RECENT RESEARCH ON THE MODE OF ACTION OF INTRA-UTERINE DEVICES IN PRIMATES

By

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INTRODUCTION

In a recent comprehensive review (Eckstein 1970) it was concluded that in rhesus monkeys, and probably also women, intrauterine devices (IUDs) exert their contraceptive activity within the uterus, either at or shortly before implantation. Of the several possible mechanisms involved in the anti-fertility action the most likely one was thought to be an inhibition of implantation through physical presence of the device and a combination of foreign-body reaction-cum-low-grade inflammation in the endometrium.

The object of the present survey is to assemble the new information that has been gathered about the mode of IUD action in primates since the previous review was concluded and to examine its implications in the light of the earlier conclusions.

Although not a great deal of experimental work on this subject has been carried out in laboratory primates during the past few years it is significant that increasing use is being made of baboons (Papio spec.). Baboons have several advantages over say, rhesus monkeys in this type of research. Among them are the larger size of their reproductive organs, an almost straight, human-like cervix which permits direct access to the uterine cavity without laparotomy and the occurrence of a well-marked sexual skin cycle from which the approximate time of ovulation can be inferred (cf. Hendrickx & Kraemer 1969, 1971). So far, however, there is no positive evidence that IUDs are contraceptive in baboons. This limits the value of findings obtained in this species.
and their relevance to the mechanism of IUD action in women. To date, such proof is only available for rhesus monkeys among non-human primates (Kelly et al. 1969a).

If the uterus is accepted as the site of primary action of IUDs in women and lower primates (cf. Eckstein 1970; El Sahwi & Moyer 1970), the contraceptive effect may be due, more specifically, to one of the following mechanisms: A) interference with implantation; B) impairment or destruction of the ovum; C) premature expulsion of the ovum or, possibly, a combination of them.

A. Interference with implantation

1. Importance of contact area

There is considerable evidence that the contraceptive efficiency of IUDs in women and other mammals is positively related to their area of contact with the endometrium. Davis & Lesinski (1970) have recently established that surface area of the device, independent of its shape, size and weight, is inversely related to pregnancy rate. They have also shown that of two devices, identical in external dimensions and shape but differing in their active surface area, the one with the greater surface area has a substantially lower failure rate. Davis & Lesinski interpret this relationship in terms of a local reaction between them (see below). Conversely, should the device get embedded during prolonged use its contact area with the endometrium will also become smaller, with a consequent reduction in contraceptive efficacy.

2. Endometrial reaction

a) The cellular response. It is widely agreed that the interaction between IUD and the endometrium induces a low-grade chronic, probably non-bacterial inflammatory reaction. This involves a predominantly leucocytic invasion of the uterine stroma and lumen which is thought to be ultimately, though indirectly, responsible for the contraceptive effect (e.g. Parr et al. 1967; Kelly et al. 1969b; cf. also Eckstein 1970; El Sahwi & Moyer 1970; World Health Organization 1971).

In women, a transient low-grade endometrial infection occurs as the result of contamination with bacteria from the cervical mucus carried into the uterus during insertion of the IUD. The primary cytological response of the endometrium is polymorphonuclear leucocytic, but later becomes increasingly mononuclear (lymphocytes and macrophages) (Moyer et al. 1970; Moyer & Mishell 1971; see also 2 b, below). Initially, plasma cells are also frequently present, but according to Moyer & Mishell (1971) they generally disappear from 6 months
after insertion and no longer materially contribute to cellular degeneration products in the uterine cavity.

A relatively high incidence of true inflammatory changes has been found in endometrial biopsies of women who developed clinical symptoms after being fitted with a stainless steel spring IUD (Ober et al. 1970). This type of device contains a high proportion of chromium and nickel, as well as smaller amounts of silicon and manganese, each of them capable of inducing a marked inflammatory response which may be responsible for or contribute to the anti-fertility effect (see also 2 c, below).

In rhesus monkeys, polymorphs are invariably present in the endometrium of both IUD-contact and non-contact areas. In the former they occur within the lining epithelium as well as beneath it, especially along the lateral angles of the uterine cavity. It is believed that they pass from there into the uterine lumen. Sub-epithelial leucocytes are usually undetectable in non-IUD uteri (Kelly et al. 1969b).

The possible embryotoxic effects of degradation products of polymorphs are discussed below (sect. B).

b) Role of macrophages. It has been recognized for several years that the material that adheres to an IUD removed from the human uterus may contain cells morphologically resembling monocytes and macrophages, in addition to polymorphs, uterine epithelial cells, etc. (e. g. Potts & Pearson 1967). More recently, Sagiroglu & Sagiroglu (1970) have called attention to the presence of large numbers of macrophages in the cell population attached to and surrounding an IUD, and claimed that they play a vital part in the contraceptive effect of the devices. By rough calculations on contact (»loopal«) smears from Lippes loops freshly removed from human uteri they claim to have found »up to 50 000« macrophages per slide, equivalent to a »million« or more per device in situ. Polymorphs, epithelial cells and fibroblasts were also present, but all in far smaller numbers. The authors believe that the loop »attracts« macrophages which consequently accumulate in the uterine lumen and are capable of phagocytosing sperm entering the uterus and, possibly, also the blastocyst should fertilization occur (Sagiroglu & Sagiroglu 1970; Sagiroglu 1971). By contrast, control smears obtained by endometrial aspiration of women without IUDs contained no or very few macrophages.

So far, Sagiroglu’s findings have not been confirmed in women. In baboons, Joshi (1971) observed macrophages in coil smears, but in far smaller numbers than those reported by Sagiroglu & Sagiroglu (1970), and generally not exceeding 500 per slide.

Neither Joshi’s nor Sagiroglu’s studies, however, provide positive evidence that the macrophages are actively phagocytic or about their relative frequency among nucleated cells in the smears. This aspect was examined in our own laboratory by injecting Indian ink into the uterus of baboons previously fitted
with plastic IUDs, removing the devices from 5 to 24 hours later and carrying out differential counts on smears prepared exactly according to Sagiroglu's technique (Breed et al. 1972a). Phagocytic activity, as inferred from the ability to ingest Indian ink particles, could be demonstrated among both macrophages and polymorphs (PMNs), even though only a proportion of them (ca. 7.6% and 27% respectively, of total nucleated cells) appeared to be actively phagocytic. The absolute number of macrophages in a given smear could not be established with certainty, since their cytological features were not always distinct enough to permit complete identification. It was, however, clear that far fewer macrophages were present in coil smears from baboons than have been claimed by Sagiroglu in human IUD preparations and that they were relatively outnumbered by PMNs. Whether the different findings can be explained wholly in terms of differences between women and baboons is uncertain. Also, while it has been shown that phagocytic macrophages and polymorphs occur in coil smears from baboons, this does not prove that these cells are equally capable of ingesting live sperm or fertilized ova.

It may be that the contraceptive effect of IUDs in women and lower primates will prove to be caused, as Sagiroglu believes, by an accumulation of phagocytic cells in the uterine lumen whereby the number of viable sperm reaching the oviduct is markedly reduced. Phagocytosis is, however, not a notable feature of the human or monkey uterus containing an IUD (e.g. Israel & Davis 1966; Willson 1969; World Health Organization 1968, 1971; Kelly et al. 1969b; Moyer et al. 1970; cf. also Eckstein 1970).

Relation to fertilization. Sagiroglu's observations also raise a more general issue. The concept implies that the antifertility effect of an IUD is exerted predominantly on the sperm. Most of the available evidence suggests, however, that IUDs are blastotoxic or anti-nidatory, and probably do not, except in a few species such as ruminants, interfere with fertilization (e.g. Hawk 1969: cf. Eckstein 1970; El Sahwi & Moyer 1970).

In rhesus monkeys, approximately equal numbers of fertilized cleaving eggs were found in the Fallopian tubes of both control and IUD females, after natural mating at mid-cycle (Marston et al. 1969a). There were also no substantial differences in the recovery of sperm from the reproductive tracts of both groups of monkeys. While no more than isolated spermatozoa were observed in the oviducts, fertilized eggs from females both with and without IUDs appeared to have comparable complements of sperm attached to the zona pellucida. Thus, the position in rhesus monkeys, and probably also in women, is that in the presence of an IUD there seem to be enough, apparently capa-

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difficult to conduct. Until they are completed, the important issue, whether fertilization occurs in IUD-fitted women and monkeys who do not become pregnant, and hence whether the devices interfere with fertilization or some later stage of pregnancy, will remain unsettled.

c) Effects of intrauterine metals. The occasional occurrence of a metal-induced true endometritis, and its possible role in the contraceptive activity of stainless steel spring devices (Ober et al. 1970), has already been referred to (see 2a).

More specifically, it has been shown by Zipper and his associates that the addition of heavy metals, in particular copper and zinc, to plastic IUDs results in a marked improvement in clinical effectiveness without increasing side effects. This approach stems from the observation by Zipper et al. (1969) that a small piece of copper or zinc placed into one horn of the rabbit's uterus can markedly decrease the number of implantation sites on that side without affecting implantations on the control side. The effect was probably exerted at, or shortly before implantation.

As used in current clinical trials, the copper devices consist of a T-shaped
plastic carrier, the vertical stem of which is covered with closely-wound pure copper wire with a surface area varying from 30 to 200 mm². Zipper et al. (1971) have recently shown that the surface area of copper in contact with the endometrium is roughly proportional to the contraceptive activity of the device (Fig. 1).

Studies to elucidate the mode of action of the copper-coated IUDs are still in a preliminary stage. They suggest that these devices, like the conventional ones, elicit an inflammatory response in the endometrium; the degree of the cellular infiltration provoked also appears to be similar to that seen in women fitted with plain 'T's or Lippes loops.

In addition, however, copper devices are thought to possess specific biochemical activities which distinguish them from the conventional 'inert' IUDs, and may account for their greater clinical efficacy. Repeated biopsies in human volunteers have shown that the concentration of copper in the endometrium is significantly increased during the late progesterational stage of the cycle; it returns to normal after removal of the device (Hagenfeldt 1970). Copper is released by ionization of the copper wire in the uterus at the rate of approximately 30 micrograms/24 h (WHO 1971) and is deposited, in the form of fine granules, in the epithelium of the endometrial glands during the luteal phase. This observation suggests a possible connection with the secretory activity of the glandular cells and, perhaps, interference by copper with progesterone and/or oestrogen metabolism (Medel et al. 1971). The concentration of copper in the cervical mucus is also elevated in the presence of copper IUDs, and the possibility that the cupric ions released by them are either toxic to spermatozoa or affect penetrability of the mucus cannot be excluded (cf. Oster 1971).

3. Sensitivity of the endometrium to decidualising stimuli

An essential and characteristic feature of implantation in rhesus monkeys is the formation of a superficial decidual reaction, or plaque, in the endometrium (Wislocki & Streeter 1938). This can be artificially reproduced by mechanical trauma both in intact females during the luteal phase of the cycle and in spayed hormone-treated ones (Rossman 1940).

As previously shown (Kelly et al. 1969b), a decidual reaction can also be induced when the uterus contains an IUD. This suggests that in primates, unlike rats (e.g. Margolis & Doyle 1964), endometrial sensitiveness to a traumatic stimulus is unaffected by the device. It has since been demonstrated that a more gentle and superficial stimulus, such as that provided by arachis oil injected through the Fallopian tube into the uterine cavity, has the same effect (Marston et al. 1971). It appears therefore that the ability of the primate endo-
metrium to undergo deciduomal transformation in response to a stimulus approximating that of the attaching blastocyst, is not impaired by an IUD. If this applies also to the human uterus it would seem that the action of an IUD in primates is not likely to depend on the prevention of the endometrial (i.e. maternal) part of the nidation process.

4. **Systemic or extra-uterine effects**

Although there is near-consensus that the chief antifertility action of IUDs in primates is exerted on the uterus itself, it has not yet been conclusively shown that luteal function remains unaltered in the presence of a device. If the latter were to cause the appearance of a luteolytic agent, or would enhance the action of a pre-existing luteolytic mechanism, it might deprive the embryo of essential progesterone during the critical stage before and including implantation. Such an effect has been clearly demonstrated in ruminants (*cf.* Eckstein 1970), and there is at least some evidence that this may also apply to women. Preliminary findings by Faucher et al. (1969) suggest that the luteal phase of the human cycle is shorter and urinary pregnanediol excretion reduced after insertion of an IUD. Marginal shortening of the cycle, but no evidence of disturbed luteal function, was also found in rhesus monkeys fitted with IUDs (*Eckstein et al.* 1969).

More direct evidence was therefore obtained in baboons (*Breed et al.* 1972c). The results showed the almost complete absence of an IUD effect on the overall pattern of the menstrual and sexual skin cycles, except for a trivial shortening in the duration of the deturgescent phase of the sexual skin and that of the cycle as a whole. Menstruation, however, was prolonged.

Similarly, plasma progesterone levels during the luteal phase were unaffected by the presence of an IUD, although the onset of menstruation was associated with a higher progesterone concentration than that in controls (Fig. 2). By implication, the devices interfered neither with the occurrence and timing of ovulation nor with the hormonal control of the cycle as a whole. It appears, therefore, that in baboons, as in rhesus monkeys, the devices are not contraceptive by impairing the life span and function of the corpus luteum.

There is surprisingly little reliable information about the effect of IUDs on the periodicity of the human menstrual cycle. An early report by Vorys et al. (1965) suggests that the cycle is shortened during the first few months after insertion of a device, after which normal cyclicity is resumed. More recently, Batta et al. (personal communication, 1971) found no significant differences in cycle length and the duration of menstruation between a small group of women with symptomless IUDs and a normal control group, observed continuously for 1–3 years.
Fig. 2.
Levels of progesterone in peripheral plasma during the menstrual cycle in baboons. 
--- o ---, without IUDs; ---●---, with IUD (Breed et al. 1972c).

B. Impairment or destruction of the unimplanted ovum

1. Embryotoxic effects

It is now clear that the presence of an intrauterine foreign body is associated with the appearance of a uterine factor which is toxic to the early embryo. This has so far only been demonstrated in rodents. It, and the further observation that the ovotoxic substance is present in the uterine lumen and can be conveyed to the contralateral horn by anastomosing it with the experimental one (Batta & Chaudhury 1968; Marston & Kelly 1969) is, however, relevant in the context of the mode of IUD action in primates.

Direct proof of the IUD-induced hostility of the endo-uterine environment to the early conceptus has been convincingly provided by de Boer & Anderson (1971), using the technique of double transfer of embryos. They transferred embryos, obtained from normal rats, to females with one IUD horn and one non-IUD horn. They recovered the embryos from these hosts after variable periods up to 4 h, and then tested their capacity to survive and implant on re-transfer to a second, pseudopregnant recipient without an IUD. Their findings show that after remaining in the IUD horn for 2–4 h only 10–15% of embryos were recoverable and survived in untreated recipients, compared with some 40–50% of embryos kept for the same time in the non-IUD horn before transfer (Fig. 3). It may be concluded that in the rat an IUD is contraceptive by inducing a uterine milieu which becomes the more destructive the longer the pre-implantation embryo is exposed to it.

The hostility persists even if the IUD is removed. Equality between the
IUD horn and the control horn was not re-established until 72 h between removal of the IUD and embryo transfer. Progesterone may, however, counteract the ovotoxicity of an IUD-environment. Thus De Boer & Anderson (1971) found a higher recovery rate of embryos from the IUD-fitted horn of spayed, progesterone-treated rats than that from the IUD-horn of intact rats. The mechanism underlying this apparently protective action of progesterone remains to be elucidated.

Compared with the uterus the environment of the oviduct appears to be innocuous in the presence of an IUD. Thus tubal eggs recovered from rats and sheep with IUDs are fertilizable, and will undergo early cleavage in their own oviducts or those of hosts (e.g., Hawk 1965; De Boer & Anderson 1971).

No experiments of this kind appear feasible in women or even, at present, in laboratory primates. An attempt has, however, been made to test the toxicity of uterine washings from baboons and rats fitted with IUDs on mouse embryos maintained in culture, and to compare their effects with those of similar washings from controls without the devices (Joshi & Kraemer 1970). These authors found that the washings from IUD-uteri of rats in dioestrus and Day 5 p.c., were more toxic to mouse embryos than those from control uteri. Surprisingly, however, flushings from baboon uteri, both with and without IUDs, collected from 5 to 9 days after ovulation, were non-toxic to
the embryos. It is clear that species not only differ widely with regard to the changes in the composition of the uterine fluids induced by the presence of IUDs, but perhaps also in the sensitivity of their embryos to such secretions. Until primate embryos become more freely available than at present*, and are shown to be manipulable in vitro, a biological test system of the kind developed by Joshi & Kraemer appears to be essential for further progress in this field.

2. Toxicity of the intrauterine environment

The nature of the specific changes in the intrauterine environment induced by IUDs remains largely conjectural. The most common view is that the devices set up a low-grade inflammatory reaction, the products of which either directly or indirectly, cause embryonic death (see sect. A, above). Attempts to isolate and identify the factor(s) responsible for this toxicity have progressed little beyond Parr's demonstration (1969) that extracts of polymorphonuclear leucocytes (polymorphs), as well as of various non-uterine, e.g. HeLa, thyroid and liver, cells are capable of killing rat morulae in vitro. This suggests that either degradation products of polymorphs, or non-specific ones present in damaged cells in general, may be responsible for the embryotoxicity. Recent studies (El Sahwi & Moyer 1971; Smith et al. 1971) indicate that there is a quantitative relationship between the number of polymorphs present in the uterine horns of rats and rabbits fitted with IUDs and the ovotoxicity of the devices. Also, since homogenized polymorphs are as toxic to mouse embryos in vitro as intact, it appears that phagocytosis is not the chief, or only, mechanism responsible for the embryotoxic activity, at least in lower mammals (Smith et al. 1971).

3. Chemical composition of luminal fluids

Attempts to study the chemical composition of the luminal fluid in the presence of an IUD, in order to isolate and identify the factors responsible for its ovotoxic activity, have so far usually yielded inconsistent or inconclusive results.

This is not wholly surprising. The normal uterine cavity of women and lower primates, unlike that of the oestrous rat, contains little if any free fluid. It must therefore be flushed out with some physiological medium in order to sample its contents. This inevitably leads to dilution of the recovered material and usually some contamination with blood. It can also be done rarely if ever routinely or serially, for instance in women.

Another problem is the surgical difficulty of reaching the lumen of the

uterus in primates. In rhesus monkeys the tortuous cervix of non-parous females precludes easy access to the uterine cavity, which, instead, has to be approached during laparotomy. Baboons are therefore preferable to them. Lastly, very little is known so far about the normal composition of luminal fluid and its periodic variations during the cycle and early pregnancy. Preliminary systematic studies at the physiologically most suitable times are therefore needed before valid conclusions about the biological significance of any changes in the intra-uterine environment brought about by IUDs can be drawn.

a) Studies in women and baboons. A comparative study of the effects of an IUD on the cellular and chemical composition of uterine flushings from rats, baboons and women has recently been carried out by Joshi et al. (1970). In both women and baboons the flushings were obtained by direct aspiration from the uterus during elective laparotomy; contamination of samples with blood was estimated to be of the order of 0.2%. It was found that IUDs evoke significant increases in the intrauterine concentrations of white blood cells and lysosomal enzymes in rats, but, surprisingly, not in either women or baboons. Moreover, there was no change in the protein content of human and baboon uterine fluid. Joshi et al. (1970) concluded that factors other than those of leucocyte origin may be responsible for the changes observed in the chemical characteristics of intrauterine fluids in baboons and women.

Their findings are at some variance with those obtained in other studies. Kar et al. (1968) examined uterine flushings, collected per vaginam, from women with and without IUDs, and reported raised levels of protein and non-protein nitrogen, independent of the stage of the cycle, in the former; no significant changes in glycolytic enzymes and other constituents of the flushings were observed. Significantly increased concentrations of total protein were also found in intrauterine flushings of women examined at 6 and 18 weeks after IUD insertion, compared with their pre-insertion levels (Moyer & Mishell 1971; see Table 1).

In a further study normal and IUD-fitted baboons were investigated at Birmingham University (Peplow, Breed, Law & Eckstein 1972, in preparation), Uterine fluid was sampled by injecting physiological saline through a special flushing device into the cavity of the uterus and then aspirating the washing. Flushings were carried out from approximately two weeks before to about two weeks after the estimated time of ovulation (cf. Hendrickx & Kraemer 1969). It was found that the concentrations of total protein, reducing sugar and proteinase activity (measured at acid pH) were consistently higher when an IUD was present, the differences being statistically significant during the early secretory stage (3–7 days after ovulation) when the devices are thought to exert their contraceptive activity. The levels of amylase, lysozyme and proteinase (measured at alkaline pH) were not significantly altered in the

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Table 1.
Mean number of white blood cells (WBC) and protein concentration in uterine flushings from women before and after insertion of IUDs.
PMN, polymorphonuclear leukocytes; MNC, mononuclear cells.
(From Moyer & Mishell 1971).

<table>
<thead>
<tr>
<th>Weeks after IUD insertion</th>
<th>Number of women</th>
<th>Total WBC/ mm³</th>
<th>PMN/ mm³</th>
<th>MNC/ mm³</th>
<th>Protein (mg/100 ml)</th>
</tr>
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<tr>
<td>0</td>
<td>38</td>
<td>316</td>
<td>168</td>
<td>148</td>
<td>193</td>
</tr>
<tr>
<td>6</td>
<td>30</td>
<td>2205⁰</td>
<td>1708</td>
<td>497</td>
<td>393⁰</td>
</tr>
<tr>
<td>18</td>
<td>10</td>
<td>3434⁰</td>
<td>2444</td>
<td>990</td>
<td>417⁰</td>
</tr>
</tbody>
</table>

* P < 0.01.

presence of an IUD at any of the cycle stages examined. In addition, the protein patterns of the uterine fluids were studied, but no significant differences in the presence, distribution or motilities of specific protein fractions were detected between flushings from baboons with and without IUDs.

These findings are in substantial agreement with those obtained in a comprehensive study of IUD-induced changes in the composition of uterine flushings from rats (Breed et al. 1972b).

b) Prostaglandins. The suggestion has been made that prostaglandins (Pgs) may be involved in mediating the contraceptive activity of IUDs (e.g. Chaudhuri 1971). This is a superficially attractive but improbable explanation. Several Pgs have been isolated from human menstrual blood and endometrium (see Pickles 1967). If the devices were to induce the release of excessive amounts of Pgs they might cause hypertonicity of the Fallopian tubes and uterus and so lead to accelerated tubal passage and eventually premature expulsion of the ovum from the uterus. There is, however, no convincing evidence that IUDs exert such actions (cf. Introduction; Eckstein 1970).

Alternatively, Pgs may act as luteolysins. Such an action has been demonstrated in rhesus monkeys in which PgF₂ caused a prompt reduction in plasma progesterone and premature onset of menstruation (e.g. Kirton et al. 1970). The fact that a positive (luteolytic) utero-ovarian relationship does not appear to exist in primates (e.g. women: Doyle et al. 1971; rhesus monkeys: Neill et al. 1969) argues, however, strongly against such an explanation. In a preliminary report, Batt et al. (personal communication, 1971) claim to have found increased pharmacological activity suggestive of the presence of Pgs in uterine fluid from women fitted with contraceptive devices. This requires
confirmation. Attempts to detect Pgs in uterine flushings from baboons in our own laboratory have so far revealed no significant changes in the presence of a device.

C. Premature expulsion of ovum

The possibility that IUDs may induce a (periodically or permanently) altered pattern of uterine motility, as a result of which the fertilized ovum is prematurely expelled, has been discussed in detail (Marston et al. 1969b,c; cf. Eckstein 1970). No significant new information on the likelihood and operation of such a mechanism in primates has been obtained in recent years (see, however, Moawad & Bengtsson 1970). Consequently, there seems no reason for altering the earlier conclusion that enhanced uterine motility is unlikely to be a major factor in the mode of IUD action in women and non-human primates (cf. Eckstein 1970; El Sahwi & Moyer 1970).

DISCUSSION AND CONCLUSIONS

The survey makes it clear that considerable progress has been achieved in IUD design and research during the past few years. With rates for unplanned pregnancy close to those of oral contraceptives and 1- and 2-year continuation rates probably superior to them, as reported in recent Dalkon shield, and ‘copper-T’ trials, the point may be near at which the clinical problem – the provision of reliable, safe and generally acceptable contraception – can be said to be essentially solved.

In the case of the mode of action of the devices such a satisfactory stage has not yet been reached. The recognition by Davis & Lesinski (1970) of the inverse relationship between surface area of the device and conception rate is an important advance, but perhaps more for the bioengineer and clinician than for the physiologist. It is clear that the aim of the IUD designer should be to combine maximal contact at the interface between device and endometrium with minimal pressure on and distortion of the uterine cavity. What the biologist wants to know is whether an increased surface area also provokes a more intense or generalized inflammatory response in the endometrium.

It seems generally agreed that the endometrial response itself consists chiefly of polymorphonuclear leucocytes and, next, mononuclear elements. There is less consensus about the composition of the luminal fluid, probably because this has been less thoroughly investigated. Some workers believe that it largely resembles the cellular exudate in the uterine stroma and epithelium, but a few think that it is made up predominantly of phagocytic macrophages.
and only residually of polymorphs, lymphocytes, fibroblasts and endometrial cells, etc. (Sagiroglu & Sagiroglu 1970). Their observations were, however, made on the material in direct contact with IUDs, and do not necessarily apply to the luminal contents proper. It is possible that macrophages aggregate in close proximity to the devices, while polymorphs do not. The former may therefore become concentrated on the IUD, but depleted in the luminal fluid itself; macrophages are also thought to have a longer lifespan than leucocytes. The issue can probably only be resolved by simultaneous study of the endometrium, ‘coil smears’ prepared directly from the device, and uterine flushings; opportunities for examining all three together in women are not likely to occur often.

There can, however, be no doubt that macrophages are present in coil smears from baboons, and that a proportion of them and of polymorphs are actively phagocytic (Breed et al. 1972a). The ability of these cells in baboons, and in women, to phagocytose viable gametes has, however, still to be established.

One of the most interesting and promising recent developments in human intrauterine contraception is the advent of copper containing, and -releasing, devices. While their clinical efficacy cannot be doubted, their biological action is only imperfectly understood. It probably depends on an endometrial inflammatory reaction similar to that induced by conventional IUDs, but may be complemented or reinforced by additional biological actions such as toxicity to spermatozoa, possible interference with implantation by an effect on steroid metabolism, etc. Interestingly, the high contraceptive efficacy claimed for the Dalkon shield may be due to the combined action of the cellular response and that of a small amount of copper incorporated into the semi-permeable plastic matrix of the device; how much metallic copper is released from it does not seem to be known.

With regard to possible systemic or extra-uterine effects by IUDs, the work reported from our own laboratory indicates that in baboons, as in rhesus monkeys, the devices do not interfere with the lifespan and function of the corpus luteum, and hence, by inference, with the hormonal control of the cycle as a whole. It is highly probable that this also applies to women.

This and the available strong evidence against the existence of a luteolytic mechanism in women (Doyle et al. 1971) and rhesus monkeys (Neill et al. 1969) make the participation of prostaglandins in the action of IUDs in primates improbable. The possibility of their involvement should nonetheless be fully investigated.

The study of De Boer & Anderson (1971) has given convincing proof that the uterine horn of a rat fitted with an intrauterine suture contains material which is lethal to the early conceptus. Preliminary attempts to demonstrate a similar toxic effect in the case of the primate uterus by use of an in vitro
technique have, however, failed. While intrauterine fluid from rats with IUDs exerted an inhibitory effect on the development of fertilized mouse eggs in cell culture, those from baboons did not (Joshi & Kraemer 1970). Their study, based on the testing of single samples, requires confirmation, and with uterine flushings from other primates including women. It can, of course, not be assumed that uterine material from primates will be toxic to non-primate eggs. It may therefore be necessary to develop more nearly species-specific test systems to settle the issue, for instance by testing flushings from macaques or baboons against their respective ova. Improved methods for routinely sampling the uterine secretions of laboratory primates and women are also greatly needed and, when available, may yield positive results. The ingenious method developed by Edwards (e. g. 1967), in which a small chamber surrounded by a millipore filter is introduced into the human uterus to monitor the luminal fluid, may offer a possible approach. Its application will, however, be complicated in the presence of a (second) intrauterine device.

The chemical, pharmacological and immunological analysis of the uterine secretions of women and lower primates, both with and without IUDs, is also urgently needed. In spite of recent studies little is yet known about the normal variations in and the effects of IUDs on the chemistry of the luminal fluids during the menstrual cycle. For instance, findings in several laboratories have shown that the protein content of these fluids during the luteal phase is raised in the presence of an intrauterine device, as might be expected on the basis of the inflammatory-response concept of IUD action (e.g. Moyer & Mishell 1971; Peplow et al., in preparation, 1972). On the other hand, Joshi et al. (1970) reported similar concentrations of leucocytes and lysozyme in uterine flushings of women and baboons either without or with IUDs. Improper sampling techniques, dilution or contamination of the uterine specimens with blood and, above all, single or infrequent tests, may have contributed to these inconsistent results. They should, of course, be fully checked and clarified.

It may be concluded that in spite of substantial progress in IUD research during the past few years, understanding about the specific contraceptive action of the devices in women and lower primates remains incomplete. It seems, however, reasonably certain that several intrauterine mechanisms are involved, and that these are already identified but have not yet been fully appreciated, whether quantitatively, in timing or in their biological significance.

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