U.S.

REPORT ON INTRAUTERINE CONTRACEPTIVE DEVICES

Advisory Committee on Obstetrics and Gynecology
Food and Drug Administration, January 1968

Advisory Committee on Obstetrics and Gynecology

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Director, Bio-Medical Division, Popu
Rockefeller University, New York, N

Christopher Tietze, M.D.
Associate Director, Bio-Medical Divi
Rockefeller University, New York, N

ON INTRAUTERINE CONTRACEPTIVE DEVICES

Advisory Committee on Obstetrics and Gynecology

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Preface

Although the Food and Drug Administration has no direct responsibility for intrauterine contraceptive devices, its Advisory Committee on Obstetrics and Gynecology was requested to review the entire subject and to submit a detailed report to the Commissioner, since increasing numbers of women are presently employing this method of birth control. The Committee was also charged with assessing the applicability of contemplated legislative recommendations designed to protect the public that uses devices that are retained within the body for many years.

Contents

Introduction

Rebirth of interest in the intrauterine devices (IUD's) as an effective, acceptable method of contraception stems from two factors. First is the availability of inert plastics that may be straightened to allow easy insertion and that return to their original shape, in which they are retained within the uterus. Second is the suggestion that the underprivileged woman is more effectively served when the need for recurrent motivation, required in most other forms of contraception, is removed. Several additional advantages of the intrauterine devices commend their use. Although their mode of action in women has not been fully elucidated, the antifertility action cannot be associated with any known systemic effect. Problems of initial distribution and followup are smaller than those associated with the oral contraceptives, and the expense of the intrauterine device is negligible. Whereas intrauterine contraception is not quite as effective as the best oral compounds, its use-effectiveness ratio is more favorable than that of traditional methods of contraception.

Complications of intrauterine devices are, of course, different from those of the hormonal contraceptives, but are approximately as common. The rates of discontinuance, furthermore, appear to be about equal in the two forms of contraception.

Data on use-effectiveness and discontinuance are more precise for the devices, since they are based largely on carefully supervised programs in the United States and abroad.

Basic and clinical research on the devices has met with fewer obstacles than those associated with study of the hormonal contraceptives. Both methods are highly effective for contraception, and each has its advantages and specific indications.

The Committee was divided into the following task forces to investigate and report on the major facets of intrauterine contraception:

Task Forces

1. Biologic Action
   S. J. Segal, Chairman
   P. A. Corfman
2. Utilization and Effectiveness
   C. Tietze, Chairman
   P. E. Sartwell
   S. G. Kohl
3. Inflammatory Reactions and Warnings
   R. B. Scott, Chairman
   E. M. Delfs
   A. T. Masi
4. Carcinogenic Potential
   R. Hertz, Chairman
   E. R. Carrington
   K. Adamsons
5. Legislation
   H. F. Fuller, Chairman
   N. J. Eastman
   L. M. Hellman

The report of each task force and the results of a questionnaire on serious adverse reactions have been reviewed and approved by the entire Committee. They are included in the appendix of the report. The findings of the task forces, with conclusions and recommendations of the the Committee, form the body of the report.

History

Intrauterine devices are far from new, having been mentioned in the writings of Hippocrates. Devices made of many different materials have been used for more than 2,000 years in a variety of gynecologic disorders, as well as to control fertility. Scientific writings on the subject were extensive during the 19th century, when devices were used chiefly for correction of uterine displacement but also for contraception. Contraindications to their use were defined. Chief among them was preexisting infection; intrauterine devices were therefore not employed for women with adnexal inflammatory disease. The question of carcinogenesis was raised, but no documented causal relation was ever established.

Resurgence of interest occurred in 1930, when Gräfenberg reported a series of more than 2,000 insertions of intrauterine devices for contraception. The failure rate with his silver ring was 1.6 percent. Although the mechanism of contraceptive action was not ascertained, Gräfenberg suggested that the devices increase functional activity of the endometrium. At the same time other workers showed that foreign bodies in the uteri of experimental animals prevented pregnancy.

The Gräfenberg ring was poorly received by the contemporary gynecologists. Although few of them had any personal experience with the ring, their objections were apparently based on unfortunate experiences with earlier intrauterine devices. The opposition was sufficiently great that the method fell into disrepute, and no further work in the field was reported for nearly 30 years. Two papers were then published, leading directly to the current revival of interest.

In 1959 Oppenheimer presented the results of years of experience with modifications of the Gräfenberg ring. His series included 1,500 patients with no serious complications. Japanese workers, including Ota, were the first to utilize plastic material for intrauterine contraceptive devices. Ishihama, also in 1959, reviewed the results obtained with the Ota ring in 20,000 women. These two reports revived interest and stimulated further research. Within 5 years many devices were designed and tested. The chief advantages of the new forms resulted from the use of relatively inert plastics and stainless steel, and from development of techniques of insertion that did not require dilatation of the cervix.

Designs

The stainless steel ring described by Hall in 1959 (figure 1C) is a slightly modified Gräfenberg ring. Several forms of metal and plastic rings have been used in Japan and Taiwan for 30 years. The most popular is the polyethylene Ota ring (figure 1B). Zipper, in Chile, devised a ring made of coils of nylon thread with a length of the thread left free as a transcervical tail (figure 1A). The first linear plastic device that could be introduced through the cervical canal was the Margulies spiral (figure 1D), developed in 1959. Shortly thereafter, Lippes designed his loop, a linear device of polyethylene (figure 1E). At about the same time other plastic devices, the bow (figure 1F) and the double-spiral (figure 1G), became available.

By early 1968 these were the only devices for which adequate testing and statistical evaluation had been completed. Others, however, have been manufactured and some are being evaluated. They include, among others, a stainless steel spring (figure 1H), a plastic "sham-

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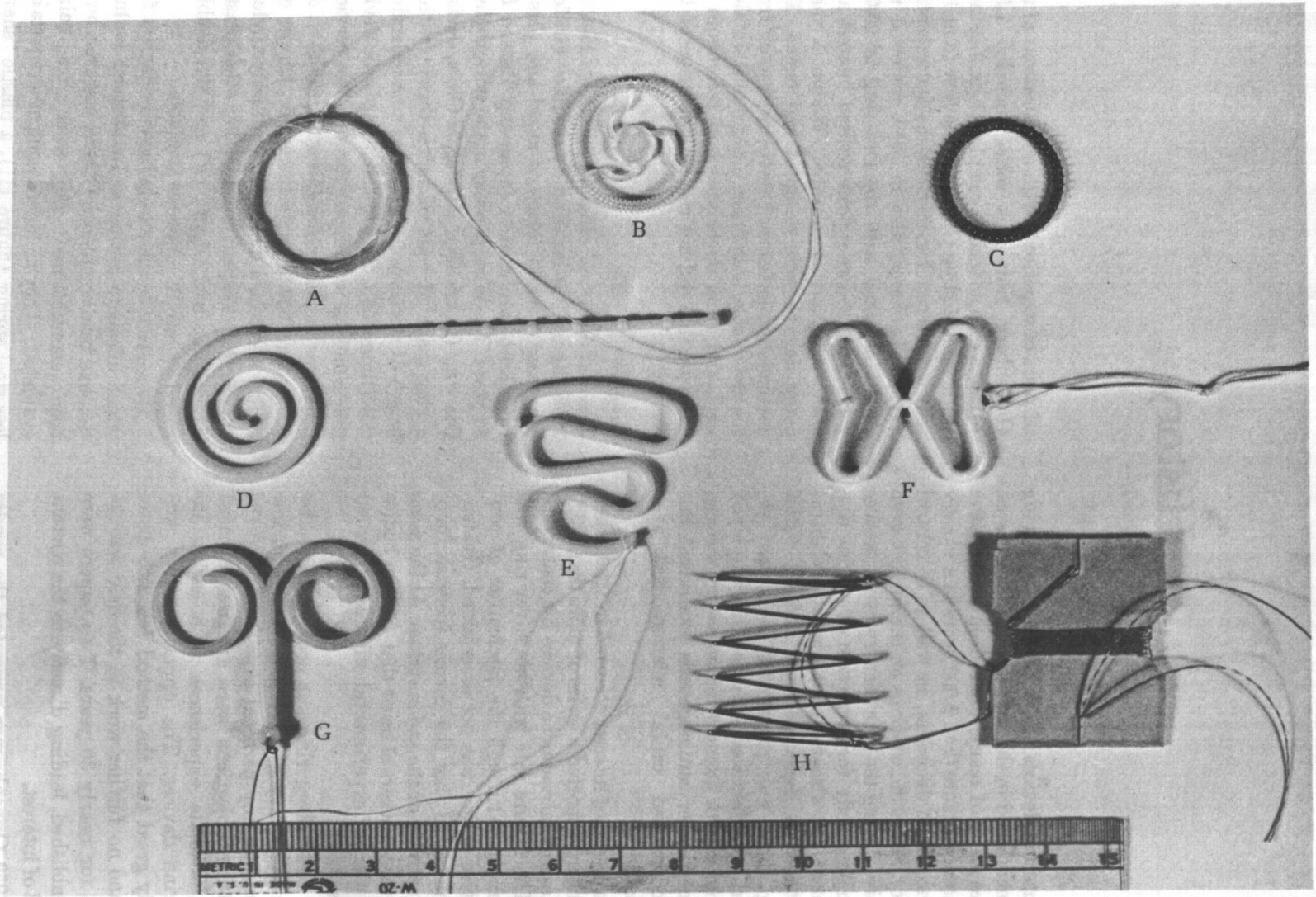
FIGURE 1



rock," and a plastic "T." The plastic is commonly a polyethylene of medium density, containing some barium to permit radiologic visualization. At least two plastic devices include a piece of metal that causes magnetic deflection when an appropriate instrument is placed near the pelvis.

Utilization

The countries listed in table 1 have nationwide family planning programs that emphasize the intrauterine devices. An absolute figure for the total number of women throughout the world who have had devices inserted in recent years can only be estimated. A reasonable figure is probably between 6 and 8 million, or nearly one-half the number of women currently using oral contraceptives.

TABLE 1

Utilization of Intrauterine Contraceptive Devices

Country*	Approximate cumulative number of IUD insertions		
	Sept. 1964	Jan. 1966	Jan. 1968
India	2, 000	320, 000	2, 000, 000
Pakistan	5, 000	50, 000	1, 200, 000
South Korea	50, 000	350, 000	1, 100, 000
Taiwan	25, 000	150, 000	370, 000

*Accurate figures for the United States are not available. By September 1964, the major manufacturers of IUD's had distributed nearly 250,000 devices. By January 1968, the total number distributed was approximately 3,000,000.

Biologic Action

The rapid acceptance of intrauterine devices for family planning has been accompanied by extensive research into their biologic effects and mode of action in fowl, in mammals including subhuman primates, and, to some extent, in man. Because of the anatomic and functional differences in the genital tracts of the various species investigated, it is unlikely that one mode of action or one particular effect will be found common to all.

Intrauterine devices have an antifertility effect in every animal tested, but differences among species have been found. In the chicken and sheep, for example, transport of spermatozoa is inhibited, thereby preventing fertilization. In the rabbit, sow, cow, and ewe, function of the corpus luteum is impaired to varying degrees. This effect appears to be unilateral and local. In animals such as the guinea pig, cow, and sow, in which sperm transport is not inhibited, fertilization may occur. Fertilized ova that implant in an untreated horn may go to full term, but those that implant adjacent to an IUD are likely to be lost. The IUD's do not inhibit ovulation, transport of spermatozoa, or fertilization in rodents and lagomorphs (rabbits or hares). Implantation, however, is inhibited—to the greatest extent in the mouse, less so in the rat, and to the smallest extent in the rabbit.

Many of the effects of IUD's in laboratory mammals and ungulates are not seen in subhuman primates or women, but the differences may be related in part to anatomic diversity of their reproductive tracts. The IUD does not prevent ovulation in either the rhesus monkey or woman, and there is no convincing evidence that the device exerts a systemic effect in primates, as it may in the rabbit and sheep. It has recently been suggested, however, that IUD's may increase or prolong secretion of oxytocin in postpartum women.

In women with IUD's there is evidence of transient endometrial inflammation. Histologic and ultrastructural studies, furthermore, suggest an alteration in cyclic maturation of the endometrium. The resulting asynchrony may be sufficient to inhibit intrauterine pregnancy. The suggestion that the device increases tubal motility in rhesus monkeys treated with gonadotropins to induce superovulation needs confirmation in large groups of normally ovulating macaques and in other species. Whether IUD's exert their contraceptive effect by interfering with fertilization in either rhesus monkeys or women is still not clear.

Efficacy

Much information is available about the efficacy of several intrauterine devices and their use-

effectiveness ratio. The data have been obtained largely as a result of a Cooperative Statistical Program (CSP) initiated in 1963 by the National Committee on Maternal Health. Adequate data are available for five types of IUD's: the Lippes loop, the Margulies spiral, the Birnberg bow, the Hall ring, and the double spiral. The period of followup is now 5 years for the largest loop (Size D) and 2 years for other devices.

These data have been derived from records of 27,600 women, covering more than 477,000 woman-months of experience. In conjunction with the material from the Taichung Medical Follow-up Study (a sample of about 6,600 women followed for more than 2 years), they provide adequate information for scientific evaluation. Both studies, furthermore, have utilized a life-table method of analysis of the data (app. 2, p. 24), which allows comparison of the results of studies of varying durations.

In the United States the most successful IUD's are associated with a pregnancy rate of from 1.5 to 3.0 per 100 women during the first year of use. These rates tend to decline during successive years. In general, the rates vary inversely with the size of the device and with the age of the patient.

A comparison of the effectiveness of the IUD's with that of other contraceptive methods requires consideration of the difference between theoretical effectiveness and use-effectiveness. Theoretical effectiveness reflects the assumption that the method is currently used according to instructions, whereas use-effectiveness takes account of human errors, which lead to inconsistent or incorrect use of the method. With IUD's, use-effectiveness approaches theoretical effectiveness, since the method requires neither daily nor periodic medication, nor any manipulation before, during, or after intercourse. The careful woman can, however, increase her chances of protection by inspecting her menstrual pads or tampons to see whether the device has been expelled, or, if the device has a transcervical appendage, by examining herself periodically.

In terms of theoretical effectiveness, IUD's are less reliable than oral contraceptives given according to the combined or the sequential regimen. The IUD's are probably not more effective than the diaphragm or condom if the conventional forms of contraception are used correctly. In terms of use-effectiveness in clinic patients, however, the IUD's have proved far more reliable than the traditional methods and only slightly less reliable than the oral compounds.

The success of any contraceptive method depends not only on the effectiveness in preventing pregnancy but also on the rate of continuation of its use. IUD's may be discontinued on the patient's request because of the desire for another pregnancy or other personal reasons, because of untoward reactions, or because the devices are involuntarily expelled.

Rates of expulsion tend to decline steeply with age and less steeply with parity. They vary inversely with the size of the device, and are higher during the first few months after insertion. Rates of removal tend to follow the same pattern as that of expulsion, but there is an additional steady incidence of removal during the 4 years for which significant data are available.

About 80 percent of women will continue to use the device for the first year, 70 percent for the second, and, from the limited data available, about 50 percent at the end of the fifth year.

Among clinic patients in the United States, rates of continuation have been much higher for the IUD's than for such traditional contraceptive methods as the diaphragm, foam tablets, and vaginal foam. The combined experience of family planning programs in a number of developing countries has been similar.

The relative rates of continuation for IUD's and oral contraceptives cannot be assessed accurately because no studies have been reported in which the two methods were offered to comparable populations in comparable circumstances. Fragmentary evidence suggests that in the lowest socioeconomic group with minimal education, rates of continuation are higher with the IUD's than with the oral compounds, but adequate information about nonclinic patients is not available.

Adverse Reactions and Safety

Chief among the minor complications of the intrauterine devices are irregular bleeding and uterine cramps or pelvic pain. They occur commonly during the first 2 or 3 months after insertion and tend to disappear with continued use. Together they constitute the reasons for about 60 percent of all removals.

More serious is the occurrence or recrudescence of pelvic inflammatory disease (PID). The prevalence of PID in the entire female population is not known exactly but it is very likely considerable; the disease is more common among the socially and economically deprived.

Some experimental animals are subject to pyometra when foreign bodies are inserted into the uterus (app. 4, p. 36). In women, there is transient infection of the uterine cavity during the first 24 hours after insertion, but the bacteria disappear rapidly (app. 3, p. 31). The incidence of PID in women using IUD's has been reported to be about 2.5 percent during the first year, falling to about 1.5 percent during the second. The rates are highest during the first month after insertion.

The Committee believes that the rate of infection can be reduced by sterile prepackaging of the devices with disposable inserters. Further studies should be done to ascertain whether antiseptic cleansing of the vagina and cervix reduces infection.

Perforation of the uterus is uncommon and is often unnoticed by the physician. Its incidence varies from 1 per 10,000 insertions reported from Taiwan, to 4 per 10,000 as reported by CSP, or 70 per 10,000 as reported from Singapore. Perforations are probably the result of trauma caused by the introducer during insertion. The Committee believes that the incidence of perforation can be reduced by careful sounding of the uterus before insertion to ascertain the depth and direction of the uterine cavity, and by routine use of a tenaculum to maintain the uterus relatively straight.

A survey of the Fellows of the American College of Obstetricians and Gynecologists (app. 6, p. 41) disclosed 15 instances of intestinal obstruction following perforation of the uterus by IUD's. The device was of the closed type in 13 and of an undisclosed type in two cases. In addition, three cases of uterine perforation with intestinal obstruction had previously been reported in the world's literature. These were all associated with a closed device. In at least four cases the device had only partially perforated the uterine wall, adding to the difficulty of the immediate diagnosis of this accident. The significance of these findings is amplified by the relative paucity of use of devices of the closed type. Perforation of the uterus with intestinal obstruction has not been reported with open devices. In view of these reports, the Committee recommends that the presently available closed devices not be used except in specially indicated circumstances.

If perforation is known to have occurred with a closed device, in ordinary circumstances the device should be surgically removed without delay. If, on the other hand, perforation occurs with an open device, removal will depend on the judgment of the attending physician.

The survey by the Committee (app. 6, p. 41) disclosed 10 deaths in which the data were sufficiently detailed to permit assessment. In the judgment of the Committee there was a causal relation between death and the insertion of the device in four instances. Basing the figure on the 10 documented cases, allowing for 50 percent under-reporting, and assuming a conservative estimate of usage, mortality might reach 0.2 per 10,000 insertions, a rate so small that it might not be disclosed even in the large series of CSP.

Plastics of the type used for IUD's have been used extensively as prostheses in various parts of the human body and have in no instances resulted in cancer. Intrauterine devices have, however, been associated with malignant tumors in rats, but the IUD has not been shown to produce a neoplasm in either the cervix or the endometrium of women, and the available reports indicate no effect of the device on the course of preexisting dysplasia.

The incidence of abortion may be as high as 40 percent if pregnancy occurs with the intrauterine device in situ. The proportion of these reported abortions that are induced, however, cannot be ascertained. When the pregnancy pro-

ceeds to full term, the device is found to be outside the membranes or occasionally beneath the placenta. The limited numbers of infants so far available for study do not have a greater than expected incidence of prematurity or malformations.

Ectopic gestation occurs about once in 20 pregnancies with the device in place. This ratio, which is 10 times the normal rate, is attributable to the substantial reduction in the number of intrauterine pregnancies. There is no evidence that IUD's cause ectopic pregnancies.

Legislation

The present legislation establishing jurisdiction over devices is limited to regulation of marketed products when there is evidence of excessive claims or hazard to health. Various intrauterine devices may therefore be marketed with only the manufacturer's supervision of the purity of the plastic and of quality control. Most devices are packaged without adequate instructions for use, and many are not marketed in sterile packages with disposable introducers.

The legislation under consideration by the Food and Drug Administration (app. 5, p. 39) for certain classes of devices secured or placed within the human body appears satisfactory when applied to intrauterine contraceptives. It will neither limit research nor prevent investigational use. It will, however, set standards of composition, reliability, and labeling that are directed toward maintenance of public health and safety and prevention of complications and untoward effects. The Committee endorses the contemplated legislation provided that contraceptive devices are not subjected to special attention.

Conclusions and Recommendations

I. Effectiveness and Utility

A. The Committee finds adequate scientific data attesting the effectiveness and utility of the intrauterine devices.

B. The intrauterine devices are highly effective in preventing pregnancy, although they are not quite as reliable as the hormonal contraceptives if the latter are taken according to instructions.

C. The rate of continuation of use is similar to that of the oral contraceptives and is far higher than that of traditional methods, at least among the socially and economically deprived.

II. Serious adverse reactions

A. Although there seems to be underreporting of serious adverse reactions, insertion of intrauterine devices carries a definite, albeit small, risk of infection and uterine perforation. Deaths arising from infection have been rare, but perforation by closed devices is followed by intestinal obstruction in a disproportionately large number of instances. *For this reason, the Committee is averse to the use of currently available closed devices, except in very unusual circumstances.*

B. The adverse reactions that require removal are mainly vaginal bleeding and pelvic pain. More serious adverse reactions associated with the IUD are rare, stemming essentially from infection and from uterine perforation during insertion.

The incidence of infection can probably be reduced by greater attention to sterile technique and by the use of a device with disposable inserter packaged as an individual unit and presterilized. *The Committee recommends more stringent procedures for sterilization of the devices and inserters and more careful techniques in their insertion.*

C. The incidence of uterine perforation can be reduced by sounding the uterus before insertion and by aligning the corpus and cervix by traction on a tenaculum.

D. There is no apparent carcinogenic effect of the devices in the human being. *Each patient, nevertheless, should have a cervical smear before insertion and should have a periodic cytologic examination.*

E. *The Committee recommends adherence to the contraindications and precautions listed in appendix 3, page 31.*

III. Legislation

A. *The Committee endorses the efforts of the Food and Drug Administration to regulate certain classes of medical devices.*

B. *Contraceptive devices should not be subjected to special attention in contemplated legislation.*

C. *The contemplated legislation regulating certain medical devices should include a means of confidential reporting of adverse reactions.*

IV. Further Research

A. Adequate data are still unavailable to answer several basic scientific and clinical questions related to the intrauterine devices.

B. *Research support should be provided as follows:*

(1) *to elucidate the mechanism of action of the intrauterine devices,*

(2) *to develop more satisfactory and effective devices,*

(3) *to study their specific acceptability by particular population groups, and*

(4) *to provide means for reducing the incidence of adverse reactions, both minor and serious.*

Report of the Task Force on Biologic Action

S. J. Segal, Ph. D., Chairman

Introduction

The rapidly increasing use of the intrauterine device (IUD) for family planning purposes has stimulated considerable research on its biological effects in experimental animals and humans. Several comprehensive reviews of the subject have appeared in recent years (4, 23, 44, 106, 117). The research shows that IUD's have an antifertility effect in every species tested but that the stage of the reproductive process influenced by their presence differs from species to species. It is not possible, therefore, to explain the mechanism of action in a manner that applies to all species studied.

The differences in action which have been observed are due in part to differences in the anatomical and physiological features of the reproductive systems among animal forms and to the marked variation in size, configuration, and composition of the devices which have been used. IUD's used in subhuman primates and humans are generally composed of stainless steel or mixtures of polyethylene and barium sulfate. They are manufactured in various shapes, such as loops, coils, bows, and rings and are usually of a size to fill the corpus of the uterus without applying lateral pressure to the uterine walls. Devices used in large domestic animals, such as sheep and cattle, are spirals of polyethylene and tend to distort the shape of the uterus; in smaller animals, such as rodents and rabbits, they may be threads of silk or nylon or larger segments of polyethylene. In earlier experimental work, when intrauterine foreign bodies were used solely as a tool to investigate such problems as decidualization and nidation, glass beads and beeswax or paraffin balls were employed.

Recently research has become focused on the mechanism of the antifertility action of the devices, with the ultimate aim of achieving better intrauterine device design for human use. A good deal of work has been done, but there are particular areas that require further investigation.

Effects in Experimental Animals

Domestic Fowl The effects of foreign objects in the avian oviduct are of interest. Early observations suggested inhibition of ovulation (54) but more recent work indicates that ovulation is not affected by the presence of intrauterine threads, but that egg pickup by the oviduct is somewhat inhibited (75, 76, 111).

Eggs which are produced are not fertilized since sperm do not ascend to the upper oviduct, and the eggs tend to have soft shells, suggesting either a rapid passage through the lower oviduct or an alteration in oviductal environment. This later interpretation is supported by the consistent finding of acute and chronic inflammation in the lower oviduct as a response to the foreign object.

Mouse The placement of a length of thread in a small segment of one horn of the bicornuate uterus of the mouse prevents the establishment of nidation sites throughout the entire length of the occupied horn, and renders the contralateral horn comparatively sterile as well. Sperm transport and fertilization are not prevented on either side of the reproductive tract. Zygote transport, however, appears to be impeded on the operated side, since fertilized ova can be recovered from the tube on the fourth day after mating, a time when they should normally have passed into the uterus. There is no gross anatomical explanation for this "tube-locking" effect; the cause remains unexplained. The basis of the sterility on the control side is also unknown, although it is presumed to be mediated through a humoral factor transmitted from the IUD-bearing horn, a phenomenon that is anatomically possible in the mouse because of an incomplete septum between the two horns at the cervical junction (29, 30).

Rat Foreign bodies in the bicornuate uterus of the rat have a less extensive effect than they do in mice. Threads of silk or nylon or devices composed of materials used in the manufacture of intrauterine devices for women will prevent blastocyst nidation in the horn in which they are inserted, but have no antifertility effect on the contralateral untreated horn (27, 28, 29, 30). The foreign body must lie freely in the endometrial cavity and the endometrium must be pierced; if the thread lies only in the myometrium it has no antifertility effect (31, 108). There appears to be no effect on the estrus cycle or on the corpus luteum (88, 105), nor is sperm transport altered (83). Upon removal of the thread, fertility is restored (73).

It appears that ova transport through the oviduct is not affected but that blastocysts degenerate or are prevented from implanting when they enter the uterine cavity at approximately day 5 (72, 85, 88). This concept is supported by observations in rats with unilateral IUD's subjected to experimental delay of implantation. Following a 6-day period of delay, implantations occur in the control horn but neither implantations nor deciduomata are found in the experimental horn (72).

Uterine threads inserted prior to the period of maximum sensitivity for decidua formation inhibit the ability of the endometrium to decidualize after stimulation with trauma or histamine injections (24, 30, 85). Timing of the introduction of a thread can be arranged, however, so as not to prevent decidua formation in response to trauma. Since similarly timed insertions of threads in mated animals have an antifertility effect, a direct effect of the foreign body on the ability of the endometrium to decidualize cannot be considered the primary action of the procedure. Furthermore, a thread will not interrupt pregnancy if it is placed in the uterus as early as the eighth day of pregnancy (67).

All of these findings indicate that the intrauterine foreign body induces some alteration in the rat uterine environment hostile to fertilized ova. Preliminary studies indicate that the formation of a surgical anastomosis between the uterine horns of the rat will allow a single suture to have a bilateral effect (17), suggesting the transfer of a humoral mediator as in the case of the mouse. Other preliminary studies show that a foreign body causes the uterine fluid to become viscous, manifesting an increase in albumin and globulin concentrations (62, 66). It is suggested that these changes in ionic strength could have a dehydrating effect on blastocysts. That earlier studies had demonstrated no effect on uterine pH (82) is not incompatible with this concept because of the highly buffered quality of uterine fluid. Indeed, there is a report of an experimental situation in which the uterine fluid from the horn of a rat uterus bearing a foreign body transmitted to an otherwise normal rat uterus the inhibitory influence of the foreign body itself (103).

Foreign bodies affect the rat uterus in other ways. They are uterotrophic (102) and produce increased muscle tone (84) unless they are too small (73). Such uterotrophism occurs after ovariectomy and adrenalectomy (102), indicating that the effect is local in nature. That the uterine weight increase is more than a nonspecific inflammatory reaction is indicated by the histological pattern of the myometrium and

endometrium and by the fact that the weight increase is not prevented by hydrocortisone (102).

Tissue slices taken from rat uteri with foreign bodies have been studied for alkaline phosphatase levels, lipids, nucleic acid, glycogen and a number of other substances (73). The only notable effect has been that slices taken from IUD-bearing horns show an almost doubled oxygen uptake shortly after insertion and that this increase declines slowly with time, a phenomenon that could reflect the initial trauma of insertion. Histological studies have shown that development of normal secretory endometrium is inhibited somewhat in the region of the foreign body and that there is considerable glycogen accumulation at the basal area of the endometrium (100). There is also some increase in cystic glandular hyperplasia (102). In one study, the chronic presence of foreign bodies produced squamous metaplasia in 20% of the experimental animals (73); and in another study prolonged exposure was found to lead to pyometra, metaplasia, and epidermoid carcinoma (22). Chronic inflammation of the endometrium has been found associated with the IUD in a number of studies (26, 43, 62). This observation has led to the suggestion that a chronic inflammatory reaction is essential to the antifertility effect in rats.

The foreign body increases uterine histamine levels (101), a finding that is probably related to the discovery by another investigator of an increase in the number of mast cells in the tissue adjacent to the IUD (17). This phenomenon is of particular interest because of the implication of histamine release for normal implantation of rat blastocysts. On the other hand, the relationship of this finding to the antifertility effect seems puzzling, if, as already noted, the blastocysts degenerate prior to the expected time of implantation.

In summary, among the experimental animals, the rat has been used most extensively to study the biological action of an intrauterine foreign body. An antifertility effect occurs, which is reversible upon removal of the foreign body. There is no evidence of a systemic effect; the antifertility action is confined to the horn bearing the foreign body. Treated animals have normal pituitary content of gonadotropins (18), normal estrus cycles, and normal corpus luteum function. Ovulation, sperm transport, fertilization, and zygote transport through the oviducts occur normally. As the zygotes enter the uterus, they either degenerate completely or pass out of the uterus *per vaginam* in a degenerative state. The cause of this hostility of the uterine environment is unresolved.

Although biochemical studies of a large number of components of uterine tissue have been carried out, no single observation stands out as particularly revealing. An inhibitory effect of the foreign body on the ability of the rat endometrium to decidualize in response to trauma or histamine may be related to the blastotoxic effect, but so far this relationship is obscure. The strongest indication of a relationship between the two effects is the observation that luminal secretions from a thread-bearing horn when instilled locally can reduce the decidualization capacity of a normal rat uterus that is in the predecidualization stage.

The occurrence of the changes caused by the foreign body requires that some part of the object be intraluminal and not merely imbedded in the myometrium or endometrium. This observation makes it difficult to consider increased myometrial activity resulting in premature expulsion of blastocysts as the primary event. That the foreign object causes an endometrial accumulation of glycogen, mobilization of mast cells, increase in total uterine content of histamine, and a transient increase in oxygen consumption is interesting, but these observations fail to suggest a direct relationship with respect to the degeneration of blastocysts. More revealing, perhaps, is the consistent polymorphonuclear leucocytic invasion of the endometrium observed in the uterine horns with foreign bodies. This circumstance may have an effect on the biochemical properties of the luminal contents, and on the ability of blastocysts to survive there.

Hamster and Guinea Pig Similar to the rat, the hamster responds to the presence of a foreign body in the uterus by failing to manifest blastocyst nidation in the treated horn. Cycle length, ovulation, sperm transport, and fertilization

proceed normally, yet the presence of the IUD does not prevent the endometrium from decidualizing in response to appropriate stimuli as it does in the rat (99).

The reproductive cycle of the guinea pig differs from that of the mouse, rat, and hamster by the occurrence of a prolonged functional phase of the corpora lutea. It is interesting to note that IUD's inhibit corpus luteum function in guinea pigs (8) much as they do in sheep and cattle. Such inhibition is not observed in other rodents, possibly because the cycle in such animals is comparatively short. In guinea pigs only the corpora lutea of the ovary on the side of the uterus bearing the foreign body are affected (34). It appears, therefore, that the luteolytic effect of the IUD is mediated locally rather than systemically.

Rabbit Some of the earliest laboratory work on the antifertility effect of intrauterine foreign bodies was done in the rabbit (14). These studies, and others (1, 2, 10, 30, 69, 88) show that the device affects fertility by interfering with normal nidation. Ova are released, fertilization occurs, tubal transport is normal, implantation takes place on both the treated and the untreated side, and embryos not immediately adjacent to the device proceed to term. Embryos adjacent to the intrauterine device, however, are lost at about the seventh day.

As in the rat, an IUD in the rabbit uterus has an uterotrophic effect not necessarily associated with an effect on uterine activity (25). Although some observers have noted evidence of inflammation with IUD use (14), others have claimed that the use of sterile technique will prevent infection without eliminating the antifertility effect (77, 78). Earlier studies (14) suggested that glandular hypertrophy is associated with the IUD, but more recent observations (69) show no significant changes in histology, and no changes in alkaline phosphatase or glycogen levels. The biochemical composition of the tubal fluid does not show any noteworthy alterations in the presence of an intrauterine foreign body (71).

Of particular general interest is the possibility that IUD's may accelerate transport of ova through the oviduct. A unique study in rabbits has shown that an intratubal thread may speed ova passage (15, 68). Other studies with intrauterine threads indicate a normal rate of passage of tubal ova (55).

The discovery in the rabbit of a prolongation of several hours in the interval after mating before ovulation in the presence of an IUD (58) indicates that the IUD influences the hypothalamo-hypophyseal complex. Evidence thus exists for a systemic effect in the rabbit, probably neurogenic. The mechanism which has been suggested for such a delay is a prevention of LH release, substantiated by direct measurement of LH content of the pituitary glands, and reported to be elevated in the presence of an IUD. This is an important observation, one of the few that indicate IUD's may have a systemic effect. But it must be remembered that rabbits are reflex ovulators and such delay in ovulation would not be apparent in other animals in which IUD's have been used, since such animals are spontaneous ovulators.

Sheep The effect of an IUD in the ewe is unique among the mammals studied since it appears to block sperm transport (19, 49), a phenomenon also seen in the hen. When a device is placed unilaterally or bilaterally, no sperm can be found in the oviduct after natural mating. Sperm injected directly into the uterus containing an IUD undergo head-tail separation, though some sperm may not be affected and fertilization does occur.

Histological studies in the ewe show that IUD's produce inflammation, leukocyte infiltration, and an increase in vascularization (35, 50, 53). Somewhat similar histological effects are seen in the goat (59). Recently it has also been shown that IUD's cause the production of an increased amount of mucopolysaccharides in the endometrium (21).

The device apparently does not affect ovulation or egg transport (49), but it does influence the size of the corpus luteum (36, 109). When a corpus luteum develops on the same side as a unilaterally placed device, the corpus luteum is smaller than normal; the administration of human chorionic gonadotropic hormone over-

comes this inhibitory effect. If the corpus luteum develops on the side opposite the IUD, it is normal in size. These observations indicate that the IUD in sheep has a distinct local effect on the adjacent corpus luteum. Humoral or neural factors are undoubtedly involved, but they have yet to be identified.

In addition to the local effects on the utero-ovarian axis, intrauterine foreign bodies in ewes are associated with elevated pituitary LH content on the day of estrus and 3 days following mating (33). These findings are somewhat similar to those observed in the rabbit and similarly suggest a neurogenic effect which may partially prevent LH release. Final conclusions cannot be drawn from this preliminary work, since normal LH curves have not been completely established for ewes.

Swine Studies with IUD's in the gilt have shown that ovulation and fertilization occur normally, and that the estrus cycle length is unchanged, but that the device inhibits full development of the corpus luteum (3, 32, 48). As in the rabbit, the principal effect on fertility appears to be on the survival of implantations. A unilaterally placed IUD inhibits corpus luteum development and implantations on both sides; this bilateral effect is similar to the effect in mice and unlike the much more restricted effect seen in sheep and cattle. Microscopic examination of the endometrium reveals an increased number of leucocytes.

Cattle The cow responds to the placement of an intrauterine device similarly in some respects to the ewe and sow; ovulation and ova transport are normal but the life span of the corpus luteum is shortened (16, 37, 52, 123, 124). Corpus luteum inhibition occurs only when the corpus luteum and the device are on the same side. This finding supports the contention that there is some local humoral or neural impulse transmitted from the affected horn to the adjacent ovary. Early studies indicated that in a related species, the water buffalo, devices inhibit ovulation (11). This is a remarkable finding that certainly requires further investigation.

The presence of an IUD prevents successful fertilization of cow ova following artificial insemination but not after natural mating (51). The meaning of this observation is not entirely clear, but the role of natural mating in the release of oxytocin for optimal sperm transport may be involved.

IUD's produce histological evidence of endometrial inflammation, and leucocytes are almost uniformly found adherent to the device when it is removed (37, 52). No alteration in the normal number of mast cells has been observed in the endometrium adjacent to the IUD (51) in contrast to the increase which has been observed in the rat. It has also been shown that IUD's in cattle cause an increase in total endometrial mucopolysaccharides in the tissues immediately adjacent to them (20). These changes, similar to those seen in the sheep, may be secondary to the occurrence of inflammation.

Rhesus Monkey As in all other species tested, in the rhesus monkey an intrauterine device appears to prevent pregnancy, but experience in attempting to establish pregnancy in IUD-wearing monkeys is too limited to establish if this is an absolute or partial effect.

There is considerable evidence that under specific circumstances the presence of the IUD in rhesus monkeys influences the reproductive process at the level of the oviduct, a finding that may be applicable to all primates. The evidence is that the IUD increases the rate of tubal transport in monkeys that have been ovulated artificially with exogenous gonadotropins and artificially inseminated (90, 91). In this situation, ova are transported through the tube in several hours instead of the 3 to 4 days normally required. Accelerated ova can be recovered from the uterus or vagina in the unfertilized state at a time when the ova of similarly treated females without an IUD are still found in the oviducts, occasionally fertilized.

Further evidence of tubal acceleration is provided by experiments in which clusters of rabbit ova, colored with a vital dye for visual identification, are placed in the ostium of the oviduct of monkeys that have been artificially ovulated

in order to standardize their hormonal state. If the recipient animal has an IUD, the egg cluster passes through the tube into the uterus in a matter of hours; in control animals, at the same postovulatory time, no significant movement of the egg cluster is discerned in a comparable period (89).

Gonadotropin-induced ovulation has the advantage of providing a fairly accurate means to time ovulation, but it involves the disadvantage of multiple ovulations, an abnormal phenomenon for the rhesus monkey. Multiple ovulations undoubtedly create an elevated estrogen secretion level which could cause accelerated tubal transport and influence the fertilizability of the ova. In order to avoid these difficulties, ovum recovery experiments have been performed with IUD-bearing rhesus monkeys following naturally occurring ovulation. Since it is difficult to know precisely when ovulation occurs in such animals, the time selected for laparotomy to recover ova can only be estimated. Nevertheless, the presence of fertilized and unfertilized tubal ova at least 3 days after the estimated time of ovulation in animals with intrauterine devices has been reported (74). Since several of these ova were found to be denuded of the corona radiata, an unusual situation for unfertilized tubal ova, it is not known whether these ova actually were fertilizable. At present, therefore, the possibility of a tubal effect exerted by an IUD in the subhuman primate remains a consideration, but is not fully established.

It has been established that ovulation occurs normally and that sperm transport is not impaired in rhesus monkeys bearing IUD's. The devices appear to have no remarkable short- or long-term effect on the endometrium except on the tissue immediately adjacent to the device where pressure atrophy and slight dysplasia have been demonstrated (63, 64, 65, 70, 114). The lack of marked inflammatory reaction to IUD's in rhesus monkeys contrasts with studies in humans where signs of inflammation have been described by a number of investigators. Recent studies indicate that IUD's have no effect on the decidua response in ovariectomized and hormonally treated rhesus monkeys (118).

IUD's do not evoke any notable histochemical or biochemical changes in the rhesus monkey uterus, except for a consistent increase in oxygen consumption rate by uterine tissue, an observation also made for the oviducts from monkeys wearing IUD's. The significance of this enhanced oxygen consumption rate is not clearly understood, but may be an expression of mild trauma to the uterus and adjacent tissues.

Effects in Women

Systemic Effects Most of the biological effects so far described with the use of IUD's by women are confined to the tubo-uterine anatomical unit. The occurrence of normal ovulatory cycles is indicated by studies of endometrial biopsies (5, 93, 121), urinary pregnanediol levels, and visualization of corpora lutea at laparotomy. Histochemical studies of ovaries from women with IUD's reveal no significant alteration in lactic dehydrogenase, succinic dehydrogenase, or glucose-6-phosphatase levels (40). There is a paucity of published data on urinary and circulatory hormone levels for women using IUD's. One report on cyclical levels or urinary FSH and LH in a limited number of cases suggests no remarkable change from expected patterns (119).

Available data suggest that the postpartum woman may respond to the presence of an IUD by an elevated secretion rate of oxytocin. In one study, a group of IUD-users continued to lactate significantly longer than a paired controlled group (39). Oxytocin levels were not studied in these women. Elevated blood levels of oxytocin or oxytocin-like substances in IUD-wearers were observed in another study; however, these subjects may have been lactating, since the work was performed in India where use of IUD's is often initiated during lactation (17). Such studies are of considerable importance and warrant extension and confirmation in light of the evidence of comparable systemic effects in some animals.

Oviduct Function and Sperm Transport Tubal patency tests establish that the presence of an IUD does not cause mechanical obstruction of

the oviduct (107). Normal motile sperm have been found in the oviducts and uteri of women bearing IUD's at least 24 hours after coitus (80), although more recent work indicates that the number of sperm may be fewer than expected (94).

It is not known whether oviduct motility is altered in women with IUD's. Some investigators have speculated that tubal motility is increased with such devices and that this effect interferes with ova or sperm transport (86, 87). Acute and chronic studies with salpingograms and other clinical tools have shown that IUD's do not cause tubal spasm or alterations in peristalsis detectable by such means (55, 107). Several statistical studies demonstrate that the ectopic pregnancy rate in women with IUD's is markedly lower than the rate without IUD's (57, 115, 116). It is postulated that this differential is due to an increase in tubal motility or some other tubal factor.

It is well known that about 2 percent of IUD wearers have normal pregnancies (115), but it is not known whether fertilization occurs in IUD subjects who do not become pregnant. Several studies have included the attempt to recover human ova at surgery by flushing the oviducts and uterus. One fertilized ovum has been found in the tube of a woman using an IUD, but the numbers of patients studied to date do not provide significant data to warrant the conclusion that the IUD affects fertilization (96, 97).

Myometrium Cineradiographic observations carried out a number of years ago indicated that IUD's may increase uterine motility, and it was postulated at that time that normal uterotubal synchrony is altered by their use (81). More recently, studies with transducers in IUD's indicate that myometrial activity may increase immediately after the insertion of the IUD but that this increase of activity diminishes with time (6). Other investigators, using microballoons (40, 61), have shown no such increase in myometrial activity after the insertion of IUD's; still another technique was employed involving an open-catheter recording apparatus and the conclusion was reached that following insertion of the device, prelabor-like activity evolves prematurely at a time corresponding with ovum implantation (7). These apparent differences in observed myometrial effects may be due to differences in techniques used. There is an isolated observation that IUD's may cause myometrial hypertrophy (56).

A study that may apply indirectly to myometrial activity involved measuring the sensitivity of IUD wearers to oxytocin by measuring the milk ejection reflex in response to the exogenous administration of this drug. No significant difference was noted in intramammary duct pressures of postpartum women with or without IUD's following the intravenous administration of a standard dose of oxytocin (41).

Endometrium Early histological studies disclosed no significant tissue alterations with the use of IUD's in humans (46, 79, 110). It was postulated on the basis of such observations that the devices acted mechanically: that they prevent implantation by an abrasive effect. Although endometritis was noted, it was thought to be a sterile reaction to a foreign body and of no significance. Several more recent studies have shown rather uniformly that there are alterations in the endometrium (5, 9, 12, 56, 60, 93, 104, 121). These studies, based on the examination of endometrial biopsies and hysterectomy specimens, show grossly a thickening of the endometrium with edema and pressure effects. Indeed, in many instances, an impression of the device may be seen on the endometrial surface. Microscopic examination shows that the endometrium directly adjacent to the device is thin and ulcerated. Frequently, there is a marked increase in polymorphonuclear leucocytes and lymphocytes with fibrin deposition. Chronic endometritis, with lymphocytes and plasma cells, is often present and large vessel channels are common. Some observers suggest that the endometrial timing lags behind the normal patterns (5). One electron microscopic study indicates an asynchrony of endometrial maturation associated with the use of IUD's (122), although the criteria for endometrial dating by ultrastructural characteristics are not fully established.

Biochemical studies of the human endometrium indicate that there is no alteration in histochemical reactions for alkaline phosphatase or glycogen, but that there is an increase in the alcyan blue staining reaction, thought to be due to an increase in mucus production (45, 47). IUD's may retard the increase in the nonphospholipid to phospholipid ratio found to occur coincident with ovulation; this change is interpreted to represent retardation in biochemical maturation of the endometrium (38). Another observation is that IUD's produce an increased beta-glucuronidase activity in menstrual blood (13).

One study has suggested the presence of endometrial squamous metaplasia in women who have used intrauterine devices for 1 or 2 years (112, 113), but other observers have not reported metaplasia or other atypical changes (47, 104).

Uterine Infection Early reports of clinical experience with IUD's were mixed concerning the occurrence of uterine infection. Some reports claimed that no inflammation or infection occurred (98) whereas others claimed that at least 10 percent of patients showed some evidence of infection (60). As noted, plasma cells and lymphocytes are almost always seen with the use of IUD's, but recent studies show that such evidence of inflammation is rarely associated with actual bacterial infection, except immediately after insertion (92, 95). These studies, which involve obtaining endometrial specimens at hysterectomy through the sterilized fundus, may have corrected the impression based on earlier work that the endometrium has a normal bacterial flora (120).

Summary of Effects in Women Studies suggest that IUD's do not have a systemic effect in human females except that they may possibly lead to prolonged or elevated oxytocin secretion. Ovulation and sperm transport are not significantly altered. It is not known whether fertilization occurs ordinarily. Tubal transport may be accelerated but there is no direct evidence for it.

The principal effect for which there is evidence is on the endometrium. Bacterial contamination occurs almost universally after insertion. Chronic infiltration of the endometrium with plasma cells and lymphocytes almost always occurs. There is tissue edema, stromal fibrosis, and increased vascularity in tissues directly adjacent to the device. Furthermore, there are reports that endometrial maturation may be delayed or asynchronous.

Summary of Comparative Biological Effects

Intrauterine devices have an antifertility effect in every animal tested, but this effect is manifested differently among the species. In the fowl and sheep, sperm transport is inhibited so that fertilization cannot occur. In the guinea pig, rabbit, pig, and cow, as well as the ewe, corpus luteum function is impaired to varying degrees; this effect appears to be unilateral and local rather than bilateral except in the pig where the effect is bilateral. In animals such as the guinea pig, cow, and pig, in which sperm transport is not affected as it is in the sheep, fertilization does occur. Fertilized ova that implant in an untreated horn may go to term, but those that implant adjacent to an IUD are likely to be lost. IUD's do not inhibit sperm transport and fertilization in rodents and rabbits, but they do inhibit implantation with increasing effectiveness as one progresses from the rabbit, through the rat, to the mouse.

Many of the effects of IUD's found in other eutherian mammals are not seen in subhuman primates or humans, but the differences in action among these groups may be more apparent than real, considering the differences in reproductive anatomy and processes. It is known that both rhesus monkeys and human females ovulate with IUD's. There is no significant evidence, to date, that devices have systemic effects in primates as they appear to have in rabbits and sheep, beyond the observation that IUD's may elevate or prolong oxytocin secretion in postpartum women. In women there is histological evidence of endometrial inflammation and alterations in the normal endometrial progression during the menstrual cycle; these changes may be sufficient to explain the prevention by IUD's

of uterine pregnancies. Observations in rhesus monkeys that devices may increase tubal motility need confirmation and extension with large groups or normal ovulating animals. Finally, it is not known whether IUD's affect fertilization in either rhesus monkeys or human females.

Many possible explanations of the antifertility action of intrauterine devices can be considered untenable on the basis of the numerous studies already done. Nevertheless, elucidation of the primary events must await the accumulation of additional facts.

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Report of the Task Force on Utilization and Effectiveness

C. Tietze, M. D., Chairman

Sources of Information

Over the past 4 years, a vast amount of statistical data relevant to clinical and field experience with IUD's has been assembled, analyzed, and made available to the medical community (9, 12). The information thus obtained makes it possible to evaluate the effectiveness, utility, and safety of intrauterine contraception for the period covered by these studies; to assess the advantages and disadvantages of several major types of IUD's; and to identify some of the factors associated with higher and lower rates of pregnancies, expulsions, and removals.

The largest source of statistical information on the IUD's is the Cooperative Statistical Program (CSP), initiated in mid-1963 by the National Committee on Maternal Health in New York, at the request and with the financial support of the Population Council. On January 1, 1967, this program was transferred to the Council's Bio-Medical Division.

During the 4 years of its existence, the CSP has published a series of progress reports (13, 14, 15). The most recent one is based on data from 30 investigators who had submitted individual case records for almost 27,600 women, covering an aggregate of more than 477,000 woman-months of experience. Of the 30 investigators, 26 are institutional and 4 are gynecologists in private practice. The institutional participants include 13 outpatient clinics in hospitals, mostly associated with medical schools, and 13 extramural clinics, of which 7 are affiliated with the Planned Parenthood Federation of America. All but three of the investigators are located in the United States, including one in Puerto Rico. About 90 percent of the 27,600 women are nonprivate patients in the United States, including 4 percent in Puerto Rico.

The CSP has adequate data for five types of IUD's: the Lippes loop in four sizes, the Margulies spiral in two sizes, the Birnberg bow in two sizes, the stainless steel ring of Hall and Stone in one size, and the double spiral in one size. The period of followup is now 5 years for the largest loop (Loop D) and 2 years for the other devices.

From its very beginning, the CSP has developed a statistical method based on the principle of the life table (3, 4, 16), which had not been previously used to any great extent in the study of contraceptive techniques. Any statistical method for measuring the incidence of pregnancies, expulsions, and removals should yield results which can be compared with those of other investigators. Since the monthly incidence of these phenomena varies with the length of time elapsed since insertion of an IUD, it is essential that *duration of use* be an integral part of the statistical procedure.

This requirement is met by the *life table method*, developed cooperatively over the past several years by Robert G. Potter, Jr. (3) of Brown University and Christopher Tietze (16) and, quite independently, by Benjamin Viel in Chile (19). The life table method is based on rates of pregnancies, expulsions, and removals

during successive months and yields *cumulative rates* per 100 users to the end of the Nth month. As a rule the values chosen for N are multiples of 12, corresponding to successive years of use.

Cumulative rates may be based on experience subsequent to the first insertion only or may be based on all experience, including reinsertion; they may be computed either as event rates or as closure rates. Event rates are based on all pregnancies, expulsions, and removals, whether or not followed by a reinsertion. *Closure rates* are based on events *not* followed by a reinsertion.

Cumulative event and closure rates may be computed either as gross rates or as net rates. *Gross rates* are designed to measure the incidence of each type of event separately, without regard to other types of events. For this reason, gross cumulative rates for the several types of events cannot be added to obtain total event or closure rates.

Net rates are computed by means of a multiple decrement table and are designed to measure the incidence of each type of event in the presence of all other types of events. Net cumulative closure rates can be added to obtain a total closure rate. Subtraction of the total closure rate from 100 yields the percentage of continuing users at the end of Nth month.

The life table method can also be applied to the experience with contraceptive methods other than the IUD. This approach permits valid comparisons between investigators, types of devices, types of users, etc., which could not be made by simpler procedures because of differences between groups in the average length of observation.

The life table method has been used in depth in the important Taichung Medical Follow-up Study, based on a large-scale family planning program initiated in Taichung, Taiwan, in 1963 (5). This material is being analyzed through collaboration between the Taiwan Population Studies Center and the University of Michigan Population Studies Center. The sample consists of about 6,600 women and the followup now extends over 2 years.

The life table method has also been used in several smaller studies, based on women who had IUD's inserted within the framework of national or local family planning programs in various countries, especially in Asia (2). Clinical investigators, on the other hand, both in the United States and abroad, have generally used simpler methods of analysis of their data. Therefore, as a rule it is not possible to compare the findings of one investigator with those of others, and sometimes it is not even possible to compare results for one group of users with those for another group. However, the literature has been reviewed and pertinent data have been evaluated in the preparation of this report.

Effectiveness

The effectiveness of a method of contraception is measured in terms of the pregnancy rates associated with its use. In the United States, according to the CSP, women using the most successful types of IUD's have had pregnancy rates on the order of 1.5 to 3.0 per 100 women during the first year of use. Other devices, since abandoned, have been associated with much higher rates. For all types of IUD's the pregnancy rate tends to decline gradually after the first year.

For any given type of IUD, pregnancy rates tend to be higher for a smaller size than for a larger size. Among plastic devices of comparable size, pregnancy rates are higher for the bows than for the loops and lowest for the spirals. Pregnancy rates tend to be higher for younger women than for older women wearing the same type of device. Within each age group, the pregnancy rates tend to increase with the number of children born prior to the first insertion.

A comparison of the effectiveness of the IUD's with that of other contraceptive methods requires consideration of the difference between theoretical effectiveness and use-effectiveness. Theoretical effectiveness reflects the assumption that the method is correctly used according to instructions, while use-effectiveness is reduced by human frailty, which leads to inconsistent or incorrect use of the method. For the IUD's, use-effectiveness approaches theoretical effectiveness, since the method does not require either daily or periodic medication or any manipulation before, during, or after the sexual act. However, the careful user can increase her chances of protection by inspecting her menstrual pads

or tampons and, if the device has a transcervical appendage, by examining herself periodically.

In terms of theoretical effectiveness the IUD's are doubtlessly less reliable than oral contraceptives under either the combined or the sequential regimen, and they are probably not more effective than such methods as the diaphragm or the condom, if the latter are used correctly at each sexual union. In terms of use-effectiveness, on the other hand, the IUD's have proven themselves far more effective among clinic patients than the traditional methods and only slightly less reliable than the oral tablets.

Expulsions

The incidence of involuntary explusion varies widely among different types of IUD's. Among the devices investigated in the CSP, the highest rates of expulsion were reported with the spirals and the lowest with the bows. For all types of devices, the smaller sizes were associated with much higher expulsion rates than the larger sizes.

The great majority of expulsions occurs in the first year of use; about one-half of the total within 4 months after insertion. More devices seem to be expelled with the menstrual flow than at any other time. If an IUD is reinserted after an expulsion, the chance of reexpulsion is two or three times as high as the chance of expulsion after the first insertion of the same type of IUD. Nevertheless, according to the CSP, about one-half of all women who experienced a first expulsion, eventually retained the device after one or more reinsertions.

Expulsion rates for all types of IUD's tend to decline steeply with increasing age of the woman and less steeply with parity. Cross-tabulation by age and parity suggests that age is the more important factor of the two. Expulsion rates are very high following insertion during the first few days after childbirth; they are lower following insertion 5–12 weeks after childbirth, and the lowest following insertion at 3 months or later.

Removals

For all IUD's, voluntary removal, at either the clinician's or the wearer's initiative, is the most important cause of discontinuation and may exceed the combined effect of pregnancies and expulsions at a ratio of 2 to 1 or more.

In the United States, removals are more often performed for "medical" rather than for "personal" reasons, but these two categories tend to overlap. The most common reasons by far are bleeding and pelvic pain, often reported together. In the CSP they accounted for about 60 percent of all removals (excluding those for planning pregnancy or associated with the research program), while other "medical" reasons accounted for 25 percent and "personal" reasons for only 15 percent.

Like the expulsion rate, the removal rate is highest in the first month after insertion. However, the subsequent decline of the rate is not so steep as noted for the expulsion rate, nor does it go so far. A significant incidence of removals has been reported throughout the period for which data are available, i.e., for 4 years after the first insertion. It has not yet been ascertained whether the types of complaints that may lead to the late removal of an IUD actually occur more frequently among women wearing IUD's than among other women in the same age groups.

The removal rate tends to decline moderately with increasing age and parity, but apparently more with parity than with age. There is no clear-cut association with type or size of IUD nor with the length of time between last confinement and insertion.

Continuation of Use

Next to the effectiveness of the method used, continuation of use is the most important condition for successful contraceptive practice. Continued use can be conveniently measured in terms of "continuation rates," indicating the proportion of couples still using the method after a specified period.

According to the experience of the CSP, continuation rates for the various types of IUD's were quite similar, averaging about 75 percent at the end of the first year and about 65 percent at the end of the second year following the first insertion. Limited data for one type of device (Loop D) suggest a further drop to about 50

percent at the end of the fifth year. These figures include women who continue to wear an IUD after one or more reinsertions.

Among clinic patients in the United States, continuation rates have been much higher for the IUD's than for the traditional contraceptive methods, such as the diaphragm, vaginal foam, or foaming tablets (17). The experience of family planning programs in a number of developing countries has been the same.

The relative levels of continuation rates for IUD's and oral contraceptives cannot be accurately assessed, because no studies have been reported in which the two methods were offered to comparable populations under comparable circumstances. Fragmentary evidence suggests that at the lowest socioeconomic level, with a minimum of education, continuation rates are higher for the IUD's than for the orals (9).

Adequate information on the acceptance of the IUD by private patients is not available. However, since other methods of birth control are usually accessible to the private patient, the question of continued use of a particular method is far less critical than it is for the clinic patients.

Side Effects and Complications

After the insertion of an IUD, the first and sometimes the second and third menstrual period tends to start earlier than usual; the flow may be prolonged and heavy. Intermenstrual bleeding and spotting may also occur. Many women experience uterine cramps and other types of pelvic discomfort. As a rule, these complaints disappear within a few months, with or without symptomatic treatment.

Medical concern about possible serious complications of the IUD has focused on six areas:

1. Carcinogenicity in respect to the *corpus uteri* and, in the case of devices with a transcervical appendage, also to the *cervix uteri* (Appendix 4).

2. Pelvic inflammatory disease either resulting from or aggravated by the introduction of a foreign body into the uterine cavity (Appendix 3).

3. Perforation of the uterus and its sequelae.

4. Sterility, either resulting from salpingitis or caused by an unknown mechanism.

5. Damage to the fetus if pregnancy occurs with a device *in situ*.

6. Ectopic gestation.

Perforation of the Uterus

Perforation of the uterus in connection with insertion of an IUD is an infrequent accident. Since most perforations are asymptomatic, however, some may pass undetected. The investigators participating in the CSP reported 90 perforations per 10,000 insertions of bows, and 4 per 10,000 for the other types of IUD's taken as a group. These percentages do not include perforations of the cervix by the stiff-beaded tail of the spiral (Gynekoil), reported in about 1 percent of all cases.

A recent report from Singapore, based on 17,900 insertions of loops, revealed 70 perforations per 10,000 insertions (18). The difference between the two findings may be due, in part, to the fact that the Singapore group X-rayed all women who had apparently experienced an unnoticed expulsion. This was not always done by the CSP investigators.

The available evidence indicates that the frequency of perforation varies with the time of insertion in relation to a preceding childbirth. The risk appears to be low immediately after delivery and highest during the early post-partum period. It then decreases progressively.

It is likely that most perforations occur at the time of insertion or as a result of trauma to the uterine wall during insertion. The frequency of perforation may be kept at a minimum by sounding the uterus to determine the location of the fundus and by placing a tenaculum on the anterior lip of the cervix. Downward traction on the tenaculum stabilizes the uterus and reduces the angle between the cervical canal and the uterine cavity. Care must be exercised to guard against completely or partially perforating the uterine wall with the inserting instrument. The rigidity of the inserter, rather than of the IUD itself, may be

the major factor in producing perforation. Migration of an IUD through the uterine wall, without prior trauma, has not been demonstrated.

Evaluation of the reported perforations reveals few serious disabilities. In several cases, devices have been allowed to remain free in the peritoneal cavity without serious consequences. Some of the perforations have been discovered as an incidental finding during a later laparotomy performed for other reasons. The device is usually situated in the omentum with a minimum of tissue reaction.

A careful survey of the world literature has revealed five instances of intestinal obstruction associated with the modern IUD's or their immediate precursors (1, 6, 7, 10, 11). All involved a closed type of IUD. In at least three of these cases, the device was found partially protruding through the uterine wall. This enabled the small bowel to slip through the ring or bow and become incarcerated.

Future Fertility

The wearing of an IUD does not appear to result in reduced fertility after it has been removed. According to the experience of the CSP, about one woman in three conceived within 1 month after removal, almost three out of four within 6 months, and almost nine out of ten within 1 year. Rates of this magnitude have been observed in samples of the general population after the discontinuation of traditional birth control methods.

An IUD will continue to prevent conception if the wearer forgets its presence or if she mistakenly believes that the device has been expelled or removed. In several instances IUD's have been withdrawn from the uterus after a number of years, with subsequent conception.

Outcome of Pregnancy

According to available statistics, the incidence of abortion is much higher among pregnant women wearing IUD's (41 percent in the CSP) than the incidence of spontaneous fetal wastage in the general population of pregnant women, estimated at 15 percent. It is possible, however, that the excess frequency of abortion among IUD users may be a consequence of induced abortion, since women who practice contraception are motivated to avoid birth if contraception fails. While the question remains unanswered whether the presence of the IUD in the pregnant uterus can cause abortion, it can be stated with assurance that the removal of an IUD during pregnancy does not necessarily have this effect.

At delivery, the IUD is usually found on the maternal side of the membranes and occasionally of the placenta, never in the amniotic sac. Not infrequently (20 percent) it is retained after the placenta has been expelled. In the absence of symptoms removal is not necessary.

In the CSP only three serious malformations and anomalies (one phocomelia, one meningocele, one strabismus) were reported among more than 300 viable infants gestated with device *in situ*, which is not significantly different from the 1.5 percent one would ordinarily expect. The reported incidence of premature births in the same series was 6 percent.

Ectopic Gestation

Ectopic as well as uterine pregnancy may occur among women who wear IUD's. Among pregnancies with device *in situ*, the relative frequency of tubal gestation is very high (about 1:20 pregnancies), but apparently normal among pregnancies following unnoticed expulsion. There is no evidence that the presence of an IUD can cause a conceptus to implant ectopically. The high relative frequency of tubal pregnancies results from the successful prevention of most uterine pregnancies.

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Report of the Task Force on Inflammatory Reactions and Warnings

R. B. Scott, M.D., Chairman

Prevalence and Incidence of Pelvic Inflammatory Disease

Exact figures on prevalence and incidence of pelvic inflammatory disease (PID) in population groups are not readily available. It is known, however, that social and economic levels of a group, as well as the sexual mores and other variables, will alter the prevalence and will drastically affect the yearly incidence. Clinical experiences have assessed these relative data; for example, the prevalence and yearly incidence of pelvic inflammatory disease may be twice to more than 10 times as high in an indigent, low socioeconomic group as in a private patient, high socioeconomic group.

Clinical Experience of Pelvic Inflammatory Disease Subsequent to the Insertion of an IUD

Tietze (24) reporting for the National Committee on Maternal Health on a cumulative study financed by the Population Council, calculates the annual rate of PID per 100 first insertions in a group of 22,403 women as follows:

Type of Device	First Year	Second Year
All loops	2.1	1.4
All spirals	2.8	1.4
All bows	2.8	2.1
Steel ring	2.5	1.7

Only a sixth of the 606 cases of PID were classified by the 33 investigators as severe and most of the others as mild. Since these reports were based upon clinical observations alone some would be doubtful or erroneous. In many instances the infection represented an acute exacerbation of a preexisting PID, a new gonococcal infection, or a septic abortion. In this study antibiotic therapy was often successful and in the majority of cases the device was not removed. Contrary to theoretical expectations, the presence of a transcervical appendage did not significantly increase the annual rate of PID. The incidence of pelvic inflammatory disease is significantly higher during the first month after insertion than in subsequent months.

A survey of individual experiences reported in the literature gives data which when averaged out differ little from the above cumulative series. Willson (26, 27, 28, 29) and his colleagues in several reports note a pelvic infection rate of 1.3 percent for private patients compared to a rate of 8 percent for clinic patients. This differential is an expected one, but we agree with Willson, *et al.* (29) that the rate in private patients is disturbingly higher than anticipated.

This subcommittee was concerned about four deaths from infections associated with the use of IUD's but as yet unreported in the literature.*

**See survey report as contained in Appendix 6.*

Laboratory Evidence of Uterine Infection Associated With an IUD

The transcervical insertion of a device into the uterine cavity probably cannot be done without introducing bacterial flora both foreign to and present in the cervical area. Bacteriologic studies of the uterine cavity containing an IUD have been limited and any such observations on transcervically obtained material must remain suspect (26).

Transfundal cultures from removed uteri containing an IUD have been reliable and informative. Mishell, Bell, Good, and Moyer (19) have reported such a study. Their findings are worthy of summary.

1. All five endometrial cultures obtained in the first 24-hour interval following insertion were positive.

2. Within 1 month following the insertion of an IUD the endometrial cavity was uniformly sterile by transfundal culture techniques.

3. Microscopic evidence of chronic endometritis bore no relationship to the presence of viable organisms in the endometrium.

The microscopic diagnosis of chronic endometritis is unfortunately one of difficult interpretation. Variables, such as the personal equation, the area of sampling, and the phase of the menstrual cycle, must be considered. Pressure compression of the endometrium, adjacent dilated vessels or lymphatic channels or both, focal and diffuse infiltration of the endometrium with polymorphonuclear leukocytes, lymphocytes and plasma cells, as well as microscopic "abscess pockets," have been reported in widely varying percentages (5, 11, 14, 16, 19, 20, 23, and 27). The clinical significance of these changes is unknown. It is tenable to consider most of these histologic findings to be remnants of the previous bacterial invasion, in addition to pressure and foreign body response secondary to the device.

Sterility Precautions by the Manufacturers and Distributors of the IUD's

Through the Food and Drug Administration, all of the U.S. manufacturers and distributors of the intrauterine devices were contacted. Information on control of sterility in the manufacture of IUD's instructions to the physicians about insertions, and plans for prepackaging in sterile units was requested.

Thus far the replies have been incomplete. When sterile packaging is practiced, the bacteriologic controls and checks seem adequate; however, no word has been received about plans for sterile prepackaging of the most commonly used device and inserter although some studies are underway. The instructions to the physician relative to sterile techniques are variable; this is understandable since many physicians enthusiastic about the devices have not set any uniform standards for insertion and have frequently discounted the need for even minimal precautions. This subcommittee feels that the instructions to the physicians should include:

Contraindications

1. Pregnancy or suspected pregnancy.

2. History of an infected abortion or postpartum endometritis within the previous 6 weeks.

3. Acute or subacute pelvic inflammatory disease.

4. Acute cervicitis.

5. Distortions of the uterine cavity due to myomas.

6. Recent history of abnormal uterine bleeding.

7. Suspicion of uterine malignancy until evaluated.

Recommendations

Papanicolaou smears should be obtained unless there is a record of one within the previous 6 months.

Precautions

1. A pelvic examination must be done to rule out contraindications and to ascertain the size, shape, and position of the uterus.

2. Sterile technique must be observed throughout the insertion procedure.

A. Sterile gloves must be used, unless the inserter and the device come as a single, prepackaged sterile unit.

B. Metal instruments (vaginal speculum, uterine sound, single-toothed tenaculum, Hank dilators #11 through 18, etc.) must be autoclaved or heat-sterilized. Plastic introducers and devices that are not received in sterile, prepackaged units must be soaked in 1:750 aqueous benzalkonium chloride solution or suitable iodine preparations for a minimum of 24 hours before use.

Summary

Exact figures on the prevalence and incidence of pelvic inflammatory disease are not available for most population groups. One study reported that following the insertion of an IUD, the incidence of pelvic inflammatory disease varied from less than 1 percent in groups of private patients to 8 percent in an indigent clinic group, with overall first year annual rates per 100 first insertions ranging from 2.1 to 2.8. The type of device or the presence of a transcervical appendage does not significantly alter the rate. Many of the pelvic infections associated with the IUD's, including acute exacerbation of preexisting pelvic infections, newly acquired acute gonoccocal disease and infected abortion, are mild. The incidence of infections is significantly higher within the first month after the insertion of a device than in subsequent months. Recognizing the limitations of the data, we nevertheless believe that the incidence of pelvic infections is higher in women wearing intrauterine devices than in a control population without the devices. Further studies, with control populations, are necessary before any definite conclusions can be reached.

Without any concerted effort we have obtained four case reports of deaths associated with overwhelming infections following the insertions (without perforations) of the IUD's. None of them have been reported in the medical literature. We wonder how many more such tragedies may have occurred that have not come to our attention.

The transcervical insertion of an IUD probably cannot be done without introducing bacteria and in many cases creating an intrauterine infection, albeit transient. By transfundal culture techniques the uterine cavity was found to be sterile one month after the insertion of an IUD. Although microscopic evidence of chronic endometritis and other histologic alterations in the endometrium are frequent, these changes bear no correlation to the presence of viable organisms and may represent the residua of previous infection or a foreign body in addition to a direct response to pressure.

Several manufacturers and distributors of the IUD's are making commendable progress toward sterile packaging and adequate sterility control. Unfortunately, there is no information about definite plans of the distributor of the most popular device.

The instructions to the physicians regarding necessary sterile precautions during insertion are not uniform. There is an unfortunate tendency for many physicians to discount the need for any but the barest minimum of sterile precaution. The recommended instructions to the physician as proposed by this subcommittee are given in this report.

Recommendations

1. Reliable figures for prevalence and incidence of pelvic inflammatory disease in various control population groups should be ascertained.

2. A national survey should be made and reporting should be encouraged in order to learn the magnitude of serious inflammatory processes associated with the insertion of IUD's.

3. Further clinical and laboratory research employing control populations should be carried out to assess the relation of IUD's to pelvic infection.

4. Sterile prepackaging of all devices and inserters that cannot be autoclaved or heat-sterilized should be mandatory.

5. Minimal standards for sterility precautions to be used by the physician inserting a device are listed (page 31).

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Appendix 4

Report of the Task Force on Carcinogenic Potential

R. Hertz, M.D., Chairman

The evidence relating to the potential effect of intrauterine devices upon the pathogenesis and clinical course of cancer of the endometrium or cancer of the cervix is fragmentary.

The expected incidence of these lesions in women of reproductive age is relatively low. Moreover, the carcinogenic response to exogenous factors in man usually requires from 2 to 10 years, and this response may be observed some years after withdrawal of the inciting agent. Accordingly, the available data concerning the carcinogenic potential of IUD use are limited with respect to both numbers of patients studied and duration of followup.

Ishihama (8) described the findings in 623 cases bearing Ota metallic rings, 350 cases with Ota polyethylene rings, and an additional 18,594 cases from 194 clinics employing various polyethylene devices. Although many of these patients retained these devices for up to 5 years, no data are given concerning the actual duration of exposure or followup. However, only one case of cervical cancer was encountered and it was not associated with significant endometrial pathology. Shimomura (22) also reports a case with similar findings after 9 years with a ring in place.

Various studies describing the local tissue response to IUD's indicate tissue changes not related to neoplasia (3, 6, 13, 14, 16, 18, 20, 24, 25, 27).

More recently Richart and Barron (19) have reviewed the available reports of Ishihama and Kagabu (9,10), Ayre (1), and Garcia (17), and conclude that these reports provide inconclusive information regarding the effect of IUD's on the progression from cervical dysplasia to carcinoma. These authors outline the statistical basis for a proper analysis of a potential effect of the use of the IUD on the progression of cervical dysplasia. The committee regards the employment of their (proposed) procedures a highly useful tool for investigations concerning the carcinogenic potential of the IUD.

Their study (19), moreover, failed to reveal any significant influence of the presence of the device on the rate of progression from dysplasia to carcinoma *in situ*. The progression rate of cervical dysplasia to carcinoma *in situ* was calculated in 114 subjects wearing IUD's and in 221 using other contraceptives or no contraceptives, for a period of 2½ years. The progression rates in these two groups, calculated by the life table method, were not significantly different, indicating that the IUD exerts no significant carcinogenic effect on the human cervix (Table 1).

Some guidance with reference to the carcinogenic potential of the IUD is derived from extended years of clinical experience with the chronic emplacement of plastic and metal materials in various parts of the body for prosthetic and cosmetic reasons. They include such a wide variety of items as: dental plates, contact lenses, nylon sutures, indwelling polyethylene catheters, glass eyes, plastic hearing aids, and vas-

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TABLE 1

Life Table and the Probability of Progressing from Dysplasia to Carcinoma *in situ*

Interval Days	Number of Patients	Number Progressing	Number Withdrawing	Cumulative Probability of Progressing
SUBJECTS WITHOUT IUD'S				
0–90	221	0	40	0
91–180	181	1	24	0. 0057
181–360	153	9	53	0. 0793
361–540	91	8	32	0. 1919
541–720	51	4	15	0. 2882
721–900	32	0	19	0. 2882
SUBJECTS USING IUD'S				
0–90	114	0	16	0
91–180	98	0	18	0
181–360	80	4	25	0. 0610
361–540	51	3	22	0. 1389
541–720	26	2	17	0. 2601
721–900	7	0	5	0. 2601

(*From reference 19.*)

cular protheses. Neoplastic changes in response to such materials have not been observed although extensively studied (2, 5, 7, 21).

Animal investigations bearing on this problem include studies in which plastic and metal materials have been placed in various parts of the body, but only a few in which the reaction of the uterus itself has been tested (4, 11, 12, 15, 23, 26). Corfman and Richart (4) have adequately summarized these varied reports and have themselves observed epidermoid carcinomas in the uterus of rats bearing polyethylene or stainless steel devices for protracted periods of time. Since these lesions may have evolved from preexisting squamous metaplasia associated with pyometra, and since IUD's in women are not usually associated with such antecedent effects, these authors conclude that the pathogenesis of these lesions in the rat has little bearing on what may be expected in women. The committee agrees with this interpretation, notwithstanding the observation of "squamous metaplasia of the endometrium in a few women wearing IUD's" by Tamada and Maruyama (25).

In summary, the committee advises the constant monitoring of women wearing the IUD's by the same methods usually recommended for all asymptomatic women, namely a semiannual pelvic examination combined with Papanicolaou smears and biopsy where indicated.

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Report of the Task Force on Legislation

H. F. Fuller, M.D., Chairman

At present the legislation establishing jurisdiction over devices is limited to regulation of marketed products when there is evidence of excessive claims or hazard to health.

In direct contrast, new drug regulations adequately establish supervision of clinical trials based on three levels of clinical investigation.

Phase I. This phase starts when the drug is first introduced to human beings for the purpose of evaluating its pharmacologic effect.

Phase II. This phase involves first clinical trials to prove the effectiveness of the drug, either as a prophylactic agent or a therapeutic agent for the specific disease indicated.

Phase III. Phase three is a widespread clinical trial. The initial commercial distribution of a product may be termed *Phase IV*. At present, industry is required to submit quarterly reports during the first year of Phase IV, semiannual reports during the second year, and annual reports thereafter.

Manufacturers of drugs must submit protocols of clinical trials for all phases. They must include pharmacologic and toxicologic studies on animals as well as previous clinical experience, if applicable, to justify the use of the drugs in proposed clinical trials.

Prior to marketing, manufacturers must submit evidence that the drug is safe and efficacious as labeled.

In the field of devices, however, the burden of proof is on the Government to demonstrate that a device is not safe or is not efficacious as labeled.

The safety of the material used, the quality control in its manufacture, and the labeling and packaging of intrauterine devices are at present the sole concern of each manufacturer. Furthermore, new devices can be introduced practically at will.

The Committee on Obstetrics and Gynecology was able to interview only the distributor of the Lippes Loop (Ortho Pharmaceutical Co.). Their procedures of quality control seemed rigid and of a high order. There is no evidence that other manufacturers do not have similar standards. Neither is there evidence to the contrary.

There is great variation in labeling, packaging, and directions to the physician as indicated in the various exhibits at the end of this report.

Because of the increasingly widespread use of devices that remain within the human body for years, the Department of Health, Education, and Welfare is considering legislative proposals to provide adequate controls of manufacturing and marketing of these devices as follows.

Therapeutic and prophylactic devices (not diagnostic devices) that are not generally recognized by qualified experts to be safe, effective, and reliable shall be submitted for preclearance with adequate data to support a conclusion that they are safe, effective, and reliable for the usage intended. The types of devices to be included under the proposed preclearance regulations are:

1. Those secured or placed within the human body or in contact with mucous membrane and

intended to be left for a substantial period of time.

2. Those intended to subject the human body to ionizing radiation, electromagnetic energy, physical, chemical, or ultrasonic energy.

3. Those intended for physical, chemical, radio, or electronic communication between a device within or connected to the human body.

4. Those that the Secretary of Health, Education, and Welfare has reason to believe are ineffective or unsafe for the conditions prescribed, recommended, or suggested in their labeling.

It is proposed that the Department of Health, Education, and Welfare have the power to establish standards of composition and performance for all classes of devices when such standards will protect the public health and safety. The proposed legislation will establish standards of manufacture that will assure the safety, effectiveness, and reliability of a number of devices without need for preclearance. The decision regarding the need for preclearance will rest with the Secretary. If, however, standards of manufacture and composition can go only part way to assure safety, effectiveness, and reliability, then the need for preclearance is obvious.

It is furthermore proposed that any interested person can call for an *ad hoc* advisory committee of experts to consider the related scientific issues when any device is under consideration.

The proposals will also give appropriate weight to any standards established by nongovernmental standardization groups.

The contemplated proposals will authorize the Secretary of Health, Education, and Welfare to exempt from preclearance any devices that, in his judgment, can be standardized within a short period of time; any devices prepared specifically to the order of a practitioner licensed by law to prescribe it; any devices adequately controlled under the Atomic Energy Act; and any devices that, because of their small number or negligible significance from the standpoint of public health seem inconsequential.

The Secretary of the Department of Health, Education, and Welfare could establish special regulations under which a sponsor, supporting the investigation of a device involving clinical trials by separate investigators, would follow the established protocol in order to develop data demonstrating safety and reliability without necessarily following the rigid requirements for preclearance.

When the Secretary or his representative suspects that any investigational plan is inadequate or needs modification, he can, under the proposals, require filing of an additional or amended plan before the investigation of the device can proceed.

At the request of the sponsor of the device, the Secretary shall promptly consult experts outside the Department on any pertinent scientific questions, or on the research design submitted.

Labeling and instructions submitted with the various devices are appended to this report.

Recommendations

1. The Task Force endorses the principles and the need for the new device legislation under consideration.

2. Intrauterine devices should be included among those covered by the proposed legislation.

3. The Task Force is opposed to any legislation directed specifically at contraceptive devices.

Survey of Fellows of the American College of Obstetricians and Gynecologists Relative to Deaths and Critical Illnesses Associated With Intrauterine Devices

R. B. Scott, M.D.

At the May 18–19, 1967 meeting of this Advisory Committee on Obstetrics and Gynecology, the Subcommittee on Information reported three deaths from overwhelming infection (without perforation) in association with the use of IUD's. The Subcommittee recommended that a national survey be made to assess the magnitude of this problem. The Chairman of this Subcommittee was directed to make such a survey and to include in the questionnaire deaths and critical illnesses from inflammation or complications of perforation in association with the use of IUD's.

The Fellows of the American College of Obstetricians and Gynecologists were selected as the survey group. They number 8,506 and in addition to Fellows in the United States included Fellows in Canada (324), Puerto Rico (70), and the Armed Forces (496). Beginning about June 15, 1967, the questionnaire, together with a personal covering letter and a self-addressed, stamped envelope, was mailed. A copy of the questionnaire is attached to this report.

By September 6, 1967, 6,449 (or 75.8 percent) of the questionnaires were returned. Of these, 5,698 Fellows (or 88.4 percent) gave negative answers in all categories, and many of these had appended comments of interest; 751 (or 11.6 percent) gave positive answers in one or both categories.

I. Deaths

As reports of deaths came in, the individual physician was contacted and a protocol of the case was requested. Of course, one death might be reported by several physicians, but it was not difficult to assign each death to a single case and hospital.

SUMMARIES OF DEATHS

Case 1. Age 28, gravida 4, para 4. Term delivery May 28, 1966. Lippes loop inserted Aug. 1 (second day of menses). Rapid illness, pelvic cellulitis, and, by Aug. 4, septic emboli, generalized petechiae, and jaundice. *Strep. viridans* in blood culture. Died 6 days after the insertion and 24 hours after total abdominal hysterectomy and bilateral salpingo-oophorectomy. Uterus showed acute purulent endometritis and myometritis. Autopsy: petechiae in skin, epicardium, myocardium, mesentery, gastrointestinal mucosa, adrenal glands, and kidneys; gangrene of toes; acute splenitis; moderate fatty infiltrates in liver; acute superficial ulcers in stomach with gastric hemorrhage; thrombocytopenia; hypoprothrombinemia; multiple recent arterial emboli and hemorrhagic infarcts in lungs with bilateral hemothorax (100 c.c.); acute passive congestion and edema of lungs;

pelvic hematoma (150 c.c.); and thrombi in small pelvic veins.

Case 2. Age 21, para 5–3–1–1–4. Term delivery Sept. 22, 1966. Device inserted Nov. 8. Foul discharge. Symptoms began Nov. 20. Pure culture beta Streptococcus, Group "A," from cervix. Septic shock, pulmonary embolism, and pulmonary edema on Nov. 22. Died Nov. 25. Autopsy: pulmonary edema, pelvic vein thromboses, parametritis, and endometritis.

Case 3. Age 34, para 4. Lippes loop inserted Sept. 20, 4 months after last delivery. Admitted Sept. 25 with vomiting, diarrhea, and abdominal pain. Laparotomy disclosed diffuse peritonitis, no perforation. Peritoneal culture and Lippes loop culture showed *Strep. viridans.* Postoperative shock, respiratory insufficiency, tension pneumothorax, cardiac arrest. Died Sept. 26. Autopsy: acute purulent bronchitis, bronchopneumonia with pulmonary edema and hyaline membrane formation, acute fibrinopurulent peritonitis with acute endometritis and salpingitis.

Case 4. Age 27. Lippes loop inserted March 2, 1967. Lower abdominal pain and bleeding May 9 and May 12–13. Received penicillin. Emergency admission May 14 *in extremis* and profound shock. Autopsy: loop in place, all cultures negative; bilateral pleural effusions; pericardial effusion; acute pulmonary edema and atelectasis; septic reaction of spleen; acute endometritis and myometritis; cerebral swelling. Cause of death: septicemia due to endometritis and myometritis.

Case 5. Age 42. Device (coil) inserted March 3, 1966. Pain, cramps, fever, and chills began almost immediately. Diarrhea and vomiting by admission March 6. Medical treatment of pelvic inflammation. Diffuse peritonitis, small bowel obstruction, and surgery March 26. Died March 28. No autopsy or culture reports.

Case 6. Age not stated. Lippes loop inserted Jan. 30, 1967 (LMP Jan. 25). Normal period April 29. Stomach cramps began May 16. Fainting spell May 19. Admitted *in extremis* and died in approximately ½ hour. Autopsy: loop in place; peritoneal culture *Pseudomonas aerogenosa* and *E. coli;* diffuse peritonitis. Most severe septic inflammation of reproductive organs spread into the abdomen.

Case 7. Age 26, gravida 5, para 4. Hospitalized for threatened abortion October 26 to November 1, 1966. Readmitted for bleeding and abdominal pain Nov. 28. Medical induction for 3 days and delivered stillborn fetus (about 20 weeks). Almost immediately unconscious and cardiac arrest. After 40 minutes heart beat restored, blood did not clot, and given 3 units of blood and 2 units of fibrinogen. Died 3 hours after delivery. Blood cultures negative and nonhemolytic streptococci from fetus. Autopsy: acute chorioamnionitis; amniotic fluid embolism; Lippes loop free in peritoneal cavity. Rent in left side of uterus showed exposed blood vessels. (Husband did not know loop had been inserted.)

Case 8. (Ledger, W. J. and Willson, J. R., "Intrauterine contraceptive devices: The recognition and management of uterine perforations," *Obstet. Gynec.* 28: 806 (1966).) Age 20, gravida 2, para 2. Lippes loop inserted 6 weeks after delivery. Returned later, loop not felt, another inserted. Conization and vaginal hysterectomy and repair for carcinoma *in situ* October 15, 1965. *Neisseria gonorrhaeae* from uterus by transfundal culture. Readmitted 12 days after surgery for pelvic cellulitis and thrombophlebitis, abscess drained, laparotomy November 10, with diffuse peritonitis, and Lippes loop not found (seen by X-ray). Died postoperatively of cardiac arrest. Autopsy permission refused.

Case 9. Age 25, gravida 4, para 3. Saf-T-Coil inserted Sept. 17, 1965. LMP Dec. 4, 1965. Bleeding and possible escape amniotic fluid April 1966. Labor July 9, 1966 for 1 hour. Four minutes after delivery of premature, female infant with deformed left lower extremity, patient developed cyanosis, convulsions, cardiac arrest, and died. Autopsy: amniotic fluid embolism; congestion, edema and atelectasis of lungs; chronic mitral valvulitis; and fibrosis, focal, around device with coils extruding through anterior fundus of uterus and leg of the Y extended into the vagina.

Case 10. Age 37. Ward patient had intrauterine device (Lippes loop) inserted 2 years prior to admission and following the delivery of her last child. Admitted to the hospital April 27, 1967 with severe pelvic infection and uterus enlarged to 16- to 20-week pregnancy size and quite tender. Profuse purulent discharge. Tentative diagnosis of infected abortion. Pregnancy test negative. Intrauterine device still in place (confirmed by X-ray). D and C done day following admission. No tenaculum marks were seen on the cervix, myomas were felt, and the uterine cavity measured 5 inches. Device was removed and a moderate amount of tissue obtained which was reported as necrotic tissue with a decidual-like reaction. Cardiac arrest and death occurred at the completion of the procedure. Cause of death on certificate: pulmonary embolism, bilateral, massive, secondary to pelvic thrombophlebitis and parametritis. Autopsy confirmed this. No information relative to bacteriology studies. Evidence of association with pregnancy was suspicious, but not definite.

Inadequately documented deaths

Case 1. Two physicians know of a death in association with perforation by an IUD and subsequent surgery. This community is small and all efforts to obtain further information have failed.

Case 2. One physician noted a death in association with perforation. Further correspondence stated that the name of the patient's physician could not be divulged since he was being sued. No additional information has been given.

ANALYSIS OF DEATHS

There are 10 definite deaths with case summaries available for analysis. Two patients (cases 1 and 2) died 6 and 17 days respectively after the insertion of an IUD of septicemia and septic emboli and the association is highly suspect. Two patients (cases 3 and 5) died 6 and 25 days respectively following the insertion of an IUD of pelvic inflammatory disease, peritonitis, and complications. The causal association is again highly suspect. One patient (case 4) died 2 months and 12 days after the insertion of an IUD of pelvic inflammatory disease and septicemia and any association would be conjecture. The same applies to deaths 3½ months and 2 years respectively (cases 6 and 10) following insertions from severe pelvic inflammatory disease and peritonitis or septic thrombophlebitis. One patient (case 8) died of overwhelming postoperative inflammation following surgery for carcinoma *in situ* of the cervix. The previous uterine perforation and insertion of another device was probably without definite relationship. Two patients (cases 7 and 9) died of amniotic fluid embolism after a second trimester delivery; the uterine perforation of a device in each instance might be related, but this is doubtful. In addition, there are one probable and one possible death with insufficient data for analysis.

II. Critical Illnesses From Pelvic Inflammatory Disease and Perforations

Of the physicians returning questionnaires, 751 (or 11.6 percent) gave positive answers as to knowledge in their communities of critical illnesses due to inflammation and/or complications of perforation in association with the use of IUD's.

The definition of a "critical illness" as reported by different observers was quite variable. Answers were not counted as "yes" if modified by saying "serious, not critical," "not admitted to a hospital," "lap for perforation" without other complications, and "colpotomy for removal of a device." Otherwise the physician's interpretation of critical was accepted.

It is obvious that many physicians in a single area would report knowledge of the same single instance of a critical illness. The hospital name was requested, and for each hospital named multiple reports were counted as a single instance, unless the information was specific as to a number greater than one. In particular instances a responsible physician at the named hospital was contacted. For example, a single instance of perforation with intestinal obstruction at University Hospital in Baltimore was reported by 21 local physicians.

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With these considerations the analysis of positive replies was as follows:

TABLE 1

Critical Illnesses

	U.S.	Canada	Puerto Rico	Total
I. Inflammation	350	16	3	369
II. A. Perforations	183	8	1	192
B. Intestinal obstruction noted	(12)	(3)	(0)	(15)
Total	533	24	4	561

Thus, the 751 positive replies represented roughly 561 separate instances of illnesses classified as critical.

Since only a "Yes" or "No" answer was requested, the types and severity of the illnesses cannot be subjected to analysis. When additional comments were inserted by the physicians, they ranged from infected abortions, ruptured ectopic pregnancies, and acute salpingitis through surgical ablation for pelvic infection, septicemia, septic shock, and subphrenic abcesses.

Fifteen of the perforations were followed by intestinal obstruction requiring emergency surgery. In the 13 cases where the physicians noted the types of devices, they were all of the closed type: 12 bows and 1 "Incon Ring." The type of device is not known in two cases. The high incidence of perforation when the Birnberg bow was inserted and the increased potential of subsequent intestinal obstruction makes surgical removal of the misplaced device mandatory and raises a serious question as to the comparative safety of this particular device.

III. Impressions from Comments Appended to the Questionnaire

A. Many physicians were satisfied with their experiences in using the IUD's. For example, in the negative group of answers a total of over 56,000 insertions was noted, although no personal experience figures were requested.

B. A rather impressive number of physicians have unfavorable memories of the Gräfenberg ring and the older types of intracervical contraceptive devices. This deters them from using the present devices and in a few instances may have been responsible for erroneously marked questionnaires.

C. Numerous remarks cited physicians in the same community who willingly, or through faulty history and examination, inserted devices during early pregnancy. This may or may not result in an abortion.

D. Many comments were made to the effect that the course of an abortion, either spontaneous or criminal, was more septic in association with an IUD.

E. The individual patient with an adverse reaction, such as bleeding or pain, will frequently go to another physician to have the device removed. This tendency may prevent the original physician from properly assessing the incidence of problems.

F. The complications from the use of IUD's provide a fertile field for malpractice suits. Four such suits were specifically noted and others were threatened or probable. The clinical data on a possible death could not be obtained because of one such suit.

Summary

About June 15, 1967, a questionnaire was mailed to 8,506 Fellows of the American College of Obstetricians and Gynecologists. They were asked if they knew of any deaths or critical illnesses in their community from pelvic inflammatory disease or complications arising from a perforation of the uterus in association with the use of an intrauterine contraceptive device.

By September 6, 1967, 6,449 (or 75.8 percent) were returned; 5,698 (or 88.4 percent) were negative and 751 (or 11.6 percent) were positive in one or both categories.

Ten deaths were reported and case summaries were available for all of these. In four instances of severe inflammatory disease, the short time

interval following insertion and the overall sequence of events indicated a definite relationship to the insertion of IUD's. In four other cases, an interval of more than a month following insertion and other factors make a direct relationship questionable. Two deaths from amniotic fluid embolism accompanied by uterine perforation of a device may have no more than a coincidental relationship. In addition, one probable and one possible death could not be adequately analyzed because of lack of information.

Critical illnesses in association with pelvic inflammatory disease and perforation were reported in 751 responses (or 11.6 percent). The definition of a "critical illness" varied with the individual reporting, and a particular case may have been reported by several physicians. After minimal editing and correcting for multiple reports from a single hospital, there seemed to be 561 (or 8.7 percent) separate instances of critical illnesses. These included infected criminal and spontaneous abortions, ruptured ectopic pregnancies, acute salpingitis, pelvic abscesses, uterine perforations with intestinal obstruction, surgical ablation for infection, septic shock with septicemia, and bilateral subphrenic abscesses.

The most impressive group were the 13 instances of uterine perforation followed by surgery for intestinal obstruction found in association with the use of a closed type of device. This high rate of serious complication from the infrequently used closed devices, when added to their high incidence of perforation, raises a serious question as to the safety of these particular devices. Surgical removal of a closed type of device perforating the uterus seems mandatory.

This questionnaire did not ask for particulars as to personal experiences, details of cases, etc.—it simply requested a "Yes" or "No" answer. Nevertheless, the appended comments were interesting and informative but without statistical significance. These comments indicated:

1. A very significant number of physicians were satisfied with their use of IUD's.

2. Prior experience with or knowledge of older intrauterine or intracervical contraceptive devices adversely influenced many physicians.

3. Many reports indicated knowledge of insertions of devices, willingly or through medical error, in women pregnant at the time.

4. The course of a spontaneous or criminal abortion in association with the use of an IUD was thought to be more frequently septic.

5. An individual patient with complications following the insertion of an IUD had a strong tendency to report this complication to another physician and request that he remove the device.

6. The complications from the use of IUD's provide a fertile field for medicolegal suits. This aspect prevented the Committee from obtaining adequate follow-through information on certain cases.

(The Committee is indebted to the Population Council, New York, N.Y., for financing the costs of this questionnaire and to the Fellows of the American College of Obstetricians and Gynecologists for their very remarkable, cooperative response to a questionnaire submitted by an individual Fellow.)

Questionnaire

1. Do you know of any patient(s) suffering from *pelvic inflammatory disease*, associated with the use of an *intra-uterine device*, who *died* or was *critically ill* in a hospital in your community?

DIED — Yes ☐ No ☐

CRITICALLY ILL — Yes ☐ No ☐

2. Do you know of any patient(s) suffering from any *complication* arising from a *perforation of the uterus*, associated with the use of an *intra-uterine device*, who died or was *critically ill* in a hospital in your community.

DIED — Yes ☐ No ☐

CRITICALLY ILL — Yes ☐ No ☐

Name of Hospital (where patient was admitted) _____

Name of City _____

Your Name (please print) _____

Return to: Roger B. Scott, M.D., 2105 Adelbert Road, Cleveland, Ohio 44106 in the enclosed, stamped, self-addressed envelope.

Bibliography of Clinical Reports on Intrauterine Devices in the English Literature From 1959 to 1967

This bibliography covers medical and sociological literature, including books, chapters of books, conference papers, and journal articles, published in the English language from 1959 to the later part of 1967. The subject matter includes clinical and pathological experience with intrauterine devices and their use in family planning programs. Basic research on laboratory animals, relating to the mechanism of action of the IUD, has not been covered.

The body of the bibliography is arranged alphabetically by single or first author and by date of publication. Republications of the same item are listed immediately after the first entry. Journal articles are identified by volume number, page, and date of issue.

The main listing is followed by an alphabetic index of secondary authors and a subject matter index. The latter is based partly on the title and partly on the general content of the entry. No attempt was made to index all subjects discussed in each entry.

The bibliography was prepared by Christopher Tietze, M.D., and Kathy Ch'iu Lyle of the Bio-Medical Division, The Population Council.

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Secondary Author Index

Subject Index

Appendix 8

List of Available Intrauterine Contraceptive Devices and Exhibits of Labeling Submitted by Some Manufacturers

Intrauterine Devices*

Device	Inventor	Manufacturer	Distributor	Patent Number and date
Ahmed	Mary Aftab Ahmed, Karachi, Pakistan.	Schueler & Co., 110 Fifth Ave., New York, N.Y. 10011.	Schueler & Co	3,306,286 (2/28/67).
Antigon	Paul Lebech and Mogens Osler, Frederiksberg Hospital, Copenhagen, Denmark.	Antigon, Svend Schrøder, 112 Bjerringbrovej, Rødovre, Denmark.	Antigon	Patent pending.
Appleby	Basil Paul Appleby, London, England.	N. V. Organon, Oss, Holland.	----------	3,319,625 (5/16/67).
Birnberg Bow	C. H. Birnberg, John L. Marco.	I.C.D. Corp., 191 Ocean Ave., Brooklyn, N.Y. 11225.	I.C.D. Corp. (outside United States and Canada: Schueler & Co., 110 Fifth Ave., New York, N.Y. 10011).	3,253,590 (5/31/66).
Butterfly	John L. Marco	Marco & Son, Inc., 601 Dow Ave., Oakhurst, N.J. 07755.	----------	
Comet	Jerome Schwartz, Franklin Reyner.	Skye-Ray Medical Supply Corp., 88-61 76th Ave., Glendale, N.Y. 11227.	Edlaw Pharmaceutical Division (Skye-Ray Medical Supply Corp.).	3,256,878 (6/21/66).

*The accuracy of this information cannot be guaranteed.

Intrauterine Devices*—Continued

Device	Inventor	Manufacturer	Distributor	Patent Number and date
Contram	Gregory Majzlin	Skyron Corp., 120 Little St., Belleville, N.J. 07109.	----------	
Contraring	----------	----------	Kalmedic Instruments, Inc., 425 Park Ave., New York, N.Y. 10022.	
Gräfenberg Ring	Ernst Gräfenberg, Berlin, Germany (1929).	Eschmann Bros. & Walsh, 22 Bartholomew Square, London E.C.1, England.	John Bell & Croyden, 50–54 Wigmore St., London W.1, England.	
Gynekoil	Lazar Margulies	Ortho Pharmaceutical, Raritan, N.J. 08869.	Ortho Pharmaceutical	3,200,815 (8/17/65).
Hall-Stone Ring	Herbert Hall, Martin Stone, Alexander Sedlis, Irwin Chabon.	Eschmann Bros. & Walsh, 24 Church St., Shoreham-by-Sea, Sussex, England.	Glaxo-Allenburys Ltd., 52 Bartor Rd., Weston, Ontario, Canada.	
Heart Shaped Device.	Pathfinder Fund.			
Helical Spring	Marc E. Chaft	Skyron Corp., 120 Little St., Belleville, N.J. 07109.	----------	
Incon	Robert Israel, Hugh J. Davis.	Ortho Pharmaceutical, Raritan, N.J. 08869.	----------	
Inhiband	Herbert Hall	----------	Ayerst Laboratories, 685 Third Ave., New York, N.Y. 10017.	3,323,520 (6/6/67).
K.S. Wing	K.S. Wing Laboratory, Japan.	K.S. Wing Laboratory, 123 Hase, Kamakura City, Kanagawa Prefecture, Japan.	K.S. Wing Laboratory.	
Lippes Loop	Jack Lippes	U.S.: Ortho Pharmaceutical Corp., Raritan, N.J. 08869.	U.S. and foreign: Ortho Pharmaceutical.	3,250,271 (5/10/66).

*The accuracy of this information cannot be guaranteed.

Intrauterine Devices*—Continued

Device	Inventor	Manufacturer	Distributor	Patent Number and date
Majzlin Spring	Gregory Majzlin	Anka Research, Ltd., 139–01 Archer Ave., Jamaica, N.Y.	----------	
OTA Ring	Tenrei Takeo Ota, Tokyo, Japan.	The Ota Ring Kenkyusho, 2–1, Kanda Ogawa-Cho, Chyoda-ku, Tokyo, Japan. Hsin Kwang Instruments, No. 19 South Yen Ping Rd., Taipei, Taiwan.	The Ota Ring Kenkyusho.	
Saf-T-Coil	Ralph Robinson	Deseret Pharmaceutical 19 East Oakland Ave., Salt Lake City, Utah.	Julius Schmid, Inc., 423 West 55th St., New York, N.Y.	3,234,938 (2/15/66).
Shamrock	C. Lalor Burdick	----------	----------	3,312,214 (4/4/67).
Silent Protector	M. H. Knoch, Bandung, Indonesia.	----------	----------	3,077,879 (2/19/63).
Soonawala	Rustom Soonawala, Bombay, India.	----------	----------	
Spira-Ring	Tenrei Takeo Ota, Tokyo, Japan.	The Ota Ring Kenkyusho, 2–1, Kanda Ogawa-Cho, Chyoda-ku, Tokyo, Japan.	The Ota Ring Kenkyusho.	
Szontagh	F. E. Szontagh, Szeged, Hungary.	----------	----------	
"T" Device	Howard Tatum	----------	----------	
Yusei Ring	Onagi Ikemi, Tokyo, Japan.	Yuseiring-sogokenkyusho, 2–8–14 Shinbashi, Minato-Ku, Tokyo, Japan.	The Wako Koeki Co., Ltd., 827, Ohtemachi Bldg., No. 4, Ohtemachi, 1-Chome, Chiyoda-Ku, Tokyo, Japan.	
Zipper Ring	Jaime Zipper, Santiago, Chile.	Shyf Plastic Chilena, Francisco Meneses 1980, Santiago, Chile.	Shyf Plastic Chilena	

*The accuracy of this information cannot be guaranteed.

Exhibit A

The New BOW

Intra-uterine contraceptive devices (IUCDs) have been intensivel investigated in recent years. A symposium organized by the Population Council (5) concluded that the devices were safe and effective when properly used.

In 1964 the BOW was reported in the literature (1). Years of research have resulted in the designs known as the New STANDARD and JUNIOR BOW. Both Bows are made of a new formulation of polyethylene and barium. The designs of both devices have been altered to give them greater resistance to breakage, enhanced resiliancy, better fit in the endometrial cavity, and greater effectiveness. A tail has been molded into the lower portion of the BOW to allow for easier detection and removal.

INSTRUCTIONS FOR USE

INDICATION: PREVENTION OF PREGNANCY

CONTRA-INDICATIONS

Acute or subacute pelvic inflammatory disease or recent septic abortion.
Pregnancy
Abnormal Uterine Bleeding
Fibromyomata Uteri
Bicornuate or septate uteri.

CHOICE OF DEVICE SIZE

The standard device is used routinely. If the uterus sounds to less than 2½", or if peristent bleeding or cramping follows introduction of the Standard Bow, then the Junior BOW should be used.

TIME OF INSERTION

Devices are best inserted during the menses. At this time the cervix is somewhat dilated, side-effects are masked, and one can be reasonably sure that the patient is not pregnant.

POST-PARTUM. If possible insertions should be delayed until the second normal menstrual period, and full involution of the uterus has taken place. Insertions prior to this time require great care, as both the perforation rate, and subsequent pregnancy rate are higher. Insertions into the uterus of a lactating female, if necessary, must be done with great care (4)

USE OF A TAILESS BOW

The tail may be cut off prior to loading the introducer. The BOW may then be loaded by folding it between two fingers and pushing it into the tubing.

LOADING THE INSERTER – FOLLOW INSTRUCTIONS

Open the package carefully, unfold the cardboard envelope, and put on the gloves. Push the plunger through the introducer Thread the tail of the bow through the notch on the plunger. Pull the plunger entirely through the introducer bringing the tail with it. Fold the lower portion of the device between two fingers and guide the bow into the introducer. Wrap the protruding tail around one finger and pull until only ¼" of the BOW protrudes from the tip of the introducer. Compress the tip of the introducer around the bow for 30 seconds so that the tip becomes closely applied around the bow and assumes an oval shape.

NOTE: The introducer should be loadea trom the long depth stop (2¼") for the STANDARD BOW.

TECHNIQUE OF INSERTION

Have ready a Tenaculum, Speculum, and Scissors.

Careful bimanual examination. - determine size, shape, and position of uterus.

Cervix is grasped with tenaculum and firm traction applied.

Uterus sounded with narrow end of plunger.

Cervix dilated with wide end of plunger.

If resistance to dilatation is encountered leave dilator in place for one minute.

Insert introducer to depth stop. If any obstruction is met stop insertion, resound, and redilate.

Place plunger in introducer. Keep traction on tail while doing this to avoid tangling in the introducer.

MAKE SURE THAT THE INTRODUCER IS INSERTED SO THAT THE FOLDED BOW IS LYING IN THE SAME PLANE AS THE UTERINE CAVITY. A device introduced at right angles to the cavity will not unfold properly.

Push on plunger slowly and gently, while holding the introducer in the other hand to prevent it from being pushed deeper into the uterus. No force should be needed to expell the device. Stop insertion and re-check technique if force is required against the plunger.

Remove plunger and wait 30 seconds for BOW to resume its unfolded shape.

Remove introducer and use sound to seat device. This makes sure that the device has not been left in the cervical canal.

Cut off tail 1" from cervical os.

REMOVING THE BOW

Pull gently on both strands of the tail. If for any reason the tail cannot be visualized, or if the tail breaks, use the removal hook. Pass the hook half way to the fundus. Rotate the hook anteriorly and draw downwards and forwards until the Bow is hooked. Steady downwards pressure will then remove the device.

PATIENT INSTRUCTIONS

Have patient read instruction sheet and explain the possible side-effects and results prior to inserting the BOW. If desired she may sign the authorization form. A return visit should be scheduled after two menstrual periods to determine the presence of the device.

CLINICAL RESULTS

Pregnancy rates between 0/hwy (3) and 5.7 cumulative per year (6) have been reported. Correcting the over-all hypothetical pregnancy rate published by Tietze (6) by eliminating insertions taking place less than 12 weeks post-partum, and insertions into a pregnant uterus, yields a rate of .8 pregnancies per 100 insertions.

Expulsion rates vary between 0% (3) and 1.1% (6)

Removal rates and the incidence of pelvic inflammatory disease vary widely from group to group but are not significant.

SIDE EFFECTS

Mild bleeding or cramping may be expected after the introduction of a device. Conventional analgesics can be used for the cramping. Adaptation takes place within two to three months.

Persistent severe backache, marked dysmenorrhea, or severe menorrhagia is generally due to utilization of too large a device, or poor placement of the device with impingement on the cervic-isthmic junction. These may be corrected by replacing the Standard Bow with the Junior Bow.

If the patient develops a persistent discharge of a non-specific nature replacement of the tailed with a non-tailed BOW is of value.

Heavy menses may be corrected by the use of large doses of ascorbic acid. (.5 or 1.0 gms q.i.d.), and Ornade^{R} (Smith, Kline & French, 1 capsule q8h)

If symptoms persist despite the above measures the bow should be removed and other forms of contraception advised.

UTERINE PERFORATION

Most perforations occur when devices are inserted less than 12 weeks post-partum (2). Careful attention to the instructions for insertion and proper-gentle technique should prevent this complication.

PELVIC INFLAMMATORY DISEASE

Can be treated in the usual fashion. Removal of the device is not necessary.

UNINTENDED PREGNANCY.

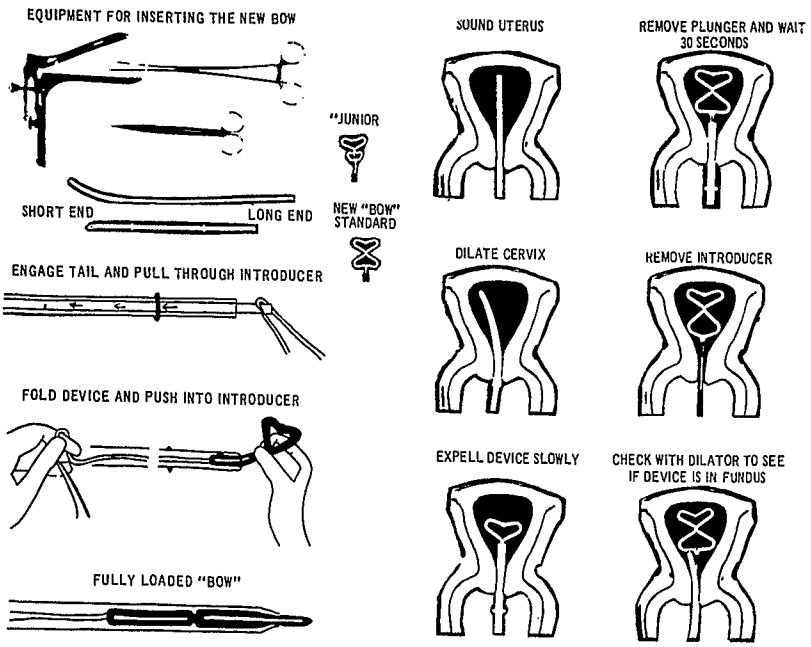
The device may be left intra-uterine without damage to the fetus. Early removal of the device results in a high percentage of miscarriage.

STERILIZATION OF EQUIPMENT

The equipment in this package is sterilized after packaging. If the package is intact the equipment can be used without additional sterilization. If for any reason re-sterilization is necessary, the equipment may be soaked in a suitable aqueous antiseptic solution (such as benzalkonium chloride, 1:1000) for a minimum of 30 minutes. This equipment cannot be autoclaved.

REFERENCES.

1. Birnberg, C.H., Burnhill, M.S., Am. J. Obst. & Gyn. 89, 137, 1964
2. Burnhill, M.S., Birnberg, C.H., Am. J. Obst. & Gyn, in press
3. Lay, C., Am. J. Obst. & Gyn., 93, 330, 1965
4. MacFarlan, S.M., Am. J. Obst. & Gyn., 94, 283, 1966
5. Segal, S.J., Southam, A.L., Shafer, K.D., editors, INTRA-UTERINE CONTRACEPTION, Internatl. Cong. Series #86 Excerpta Medica Fo ›ndation, 1965
6. Tietze, C. Cooperative Statistical Program for the Evaluation Of IUCDs, Fifth Progress Report, February 28, 1965



ADDITIONAL SUGGESTIONS FOR USING THE NEW BOW.

1. REMOVING TAIL

If you prefer to use the bow without a tail, simply pull on one strand of the tail and the entire tail will pull out.

2. SECURING TAIL – TIE STRANDS TOGETHER.

The bow should be removed by pulling on both strands of the tail at the same time, otherwise the tail may pull out.

To prevent this, the two strands of the tail may be tied together just below their exit point on the bow.

3. FACILITATING LOADING

You may find it easier to pull the bow into the introducer if you tie a knot in the loose ends of the tail so that the finger may pull against the knot.

4. MAKING INTRODUCTION EASIER.

If the dilator end of the pusher can be inserted to its end (2½") with ease the Standard Bow may be inserted without difficulty. If more than ½" protrudes the Junior Bow should be used.

If the dilator fits tightly and the introducer cannot be inserted, let the dilator stay in place within the cervical canal for one minute. On rare occasions a Hegar 6 or 7 dilator may be needed in addition to the dilator on the plunger.

THE BOW *** AN INTRAUTERINE CONTRACEPTIVE DEVICE INFORMATION FOR PATIENTS

The bow is an intrauterine contraceptive device. It is one of the the newest forms of birth control. It has been carefully tested. Many thousands of women all over the world are using *bows* successfully. Scientific studies show that the present devices, while not 100% effective, are among the most effective means of birth control available.

When the doctor places *the bow* in the womb, and for a short time thereafter, some women may experience a few cramps similar to those of of a menstrual period. If you have cramps or backache take two aspirin tablets every three or four hours until the discomfort stops. If the discomfort is not relieved, which is most unlikely, contact your doctor for additional advice.

There may be a slight alteration in your menstrual period; your first few periods may come sooner or be heavier than usual or there may be a little bleeding between periods. Your periods may be preceeded or followed by several days of staining. If the bleeding seems heavy take vitamin C tablets (500mg) three times a day and try to rest as much as possible. Spotting or bleeding after insertion of a device is not serious. The womb adapts to *the bow* and within two or three periods the bleeding episodes disappear.

Mild backache or cramping can be relieved by applying a heating pad to your back and taking aspirin.

Very rarely the womb may eject the device. This usually is accompanied by cramping and generally takes place during a period. If this happens another birth control method should be used until you contact your doctor.

The bow may be left in place indefinitely but should be checked annually by your doctor.

When you wish to become pregnant *the bow* can easily be removed by your doctor. The use of the device does not affect future children or your ability to have them.

CUT ALONG DOTTED LINE

AUTHORIZATION FORM FOR INSERTION OF AN INTRAUTERINE CONTRACEPTIVE DEVICE

Patient _____ Age_____

Address_____Date_____

I have read and understand the information on intrauterine contraception and hereby request and authorize the insertion of an intrauterine *bow* by

Dr._____

Signed _____

Witness_____

Contents sterile if package is intact

5

the NEW BOW

an improved INTRAUTERINE CONTRACEPTIVE DEVICE

– CONTENTS –

One bow
Pair of gloves
Introducer
Additional equipment needed:
Scissors, speculum and tenaculum

- MORE DURABLE PLASTIC
- MOLDED IN TAIL
- DESIGN CONFORMS TO CAVITY
- SIMPLE INTRODUCER
- COMBINATION SOUND-LOADER-DILATOR-PLUNGER

The Bow Patented*

For Physicians Use Only

READ DETAILED INSTRUCTIONS BEFORE INSERTING DEVICE

OUTLINE OF INSERTION TECHNIQUE

1. Have patient read information sheet and sign authorization form (Optional).
2. Have tenaculum, speculum, and scissors ready.
3. Open package, remove gloves and the inner package.
4. Load introducer, and remove plunger.
5. Perform a careful bimanual examination, noting position of uterus, its size and shape.
6. Visualize cervix, grasp with tenaculum. Sound uterus with narrow end of plunger, then dilate cervix with wide end of plunger.
7. Replace plunger in inserter keeping tension on tail – Introduce inserter gently and *keep device in plane of uterus.*
8. SLOWLY EJECT DEVICE by pressing on plunger.
9. REMOVE PLUNGER – WAIT 30 SECONDS.
10. Remove introducer--Cut Tail to one inch length.

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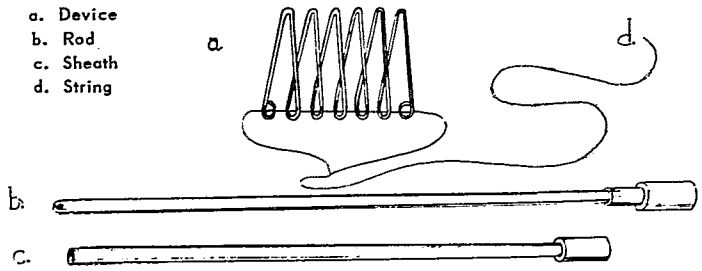
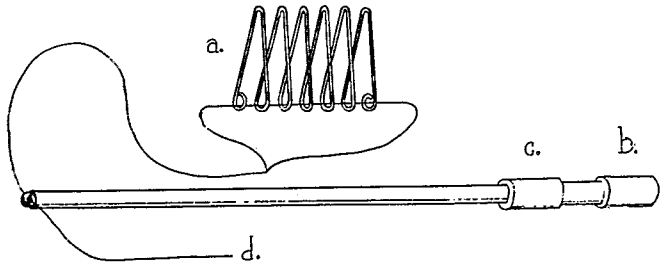
Instructions for using the "MAJZLIN SPRING"[T.M.] IUCD

World Wide Patent Pending No. 554,765 ©1966

a. Device
b. Rod
c. Sheath
d. String

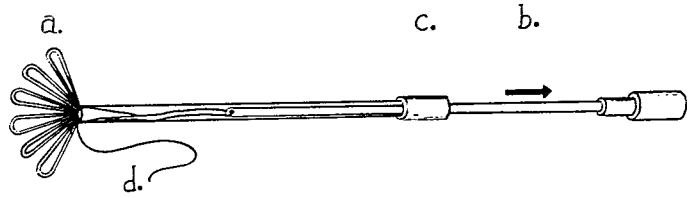


1. After removing the device from the envelope, unwind the string.

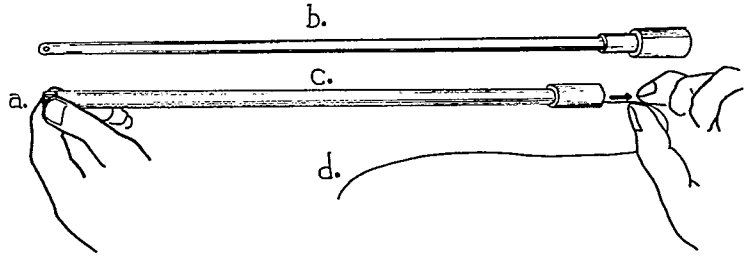


2. Make certain that the rod of the inserter is in the sheath of the inserter.

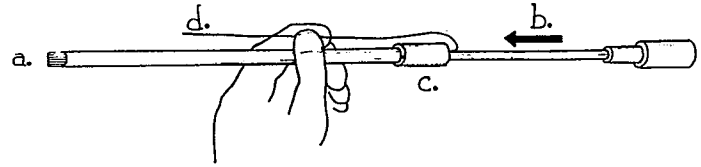
3. Moisten the ends of the string and thread through the hole at the end of the inserter rod. Do this on a flat table.



4. Slowly pull the threaded rod out of the sheath.



5. Slowly pull the string with one hand while guiding the device into the sheath with the other hand, so that the horizontal plane of the device faces the curve of the sheath. Leave 2 mm of the device protruding from the sheath, thus giving it a smooth end.



6. Fold the loose end of the string against the sheath, hold it with one hand while inserting the rod back into the sheath up to the device with the other.

Exhibit B

7. Examine the patient bimanually. Expose the cervix, cleanse the cervix with an antiseptic, grasp with tenaculum or 7" long allis forceps, and ascertain the direction of the cervico-uterine canal with a probe. Bend the inserter with the device in it to conform to the direction of the canal.

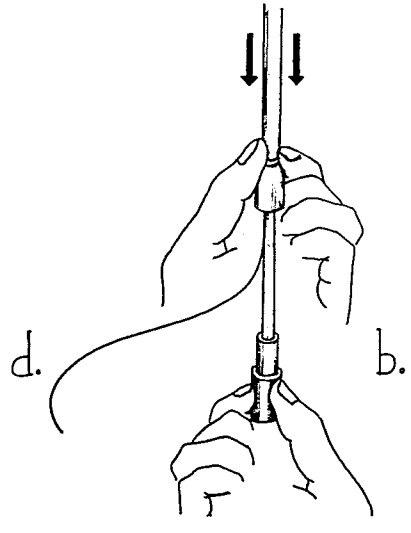
8. Boil the entire unit for at least ten minutes.

9. Insert the unit until you feel the fundus of the uterus.

STOP AT THIS POINT

CAUTION: DO NOT PUSH THE ROD OF THE INSERTER TO RELEASE THE DEVICE

FOLLOW THE NEXT INSTRUCTIONS VERY CAREFULLY



10. Hold the knob end of the sheath of the inserter in one hand and the knob end of the rod in the other. SLOWLY PULL THE SHEATH DOWN TOWARDS THE KNOB END OF THE ROD. This will release the device in situ.

11. Pull the rod out completely.

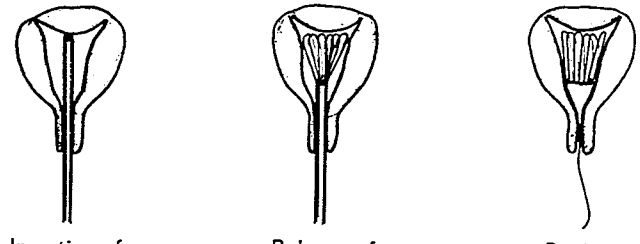
12. Pull the sheath out completely.

13. Cut the string 2½ inches from the external cervical os.

14. Remove the tenaculum or allis forceps, and the speculum.

THE DEVICE IS NOW IN THE FUNDUS OF THE UTERUS.

15. Wash the inserter with soap and water before re-using.



Insertion of sterile unit

Release of device

Device in situ

Manufactured in U.S.A. by
ANKA RESEARCH LTD.
139-01 Archer Ave., Jamaica, N.Y.
(212) 657-2222

SAF·T·COIL 33·S
INTRA-UTERINE CONTRACEPTIVE DEVICE

INFORMATION FOR PHYSICIAN

INDICATIONS:
Prevention of pregnancy

CONTRAINDICATIONS:
Pregnancy or suspicion of pregnancy
Suspicion of carcinoma
Acute cervicitis
Acute or subacute adnexal disease
Fibroids with distortion of uterine cavity, particularly submucous fibroids
Menorrhagia or any unexplained bleeding

TO FACILITATE INSERTION OF THE SAF-T-COIL 33-S, HAVE AVAILABLE THE FOLLOWING STERILE INSTRUMENTS:

1. Uterine Sound or a cervical dilator
2. Tenaculum (for positioning the cervix, if necessary)
3. Vaginal speculum
4. Clipping forceps or scissors

A complete and thorough pelvic examination should be performed to rule out contraindications. It is also essential to determine size and position of the uterus. A Pap smear can also be taken.

GENTLY PROBE THE CERVICAL CANAL with a Uterine Sound or a small dilator to further determine if the uterus is anteverted or retroverted. The Uterine sound or dilator will slightly dilate the cervix and align the cervical canal. This procedure will expedite passage of the insertion tube.

see FIG. 1 **OPEN THE STERILE PEEL-PACKAGE. WITH THE SAF-T-COIL ON THE PACKAGE-INSERT CARD, GRASP THE PROTRUDING END OF THE PLUNGER AND SLOWLY PULL THE SAF-T-COIL 33-S INTO THE INSERTION TUBE UNTIL THE NODULE ON THE END OF THE COIL CONTACTS THE DISTAL END OF THE INSERTION TUBE AND REMAINS RELIABLY IN PLACE.** The **SAF-T-COIL 33-S** is mounted on the card so that the coils will pull into the insertion tube in the same plane as the tabs on the blue stop. Do not keep the **SAF-T-COIL 33-S** in the insertion tube more than 8 or 10 minutes as it may lose its memory.

see FIG. 2 **INSERT THE DISTAL END OF THE LOADED INSERTION TUBE GENTLY INTO THE CERVICAL OS. ADVANCE THE INSERTION TUBE INTO THE UTERUS UNTIL THE BLUE STOP LIGHTLY CONTACTS THE EXTERNAL OS. THE BLUE STOP IS SET AT AN INCH AND A QUARTER FROM THE DISTAL END OF THE INSERTION TUBE FOR THE NORMAL UTERUS, BUT IS ADJUSTABLE WHEN THE CERVICAL CANAL IS FOUND TO BE OF GREATER LENGTH. ROTATE THE INSERTION TUBE UNTIL THE TABS ON THE BLUE STOP LIE HORIZONTALLY. THIS WILL INSURE A FRONTAL PLANE PLACEMENT OF SAF-T-COIL 33-S WITHIN THE UTERUS UPON EJECTION.**

see FIG. 3 **HOLDING THE INSERTION TUBE WITH ONE HAND, VERY SLOWLY AND GENTLY ADVANCE THE PLUNGER WITH THE OTHER HAND UNTIL THE END OF THE PLUNGER REACHES THE PROXIMAL END OF THE INSERTION TUBE.** The **SAF-T-COIL 33-S** is now in place.

Wait one full minute to allow the **SAF-T-COIL 33-S** to regain its original shape.

see FIG. 4 **TO FACILITATE CLIPPING TO THE CORRECT LENGTH, GENTLY WITHDRAW THE INSERTION TUBE AND PLUNGER UNTIL THE SUTURE THREAD IS FULLY EXPOSED. THE SUTURE THREAD MAY NOW BE CUT WITH SCISSORS. AS MUCH AS TWO INCHES OF THE SUTURE TAIL CAN BE LEFT PROTRUDING FROM THE EXTERNAL OS.** This tail can be shortened at a later date, if desired.

THE INSERTION TUBE AND PLUNGER CAN NOW BE WITHDRAWN AND DISCARDED.

The **SAF-T-COIL 33-S** may be inserted or removed at any time. The recommended time for insertion is the third to fifth day of the cycle. It need not be removed, unless the side effects become too severe or the patient wishes to become pregnant. We do not recommend insertion before the sixth week postpartum.

The **SAF-T-COIL 33-S** can be removed by gently pulling on the exposed sutures.

The patient should be instructed to return to you after her first period and every six months thereafter for an examination.

Instruct the patient to examine herself and suggest she do so routinely. The **SAF-T-COIL 33-S** may fit each patient differently, however, one or two sutures should always protrude from the cervix.

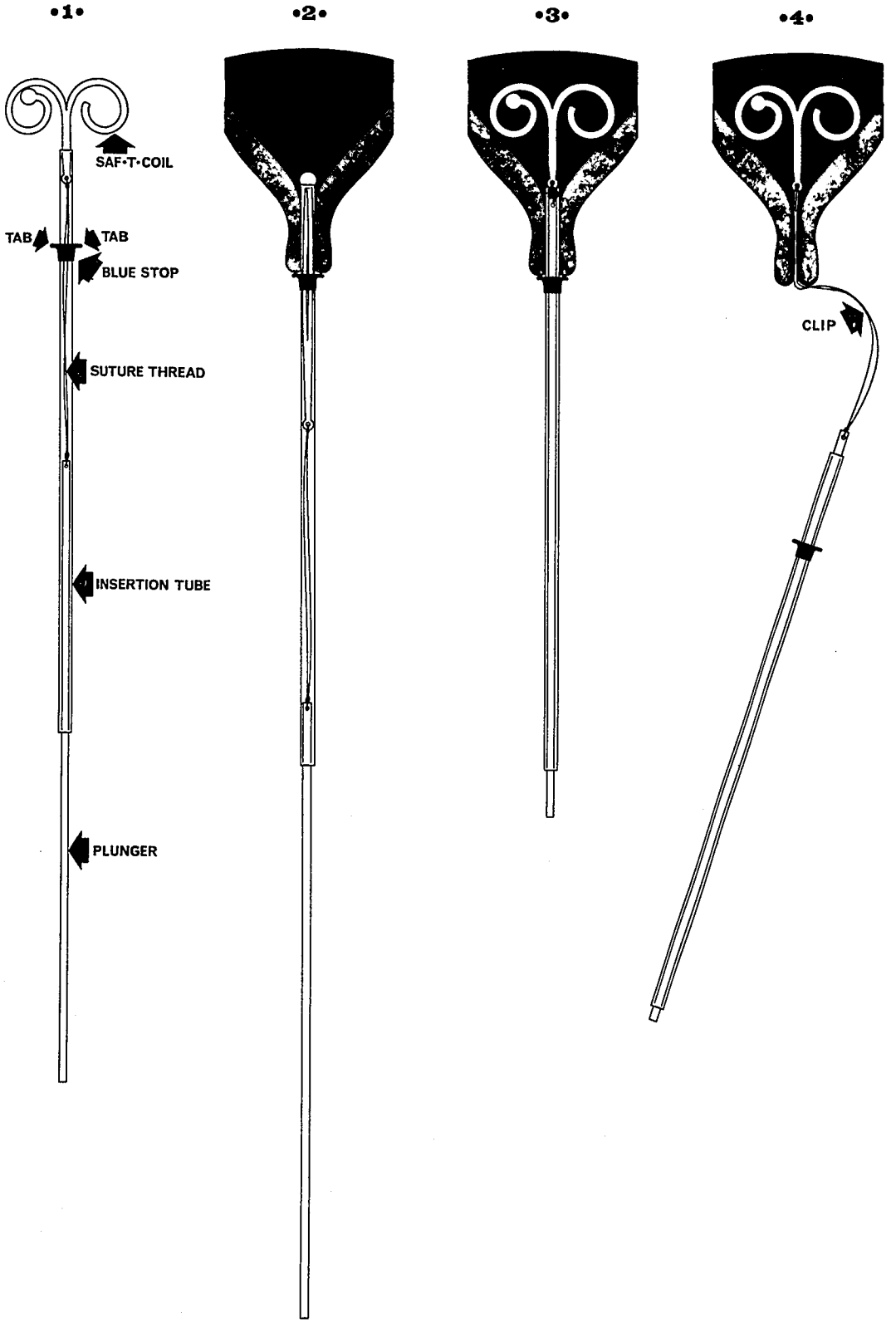
This length may vary during the cycle. If, upon examination, she thinks the **SAF-T-COIL 33-S** is coming out, instruct her to return to your office.

Inform the patient that cramping may occur after insertion and during the first and possibly the second menstrual periods. This cramping can be controlled with simple analgesics.

The patient may experience irregular bleeding for one or two menstrual periods and occasional spotting between these periods. The first period after insertion may come early and the flow may be heavier than usual.

Jan. 15, 1966

(See reverse side for figures)


•1•
•2•
•3•
•4•
SAF•T•COIL
TAB
TAB
BLUE STOP
SUTURE THREAD
INSERTION TUBE
PLUNGER
CLIP

SAF T COIL 33S

Instructions to Patients

You have been fitted with the very latest development in a method of family planning that has been in use for over forty years. More than a million women throughout the world have used this method successfully.

At any time you want to become pregnant, simply return to the office, and the device will be removed. At first, you will probably notice a difference in your periods. In some women, during the first, and occasionally the second period, the flow is quite heavy for a day or so.

Some women may have spotting or bleeding after insertion and before the next period begins. Although such bleeding or spotting is a nuisance, experience has shown that it is for short duration and has no serious after-effects. If you are concerned in any way, by all means let's discuss it. It will be very helpful if you keep a calendar of between-period bleeding as well as noting your regular periods.

If you have never had a baby, you will probably have cramps. They may even be fairly severe for a day or so. However, there are medicines which will help you feel comfortable until the "breaking-in" period is over. Please let me know right away if you have any trouble.

If your device is in its correct position, neither you nor your husband should be able to feel the device during relations.

At least once a week you should examine yourself to see if the device is in place. Thoroughly wash your hands, then sitting on the edge of a chair or in a squatting position, use your middle finger, and feel for the threads deep in your vagina. If you do not feel the threads, return to the office immediately for a check-up.

Never stop checking yourself. Only in this way can you be sure you are protected.

632-10-397-3 PV3-44

Patient Instructions

For Mrs._____

You have been fitted with the new **SAF-T-COIL 33-S** Intra-Uterine Contraceptive Device, which can remain in the uterus indefinitely.

In some patients, the first, and occasionally the second period may come early, and the flow may be heavy for a day or two. Spotting may also be bothersome. Studies have shown this to correct itself rapidly and without complications. An occasional patient may experience some discomfort or cramping during the first day or two. If this occurs, a mild analgesic will usually restore your comfort.

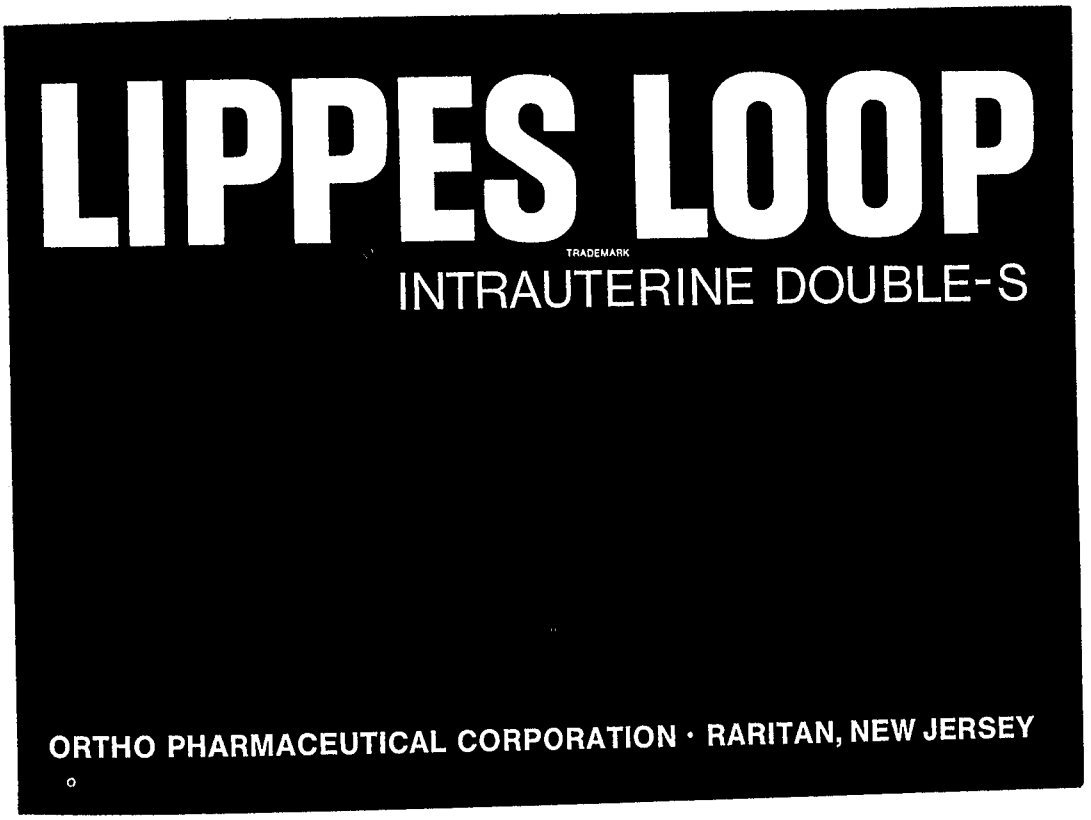
You should regularly check the position of the **SAF-T-COIL 33-S** by self-examination. With scrubbed hands, and in a squatting position, use your middle finger to feel for the thread protruding from the uterus, deep in the vagina. The **SAF-T-COIL 33-S** is designed so that you may feel one or both threads with your finger tip. Do not pull the threads.

If, at any time, you feel that the device is not in its proper position, return to my office for an examination. In any event, you should return for an examination and any possible adjustment of the **SAF-T-COIL 33-S** that may be necessary following your first period and at regular six-month intervals thereafter.

The date of your next visit to my office should be _____

Dr._____

AUG. 1, 1966



LIPPES LOOP
TRADEMARK
INTRAUTERINE DOUBLE-S

HISTORY AND BACKGROUND

The medical literature[1] is replete with references to the antiquity of intrauterine devices.

About forty years ago German physicians began to use various intrauterine devices for contraceptive purposes.[2,3] Numerous authors discussed the use and utility of the devices of this period.[4,5,6,7,8,9,10,11,12,13,14] However, for all practical purposes of medical record the present era of intrauterine contraception started in 1929, with the introduction of the Gräfenberg[15,16,17] ring. Although Gräfenberg had enthusiastic supporters,[18,19,20,21,22,23,24,25] many medical authorities rejected the method, frequently for theoretical considerations[26,27,28] and Gräfenberg himself was forced to abandon the method after he came to the United States.

Elsewhere, clinical work continued with a variety of intrauterine devices and reports appeared attesting to their usefulness, efficacy, and harmlessness.[29,30,31,32] Many of the objections to earlier devices were based on the materials available, and the necessity for dilatation of the cervix for placement. Interest has been re-awakened in intrauterine contraception with the advent of a method[34] which does not demand dilatation for introduction. Increasing awareness of world population problems has also stimulated interest in development of safe, reliable, contraceptive methods, including intrauterine devices.

Potentially, intrauterine contraception offers significant advantages for selected populations and individuals.[33] Such advantages include disassociation of the contraceptive method with coitus, subjective unawareness of the presence of the device, and freedom from the necessity of constantly replenishing contraceptive supplies.

CLINICAL EXPERIENCES

Safety and effectiveness of LIPPES LOOP Intrauterine Double-S, were first reported in 1962 by Satterthwaite[35] and Lippes,[36] in a conference sponsored by the Population Council in New York City. In a second conference in 1964, Tietze[37] reported on the first year of a co-operative statistical program, sponsored by the Population Council, and undertaken by the National Committee on Maternal Health, as a part of a comprehensive investigation of intrauterine contraceptive devices. A summary of the results reported for LIPPES LOOP is presented in Table I.

Table I

Size of Device	Number Patients	Women-mos. of Use	Unplanned Pregnancies	Pregnancy Rate*
Loop D	4100	27,772	33	1.3
Loop A	931	10,855	57	5.5

*Cumulative rate[38] per 100 cases during first year after insertion.

The 90 unplanned pregnancies reported in this group of 5031 women occurred with the device *in situ* or following unnoticed expulsion. The high effectiveness of LIPPES LOOP Intrauterine Double-S in preventing pregnancy can best be demonstrated by comparison with the number of pregnancies experienced in a population exposed to unprotected coitus. Accepting a pregnancy rate[39] following unprotected coitus of 80[40] per 100 women-years of exposure, the clinical population in the above studies would have experienced over 2500 pregnancies. The 90 unplanned pregnancies represent a dramatic reduction when compared with this expectancy.

Continuing research[41] confirms the high effectiveness of LIPPES LOOP Intrauterine Double-S in preventing pregnancy. Lippes[42] reported pregnancy rates of 1.0 for Loop D, 4.8 for Loop A, and 0.8 for Loop C, in studies with 2270 patients for more than 20,000 women-months of use.

Safety

Peng[43] and Razzak[44] described the lack of histological changes in the endometrium of patients with intrauterine devices in place for several years. These observations tend to further confirm those of Oppenheimer[29,45] and Ishihama[30,46] who did not encounter a single case of endometrial carcinoma in over 20,000 patients in whom devices had been placed, some for as long as 20 years.

Lippes[47] took 300 biopsies on 300 patients (150 on controls and 150 on loop wearers). The results revealed no sign of anaplasia, metaplasia nor any other sign that might suggest carcinogenesis. No difference in bacterial cultures from the uterine cavities of patients using intrauterine contraceptive devices when compared to similar cultures from controls was reported by Willson, Bollinger and Ledger.[48,49]

Mechanism of Action

The mechanism of action of LIPPES LOOP Intrauterine Double-S is unknown. Several theories have been advanced, the most promising of which is alteration in the motility of the fallopian tubes.

Spontaneous Expulsion

Expulsion of LIPPES LOOP occurs in some patients spontaneously. This expulsion occurs most frequently during the first and second cycle of use, usually at the time of the menses. A small percentage of expulsions can occur at any time, even several months after insertion. An unnoticed spontaneous expulsion of the device usually is followed promptly by pregnancy. Table II[42] shows the monthly and cumulative rates of expulsion per 100 patients.

The threads attached to the lower tip of LIPPES LOOP are designed to assist the patient and the physician to recognize an expulsion early. The patient should be taught to palpate the threads by self-examination. The physician can verify the position of the device by palpation, direct visualization or x-ray.

Table II: Rate of expulsion per 100 patients

	Months since insertion					
Monthly Rate	**1**	**2**	**3**	**4-6**	**7-9**	**10-12**
Loop C	0.5%	2.1%	1.2%	0.6%	0.1%	0.9%
Loop D	1.3%	1.3%	0.7%	0.8%	0.5%	0.2%
Cumulative Rate						
Loop C	0.5%	2.6%	3.8%	5.5%	5.8%	8.3%
Loop D	1.3%	2.5%	3.2%	5.5%	6.9%	7.4%

Removal for Relevant Reasons

As with all devices and medications used in medicine, many factors influence continued use in a specific individual; LIPPES LOOP Double-S has been removed from patients for a wide variety of reasons. Menometrorrhagia and cramps account for the largest group of these reasons. Figure 1[50] shows monthly rates of removal for Loop D.

Removal for these reasons has in general reflected a very conservative management of the problems as they occur. Further experience will undoubtedly be associated with fewer removals in this category.

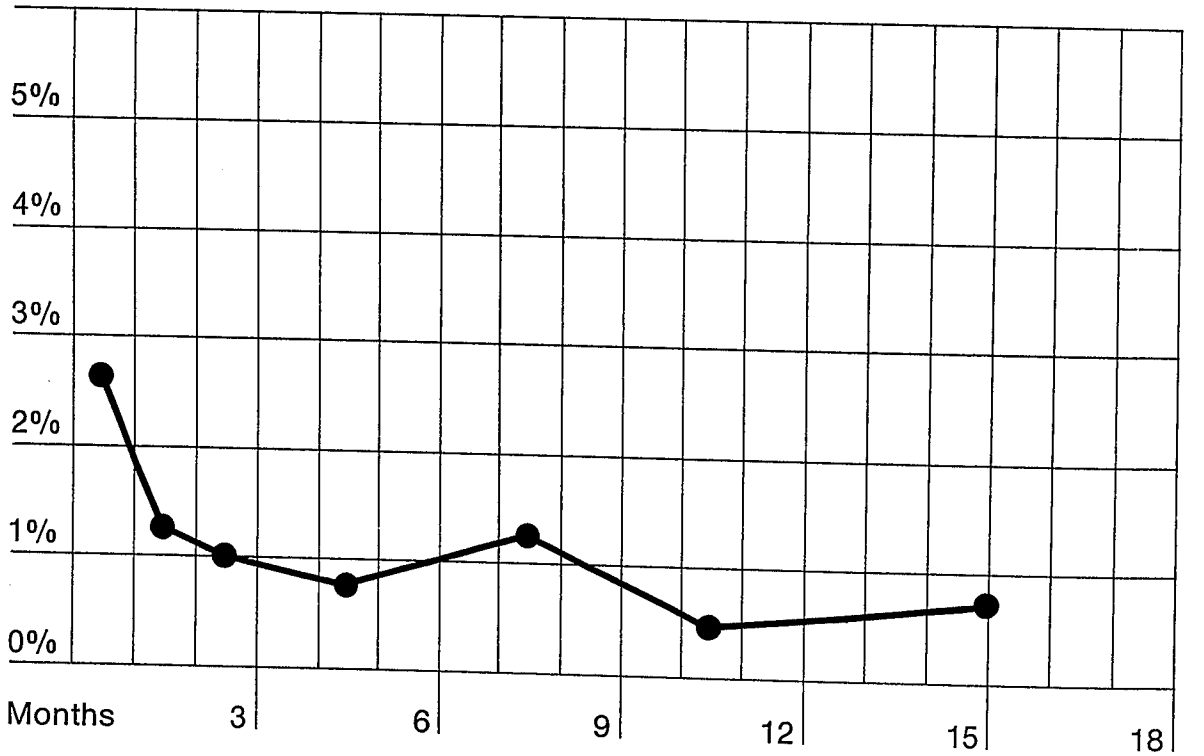
Side Effects

I. Effect on Menstrual Patterns

Post-insertion: Almost all patients will experience varying amounts of vaginal bleeding after insertion of LIPPES LOOP Intrauterine Double-S. In approximately 25% of patients, this post-insertion bleeding will cease in a few hours.

Intermenstrual Bleeding: Spotting or light bleeding occurs intermenstrually in approximately 25% of patients in the first cycle after insertion. A few patients may experience mid-cycle spotting for several consecutive cycles.

Figure 1: Monthly Rate of Removal (Loop D)



Menstrual Periods: Variation in the first post-insertion menstrual period is frequent. Most patients will experience an early menstruation, frequently with a spotting or brown discharge for 2 days before the menses. The first menstrual flow will be longer or slightly heavier than usual, and on occasion the bleeding may be extremely heavy. If this bleeding persists, removal of the loop may be considered. A few patients may have a heavier than normal bleeding during the second post-insertion menstrual period. The bleeding pattern is usually normal by the third period. Pelvic pathology should be considered if heavy bleeding occurs beyond this point.

II. Cramps

Insertion of LIPPES LOOP in multiparous women is essentially devoid of pain. Slight cramps lasting a few minutes are reported by about 10% of women in this group and rarely require analgesics.

In contrast, most nulliparous women complain of

moderate to severe cramps which may last for several days following insertion. Analgesics are often required for relief of discomfort in this group; occasional removal of the device may be necessary.

III. Syncope

Syncope may occur post-insertion particularly in nulliparous women; it is uncommon in the multipara. A few minutes in a horizontal position may be needed for stabilization in some patients.

IV. Pelvic Inflammatory Disease

Lippes[42] reported 23 patients with tentative diagnoses or histories of pelvic inflammatory disease among 1673 patients fitted with LIPPES LOOP Intrauterine Double-S. Of these 23, the tentative diagnosis was unsupported by laboratory corroboration in 8; 3 were found to have urinary tract infections; 1 had appendicitis; 1 had regional ileitis; and 1 had a postoperative wound infection with septicemia following a posterior colporraphy.

The remaining 9 cases recovered promptly; in half of these recoveries, the device was not removed.

The base line rate of pelvic inflammatory disease in the population studied is not available. It is estimated that the rate reported with LIPPES LOOP Intrauterine Double-S in place is essentially that which would have occurred without the loop.

PRODUCT DESCRIPTION

LIPPES LOOP Intrauterine Double-S

LIPPES LOOP sizes and appropriate use:

LOOP A — 22.5 mm. Blue threads. Weight 290 mg. **For nulliparous females only.**

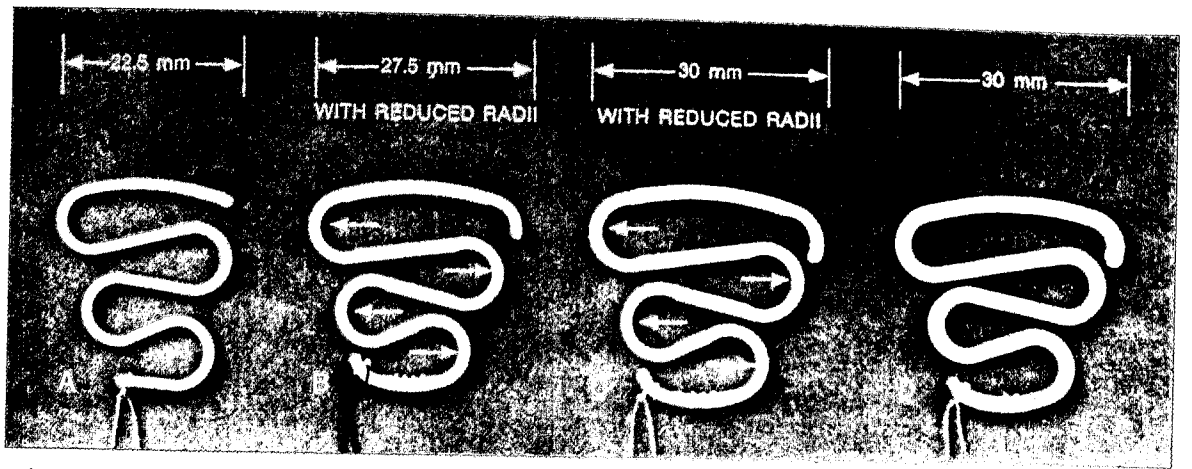
LOOP B — 27.5 mm. WITH REDUCED RADII. Black threads. Weight 526 mg. Reserved for women who have had premature pregnancy losses and multiparous females whose uteri sound out less than 6 cm.

LOOP C — 30 mm. WITH REDUCED RADII. Yellow threads. Weight 615 mg.

This is suitable for almost all multiparous females. **For women with one or more children, LOOP C should be the first choice loop.**

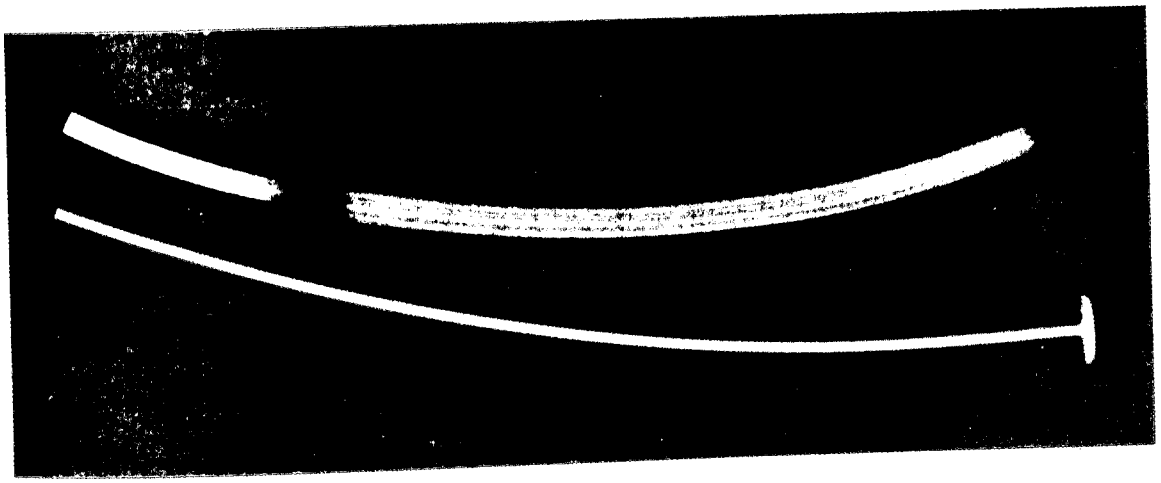
LOOP D — 30 mm. White threads. Weight 709 mg. Useful as a replacement when Loop C is spontaneously expelled.

Loop B should be used when Loop C is removed for bleeding or pain. The physician is advised to wait 2 to 4 weeks between removing a loop for bleeding and reinserting a second loop.



LIPPES LOOP Inserter

The inserter is tubular with an oval cross section about 4 mm in external diameter. Flanges serve to mark the correct distance for insertion as well as to indicate the position of the loop when it enters the uterine cavity.



DIRECTIONS FOR USE

Indication for use:

Prevention of pregnancy

Contraindications:

Any acute or subacute adnexal disease. Pregnancy. Large fibroids with distortion of cavity—especially submucous fibroids. Menorrhagia or unexplained abnormal bleeding. Suspicion of carcinoma. Bicornuate or septate uterus. Recent history of pelvic inflammatory disease.

Before attempting placement of LIPPES LOOP Intrauterine Double-S, the physician should become thoroughly familiar with the following Directions for Use:

1. Perform a thorough pelvic examination to deter-

mine freedom from overt disease and to determine position and shape of the uterus. **Rule out pregnancy and other contraindications.**

2. It is imperative that sterile technique be maintained throughout the insertion procedure.

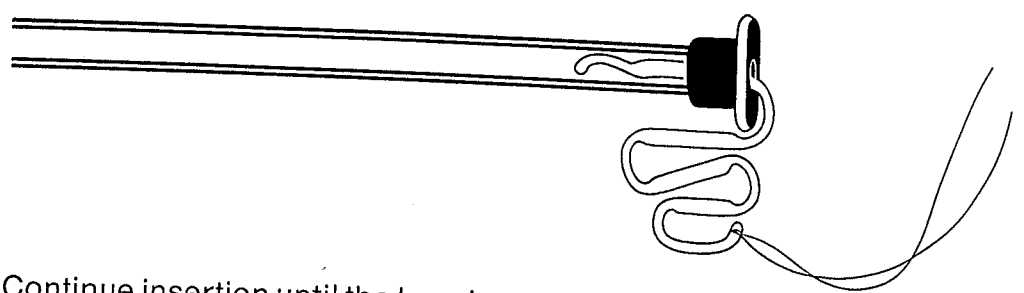
Sterilize LIPPES LOOP and Inserter for **at least 24 hours** in a 1:750 aqueous benzalkonium chloride solution. The loops may be left in solution indefinitely. **Do not boil or autoclave either the loops or the inserter.**

3. With a speculum in place, insert a sterile sound to determine the depth and direction of the uterine canal. Be sure to ascertain whether the uterus is anteflexed or retroflexed.

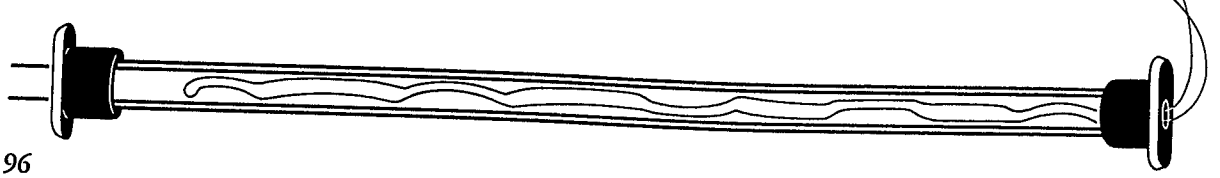
Occasionally a tenaculum is required if the uterine canal needs to be straightened. If a cicatricized cervix must be dilated, use a sterile Hank's dilator rather than a Hegar's; dilatation to a Hank's 16 to 18 is sufficient.

4. How to prepare LIPPES LOOP Inserter.

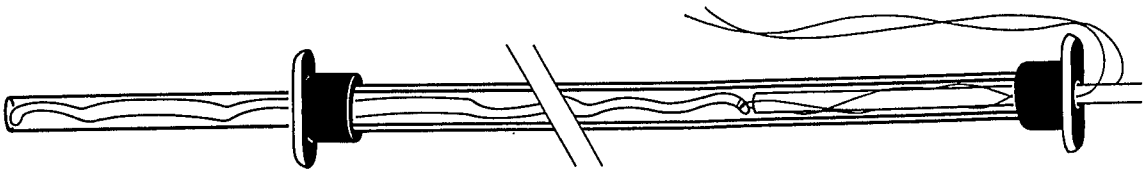
Use sterile gloves. Insert the larger end (the end opposite the threads) of the loop into the end of the inserter which is capped with a flanged indicator.



Continue insertion until the loop is entirely within the inserter.



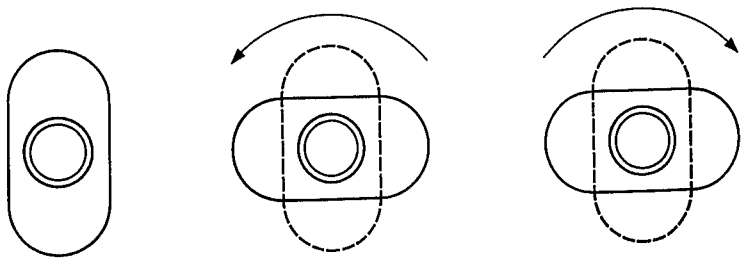
Push plunger in until the loop is at the end of the tube. Do this not more than one minute before use.



5. How to insert LIPPES LOOP.

Insert the loaded inserter **gently** into the cervical os up to the first indicator (4.4 cm), with the flanges in a vertical plane.

Turn the inserter until the flanges are in a horizontal plane.



Without undue pressure, push the plunger **slowly** as far as it will go.

LIPPES LOOP should now be in place.

Withdraw the plunger completely to avoid binding or pulling on the threads.

Remove the inserter tube.

The threads should extend about 3 cm into the vagina.

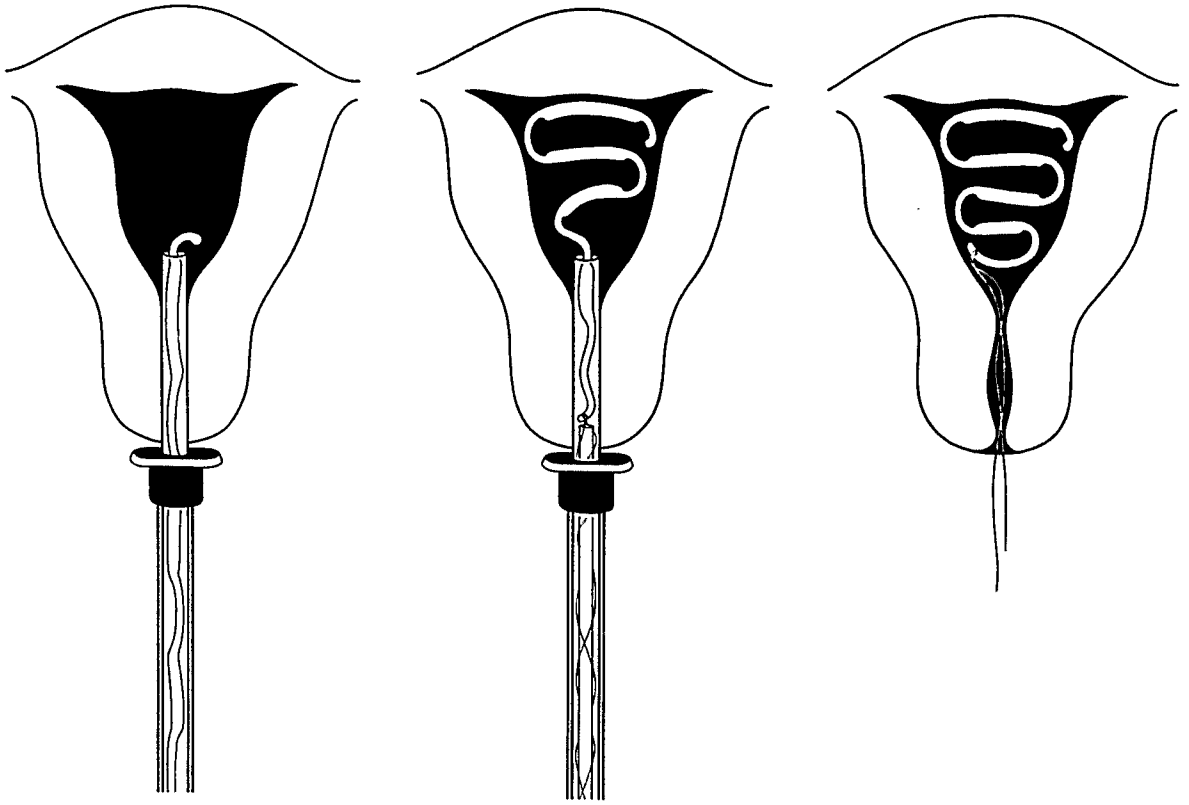
Time of Insertion.

LIPPES LOOP should be inserted preferably the last one or two days of a menstrual period or the two days following the last day.

Do not insert LIPPES LOOP sooner than 45 days after a delivery or an abortion.

In lactating patients with amenorrhea, insertion should be 45 days or more postpartum.

To remove LIPPES LOOP Intrauterine Double-S, pull gently on the exposed threads.



PATIENT INSTRUCTIONS

The physician should discuss the following with the patient:

1. Show patient how to examine herself, in a squatting position, **once a week,** with washed hands, so that she can learn how to confirm by feeling the threads that she is properly protected.

2. Instruct patient to return to you immediately if at any time she cannot feel the threads.

3. Warn the patient that she may experience cramps after insertion of the device.

4. Tell her that she may bleed occasionally for several days (two weeks is not uncommon).

5. Inform the patient that her first and, probably, her second period after insertion may come earlier than she expects.

6. Tell her that both periods may be heavy and could last longer than they would normally.

7. Advise her that if she should become uncomfortable, ordinary analgesics will help to relieve the pain.
8. Suggest that she return to you for re-examination one or two months after insertion and annually thereafter.

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AVAILABILITY

LIPPES LOOP Intrauterine Double-S

■ Introductory Package Contains:

1 Loop A—22.5 mm.
2 Loop B—27.5 mm. WITH REDUCED RADII.
14 Loop C—30 mm. WITH REDUCED RADII.
3 Loop D—30 mm.
1 LIPPES LOOP Inserter

Also available:

■ LIPPES LOOP Inserter,packaged individually.

■ LIPPES LOOP Intrauterine Double-S, All sizes, packages of 10, 50, and 100, one size only each package.

Ortho Pharmaceutical Corporation
Raritan, New Jersey 08869

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