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Oral contraception and intrauterine devices in family planning

by

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Lebensraum is very rapidly becoming a problem on this planet of ours and this cancer which is threatening to engulf us all during the next half century is indeed considerably more serious than mitotic disease itself. Sir Theodore Fox, in his new position as the Director of the Family Planning Association of the U.K., has made it clear that cheap and effective methods of family planning are indeed more urgently necessary than perhaps any other development. This last decade has seen revolutionary changes, not only in fertility control, but also in the hormonal factors which control ovulation, although at the present time the knowledge of mechanism of cortico hypothalamic factors is sadly lacking.

The last decade has seen the development of the oral contraceptive, and more recently there has been a reawakening of interest in intrauterine devices—and appropriate to this day and age the new devices are made of polyethylene. I would like to discuss and compare these methods which are clearly more effective than previously available methods.

With respect to cheapness or cost I would ask "how cheap is life—how cheap is malnutrition, subnutrition, starvation and death". Our Governments wage war on the invader and the expenses are borne by the State. If we are to survive, our children, our culture, our countries and civilisation, in this World, is it not time that our Governments waged war on these preconceived millions so that we that live might live and have complete regulation of our population growth compatible with the economic growth of the country in which we live. The tax on life is already heavy, let us by intelligent thinking control this burden by preplanning From this outlook it would seem to me that the expense of the present effective methods of family planning are extraordinarily cheap—or putting it another way "what price-tag would you put on life".

The factors affecting the population growth are shown in the table below:

FACTORS AFFECTING POPULATION GROWTH

Population rises

Improved health

Better		poor health
	antenatal care	bad housing
	paediatric care	poor medical supervision
	public health	no drugs
	nutrition	no antibiotics
	medical care	poor nutrition
	geriatric care	malnutrition
	drugs	

education
war
sterilisation { male / female }
abortion
contraception

The present World population of over three billion can be expected to exceed six billion by the end of the century. This figure of over six billion (six thousand million) is all the more

shattering when it is appreciated that by the middle of the nineteenth century, the World population had only just reached one billion.

Should this geometric progression continue, we can expect the population to double again in the first thirty years of the next century. The estimated growth is shown below:

Estimated Growth of World Population in Billions	
1963	3
2000	6
2030	12
2060	25
2100	50

Clearly improved public health measures, better ante and post natal care and development in medicine have been partly responsible for a marked reduction in the death rates. This is particularly so in the most sophisticated countries in the World, and a similar effect can be expected in progressively developing societies. This is shown in the next table:

Maternal Mortality Deaths per 100,000 live births (1961)			
Sweden	21	Mexico	195
United Kingdom	34	Ceylon	261
U.S.A.	37	Kampala (Uganda)	1370
Japan	120	India	2440
Egypt	135		

As a result of improved obstetric care accompanied by the use of antibiotics and chemotherapy, not only has the maternal mortality rate fallen, so that mothers who might have succumbed are now able to have further pregnancies, but also better paediatric and neonatal care has produced a tremendous reduction in infant mortality as shown in the following figures for England and Wales:

Year	1871	1961
INFANT MORTALITY (per 1,000 live babies in England & Wales)	156	21.4
MATERNAL MORTALITY	4.8	0.34

I do not propose to discuss sterilisation or abortion, although I understand that more than 100,000 Americans chose sterilisation last year as a method of limiting their family growth. In Madras, India, sterilisation of the male has been practised and the acceptability of the method has been shown by the increasing number of males attending the clinic for the procedure. According to Chandrasekan, however, the average age of the males, unfortunately, has been 37 years, an age when male fertility is already declining. It is perhaps pertinent to point out that in a study of oral contraceptives, the average age of the women attending the clinics elsewhere in India has been 22 years.

The necessity of limiting the growth of the family has long been recognised. Indeed Socrates more than two thousand years ago described the small village community where the villagers worked barefoot in the fields tending to their animals and crops in the summer and spinning cloth to keep themselves warm in the winter. He concluded that "a prudent fear of poverty and war will restrain them from begetting children beyond their means".

This demographic problem must indeed be solved. Apart from euthenasia and the suicidal method adopted by the lemmings, methods not likely to find much support, the situation must be tackled from three angles:

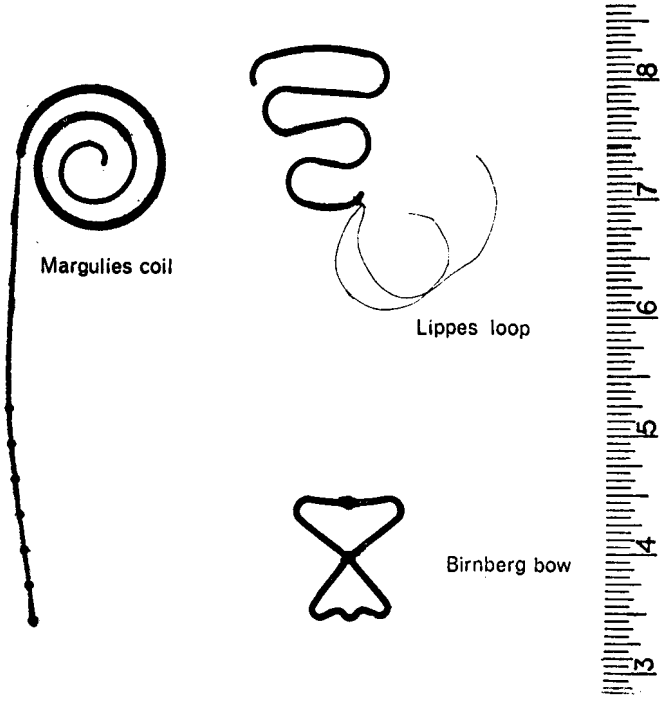
Solution to the Population Explosion

1. Increased Food Production.
   Intensive farming of land and sea.
   Scientific methods applied to food production.

2. Increase of Available Living Space.
   Fewer houses and more skyscraper flats.
   Development and irrigation of present deserts and other lands not considered suitable at the moment for habitation.
   Colonisation of other planets?
3. Reduction of the World Population
   Education
   World conflagration
   Sterilisation { male / female }
   Legalised abortion
   Effective contraception

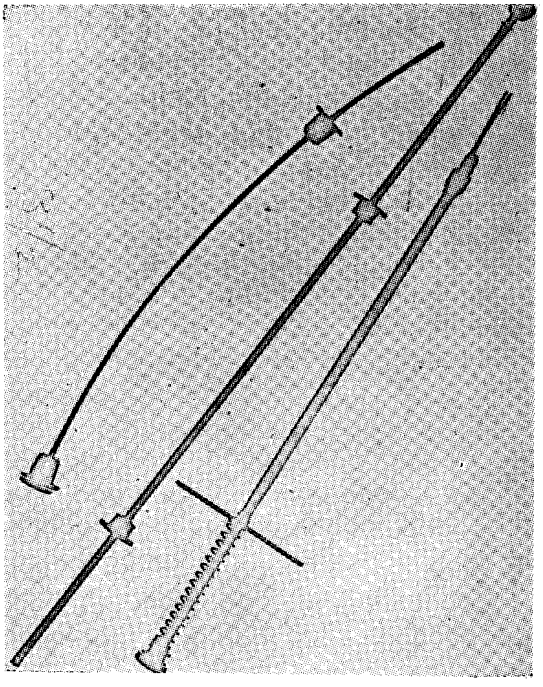
The first reference to contraception that I can find comes from the Ebers Papyrus, 1550 B.C. From this compendium of medical writings is this reference to a medicated tampon, perhaps the first properly designed intravaginal device. The prescription calls for a mixture of the tips of the shrub acacia dipped in honey. The compound is then inserted into the vagina. It is perhaps interesting to note that under fermentation acacia breaks down to lactic acid—as we all know a potent spermicidal agent.

From the same part of the World came the first intrauterine device, for the Arabs since ancient times have frequently placed small stones in the uterus of their female camels. Strangely enough the female camel then behaved as though she were pregnant and did not respond to the advances of the male. Although the intracervical device for the treatment of dysmenorrhoea was in use at the end of the last century, it was not until 1928 that the completely intrauterine device came into being following the experimental studies of Grafenberg. Undoubtedly the metal ring proved to be effective particularly in the hands of a few expert gynaecologists—as indeed Oppenheimer published a study in 1959 on 329 patients so treated for as long as 18 years. A similar study with excellent results, involving some 19,000 subjects, was published in Japan by Ishihama in the Yokohama Medical Journal, in the same year. In general, however, the Grafenberg ring did not find favour, not only did pregnancies occur, but many cases of chronic endometritis followed, and many cases have been reported of these rings finding their way into the peritoneum, and even leading to strangulation of a bowel viscus. The development of the present



plastic (polyethylene) I.U.Ds. came in about 1959-1960. Since this time there have been an increasing number of studies published and conducted. There are mainly three devices in use:

Various modifications of these devices have been used including the Japanese Ota ring. In Sydney, Australia, a modification of the Margulie's Spiral, designed by Bowman, is undergoing study. The devices are introduced with the special introducers shown below:



With the exception of the Birnberg Bow the other devices have to be fed into the introducer by hand. The difficulty with the Birnberg Bow is its subsequent removal should this be necessary. Dilation of the cervix is not usually necessary, but the devices cannot be readily introduced through the nulliparous cervix. So far most of the studies have been conducted by experienced physicians and according to Guttmacher some 60 devices can be introduced by one investigator daily.

The studies with these devices have been almost entirely as a result of investment by the Population Council of New York. Most of the studies have been conducted in the United States, Hong Kong, Fiji and the United Kingdom. There is now data on over 17,000 women in studies involving over 11,000 years. Soon Ok Kim reported a study in Korea where Lippe's Loops were inserted in over 1,000 women and there was only one pregnancy which followed an unnoticed expulsion—a pregnancy rate over 2,500 months of 0.5 per cent. Last September, some 11,000 devices were inserted in Korea, 4,000 in Taiwan and another 4,000 in Thailand. Other studies are now continuing in Egypt, Singapore, Australia, Korea, Taiwan and Thailand. The low pregnancy rate reported by Soon is considerably better than achieved by others, and Tietze reports a true pregnancy rate of 5.5 per cent, and a hypothetical figure—taking into account those pregnancies which may occur following the expulsion of the device without the knowledge of the patient—of 11.3 per cent.

How do the devices work? This is not at all clear, but various suggestions have been made and these are summarised in the following table:

Mode of Action of I.U.D.
Device accommodates to uterine cavity
May increase uterine muscle activity and prevent nidation. (Tietze)
May lead to increased passage of ova along Fallopian tube. (Mastroianni & Hongswood)
May disturb passage of spermatozoa through uterine cavity
May induce hyperoestrinism. (Pincus)

I believe it is not unlikely that various biochemical factors may operate with subsequent alteration in the endogenous hormone secretion patterns. This is suggested by various experiments and studies in rats, rabbits, and cows (and also the camel). In the rat, ovulation takes place normally and the ovum passes down the uterine tube, but disappear in the uterine horn where a thread is placed. The zygote in the other horn develops normally. In the rabbit, the zygote may nidate in the presence of an intrauterine foreign body, but not always. The imbedded zygote does not, however, develop due to

failure of the corpus luteum to survive. In the cow, the corpus luteum undergoes early atrophy so that nidation does not take place.

Alternatively, the devices may interfere with endometrial enzyme systems. This could be a direct action but the possibility of mediation through hormonal pathways must also be considered.

Various problems arising with these devices and the incidence are shown in the next tables:

Problems with Intra-Uterine Devices
EXPULSION
VOLUNTARY REMOVAL — Medical Psycho- logical
PREGNANCY
HAEMORRHAGE
PAIN
PELVIC INFECTION

Incidence of Reactions with I.U.D.	
EXPULSION	10 %
PREGNANCY	2.6 %
MENORRHAGIA	5-10 %
PELVIC INFECTION	2.6 %
PAIN	5-10 %

In all it would seem that the devices will be satisfactory in 80 per cent of patients, but that 20 per cent will for one reason or another reject them. Some 3 per cent of these will become pregnant, 10 per cent will expel the device and a further 7 per cent will have had such reactions as to make removal necessary.

Of those women where the device has been removed and no contraception practised, some 20 per cent conceived within six months. This figure is perhaps a little lower than, but not very dissimilar to, the figure quoted by Satterthwaite following the use of oral contraceptives.

I would now like to discuss the possible risk of malignancy. So far there is insufficient evidence that the devices increase the risk of cancer, although preliminary evidence from the Puerto Rican studies might indicate this risk. At the moment the numbers are too small, but I thought that you might like to see this data obtained from Drs. Pincus and Garcia, from data obtained in the Puerto Rican studies.

The following table shows the high incidence of positive Papanicolaou smears in the Carribean areas. It is, of course, well appreciated that genital carcinoma is not uncommon in that part of the World, for reasons that are far from clear.

Suspicious Papanicolaou Smears in Various Areas Before Contraceptive Use

(From Pincus & Garcia)*

Area	No. of Women	Suspicious Smears per 1,000 Women
Rio Piedros	1920	29.2 ± 3.8
Humacoa	1527	30.8 ± 4.4
Port-au-Prince	1091	29.3 ± 5.1
Mexico City	297	3.0 ± 3.2
San Antonio	289	10.3 ± 5.9
Colombo, Ceylon	250	12.0 ± 8.7

* Taken from Pincus and Garcia "Preliminary Findings in Hormonal Steroids and Vaginal, Cervical and Endometrial Histology."

Suspicious Papanicolaou Smears in Women Before Using Contraceptive Procedure Compared with Women Using Oral Progestins in the Carribean Area

(From Pincus & Garcia)

	No. of Women	Suspicious Smears per 1,000 Women
Premedication	4,538	29.8 ± 2.5
Norethynodrel with Mestranol	1,346	26.7 ± 4.4
Ethynodiol Diacetate with Mestranol	230	21.7 ± 9.7
Norethisterone with Mestranol	113	26.6 ± 15.3

The Development of Suspicious Papanicolaou Smears in Women with Negative Smears Before Contraceptive Use.

(From Pincus & Garcia)

Method	No. of Women	Suspicious Smears per 1,000 Women
Vaginal	208	72.1 ± 18.0
Oral Progestin	873	21.3 ± 10.5 28.6 ± 16.4
Intrauterine Devices	500	54.0 ± 10.0

It is noted from the following table that there is no increase in positive or suspicious smears in women using oral contraceptives over the level in the pre-treated group.

The incidence of suspicious smears, although increasing with all methods of contraception adopted, shows a higher incidence in those women choosing vaginal or intrautherine methods. It could be that there will be little difference in the final figures and that the use of oral progestins only slows down the rate of appearance of positive smears. Only time will tell.

Prospective endometrial studies have shown that endometrial dysplasia, mostly cystic and adenomatus hyperplasia and anaplasia, decrease significantly in women who subsequently use oral contraceptive methods of family limitation.

The Incidence of Endometrial Dysplasia in Women Before and Following the Use of Contraceptive Procedures

(From Pincus & Garcia)

Area	Contraceptive Method	No. of Women	% with Dysplasia
SAN JUAN	Premedication	231	5.1 ± 1.5
	Oral Progestin	579	1.5 ± 0.51
HAITI	Premedication	872	9.1 ± 0.97
	Oral Progestin	336	3.8 ± 1.04
	Vaginal	131	6.4 ± 2.14

In considering the possible risk of intrauterine devices three points must be established:

1. Does the device produce chronic irritation and will such irritation lead to a premalignant condition.
2. How do the devices work. It is not inconceivable that they work through some biochemical or hormonal pathway or at least stimulate an altered enzyme or hormonal pattern. If this is so we may not be in a position to state that the devices do not lead to a malignant or premalignant state for many years. (Experience with oral contraceptives at the moment would suggest that these compounds do not increase the incidence of malignancy and moreover there is mounting evidence that progestins may have anti-tumour activity).
3. Do we have the time available to consider long-term and possibly hypothetical risks. Can we afford to continue the small-scale human experiments for 20 years before beginning the mass use not only of coils but also oral contraceptives.

I would now like to turn to oral contraceptives, where experience now extends to more than ten years. Following the early experimental studies reported by Pincus and Chang, it became clear that the addition of oestrogen produced more regular menses. After discarding progesterone, the early studies were conducted with 19-Nor steroids combined with oestrogen. Since this time, other progestins have been used and have been found to be equally effective with respect to ovulation inhibition. These progestins fit into four groups:

1. **Testosterone Derivatives**
   (a) ethisterone
   (b) dimethisterone
2. **19—Nor Steroids**
   (a) norethisterone
   (b) norethynodrel
   (c) norethisterone acetate
   (d) ethynodiol diacetate
3. **Deoxy Steroids**
   (a) lynestrenol
   (b) allylestrenol
4. **17-a-Hydroxy Steroids**
   (a) medroxy progesterone acetate
   (b) 17-a -hydroxy progesterone caproate
   (c) megestrol acetate
   (d) melengestrol acetate
   (e) chlormadinone

The functions of the different fractions of the combined tablets are:

1. Inhibition of ovulation
2. Control of the endometrium

With the gradual reduction in progestin dosage, it is now recognised that follicular suppression is due to the oestrogen component, whereas the progestin is responsible for the maintenance of the endometrium, withdrawal of which leads to endometrial shedding.

Individual Roles of oestrogen and progestogen

Oestrogen
Suppression of Follicle

Progestogen
Control of Endometrium

Although much is known about the modes of action of the progestin/oestrogen combinations, there are many aspects which still need further elucidation. However, certain parameters have been measured which cast some light on the subject. The low urinary excretion of

(a) oestrone, oestriol and oestradiol

(b) pregnanediol

suggests inhibition of follicular growth. This is confirmed by the appearance of small pale ovaries at laparotomy. No corpora lutea have been seen on section in the human female. Although high doses of norethisterone and norethynodrel have inhibited total urinary gonadotrophins, according to Pincus, this has not been observed by Lorraine et al. following the use of oral contraceptives. This may, of course be due to the crudity of the method.

Mode of Action of Oral Contraceptives

Inhibition of follicular maturation & corpus luteum formation suggested by

1. low urinary excretion
   (a) oestrone, oestriol, oestradiol
   (b) pregnanediol
   (c) prevention of L.H. peak (Stevens)
2. absence of corpora lutea on examination of ovaries.

From the data presently available, it would appear that the action of these compounds is not just a direct inhibiting effect on the ovary, but a more central action acting through the hypothalamic pituitary pathway (Pincus). The thermogenic response to the medication may also be regarded as further evidence of the site of action (Fenn).

Other mechanisms may also play an important role in the anti-fertility effects of these compounds.

The atypical endometrium produced by the compounds may interfere with the nidation of the fertilised ovum, and the progestin, by preventing the normal thinning of cervical mucous, may prevent the passage of spermatozoa through the cervical canal. Although these ancillary effects may be of some importance in a few instances, the weight of evidence from carefully conducted studies shows that oral contraceptives inhibit ovulation in virtually 100 per cent of women who take them faithfully.

Other Mechanisms of Action

1. Atypical endometrium may prevent nidation
2. Altered viscosity of cervical mucous may prevent passage of spermatozoa.

Three regimes may be followed with oral contraception:

1. *Combined* progestin/oestrogen medication taken for 20 or 21 days each menstrual cycle.
2. *Sequential* regime. With this method oestrogen alone is taken for 10-16 days, followed by a progestin/oestrogen combination for 11-5 days.
3. *Serial* regime. This is similar to the above, but seven placebo tablets are given following the active medication. This is designed to make up a 28 day cycle.

These regimes may be shown diagramatically as below:

Schematic Presentation of O.C. Administration

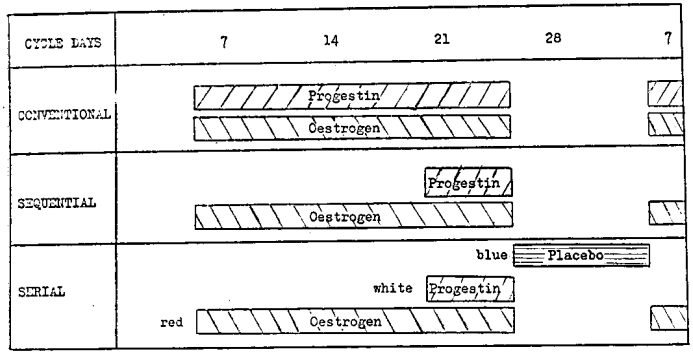
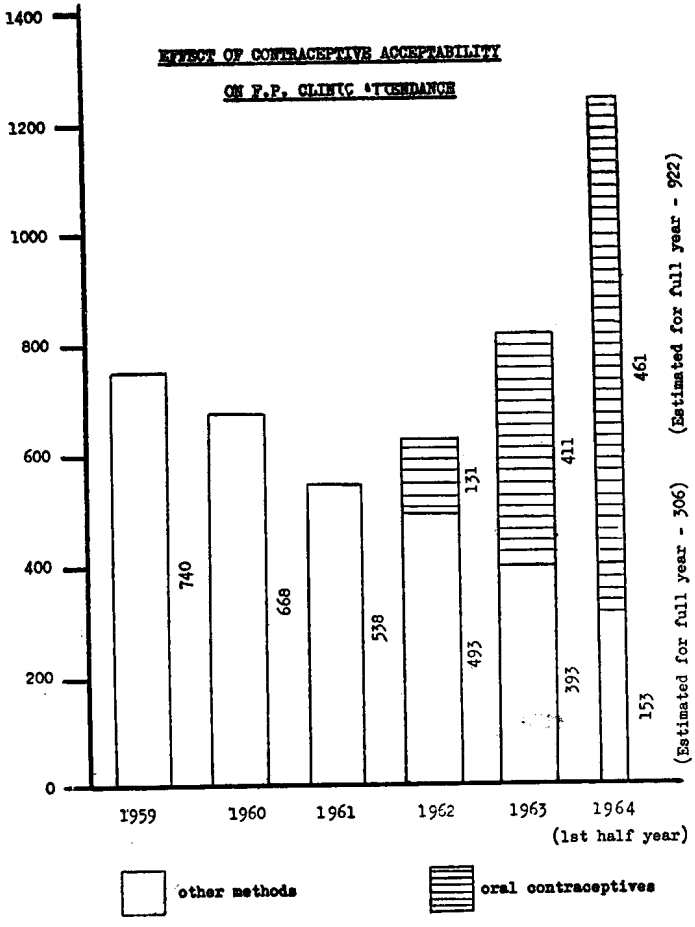


Figure 8



In the early studies relatively large doses of synthetic progestins were used to inhibit ovulation. Cycle control was not very satisfactory, but was improved when small amounts of oestrogen were added. It became apparent that many of the reactions experienced by women using these oral contraceptives were due to the progestin component of the tablet. With a reduction in the dosage of the progestin, the incidence of these reactions was lowered. It soon became apparent that the role of the oestrogen fraction was more important in the low dose progestin regimes, as shown by Eckstein et al. in the Birmingham experiment using norethynodrel where 14 women out of 48 conceived while taking the medication. In recent years it has become more apparent that the newer low dosage oral contraceptives rely practically entirely on the oestrogen content for ovulation inhibition. For this reason the percentage of oestrogen in the tablet has had to be increased. Apart from a reduction in many of the side reactions, the smaller progestin content with a relative increase in the dosage of oestrogen has provided better cycle control.

The aesthetic advantages of oral contraceptives, accompanied by a degree of effectiveness which closely approximates to 100 per cent, have been readily appreciated by women in many parts of the World. The degree of acceptability of this method over older conventional methods is illustrated in the following diagram with respect to clinic attendance and contraceptive regime requested. (see figure 8)

It could be argued that the degree of acceptability is a measure of the frequency and severity of side reactions. The increasing demand for oral contraceptives over conventional methods suggests that the reactions to the medication are rarely troublesome, or that the aesthetic advantages and simplicity of the method outweigh the disadvantages.

Clearly, a percentage of women do complain of untoward reactions, particularly during the early cycles of medication. On the other hand, many women who have previously experienced various menstrual disorders have noted an improvement in the medicated cycles.

Although many investigators have commented on this 'bonus' effect of oral contraceptives, detailed evaluation of side reactions

SIDE EFFECTS OF ORAL CONTRACEPTION	
BAD	**GOOD**
Nausea & Vomiting	Freedom from Anxiety
Breast Tenderness	Regularity of Cycles
Shortened Cycles	Withdrawal Bleeding usually less particularly in women with heavy menstrual loss
Amenorrhoea	Dysmenorrhoea less or absent
Headache	Premenstrual Symptoms often Improved
Depression	Improvements in Skin and Hair have been noted

has mainly concerned the unwanted and unpleasant effects. Of the products approved by the Family Planning Association in the United Kingdom Mears has reported on the percentage of reactions associated with these compounds. This data is shown below:

The following two tables show the latest list of approved and available oral contraceptive tablets. The figures quoted for the amount of side effects apply to one year to make for easier comparison, though after this time there are minor differences in weight change, amount of menstrual loss, and incidence of amenorrhoea.

The commonest side reaction is nausea which fortunately rarely persists for more than a few days at the beginning of the first one or two cycles. The incidence seems to be similar for all products as demonstrated by Wiseman:

A more worrying manifestation is that of amenorrhoea. Although this may not be harmful it can lead to needless anxiety on the part of the patient who may fear that she has conceived. If the new course of tablets is not started correctly, ovulation escape may occur, and the medication induced amenorrhoea may indeed be followed by pregnancy amenorrhoea. Apart from this hazard, the majority of women still believe that in the absence of pregnancy, the menses is a very necessary phenomena. In certain parts of the World, menstrual blood is regarded as bad blood, to be expelled and certainly not retained.

Although amenorrhoea is an unusual reaction in women using oral contraceptives, it none-the-less occurs in a small percentage of cycles. The incidence appears to be related to the dosage of the progestin and the duration of use. The incidence of amenorrhoea reported by Wiseman is shown below:

This incidence varies from the figures quoted by Mears and demonstrates the observed variations, a factor frequently forgotten. Clearly, many factors may account for differences in the incidence of reactions quoted by different observers. One such difference has been beautifully demonstrated by Wiseman, comparing percentage reaction rates in trial patients, when the tablets were provided free, against a similar group of women who paid for the medication:

Little information is generally available on menstrual symptomatology and cycle data in normal non-medicated women, and without proper and complete baseline information, it may be difficult to formulate correctly the effects of medication. A review of the available data on cycle length shows that more than 13 per cent of cycles are of 24 or less days of duration, whereas over 20 per cent are more than 31 days.

Against this background it would appear that medicated cycle length approximates more closely to the mean. Attention to this point has already been drawn by Garcia.

Side Effects at One Year

PRODUCT	% Nausea 1st Cycle	% Breast Discomfort	% Weight Change 3 lbs & Over +	% Weight Change 3 lbs & Over —	% Headaches
ANOVLAR	22	16	20	6	11
CONOVID	36	16	40	12	10
CONOVID E	48	9	28	17	3
LYNDIOL	40	6	25	16	9
NORLESTRIN	32	4	60	30	6
ORTHONOVIN	29	6	68	33	4
OVULEN (at 6 months)	20	14	50	nil	nil
VOLIDAN	25	4	26	33	7

PRODUCT	% Cycles of Spotting	% Cycles of B.T.B.	% Change in Flow +	% Change in Flow —	% Cycles of Amenorrhoea
ANOVLAR	5	3.8	8	74	1
CONOVID	14	17	8	22	5
CONOVID E	11	34	8	20	3
LYNDIOL	1.7	1.6	nil	46	5
NORLESTRIN	7	7	6	70	3
ORTHONOVIN	4	5	nil	58	0.5
OVULEN (at 6 months)	3	8	14	50	2
VOLIDAN	7	11	10	70	0.5

Incidence of Nausea in 1st Cycle of Medication
Showing Marked Similarity of All Preparations
(Slough F.P.A. June 1964)

PRODUCT	CONOVID E	Ethynodiol Diacetate		VOLIDAN	ORTHONOVIN	LYNDIOL
		1 mg. OVULEN	2mg. METRULEN			
Number of 1st Cycles completed	686	102	100	49	43	25
Nausea %	31	30	32	31	33	32

From: Wiseman, A., Four years experience with Ovulation Inhibitors in Clinical Trial and Routine Use, International Symposium, Sydney, October, 1964

Incidence of Amenorrhoeic Cycles with Various Preparations
(Slough F.P.A. June 1964)

PRODUBT	CONOVID E	Ethynodiol Diacetate		VOLIDAN	ORTHONOTIN	LYNDIOL
		1 mg. OVULEN	2 mg. METRULEN			
Total cycles completed to maximum of six	3213	173	584	195	44	109
% amenorrhoeic cycles	1	1	1	1	1	10

From: Wiseman, A., Four Years Experience with Ovulation Inhibitors in Clinical Trial and Routine Use, International Symposium, Sydney, October, 1964

The Incidence of Side Effects in Women Using Oral Contraceptives—Fee Paying (Clinic) Compared with Non-Fee Paying Patients (Trial)

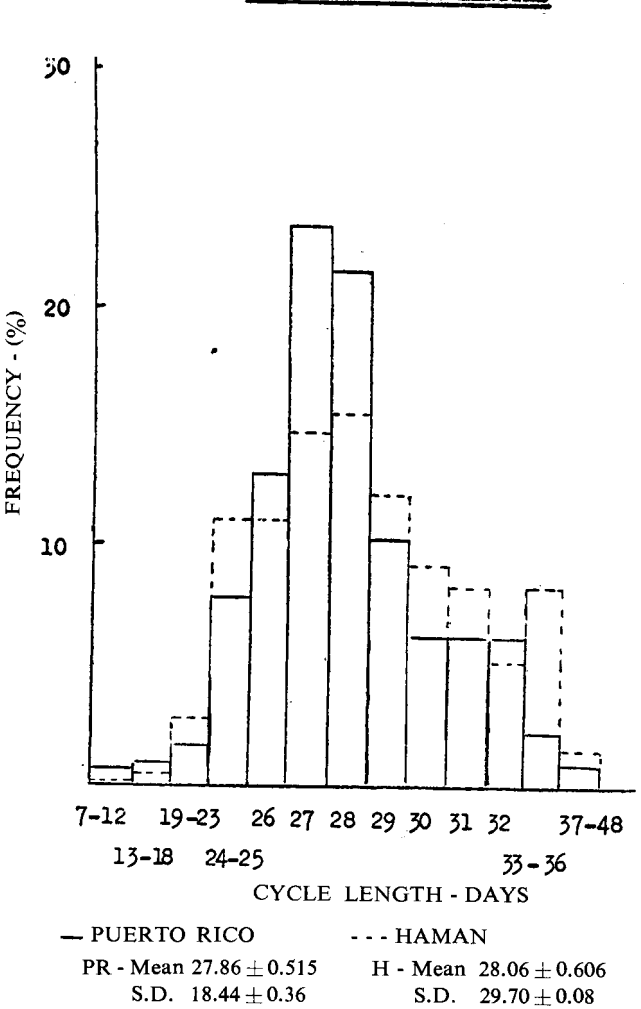
Side Effect	Patient	Percentage Incidence Rate			
		Cycle one	Cycle two	Cycle three	Cycles 4-6
B.T.B.	trial	40	36	35	26
	clinic	20	23	13	13
Spotting	trial	21	18	14	9
	clinic	12	5	4.6	1.6
Nausea	trial	38	10	nil	1
	clinic	20	3	nil	nil

From: Wiseman, A., Four Years Experience with Ovulation Inhibitors in Clinical Trial and Routine Use, International Symposium, Sydney, October 1964

Source of Data	Percentage Cycle Length		
	24 days or less	25-30 days	31 days or more
1. Issmer, 1889	9.2	78.3	12.5
2. Latz and Reiner, 1937	11.8	57.3	12.9
3. King, 1933	14.3	64	21.7
4. Engle and Shelesnyak, 1934	24.0	35.9	40.1
5. Haman, 1942	9.6	71.4	19.0
Total	13.8	65	21.2

With the introduction of lower dosage progestin/oestrogen combinations, cycle control has tended to improve. Other reactions have also been less severe including breast tenderness, headaches, depression and loss of libido.

A further reduction in progestin dosage has become possible with the introduction of the sequential and serial regimes. That oestrogen can be relied on for the inhibition of ovulation has been shown by Greenblatt, Goldzieher, Walker and McBride. In this respect it would appear that the ovulation inhibiting dose closely approximates to 0.1 mg. of ethinyloestradiol or mestranol and doses below this might allow ovulation escape. The relegation of the progestin to the end of the cycle in order to regulate withdrawal bleeding may be said to produce a more physiological state. Apart from the changes in endometrial histology discussed below, sequential and serial regimes have clearly demonstrated that the majority of side reactions are related to prescribing the progestin from early in the cycle. Some 4,000 women have now been studied where B.D.H. compounds have been used:



Sequential (Serial) Studies	
TOTAL NO. OF WOMEN STUDIED IN SEQUENTIAL REGIMES	3771
NO. OF WOMEN WHERE OESTROGEN DOSAGE 0.1 mg.E.E.	3148

The incidence of reactions with the sequential and serial regimes can be seen to be very low indeed, and certainly lower than has been reported with combination products:

It is perhaps interesting to note that the incidence of nausea has been considerably lower than with progestin/oestrogen combinations. This would suggest that the progestin must contribute to the higher incidence with the combined tablets. Libido has always been a difficult parameter to measure but the observation that patients switched to sequential or serial regimes have reported increased marital interest is perhaps more significant. There have been no reports of decreased libido on this regime. Although referred to as breakthrough bleeding, the incidence of this reaction on the low dose B.D.H. regimes has indeed been no higher than one per cent. Such bleeding has not been so marked for the patient to stop medication. It has rarely been more than slight staining or spotting.

Reactions with Serial (Sequential) Formulation

	Nausea	B.T.B.	Amenorrhoea	Breast Tenderness	Libido
FIRST CYCLE	13%	Less than 1%	nil	nil	No decrease*
LATER CYCLES	1%	Less than 1%	nil	nil	

* Increase in libido noted in patients transferred from tablets containing progestin/oestrogen combination.

Oestrogen and Progestin Content of Oral Contraceptives (Sequential or Serial)

Product	Oestrogen		Progestin			
	Ethinyl-oestradiol	Mestranol	Chlormadinone	Dimethisterone	Megestrol Acetate	Norethyn Odrel
FEMINOR		0.1				5
OVIN	0.1			25		
OVISEC	0.1				5	
SEQUENS		0.08	2			

Data on Sequential Studies

(0.1 mg of EE for 16 days; 0.1 mg of EE + 5 mg of megestrol acetate for 5 days)

No. of women	No. of cycles	No. of women withdrawn	%of total women withdrawn
664	2056	16	2.4

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Various sequential regimes are available on the market, notably in Australia and New Zealand. These are shown with their constituents below:

Ovisec is a serial method where the active medication is followed by seven placebo tablets so making up a 28 day cycle. With this formulation sixteen tablets each containing 0.1 mg. ethinyloestradiol are taken, one each day, followed by five tablets containing the same dose of oestrogen with 5 mg. of megestrol acetate. Cycle data and the incidence of reactions is shown below:

In earlier studies with sequential regimes there were a number of pregnancies. From these studies it became apparent that the oestrogen dosage was important and critical. Ovulation escape in some instances occurred either late or very early in the next cycle following the addition of the progestin. This has suggested that the progestin acting as an anti-oestrogen may depress the oestrogen activity below that necessary for ovulation inhibition. For this reason it also became apparent that the dose of progestin used should be small and only sufficient to produce predictable withdrawal bleeding. Studies have been proceeding in various parts of the World using 0.1 mg. ethinyloestradiol daily for sixteen days of the cycle, followed by a combination of this dosage of oestrogen with 1 mg. of megestrol acetate for a further five days. The intervening days are filled in with seven placebo tablets. This tablet has given rise to no pregnancies and an incidence of reactions very much lower than previously reported with the combination tablets.

Although experience with the serial method is much less than that obtained with combination products, evidence gained from studies in some 4,000 women suggests that this new

Reasons for Withdrawal			
No. of women withdrawn	**Nausea and/or vomiting**	**B.T.B.**	**Other**
16	13	1	2 (1 hairloss, 1 feeling of pregnancy)

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Data on Incidence of Reactions in Sequential Studies

(0.1 mg of EE for 16 days; 0.1 mg of EE + 5 mg of megestrol acetate for 5 days)

No. of women: 664 No. of cycles: 2056

Side effect	No. of women	No. of cycles	% total women	% total cycles
Nausea	21	21	3.1	1.0
Nausea and vomiting	6	6	0.9	0.3
Shortened cycles (B.T.B.)	8	12	1.2	0.5
Amenorrhoea	0	0	0	0

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method offers distinct advantages over previous methods at a progestin dosage considerably lower than any other compound currently available. The reduction in the progestin dosage to a total amount of 5 mg. for the cycle accompanied by a negligable incidence of side effects confirms the experience of others with combination products where the smaller dose of progestin included in the tablet has lowered the reaction rate.

Summary

In comparing oral contraception and intrauterine devices:

1. Effectiveness

The tablets are clearly more effective than the intrauterine devices:

Effectiveness of Various Methods of Contraception
Average Pregnancy Rate per 100 Women Years

Method	Percentage
DOUCHE	31
SAFE PERIOD	24
JELLY	20
COITUS INTERUPTUS	18
CONDOM	14
DIAPHRAGM	12
INTRAUTERINE DEVICES	2.6-5
ORAL CONTRACEPTIVES (Conventional)	0.1-1.0

From: Wiseman, A., Four Years Experience with Ovulation Inhibitors in Clinical Trial and Routine Use, International Symposium, Sydney, October 1964

2. Side Effects

About 20 per cent of women using oral tablets get some side reactions and although the incidence drops with succeeding cycles a number of women drop out from the trials, so providing a better figure with respect to reactions. The incidence of such reactions with serial and sequential methods seems to be far less, but even here a figure of 10-12 per cent can be expected initially.

Some 20 per cent of coil patients drop out for side reactions or unwanted pregnancy. So the figures would appear to be similar. There is some suggestion that the women who do not tolerate the tablets do not do much better with intrauterine devices, but this needs to be explored further.

3. Subsequent Fertility

This appears to be the same for pills and intrauterine devices.

4. Pelvic Infection

There is the suggestion that intrauterine devices may increase the risk of infection and endometritis. This may be true, but the need for a prospective study is again necessary here. If this is true, then one can expect a higher rate of infection when such devices are generally released—particularly so if it is planned that they be inserted by lay people.

There is no evidence that I am aware of that pills increase pelvic infection, although on that score there have been reports of monilial infections in women treated with progestins on pseudo-pregnancy regimes (Wright).

5. Post Partum Use

The coils are not usually inserted in post partum women until six weeks, at which stage the mother may already be pregnant or certainly be too busy to attend the clinic again. On the other hand women could be provided with pills at the time of parturition and given sufficient to last three months.

6. Newly Wed and Nulliparous

The intrauterine devices cannot be used easily here as the cervix is not patulous. This is another advantage for the pills.

7. Mode of Action

Far more is known about pills in this direction than with the intrauterine devices. Pills have now been in use for twelve years and intrauterine devices for only five, excluding the data on the Grafenberg ring.

8. Cancer

This is not yet known, but early information from the Puerto Rican studies would suggest that the risks with intrauterine devices may be higher than already found in pill users.

9. Cost

Clearly the intrauterine devices are cheap and this is a great advantage. Women can be fitted and seen at long intervals—but so for that matter can the majority of pill patients, certainly those women using serial and sequential regimes.

In conclusion I would suggest that there is probably a place for both methods. The pills perhaps for the young woman throughout her reproductive life, then when she has planned her family an intrauterine device can be fitted. By this time we shall perhaps have learnt a lot more from detailed studies of intrauterine devices that are now proceeding in many parts of the World.