SPECIAL REQUIREMENTS FOR TOXICOLOGICAL TESTING OF METAL-RELEASENING INTRAUTERINE DEVICES

By

Robert Gordon McConnell

ABSTRACT

Intrauterine devices (IUD's), intrauterine drug reservoirs (IUDR's), and metal-releasing intrauterine drug reservoirs (MR-IUDR's) with anti-fertility activity in the animal and human are considered as separate entities. General requirements for toxicologic and teratologic testing of such agents in animals are presented. A comparison reveals the relative advantages and disadvantages of simian, canine, lagomorph, and rodent species. A pretreatment review of obstetric-gynaecologic status and history of each animal is emphasized. Designing of appropriate replicas of the clinical device for use in predictive animal studies requires comparative data on uterine morphology, device-endometrium spatial relationships, and drug release rates. Adult, maternal and foetal tissue metal levels may be important; the analytical methods for detecting and localizing cellular and subcellular wet tissue metal levels are available. Existing in vivo mutagenicity assay procedures are poorly adapted to intrauterine drug testing. Method modifications are explored briefly. A sequence for the animal safety testing of an intrauterine antifertility agent, and its interrelation with clinical research, is outlined.

Introduction

Intrauterine and/or inter-uterine antifertility effects may be elicited clinically by chemically-inert foreign objects, by locally-released drugs (metallic or non-
metallic), or by a single unit possessing both properties. In a recent publication
(Gardner 1973) the Food and Drug Administration indicated which types of
intrauterine devices are now classified as drugs in the USA. It was a definition
by exclusion, and stated essentially that those intrauterine devices which are
not fabricated solely from inactive materials, or which contain substances con-
tributing to contraception through chemical action on or within the body, or
are dependent upon being metabolised for the achievement of the contraceptive
purpose, are classified as new drugs.

Briefly then, an intrauterine device (IUD) might be considered a chemically
inert foreign body which elicits an antifertility effect when reposing in utero.
An intrauterine drug reservoir (IUDR) elicits its antifertility effect partially
or wholly through chemical action within or on the body, by a chemical agent
released in utero from the device. A metal-releasing intrauterine drug reservoir
(MR-IUDR) likewise elicits such an effect via a metallic agent released from
the device. Thus the IUD, the IUDR, and the MR-IUDR may be considered
separate, defined entities. An IUD initiates its effect locally; an IUDR or
MR-IUDR might act locally and/or systemically.

Numerous publications indicate the relative antifertility effectiveness of
copper, zinc, cadmium, nickel and various other metals when deposited in the
uterine cavity of rodent and lagomorph species (Chang et al. 1970; Tatum
1972; Zipper et al. 1969). Copper and/or zinc releasing antifertility devices are
being employed in humans (Hagenfeldt 1972; Salaverry et al. 1973; Tatum
1972; Zipper et al. 1971). Safety assessment of such agents in animals presents
some unique and interesting challenges.

General toxicological requirements for testing various types
of intrauterine devices or drugs

Recognizing that preclinical safety studies are valuable as such only insofar
as they are predictive of what will occur in the human, the design of each
experiment deserves careful thought. Numbers of animals to be employed,
selection of species, determination of "dose" and route of administration, and
monitoring of the anatomical location, continued "activity", and integrity of
the device may all require a bit of ingenuity.

Toxicology studies with antifertility agents in animals are unique, in that
the reproductive process with which these agents are intended to interef
clinically is present intact, and functioning normally at initiating of the study.
A major concern is whether the reproductive process is sufficiently comparable
to the human, and can be altered in a manner sufficiently comparable to the
human clinical situation, that the animal model will possess predictive utility.

Selection of species, duration of each study, and number of animals employed
per treatment group should be consistent with accepted drug toxicology testing
procedures. The need for technical experience and historical control data will preclude immediate use of exotic species, irrespective of otherwise seemingly attractive features. The most relevant animal species should be one which possesses a reproductive system comparable to the human; the chemical disruption (imbalance) imposed should be chronologically similar to that being imposed in the human.

The sub-human primate possessing a unilocular uterus and exhibiting a menstrual cycle similar to the human is a logical consideration. However, the bicorulate uterus of the rodent or lagomorph offers the opportunity for making contralateral cornu comparisons of intact vs. device-bearing, or perhaps IUD vs. IUDR-bearing horns in each animal, in addition to comparisons between treatment groups. A representative species of each type might be employed. The beagle dog's well known propensity for developing cystic endometrial hyperplasia, and purulent endometritis, and the temporal dissimilarity of its oestrous cycle endocrine balance to the human menstrual cycle, constitute possible constraints on its use.

The duration of each study should be sufficient to satisfy the study objectives. In tumorigenicity studies of drugs, 50 animals are generally used per treatment group. Post-operative mortality is a variable to be considered.

Age is also an important consideration; the use of sexually-immature animals would be at variance with human clinical use of these antifertility agents. Studies implemented with young, sexually mature rodents may be continued over the average lifespan of such species. In contrast to clinical use, the test devices will probably remain in utero beyond the cessation of reproductive capability, since removal generally requires hazardous surgical intervention.

Information on the obstetric and gynaecologic status and history of each animal is especially important, to ensure homogeneity of the animal population employed. Evidence of normal oestrous or menstrual cycling is essential in most studies (Shaw et al. 1972). Evidence of a cytologically normal cervix, as well as an accurate estimate of animal age, is recommended in all primate studies. Proven fertility may be required in certain reproduction studies. Unsuitable animals are, of course, eliminated from the study population prior to random assignment of animals to control and treated groups. All clinical laboratory procedures customarily employed in assessing the health status of animals should be performed.

Device-to-uterine cavity spatial relationships are an important consideration regarding both antifertility activity and endometrial trauma elicited by a “foreign body” device. This aspect must be considered with both IUD's and IUDR's. Close replication of the human uterine spatial relationships is unlikely to be accomplished even with larger subhuman primate species. A compromise is effected between the drug “dose” and device configuration desired, and that permitted by the size and shape of the animal uterine cavity.
Regarding size, shape, and surface contour of the device, the design selected should enable minimizing areas of continuous device – endometrium impaction; it is advisable to avoid having the device "head" continuously in apposition with the endometrium and the "tail" constantly engaging the endocervix. The inert IUD and the chemically-active IUDR must be identical in size, shape, and surface contour if valid comparisons are intended.

Tortuosity of the cervico-vaginal tract and/or size of the cervical os precludes trans-vaginal insertion of most devices. Instead, they are inserted surgically employing a trans-abdominal approach, and will subsequently be retrieved by the same approach, as necessary. They may be "suspended" in utero from a short suture which also closes the uterine incision. The stress imposed by such an operative procedure is undesirable but unavoidable; a sham-operated control group is essential, and should receive the same incision closure technique applied to the device-bearing animals. The use of a retaining suture is valuable; it allows confident selection of postmortem tissue specimens from those endometrial sites which received maximal physical contact with the device, or those receiving most direct exposure to a drug released. It also enables placement of the device between implantation sites in the pregnant animal.

Periodic verification of device retention is required, and is facilitated by inclusion of a radiolucent material in the device composition.

*Specific requirements for testing metal-releasing intrauterine drug reservoirs (MR-IUDR's)*

Assume that the IUDR of interest possesses antifertility properties both by way of its foreign body activity and through releasing a biologically active metallic chemical. Both transient and cumulative gradients of the chemical distributed are of importance. Toxicology concerns related to distribution of the chemical agent in the non-pregnant animal, the pregnant animal and the developing foetus, and of effects peculiar thereto, need be anticipated.

The kinetics of intrauterine drug release and inter-uterine drug absorption, and the possibility of combined local foreign body effects plus local and systemic drug effects, make extrapolations from data based on drug administered orally to drug administered by the intrauterine route especially unreliable.

When studies of hormonal balance, as revealed by serum gonadotrophin or hypothalamic-releasing factor levels, are appropriate, they should be performed prior to long term toxicity testing and should form the basis for selecting a given species for subsequent use. It is likely that precise definition in meaningful biological terms of those endocrine parameters altered in the treated patient, with subsequent comparable assessment of the experimental animal model, will enable identifying those animal species most likely to

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possess predictive utility. Drug dosages administered to such species should be confined to levels which elicit the identified hormonal imbalance.

Conventional toxicologic testing of drugs involves exposing groups of animals to various multiples of the human dose. Although testing of IUD’s and IUDR’s is poorly amenable to such an approach, step no. 1 would be to define the human dose. Mg/kg body weight/day is conventional, but may bear little or no relationship to biological effectiveness. Should the “dose” be expressed in mM/m² of body surface? or mM/m² of endometrial surface? Should the unit of time be drug released daily, with the implicit assumption that the rate will remain constant over the reproductive lifespan?

The rate of release of metal from many MR-IUDR’s in humans is proportional to the surface area of metal presented (Tatum 1972; Zipper et al. 1971). Subsequent to determinations of human and animal release rates, a device providing appropriate multiples of the human dose could presumably be devised. The device configuration should be an appropriate replica of the clinical device. The small size of the subhuman primate uterus may limit the use of such a device, however.

Preparation of this IUDR for animal use will probably provide most drug toxicologists with their first opportunity to collaborate with a mechanical engineer, as well as a pharmaceutical formulations expert, in the preparation of the dosage form to be used in animal toxicology studies. If so, a brief but thorough orientation session outlining the primary objectives and basic inherent constraints in each area will prove valuable and mutually satisfying.

The IUDR design specifications may necessarily require individualization for each species studied. Subsequent interspecies comparison of results, to be meaningful, requires that certain basic parameters be maintained equivalent throughout all test species. For instance, the rate and amount of drug exposure of the surface and glandular endometrial epithelium need be equivalent. It should be recognized that endometrial epithelium is replaced (regenerated) at notably differing rates in different species. This factor may an important consideration in comparative mammalian studies of intrauterine antifertility devices.

Drug distribution studies are greatly facilitated by the availability of a sensitive, precise analytical method for detecting the test agent. Such a method may enable the investigator to determine whether drug accumulation occurs, and indicate the precise location and perhaps the nature of the accumulation. Such studies may be compromised somewhat if the “drug” is available from dietary sources as well as from the intrauterine reservoir, unless the detection procedure can differentiate between such sources. Tissue distribution data on “drugs” that are normal components of some tissues cannot be reliably interpreted without extensive concurrent and historical control data.

Neutron activation analysis, widely used in studies on trace element distribu-
tion in cardiovascular diseases (Karvonen 1972), has also been employed in evaluating endometrial copper distribution in humans bearing MR-IUDR's (Hagenfeldt 1972). Analyses may be performed on wet tissue specimens of 10 to 50 mg size. Electron probe microanalysis is likewise useful for tissue distribution of metals e. g. copper, zinc, cadmium, and others (Golberg 1973).

A toxicology study of an IUDR in a simian species might include one group of sham-operated controls, one group of placebo (inert) IUD-bearing controls, and one or more groups of IUDR-bearing animals. This allows comparing the effects of the operative procedure only, the chemically-inert IUD, and the chemically-active IUDR. Use of a non-simian species with a bicornuate uterus, with the operative procedure performed on one horn only, allows comparison of surgically-manipulated and intact horns in individual animals, in addition to the group comparisons indicated above.

An objective response to the practising physician's request for advice on what action to take when an IUDR-bearing woman becomes pregnant is needed. Obvious ethical considerations preclude performance of prospective clinical research studies designed to provide data on this situation. Thus, in the absence of adequate retrospective human data, studies in the animal become especially important.

Studies of effective antifertility agents of this type in the pregnant animal are performed with some difficulty, since the presence of an IUD and especially of an IUDR reduces the number of foetuses recoverable from the device-bearing uterus. Again, the bicornuate uterus offers some important advantages. Devices may be placed between implantation sites in the pregnant uterus. Tissue levels of drug may be studied in foetuses delivered by Caesarian section. Comparisons between various locations within the IUDR-bearing horn, and between IUDR-bearing and intact horns may be made.

Devices may be inserted bilaterally near the uterotubal junction in rodents or lagomorphs shortly following implantation. Survival of a foetus generally is directly proportional to its distance from such a device. The animals may be allowed to deliver naturally after removal of the device, and the physical and sexual development and behaviour of the offspring observed. The proximity of any such pup to the IUDR during in utero development is, of course, unknown. The number of pups per litter may be markedly reduced in studies of this nature.

The reproductive capability of animals may be determined prior to insertion and again following removal of an IUDR. Such a study may provide useful data regarding the impact of an IUDR or other device on subsequent fertility. The device employed should be properly designed for the uterus being treated, and adequate post-surgical recovery should be allowed before re-mating or inseminating. Oestrous cycling should be verified, as appropriate.

Currently available mutagenicity test procedures in animals are of unproven
predictive utility regarding the human response. These procedures may be adapted for the testing of IUD's or IUDR's if desired, but improvements in predictive utility probably will not result from such alterations.

The standard dominant lethal test involves treatment of the male prior to mating, and is not applicable. It is unlikely that the standard host-mediated and cytogenetic assays would be useful in detecting mutagenic effects in the maternal system, unless drug levels in serum are detectable in the IUDR-bearing animal. Substitution of the uterine cavity for the peritoneal cavity as recipient of the cell indicator system of the host-mediated assay offers little promise, since the theoretical advantage of the intraperitoneal location is to allow exposure of the cell indicator system to both drug and drug metabolites. The uterine cavity, being “outside” the body, fails to provide comparable exposure.

Injection of the cell indicator system into the amniotic sac surrounding the IUDR-exposed foetus might be theoretically equivalent to the peritoneal cavity, and offer an approach toward detecting foetal mutagens. I have no firm basis for recommending such an approach, however. Performance of either the cytogenetic or micronucleus assays on foetal or neonatal bone marrow specimens might constitute a more meaningful approach. Interpretation of the data derived, in terms of projected human risk, might be rather precarious.

Discussion and conclusions

In the development of a new anti-fertility drug, safety testing in animals precedes human exposure, continues concurrent with human safety and efficacy studies, and usually continues long after the agent is marketed. Since such a program is both lengthy and expensive, the rational mind requires that it provides a reliable prediction of the nature and extent of risk to the human. To contribute less than this provides reason for society to question its real value.

Acute toxicity studies should not be performed with MR-IUDR’s unless a meaningful experimental design can be envisioned. Data from comprehensive subacute studies in two or more species should be available prior to initiating studies in the human. The duration of such subacute studies should exceed the treatment (device-bearing) duration of the initial clinical studies planned. They should be performed in appropriate animal populations (comparable as to age, sex, reproductive status), and should provide appropriate clinical laboratory data and extensive postmortem data. A scrupulous evaluation of local uterine effects, employing both morphologic and chemical analytical methods, need be performed. Additional comprehensive toxicology studies of longer duration precede subsequent longer term clinical studies.

An evaluation of the carcinogenic and mutagenic potential of the test agent is made prior to initiation of human studies. Actual laboratory testing is per-
formed at that point only if a mutagenic or carcinogenic activity is suspected, based on chemical structural relationships to known mutagens and carcinogens. Long term ("lifespan" or 2 year) studies in rodent(s) and non-rodent(s) would otherwise be initiated after clinical efficacy of the agent has been established preliminarily.

Teratology and reproductive studies need precede exposure of the human female possessing reproductive capability ("potentially pregnant") to the test drug.

Continued interaction of toxicology, clinical, drug metabolism, and pharmacological research project monitors via a committee charged with designing all preclinical safety studies is one industrial means of providing reasonable assurance that all relevant animal and human toxicology data will be carefully correlated. It is suggested that such a multidisciplinary industrial committee be constituted for each individual potential product, when identified as such by the appropriate research staff, and that it be continued indefinitely throughout the development and marketing of such product.

If the toxicologic assessment of a new drug proceeds according to the sequence outlined above, and if it is jointly reviewed periodically by individuals with expertise in the disciplines cited, a minimal amount of assistance from regulatory authorities is required. A failure to allot sufficient multidisciplinary expertise to each project may result in a poorly coordinated drug development program, with time loss to permit additional animal studies being a probable consequence, and unnecessary human risk as a relatively remote but possible consequence. Within a given category of therapeutic activity, drugs with different mechanisms of action and/or markedly differing chemical structures exist. It is important that standardization of toxicology test procedures does not act as a constraint on the toxicologist, preventing him from implementing in the first instance that research approach which enlightened scientific rationale envisions as being most applicable to the problem at hand.

The publication of preclinical safety studies in the scientific literature is desirable and is encouraged by most drug firms. Drug toxicology laboratories have, as a primary task, the performing of studies and reporting of results to their clinical staff and to various regulatory agencies. Transcribing such reports to constitute suitable journal submissions requires considerable additional effort, generally does not contribute visibly to development of the drug concerned, and must be accomplished on a time-available basis. Being academically trained scientists, such authors are inculcated with both a high regard for the peer review system, and an awareness of the value of data dissemination to the full scientific community. Their activities in publishing, however, will reflect the competing influences of numerous job demands.
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DISCUSSION

Berliner: Just a comment of information on the history of the regulatory status of the IUDs. When the first IUDs made their appearance a few years ago, they had to be classified as devices, according to existing regulations, and therefore pre-clinical and pre-marketing clearance through appropriate animal and clinical investigations were not required. In 1971, a directive was issued that “treated” IUDs, that is those containing an active agent, be it a drug or a metal carried on the device in some manner, were to be considered drugs and that they would fall under the clearance requirements for new drugs. At that time, two IUDs bearing copper wire were already on clinical trials. Their sponsors complied with the new regulations by submitting INDs for their products containing reports on the toxicity tests in animals and on the clinical investigations. These had been conducted without guidelines from the agency. The Advisory Committee for Obstetrics and Gynaecology was informed of these, and was asked for recommendations for pre-clinical investigations that would become requirements for IUDs of this type. The main recommendation was that such devices should be investigated in animal species with oestrous cycles, and that emphasis should be on local effects on the uterine tissues, and systemic effects, absorption, tissue distribution and excretion patterns, and so forth. Long range tests were not suggested. Considerable information in these areas had been accumulated and reported, but the Committee recommended several additional investigations in support of the safety and of the efficacy of these devices. Thus, one could say, this situation has been handled with a good deal of flexibility. Guidelines are being worked on by a committee composed of representatives from the industry and FDA. The status of untreated IUDs is also undergoing a change. They are presently under investigation by congressional committees, and legislation is before Congress to bring them too under the drug regulations pre-clinical tests to ascertain their safety before initiation of clinical investigations.

Lipsett: Dr. McConnell, what is the extra efficacy of the copper IUD that one can attribute to the copper? Secondly, is it known what a device which acts only as a repository for the copper, but does not act as an IUD, will do in terms of preventing fertility in experimental animals? Thirdly, can you tell me the amount of copper that
is absorbed from the copper IUD in relationship to the normal daily copper absorption?

*R. G. McConnell:* Extra efficacy attributable to the copper has been demonstrated in humans and in animals ([Tatum 1972; Zipper et al. 1971; Zipper et al. 1969]). Species variability was evident in the animal studies ([Chang et al. 1970]).

Dr. Lipsett's second question regards the anti-fertility effect of repository copper unaccompanied by an effective IUD, or foreign body, activity. What type of intra-uterine device would not constitute a foreign body of some sort?

*Lipsett:* Obviously, anything in the uterus is a foreign body, but I am thinking of a very small amount of plastic that would release the appropriate amount of copper so that one could look at the effect of the metal alone.

*Hertz:* I have been in very close proximity to the development of copper T through Dr. Tatum, so I think I can offer an answer to Dr. Lipsett's inquiry. First, with respect to the additive effect of putting copper on the T. With the T alone, which was well tolerated but poorly retained, pregnancy rates ran about 18 per 100 woman years and the discontinuation rate due to ready loss of the T was very high. When copper is added to the T, the retention rate goes up to a very high level and the pregnancy rate drops down — according to various reports made — to anywhere from 2 to 6 pregnancies per 100 woman years. So that there is no question that the copper adds to the effectiveness of a poorly retained, small, easily inserted IUD. Experimentally, Dr. Chang has shown that a copper wire will be retained in the uterine lumen of the rat or the rabbit, whereas a nylon thread of the same dimensions will be readily expelled. There is some inhibitory effect of the copper on uterine motility in response to a foreign object. As to the effectiveness of a metal repository of not sufficient size, the experience with the T alone shows on clinical grounds — as well as other very minute IUDs which have been proposed and developed — that once you come below a certain minimal size, the loss, unless this can be combined with some inhibitory effect on the uterine motility, will be so great that the effectiveness is very low.

As to the absorption of copper on a daily basis, studies have been made, not so much on absorption as on loss from the device. The daily loss of most devices varies with the amount of surface added in terms of copper. It has been shown that as the copper surface is increased, the contraceptive effectiveness is also increased. The original copper T had about 200 mm² of copper and lost about 10 micrograms of copper per day. What proportion of this loss was in the vaginal secretion rather than absorption remains to be worked out. There are some data from the Einstein Medical School group which indicate that, using radioactive material, the plasma copper rises during the presence of the copper T in the uterus. The extent of that absorption remains to be evaluated. I think Dr. Mishell has extensive experience with it.

*Mishell:* We have performed serum studies of copper in patients before and after insertion of an IUD. There is no increase in the serum level of copper or in ceruloplasmin levels. Although copper is lost from the devices, the amount is less than the daily intake of copper in the diet. Secondly, the pregnancy rates with the copper devices are less with a larger amount of copper on the device, so that the more copper released per day appears to significantly lower the pregnancy rate. I question whether the addition of copper changes the expulsion rate of the devices. The rates were too small to make the differences significant.
I would like to ask one question, Dr. McConnell, that has been bothering me, about the requirements of the FDA, and I think it is a matter of definition. First of all, I do not believe that the plastic devices that were introduced about ten years ago are inert devices. These devices do have materials in addition to the plastic. They are impregnated with barium sulphate that is released, albeit at a relatively slow rate. I think that your division of intrauterine drug reservoirs and intrauterine devices might be more one of degree than one of specific categories. For example, there was an older device made of steel, which obviously was releasing iron. Therefore I believe that all intrauterine devices that were considered to be inert are in fact not so, and I think that might have something to do with their mechanism of action. As an example, there are two different plastic devices of identical shape and design, one made of polyethylene, in the form of a loop, and the other made of a different plastic. This latter device has a significantly lower pregnancy rate than the polyethylene device, and it must have something to do with the composition of the plastic and its action in the cavity.

R. G. McConnell: I certainly do not disagree with your comment, Dr. Mishell, on the classification being relative, not absolute. Retrospective classification of the various metal devices now classified as IUDs would place them in the IUDR category, provided they are releasing a metal material which exerts a biological effect. The possibility of release of chemical materials from allegedly inert (by definition) plastic devices concerns most toxicologists, I am sure. This is the basis, of course, for the experimental protocol that I described, allowing one to differentiate between toxic effects of the plastic frame and of the IUDR (plastic frame plus metal).

Bryson: This speaks to the inertness question. To the extent that copper wire is not expelled from the uterus and plastic devices are expelled under similar conditions further illustrates the rejection phenomenon linked with the similarity of foreign bodies to their adjacent biological components.

With respect to experimental design, it was mentioned that comparison between surgically manipulated and intact uterine horns in bicornuate animals might be suitable. I do not think the effects could be justifiably compared in the same animal. I would like to introduce a caveat. Although rabbits and rats have two separate uterine horns, the antifertility effect is usually confined to the ipsilateral horn. Mice, on the other hand, have a short uterine body above the cervix, where the two uterine horns unite, and usually the antifertility effect of an intrauterine device is induced bilaterally. The extent of uterine tissue reaction to foreign bodies not only varies between species, but between strains, and also individual animals. These variations are considered to be genetically mediated. Furthermore, the possible endocrine perturbations that have been suggested in some studies (Sahwi & Moyer 1970) using intrauterine devices, would be pejorative to observations of a surgically intact horn as the control.

Zaffaroni: I think it is important to keep two points in mind. First, that there were no regulatory procedures at the Food and Drug Administration for manufacturing, testing and approving IUDs before they were introduced in medical practice. As reported by Dr. Berliner, such procedures are planned to be instituted in the near future. Second, there has been practically no research and development work by pharmaceutical companies in the area of IUDs. It is only very recently that we have seen serious interest in this field by two drug companies. Because of this, we have not had in the past well-standardized IUDs, reproducible manufacturing procedures
and rigid standards in quality control. It is likely that there has been significant variation in polymer composition, flex modes, etc., and that these variations may account for variable levels of clinical effectiveness.

Another point that I would like to make relates to Dr. Mishell’s remarks about the possibility that existing IUDs might not be totally inert devices. The fact that two different devices of exactly the same shape but made with different polymers will produce different levels of fertility control might be due to factors such as flex mode. A harder and stiffer material would likely exert a more substantial pressure and distortion of the uterine cavity. These factors might well be responsible for the difference in biological effectiveness. It is well to keep in mind that shape and size are but just two of the variables in the design of an IUD. The chemistry of the polymer surface, whether hydrophilic or hydrophobic, neutral or ionic, are elements to be considered. The polymer surface might act as a sequestering agent for certain key molecules present in the cavity.

In closing, I would like to call attention to the difficult problem of testing for solid state carcinogenesis when it relates to IUDs. This requires almost absolute and total reproducibility of the spatial relationship between the IUD and the cavity in the experimental animal and the human.

Goldzieher: I think we probably can lay the idea of “inert” plastics to rest. Plastic devices accumulate leucocytes and macrophages around them, which is an evidence of biologic activity. As Dr. Zaffaroni pointed out, the concretions of calcium salts indicates chemical activity as well.

Dr. McConnell, did I understand you to say that size and shape considerations in animal tests could be used in some way to infer human possibilities? It is my impression that the modes of action of IUDs vary from species to species. This makes it rather questionable, whether such experiments are relevant to the human situation.

R. G. McConnell: I hope that I did not give the impression that consideration of the size, shape, surface contour, and other physical properties of the device would enable finding an animal model predictive of the human antifertility response. I referred only to toxicity or drug safety studies. My concern over the device design was simply that, from the standpoint of mechanically inducing endometrial trauma, it resembles the best possible compromise between the type of device inserted in the human and the type of device suitable for a particular animal species. One need recognize that with the metal-releasing device, the release of metal is basically a function of the surface area exposed. This prohibits using a little device. A large surface area is necessary for a sizeable dose of metal, and this creates an obvious dichotomy for the toxicologist.

Benirschke: We have heard from Sir Austin Bradford Hill that one consequence of IUDs may be pelvic inflammatory disease and ectopic pregnancy. I wonder if any of your animal models has any predictive ability with respect to PID and ectopic pregnancy?

R. G. McConnell: We have not encountered problems with PID, and I cannot readily suggest a study design in animals for predicting PID or ectopic pregnancy effects.

Remmer: Nobody has brought up the question of the irritating action. Toxicologists know that copper released in small amounts as ion irritates the tissue locally. Now the question is, what type of irritating action has been seen? If copper acts chronically, an inflammation reaction should occur.
R. G. McConnell: With IUDs there is frequently a mild inflammatory endometrial infiltrate. If it should be a chronic inflammation, this might constitute evidence of irritation. Again, it would be useful to compare the "inert" plastic frame with the metal device one is interested in, thus evaluating the metal component.

Remmer: What type of inflammatory reaction occurs? That is a most important problem. The use of this type of device is really limited by its local toxic action.

Goldzieher: This concept of an inflammatory reaction should not get out of hand. Plastic intrauterine devices in the baboon cause a minimal subsurface infiltration with occasional leucocytes; there is an extensive migration of macrophages and foreign-body cells onto the surface of the device. The endometrium, of course, is shed every month. The human endometrium which gets shed has a leucocytic infiltration, which normally begins on cycle day 24. Therefore the simple existence of leucocytes in the subsurface zone of the endometrium is probably not terribly meaningful.

Diezfalusy: In addition to the paper by Dr. Hagenfeldt which was quoted in Dr. McConnell's paper (Hagenfeldt 1972a), she has published since then a great deal of information on the effect of intrauterine copper (Hagenfeldt 1972b). She has shown specific changes in certain endometrial enzymes and a significant increase in endometrial protein concentration which persisted for at least a month after the removal of the device. This may be a slight indication that there are changes induced by the copper-T device which do not disappear immediately.

Concerning the other point, which was raised by Dr. Hertz and answered by Dr. Mishell, I would like to say that Dr. Hagenfeldt by using very sensitive methods, was not able to find an increase in circulating copper levels and she found that the release from the copper-T device is biphasic. During the first two months, relatively more copper is released. After this, it is stabilized, and in her estimate the mean daily loss from the IUD, the 200 mm² device, was 50 micrograms per day.

Mishell: In the human there is an inflammatory reaction in the endometrium that appears to diminish during the period of time that the device is in place. Nevertheless, by doing uterine flushings the most significant reaction is the increase in polymorphonucleoleucocytes inside the endometrial cavity. The increase in number is about 700–800 % over pre-insertion levels. It is our belief that the breakdown of these inflammatory cells releases some substance which causes the antifertility action of the so-called "inert" IUDs and that some of this material is transmitted into the oviduct and causes the diminished incidence of tubal pregnancies. The incidence of tubal pregnancies is not reduced as much as the incidence of intrauterine pregnancy, because there is less of this inflammatory reaction that comes up in the tube.

Remmer: I think it was very important to raise these questions, because now we have to ask ourselves what really is the advantage of these metal releasing intrauterine devices compared with the plastic ones.

Mishell: The comparative studies that have been done so far with the copper 7 device and the copper-T 200 show that their basic advantage is that their shape is such that insertion can be performed without pain into women who have not born children, while their pregnancy rates are approximately the same as with the so-called "inert" devices. I think that the main advantage of the metal-bearing devices is that they can be used as an acceptable alternative to oral contraceptives by women who have not born children.
Further studies are going on with devices containing more copper than the devices that are at present under fire for an NDA. Preliminary data that are thus far subjected to life table analysis indicate that devices with additional copper than the 200 mm² of surface area have significantly lower pregnancy rates. The latest device that has been tested, the so-called TCu 380 A, has a pregnancy rate of only 0.2 per 100 women in one year in a study performed in our clinic.

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