]

28. _____ [35-36]

29. _____ [37-38]

30. _____ [39-40]

PREGNANCY AND MENSES

[41-42]

31. Ever pregnant: (0) no 1) yes [43]

32. Date last pregnancy ended: *day* *month* *year* [45-50]

33. Outcome of last pregnancy: 1) live birth 2) stillbirth 3) induced abortion 12 weeks or less 4) induced abortion over 12 weeks 5) spontaneous abortion 6) septic abortion 8) other _____ [52]

34. Breast-feeding now: 0) no 1) yes [53]

35. Menses since last pregnancy: 0) no → *SKIP to item 43* 1) yes [54]

36. Onset date of last menses: *day* *month* *year* [55-60]

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LAST THREE MENSTRUAL CYCLES

37. Average length of cycle in days: 88) irregular [62-63]

38. Average duration of flow in days: *(8 or more = 8)* [64]

39. Average amount of flow: 1) scanty 2) less than normal 3) normal 4) more than normal 5) excessive [65]

40. Dysmenorrhea: 0) none 1) mild 2) moderate 3) severe [66]

41. Intermenstrual bleeding: 0) none 1) staining/spotting 2) moderate 3) severe [67]

42. Intermenstrual pain: 0) none 1) mild 2) moderate 3) severe [68]

Interviewer's name _____ [79] 1 [80]

MEDICAL DATA

43. Hematocrit: 99) not done [11-12]

44. Hemoglobin in grams: 99) not done [13-14]

45. Blood pressure: systolic [15-17] 999) not done diastolic [18-20]

46. Weight in kg: *(98 and over = 98)* 99) not done [21-22]

47. Height in cm: 999) not done [23-25]

48. Primary pre-existing medical condition: _____ [26-27] [28]

PRESCRIPTION

49. Contraceptive prescribed today: 1) daily combined orals 2) daily sequential orals 3) daily minipill 4) monthly orals 5) injectables 6) vaginal ring 7) implants 8) other _____ [29]

50. Identification of contraceptive by name or code: _____ [30-33] _____ [34-35]

51. Number of cycles given this visit:

52. How patient will receive next supply: 1) at follow-up visit 2) clinic depot 3) community depot 4) store 5) mobile unit 6) home delivery 7) mail 8) other _____ [36]

53. Today's date: *day* *month* *year* [38-43]

54. Date contraceptive started: [44-49]

55. Who prescribed the contraceptive: 1) doctor 2) nurse 3) midwife 8) other _____ [50]

Prescriber's name _____

56. Appointment for first follow-up visit: *day* *month* *year* [51-56]

NOTE: If necessary, retain this form until the first follow-up contact to record starting date of contraception.

Form number: 005126 [56-65] 2 [80]

COMMENTS: _____

SC001—kkx057 7/

SC003—kkx059 7/

INTERNATIONAL FERTILITY RESEARCH PROGRAM

SYSTEMIC CONTRACEPTIVE STUDY
FOLLOW-UP RECORD

APPENDIX C-2

PATIENT IDENTIFICATION: 1. Hospital or clinic no. _____ 2. Follow-up date _____ (day month year)

3. Patient's name _____ Telephone _____

4. Address (if changed) _____

STUDY IDENTIFICATION

5. Center name _____ and number: 1-3
6. Study name _____ and number: 4-6
7. Patient order number: 7-10
8. Admission form number: 11-16
9. Follow-up visit number: 17-18
10. Number of contraceptive cycles completed: 19-20

CONTACT DATA

11. Type of contact: 1) clinic visit 2) home visit 3) moved 4) unable to locate 5) died, cause _____ 8) other _____ 21
12. Reason for this contact: 1) scheduled 8) other _____ 22
13. Date of this contact: 23-28 (day month year)
14. Date of last contact: 29-34 (day month year)

LAST COMPLETED MENSTRUAL CYCLE

15. Menses since last visit: (0) no 1) yes 35
    - 16. Onset date of last menses: _____ (day month year)
    - 17. Length of cycle in days: 36-38
    - 18. Duration of flow in days: *(8 or more = 8)* 39
    - 19. Amount of flow: 1) scanty 2) less than normal 3) normal 4) more than normal 5) excessive 40
    - 20. Dysmenorrhea: 0) none 1) mild 2) moderate 3) severe 41

MENSTRUAL COMPLAINTS SINCE LAST FOLLOW-UP VISIT

21. Intermenstrual bleeding: 0) none 1) staining/spotting 2) moderate 3) severe 42
22. Intermenstrual pain: 0) none 1) mild 2) moderate 3) severe 43
23. Number of amenorrheic contraceptive cycles: 44

PREGNANCY

24. Breast-feeding now: 0) no 1) yes 45
25. Pregnancy since last visit: (0) no 1) yes → *Complete Pregnancy Confirmation Form* 46
    - 26. Pregnancy diagnosed by: 1) pregnancy test 2) physical examination 3) history only 4) combination, specify _____ 8) other _____ 47
    - 27. Estimated date of conception: _____ (day month year)
    - 28. Pregnancy outcome: 1) currently pregnant 2) live birth 3) stillbirth 4) induced abortion 12 weeks or less 5) induced abortion over 12 weeks 6) spontaneous abortion 7) septic abortion 8) other _____ 48

MEDICAL DATA

29. Hematocrit: 99) not done 49-50
30. Hemoglobin in gm: 99) not done 51-52
31. Blood pressure: 999) not done — systolic 53-55; diastolic 56-58
32. Weight in kg: *(98 and over = 98)* 99) not done 59-60

SPECIAL STUDIES

33. _____ 34. _____ 63-64 / 65-66

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CONTINUATION DATA

35. Contraceptive to be used until next visit. Specify by name or code: _____ 68-71
36. Contraceptive type: 1) daily → *Record in Box A* 2) nondaily → *Record in Box B* 72

Box A—Daily contraceptive
Record for last 28 days or since last visit, whichever is less.

37. Maximum number of consecutive days missed: *(8 or more = 8)* 73
38. Total number of days missed: 74-75
39. Total number of days dose doubled: *(8 or more = 8)* 76

After completion of Items 37-39, SKIP to Item 43

79
3 80

Box B—Nondaily contraceptive

40. Duration of protection of last administration in days: 21-23
41. Number of days since last administration: 24-26
42. Administration this visit: 0) no 1) yes 27

43. Patient terminated from study: (0) no 1) yes 28
    - 44. Date of last use _____ (day month year) 30-35 (day month year)
    - 45. Decision to discontinue made by: 1) patient 2) doctor 7) end of study period 8) other _____ 36
    - 46. Primary medical reason for discontinuing: _____ 37-38
    - 47. Primary nonmedical reason for discontinuing: 1) desires to become pregnant 2) will move away 3) adverse publicity 4) no further need 5) husband objects 6) cannot visit clinic, reason _____ 7) no supply, reason _____ 8) other _____ 9) end of study period 39
    - 48. Other method of fertility control accepted or planned by patient: 0) none 1) IUD 2) systemic, type _____ 3) female sterilization 4) male sterilization 5) condom 6) withdrawal/rhythm 7) foam/diaphragm/jelly 8) other _____ 40-41
    - 49. Primary reason for irregular use: 0) not irregular 1) discontinued 2) forgetfulness 3) side effects 4) clinic supply not available 5) temporarily not needed 6) supply misplaced 8) other _____ 42
    - 50. How patient received last supply: 1) at follow-up visit 2) clinic depot 3) community depot 4) store 5) mobile unit 6) home delivery 7) mail 8) other _____ 43
    - 51. Has patient recommended this systemic contraceptive to anyone since last visit: 0) no 1) yes 44
    - 52. Appointment for next follow-up visit: 46-51 (day month year)

Interviewer's name _____

COMMENTS: _____

4 80

SC003—kkx059

INTERNATIONAL FERTILITY RESEARCH PROGRAM

SYSTEMIC CONTRACEPTIVE STUDY
PHYSICAL EXAMINATION RECORD

APPENDIX C-3

PATIENT IDENTIFICATION: 1. Hospital or clinic no. _____ 2. Today's date _____ (day month year)

3. Patient's name _____ Telephone _____

4. Address _____

STUDY IDENTIFICATION

5. Center name _____ and number: [ ][ ][ ] 1-3
6. Study name _____ and number: [ ][ ][ ] 4-6
7. Patient order number: [ ][ ][ ] 7-10
8. Admission form number: [ ][ ][ ][ ][ ][ ] 11-16
9. Follow-up visit number: 00) admission [ ][ ] 17-18
10. Number of contraceptive cycles completed: [ ][ ] 19-20
11. Day within present cycle: [ ][ ] 21-22
12. Date of this visit: [ ][ ] day [ ][ ] month [ ][ ] year 23-28

SIGNS AND SYMPTOMS

Record for last 28 days or since last visit, whichever is less.

13. Spotting/breakthrough bleeding: 0) none 1) yes, early cycle 2) yes, midcycle 3) yes, late cycle 4) yes, more than one phase of cycle [ ] 29
14. Estimated number of days of spotting/breakthrough bleeding: 00) none [ ][ ] 30-31
15. Nausea: 0) no 1) yes [ ] 32
16. Vomiting: 0) no 1) yes [ ] 33
17. Dizziness: 0) no 1) yes [ ] 34
18. Headache: 0) no 1) yes [ ] 35
19. Hair loss: 0) no 1) yes [ ] 36
20. Backache: 0) no 1) yes [ ] 37
21. Diarrhea: 0) no 1) yes [ ] 38
22. Constipation: 0) no 1) yes [ ] 39
23. Abdominal pain: 0) no 1) yes [ ] 40
24. Abdominal bloating: 0) no 1) yes [ ] 41
25. Swelling (edema): 0) no 1) yes [ ] 42
26. Leg pains or cramps: 0) no 1) yes [ ] 43
27. Fatigue: 0) no 1) yes [ ] 44
28. Irritability: 0) no 1) yes [ ] 45
29. Depression: 0) no 1) yes [ ] 46
30. Breast discomfort/tenderness: 0) no 1) yes [ ] 47
31. Change of appetite: 0) none 1) increased 2) decreased [ ] 48
32. Acne and/or oily skin: 0) none 1) increased 2) decreased [ ] 49
33. Rashes: 0) no 1) yes [ ] 50
34. Facial pigmentation (chloasma): 0) no 1) yes [ ] 51
35. Sexual desire: 1) unchanged 2) increased 3) decreased [ ] 52
36. Vaginal itching: 0) none 1) yes [ ] 53
37. Vaginal discharge: 0) none 1) unchanged 2) increased 3) decreased [ ] 54
38. Other: _____ [ ][ ] 55-56
39. Diagnosis and treatment of physical conditions associated with symptoms listed above: 0) none 1) yes, specify _____ [ ][ ] 57-58
40. Examiner's name _____

PHYSICAL EXAMINATION

41. Time of examination: 1) admission 2) cross-over of contraceptive 3) termination [ ] 61
42. Urine albumin: 0) no 1) yes 2) not tested [ ] 62
    sugar: 0) no 1) yes 2) not tested [ ] 63
43. Eyes: 0) normal 1) abnormal, specify _____ [ ] 64
44. Skin: 0) clear 1) acne 2) chloasma 3) hirsutism 4) combination of abnormal conditions, specify _____ 8) other _____ [ ] 65
45. Thyroid: 0) normal 1) abnormal, specify _____ [ ] 66
46. Breasts: 0) normal 1) abnormal, specify _____ [ ] 67
47. Lungs: 0) normal 1) abnormal, specify _____ [ ] 68
48. Heart: 0) normal 1) abnormal, specify _____ [ ] 69
49. Abdomen: 0) normal 1) abnormal, specify _____ [ ] 70
50. Pelvis, vagina, perineum: 0) normal 1) leukorrhea 2) inflammation 3) 1 and 2 8) other _____ [ ] 71
51. Cervix: 0) normal 1) cervicitis 2) erosion 3) nabothian cysts 4) combination of abnormal conditions, specify _____ 8) other _____ [ ] 72
52. Uterus: 0) normal 1) suspected fibroids 8) other _____ [ ] 73
53. Adnexae: 0) normal 1) thickened 2) tender 8) other _____ [ ] 74
54. Rectum: 0) normal 1) abnormal, specify _____ [ ] 75
55. Pap smear: 0) normal 1) atypia 2) dysplasia 3) carcinoma *in situ* 4) invasive carcinoma 8) other _____ 9) not done [ ] 76
56. Varicose veins: 0) none 1) yes, nonthrombosed 2) yes, superficial thrombosis 3) yes, deep thrombosis [ ] 77
57. Abnormalities of the extremities: 0) none 1) edema, specify _____ 2) ulcers, specify _____ [ ] 78
58. Other apparent abnormalities: 0) none 1) yes, specify _____ [ ] 79

[5] 80

COMMENTS: _____

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INTERNATIONAL FERTILITY RESEARCH PROGRAM APPENDIX C-4

SYSTEMIC CONTRACEPTIVE ABBREVIATED DAILY SYMPTOM GRID

PATIENT IDENTIFICATION: 1. Hospital or clinic no. _____ 2. Date completed _____ *day month year*

3 Patient's **name** _____ Telephone _____

4. Address _____

5. Center number: 0 1–4

6. Study number: 0 5–8

7 Patient order number: 9–13

8. IFRP admission form number: 14–19

9. Cycle number: 20–21

10. Symptom grid number within cycle: 22

11 Date of **first contraceptive** cycle day in this cycle: *day* *month* *year* 23–28

12. Contraceptive identification: _____ 29–32

13. Frequency of contact: 1) once a month 2) twice a month 8) other, specify _____ 33

14. Contraceptive **cycle days when contacts** for this grid were made: 999) not applicable
First contact 34–36
Second contact 37–39

15. Contact: 1) self 2) telephone 3) home visit 4) clinic visit 5) home and clinic visits 8) other, specify _____ 40

DAILY SYMPTOM GRID

Calender month:

Calendar day:

Contraceptive cycle day: 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31 32

For Items 16-23, code as indicated on days when condition occurred.

16. Contraceptive pill: 0) pill missed 1) pill taken 2) 2 or more pills taken 0

17. Bleeding: 1) breakthrough/spotting 2) withdrawal/ menses 1

18. Vaginal **discharge**: 1) yes 2

19 *Nausea*: 1) yes 3

20. Vomiting: 1) yes 4

21. Headache: 1) yes 5

22. Fatigue: 1) yes 6

23. Breast tenderness/ swelling: 1) yes 7

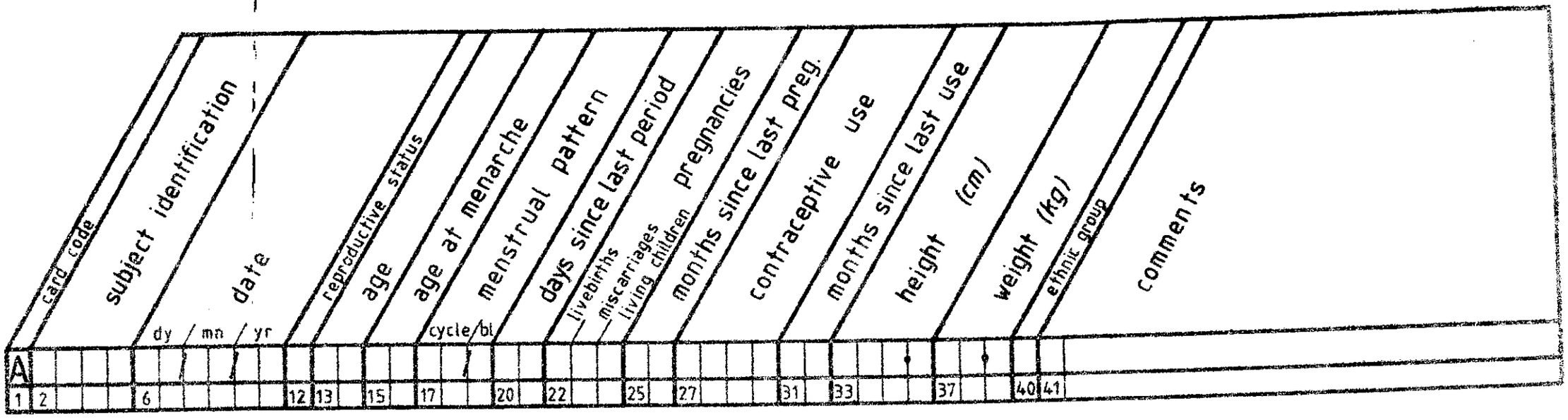
24._____ 8

25._____ 9

41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60 61 62 63 64 65 66 67 68 69 70 71 72 80

RETURN TO: International Fertility Research Program, Research Triangle Park, North Carolina 27709 USA

SC012 10/78



Subject's name _____ Census no. _____

ICDDR,B Endocrinology Study

BS 2/79 A-3

DR.B

Endocrinology Study

Subject Identification ☐☐☐☐

198_

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
January																															
February																														X	X
March																															
April																															X
May																															
June																															X
July																															
August																															
September																															X
October																															
November																															X
December																															

Please record menstrual-cycle events as follows:-

N = no menstruation S = slight bleeding (spotting) B = normal menstruation H = heavy bleeding

+ = ovulation pain E = emotional event x = missed pill (Pill users only)