Intrauterine Device (IUD) Associated Pathology: A Review of Pathogenic Mechanisms

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INTRAUTERINE DEVICE (IUD) ASSOCIATED PATHOLOGY:
A REVIEW OF PATHOGENIC MECHANISMS

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Abstract

This paper summarizes our studies of
IUD-related disease with those previously
published by others. Our data are based upon 51
IUDs and 42 index cases of IUD-related disease
demonstrating specific processes. Gross,
dissecting microscope, scanning electron
microscope and X-ray microanalysis examinations
were made of selected IUDs and associated
tissues. Tissue associated with the IUDs
revealed inflammation in 59.4%, calcific
material in 6.3% and no abnormality in 34.4%.
IUD-associated tissue responses were accompanied
by changes of the IUD; these changes involved
deposition of substances upon the IUD surface
and degradation of the IUD itself. Disintegra-
tion of the IUD, its string or both, has been
repeatedly observed. The material deposited
upon the surface of the IUD included proteins
and calcium salts. The changes which involve
the IUD and the host appear to be operative in
the genesis of IUD-related disease.
Inflammatory changes and infections are the most
common IUD-related disease processes and are
also the mechanisms commonly associated with the
most serious complications of IUD use, reproduc-
tive failure and death. We propose that serious
IUD-related disease is caused by or is a direct
consequence of processes which alter the IUD and
which potentiate inflammation and infection. A
model amenable to testing is proposed.

Key words: Intrauterine device, IUD, IUD-related
disease, microanalysis, morphologic analysis,
pathogenesis, scanning electron microscopy,
transmission electron microscopy, ultrastructure.

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Introduction

In the US* many people prefer non-permanent
methods of contraception. The IUD, despite
related health problems, remains a popular,
reversible means of birth control in this
country. In the decade from 1973 to 1982 use of
OCPs decreased by 45.2% while use of the IUD
decreased by only 26.0%. The IUD is also the
mainstay of state supported contraception
programs in a number of so-called emerging
nations (29).

IUD usage may be traced back to ancient
times and is paralleled by the appearance of
IUD-related diseases (Table 1) (74). The social
and economic ramifications of such diseases are
greater than one might imagine. In 1985, AH
Robbins Co., producer of the Dalkon shield IUD,
filed for protection under Chapter 11, citing
immense legal costs and settlements as the pre-
cipitating cause of financial failure. By
1986, G.D. Searle and Co., the makers of the
Cu-7 and Tatum-T IUDs, and Ortho, manufacturer
of the Lippes Loop, had announced the withdrawal
of their devices from the market for similar
reasons.

It is impossible to objectively measure the
human suffering associated with IUD-related
disease but reasonable estimates of the finan-
cial cost may be computed. Table 2 indicates
the means by which Gupta (20) computed the
minimum total direct cost of IUD-related PID at
almost 75 million dollars per year. When all
varieties of IUD-related disease are included, as
well as indirect costs such as time lost and
decrements in productivity, the total economic
cost of IUD-related disease in the US may be much
higher.

This review summarizes and compares our
studies of IUD-related disease with those pre-
viously published. The body of literature
appears sufficiently comprehensive to permit
conclusions, derivation of hypotheses regarding
the origin of IUD-related disease and the
generation of recommendations for the future.
The uniquely human nature of IUD usage, the
absence of an animal model with which to explore
hypotheses and ethical constraints on human

*See List of Abbreviations at the end of the paper.

TABLE 1

HISTORY OF IUD USAGE AND COMPLICATIONS

HISTORY OF INTRAUTERINE CONTRACEPTION		HISTORY OF IUD COMPLICATIONS	
Setting	Event	Setting	Event
Oral history	Smooth pebbles in camels' uteri (Asia Minor).		
400 BC	Hippocratic writings describe ebony, glass, gold, ivory, pewter, wood and wool IUDs.	400 BC	Hippocratic writings record sepsis, death associated with IUD use.
1100 AD	Avicenna writings discuss use of IUDs.		
late 1800s	Diamond-studded, platinum IUDs.		
1909, 1923	Richter, Pust - silkworm gut IUDs.	1900-1930s	Pelvic sepsis and death.
1930	Grafenberg - silkworm gut and silver wire IUDs.	1928, 1930	Barth, Tietze: fatal pelvic actinomycosis.
1930s	Ota (Japan) ring.		
1936	IUDs banned in Japan by governmental edict.		
1950s	Plastic IUDs with "memory": Margulies spiral, Lippes loop, Birnbeg bow, Saf-T-Coil. Metal devices: Majzlin spring, M device. Nylon coils (LEM device).		
1960s-70s	Copper-7, Copper-T, Dalkon shield.	1960s	Margulies spiral: rigid tail led to male dyspareunia. Birnbeg bow: bowel obstruction after uterine perforation. Majzlin Spring: myometrial embedment. LEM: in situ fracture and embedment.
1970s	Progestasert™ Antigon-F, Ypsilon, fluid-filled devices.	1970s	Dalkon shield: mid-trimester septic abortion. Medicated devices: moderate inter-menstrual spotting.

U.S. Department of Health, Education and Welfare, 1978 (74)

TABLE 2

OBJECTIVE ECONOMIC CONSEQUENCES OF IUD-RELATED DISEASE

Annual estimated cases of acute PID in the US		850,000
Annual rate of PID in women 14-34 years old		1.26%
Estimated percent of women using IUDs		8.7 %
Annual rate of PID in women using IUDs		4.4 %
Annual rate of PID in women not using IUDs		1.0 %
Per cent PID cases attributable to IUD usage		22.0 %
Annual estimated cases of PID due to IUD usage (0.22X850,000)		187,000
Estimated hospital admissions of PID patients		25.0 %
Estimated per case hospitalization cost	$1,000	
Cost of IUD-related PID hospitalization (187,000X0.25X$1,000)	$46,750,000	
Estimated PID cases with outpatient care		75.0 %
Estimated per-case outpatient cost	$200	
Cost of IUD-related PID outpatient care (187,000X0.75X$200)	$28,050,000	
TOTAL MINIMUM DIRECT COST OF IUD RELATED PID	$74,800,000	

Gupta, 1981 (20)

experimentation necessitate a retrospective analysis. We shall accomplish this by exploring:
1. the clinical nature of IUD-related disease;
2. the relationship between clinical and pathological findings; 3. the role of morphological and microanalytical techniques in clarifying the genesis of IUD-related disease.

Materials and Methods

The data presented herein include information derived from cases not previously reported as well as a series of IUD-related actinomycosis cases previously published (62). Our cases are derived from 415 IUDs collected from Hermann Hospital/The University Hospital, the ambulatory care clinics of The University of Texas Medical School at Houston, Texas, public family planning clinics of the city of Houston and those contributed by private practitioners of medicine. This collection was initiated in 1977 and continues to date. Each of the IUDs collected has been examined grossly by one of us (WAS) and in approximately 50% of the cases materials and tissues adherent to the IUD have been submitted for routine, light microscopic histopathological analysis. The data presented here are based in part upon 51 IUDs collected during 1985. Tissue specimens from 31 of these cases (60.8%) were examined in detail by LM for this study. The study also includes data derived from 42 index cases carefully selected from the collection. The index cases consist of the following: 9 cases of IUD-associated actinomycosis, 1 case with characteristic cytopathological findings of IUD-related PID, 1 case of 'encrusted' IUD characteristic of long-term IUD use, one case characteristic of intra-endometrial calcific material associated with IUD use, 28 cases not associated with disease where the IUDs were worn for twenty months or more, and IUDs from two women with characteristic IUD changes and PID.

The nine cases of IUD-associated actinomycosis, specimens from which were studied by LM, SEM and histochemical methods, have been reported previously (62). Routine histological examinations of paraffin-embedded tissues from the 1985 cases included H&E, PAS with and without diastase digestion, Brown-Brenn, Ziehl-Neilsen, and GMS stains. Special preparations of tissues, IUDs or IUD-strings from the index cases included von Kossa, ARS and Bunting's MoB stained sections, a Papanicolaou stained CV smear, and IUD surface crusts stained with ARS.

Careful gross, dissecting microscope and SEM examinations were made of selected IUDs. Paraffin-embedded sections of IUD tails and IUD-associated 'crusts' stained with H&E, ARS, GMS and MoB were examined by routine light and polarization microscopy. Portions of the IUDs and their tails as well as the ARS stained IUD were examined by SEM and XRMA.

IUDs were prepared for SEM by gently cutting each specimen into pieces approximately 1 cm in length. Each piece was fixed in phosphate buffered, 2% glutaraldehyde; osmium post-fixation was not done to avoid osmium peaks during XRMA. Specimen pieces were rinsed in buffer, washed thoroughly in distilled water, dehydrated with graded ethanols and critical point dried from liquid carbon dioxide using a Bomar SPC-1500 critical point drier. Specimens destined for XRMA were mounted with carbon paint on 25 mm carbon stubs. Specimens for detailed morphologic analysis were postfixed with an osmium/semithiocarbohydrazide technique (45,60) and critical point dried as above. Specimens for XRMA were coated with 100-150 Å carbon using an Edwards 306 sputter coater. Specimens for detailed morphologic analysis were coated with 200-300 Å gold-palladium under an argon atmosphere in an Edwards 306 sputter coater. Coated samples were examined in a JEOL SEM 35 scanning electron microscope equipped with a beryllium window probe for XRMA. The system was standardized using a copper grid mounted on an aluminum stub. Specimens were examined for non-cellular material as well as cells and deposits on or changes of the IUD surface. The presence of non-cellular material, cells or microorganisms was recorded photographically. Following SEM examination, XRMA was done at a working distance of 39 mm. Spectra were acquired from various points on each IUD including sites with crusted deposits and apparently uninvolved areas of the tail, body and head of the IUD; peaks within the spectra were labelled after acquisition. The spectra obtained from the specimens were compared with those derived from identical IUDs which had never been worn and which remained in the manufacturers' packages until processing.

Results

The IUDs received during 1985 included the following types: Lippes loop, Dalkon shield, Saf-T-Coil, Cu-7, Cu-T and Margulies spiral. The numbers of each IUD type and their frequency are shown in Table 3; this table also contrasts the 1985 cases and the index cases with the numbers and frequencies of IUD types collected during the period 1977-1986.

Of the 51 IUDs collected, 9 were received without adequate historical documentation while 42 were accompanied by sufficient clinical history to allow correlation between clinical and pathological findings. The original gross descriptions of the IUDs were insufficient in 24 cases; upon later examination by one of us (WAS), 10 of these 24 cases (41.7%) were found to have deposits on the IUD (Fig. 1) or string surfaces or there were structural changes of the IUD or string. A total of 28 cases had grossly recognizable structural changes; each of these IUDs had been in place for no less than 2 years. The gross structural changes seen included deposits of calcareous material (Fig. 2), total breaks of the IUD, chips and cracks of IUD surface, absence of, breaks of or deposits upon the IUD string, and combinations of the above.

Thirty-two IUDs (62.7%) came with sufficient amounts of attached tissues to permit histopathological examination. In 24 of these

TABLE 3

TYPE AND FREQUENCY OF IUDs COLLECTED AND STUDIED

Cases presented, N=51; 1985

Type	N (%)
Lippes loop	21 (41.2%)
Cu-7	20 (39.2%)
Cu-T	6 (11.8%)
Margulies spiral	2 (3.9%)
Saf-T-Coil	1 (2.0%)
Dalkon shield	1 (2.0%)

Lippes loop + Cu-7 = 80.4%

Index cases, N=42; 1977-1986

Type	N (%)
Lippes loop	27 (64.3%)
Cu-7	9 (21.4%)
Saf-T-Coil	2 (4.8%)
Dalkon shield	3 (7.1%)
unknown[*]	1 (2.4%)

Lippes loop + Cu-7 = 85.7%

Total collection, N=326; 1977-1986

Type	N (%)
Lippes loop	98 (30.1%)
Cu-7	155 (47.5%)
Cu-T	6 (1.8%)
Margulies spiral	3 (0.9%)
Saf-T-Coil	25 (7.7%)
Dalkon shield	25 (7.7%)
Progestasert	6 (1.8%)
unknown[*]	8 (2.9%)

Lippes loop + Cu-7 = 77.6%

[*]Not identified because of destruction or does not fall within recognizable category.

32 cases (75%), adherent tissues were obtained from the surface of the IUD itself. In 8 of these cases (25%) tissues were obtained from a coincident diagnostic or therapeutic procedure (eg., total abdominal hysterectomy, dilatation and curettage or endometrial biopsy, or tubal ligation). In 19 cases (37.3%) there was no evidence of material attached to the IUD which could be used for histopathological examination.

Histopathological examination of adherent or associated tissues revealed chronic inflammation in 28.1% of cases, acute inflammation in 31.3% of cases, calcific material in 2 instances (6.3%), and no evidence of histologic abnormality in 11 instances (34.4%). In both specimens where calcific material was found in adherent endometrial tissues, the IUDs had been in place for at least 20 months. In none of the cases were organisms found in histologic preparations. In one case with tubal ligation there

TABLE 4

IUD-RELATED ACTINOMYCOSIS

Definition of the syndrome:
Actinomycotic pelvic infection associated with IUD use; ranges from organisms in CV smears (4.0-25.5%) to pelvic abscesses (0.4-1.4%).

Characteristics of the syndrome:

1. Age range: 23-54 years.
2. Symptoms: pain, fever, sweats, menstrual irregularities.
3. Signs: pelvic mass, fever (38-40.5 C), non-specific.
   Duration: 3 days - 14 months.
4. IUD types: variable - reflects patterns of use.
   Duration: 6 months - 25 years; 84.7% $\geq$ 3 years.
5. Extent of disease: 62.5% uni- or bilateral tubo-ovarian abcess.
6. Surgical therapy: 65.6% with subsequent total loss of reproductive capacity.

Schmidt et al., 1980 (63)

was concomitant chronic inflammation in a Fallopian tube segment.

The 9 cases of IUD-associated actinomycotic disease have been reported elsewhere (62) (Table 4). These nine cases demonstrate that female reproductive system actinomycotic disease is related to IUD use. The occurrence of this infectious disease, which is otherwise rarely encountered in the female reproductive tract, is directly related to the duration the IUD has been worn. In our nine cases, and in similar cases reported in the literature up to that time, 80% of the women afflicted with IUD-related actinomycosis had worn their IUDs for more than three years. This infection is serious, commonly results in permanent infertility and is not related to life-style, sexual habits, race, socioeconomic status or the type of IUD used.

In three of our nine Actinomyces cases we observed characteristic Gupta bodies (20-22,24) in CV smears. Gupta bodies, actually complex colonies of microorganisms including Actinomyces and other pathogens, may be seen in IUD-related PID caused by organisms other than Actinomyces (20). One index case demonstrates the appearance of such organisms on CV smears. The patient, a woman who had worn her Saf-T-Coil for 13 years without replacement, was treated for severe PID within one month of finding the cytopathologic changes on her CV smear (Fig. 3).

Birefringent, crystalline, ARS positive staining material is often encountered in endometrial tissues from women with long term (>2 years) IUD use (33). Both H&E and ARS
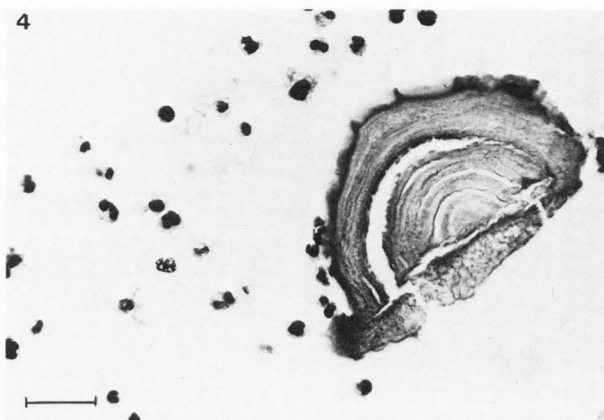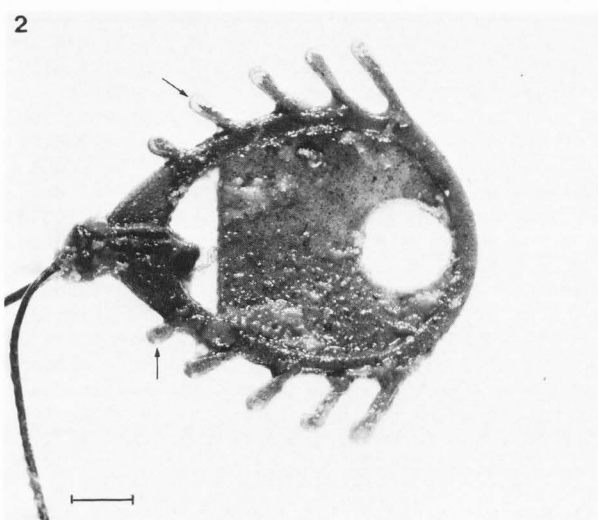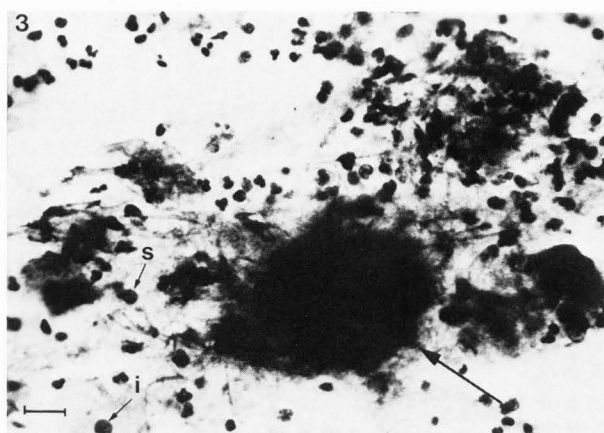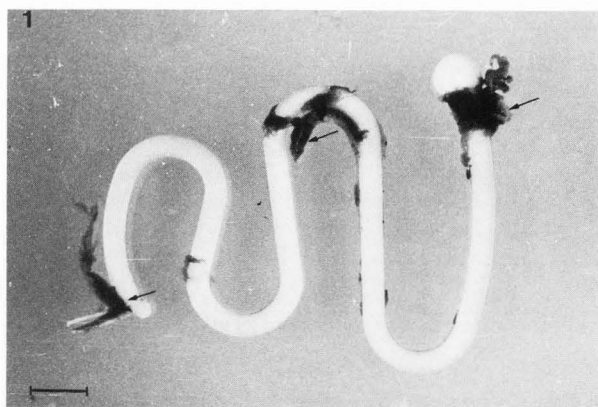
Fig. 1: A Lippes loop IUD after removal; arrows indicate adherent tissue which may be removed for histologic examination. Bar = 2cm

Fig. 2: A Dalkon shield IUD; there is adherent tissue and an extensive biodeposit. The small white flecks, seen as confluent white areas on the distal ends of the arms (arrows), are characteristic of surface depositions of calcium salts.   Bar = 3cm

Fig. 3: Light micrograph of a CV smear stained with Papanicolaou technique. The centrally located fuzzy structure (arrow) is a cluster of bacterial organisms - a Gupta body. Superficial (arrow-s) and intermediate (arrow-i) epithelial cell nuclei are seen; many PMNs are present. Bar = 40μm

Fig. 4: Light micrograph of a multilammellar, calcific body seen in a paraffin section of endometrial tissue associated with an IUD. The patient was asymptomatic and her IUD had Ca concretions on its surface. H&E. Bar = 40μm

stains identify calcium salts in these birefringent materials. One of the index cases provides a characteristic appearance of these crystalline substances in H&E stained sections of endometrial tissue (Fig. 4). These calcific materials seem to form on the surface of the IUD. Figure 5 demonstrates an ARS stained IUD which had been in place for more than 2 years. This IUD and its string were also examined by SEM and subjected to XRMA. The deposits of material on the IUD string surface are shown clearly in Figure 6. These deposits demonstrated spectra of Ca, P, S, and Cl when subjected to microanalysis; Figure 7 demonstrates a typical Ca distribution map for the string deposits.

Surface deposits are observed commonly on IUDs which have been in place for at least two years and virtually uniformly on those in situ for three or more years. The crusts are not, however, pathognomonic of IUD-related disease. Twenty-eight of our index cases were received from an OB/GYN practice composed of high-middle to upper socioeconomic class women of uniformly conservative, monogamous life style (as defined by the contributing physician). None of these women, all of whom had their IUDs in place at least 20 months (range: 20 months-13 years), were symptomatic. In this group of 28 IUDs, there were ten which had obvious surface deposits of calcific nature which were grossly identical with those previously published (33).

Fig. 5: A Lippes loop IUD removed from a patient after 4 years of continuous use. The IUD is ordinarily clear white. Calcium deposits (arrow) have been stained with ARS. The IUD is fragmented because pieces have been taken for SEM and XRMA. Bar = 2cm
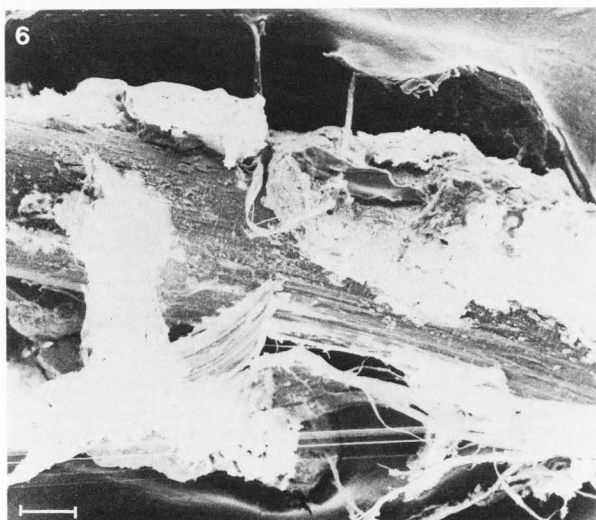
Fig. 6: Scanning electron micrograph of a portion of the string from an IUD. This specimen was coated with carbon only. There is an obvious coating of the surface of the string; this coating has a fibrillar appearance and is fragmented. Bar = 10μm
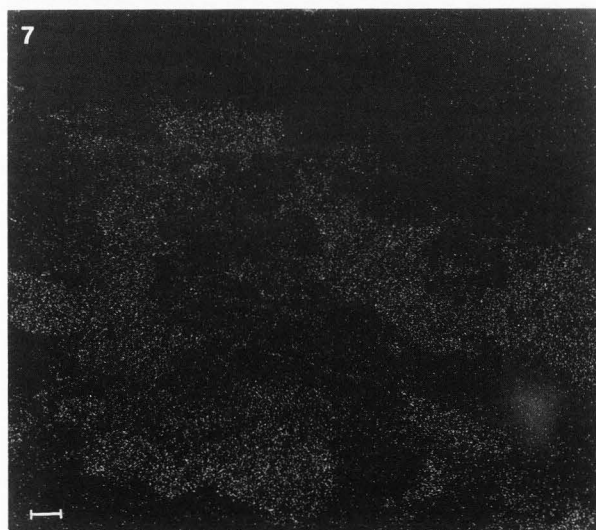
Fig. 7: Map of Ca localization on the string shown in Fig. 6. Note the correspondence of the Ca localization with the deposits on the surface of the IUD shown in Fig. 6. Bar = 10μm

In several index cases we carefully examined the deposits on both the IUDs and the strings. Amongst these cases, two women had multiple sexual partners, had worn their Lippes loop IUDs for ten years, had prominent deposits on their IUDs and had unusual female reproductive tract infections. One patient had actinomycosis and aspergillosis and the other had actinomycosis and botryomycosis. The organisms were demonstrated in CV smears (Gupta bodies), on histologic sections of endometrial tissues, on IUD surfaces and within the crusts on IUD body and tail (Fig. 8).

The crusts on these IUDs and their tails were studied in detail. The crusts were present on the surfaces of the IUDs and on the strings at about the level of the exocervical os where the string exits from the endocervical canal (Fig. 9). Portions of the strings with attached crusts were sectioned histologically after paraffin embedment. Parts of the crusted IUDs and their strings were examined by SEM and XRMA.

The paraffin sections of the crusted strings demonstrated a complex deposition within which microorganisms were easily found. The depositions consisted of dense, amorphous, PAS positive material adjacent to the string or IUD body, a layer of calcific material staining red with ARS, black with von Kossa and blue with the MoB stains, an outer layer of mucoid material and a thin surface coat of cells, cell debris and birefringent ARS positive crystals (Figs. 10 & 11). In both instances the deposits stained blue with the MoB and black with the von Kossa techniques, indicating phosphate rather than carbonate salts of calcium; Ca, P and S peaks were also seen on XRMA.

We commonly find Ca salts in materials adherent to IUDs which have been in place longer than 2 years, whether or not there is IUD-related disease. Conversely, we have not encountered prominent IUD surface depositions with or on IUDs in place less than 12 months. When microorganisms are found they are always associated with the IUD or string surface deposits (Figs. 12-15). Typically, a mixture of organisms is seen. The mixture usually includes Brown-Brenn positive and negative species; GMS positive types of microorganisms, including
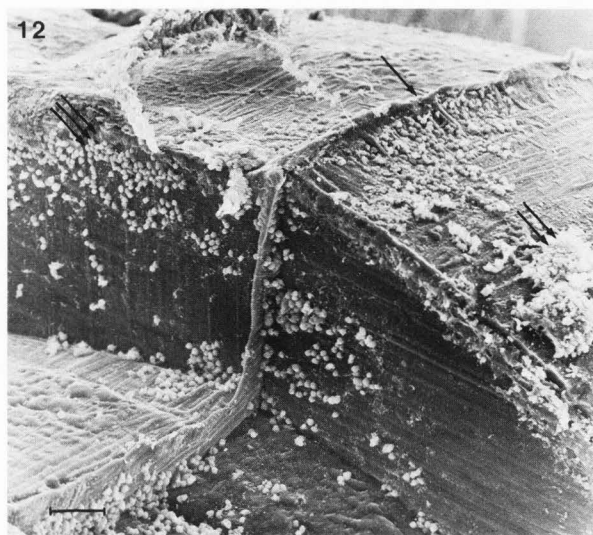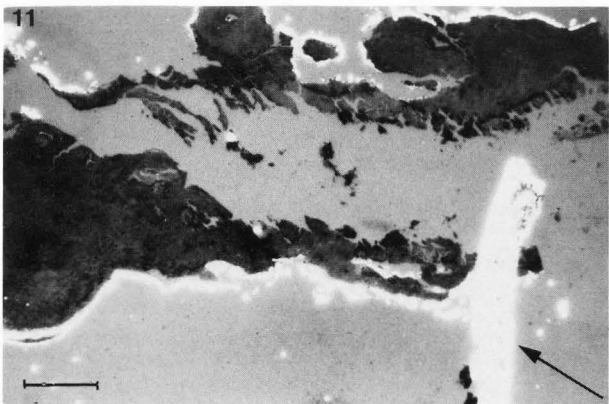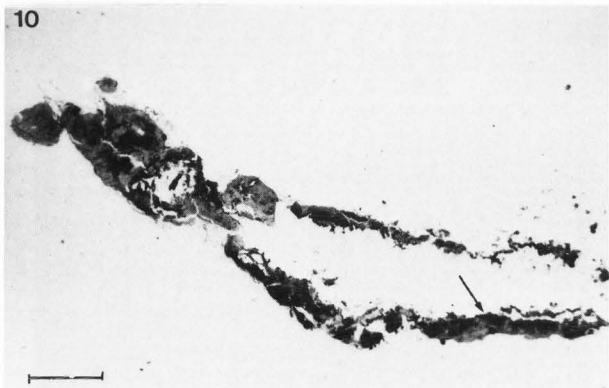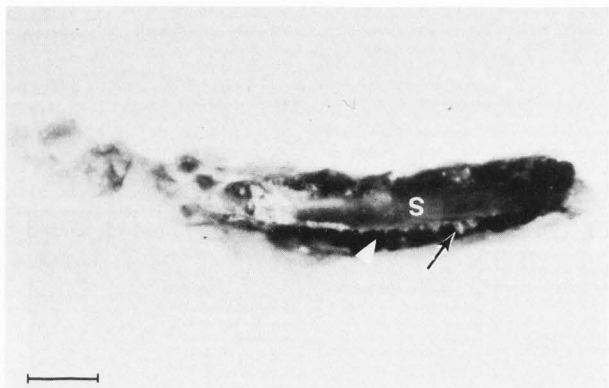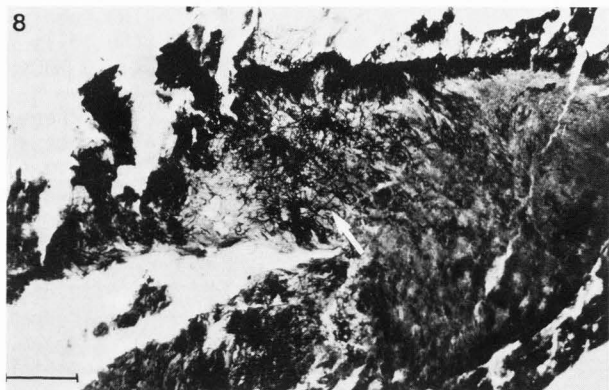
Fig. 8: LM of crust removed from an IUD of a patient with actinomycotic infection. The Actinomyces organisms are stained with silver and appear as long, slender black filaments (arrow). Gomori methenamine silver. Bar = 40μm

Fig. 9: An IUD string with surface deposits, embedded in paraffin. Multiple sections have been taken from the block. The block face reveals the cut surface of the surface deposits and the string itself. The proteins appear brown (arrow head), the string (S) is partially opaque and the Ca deposits have a white granular appearance (arrow). Bar = 1mm

Fig. 10: Light micrograph of a section taken from the block shown in Fig. 9. The string, made of plastic, washed off the slide during staining and left a central clear space around which the surface deposit is found. Proteins in the surface deposit stain red (arrow). H&E. Bar = 40μm

Fig. 11: LM of a section parallel to that seen in Fig. 10. The section has been stained identically but is viewed with polarized light. The bright band of material at the arrow is a remnant of the sectioned IUD string. The periphery of the material deposited on the string is birefringent. The birefringent material stains with ARS and is apparently a Ca salt. H&E. Bar = 40μm

Fig. 12: SEM of the elbow region of a Cu-7 IUD. The median ridge (single arrow) is from the mold in which the IUD was made. There are a variety of deposits upon the surface of the IUD. The double arrows indicate non-cellular deposits characteristic of proteo-calcareous material. Large numbers of cells are scattered over the surface of the IUD (triple arrow). Bar = 10μm
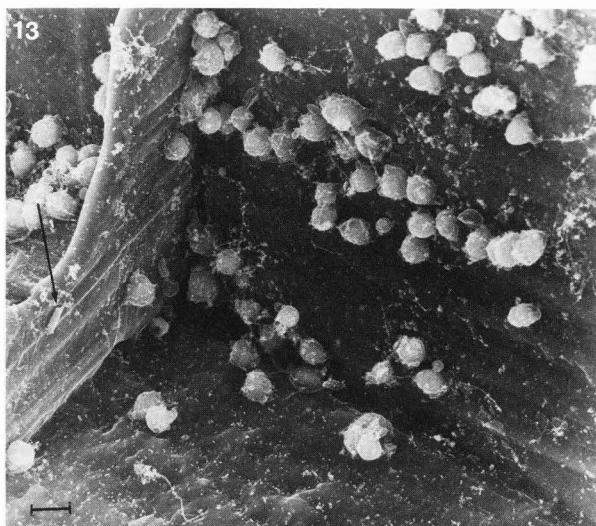
Fig. 13: Higher magnification of the IUD seen in Fig. 12. Detailed view of the cells suggests the presence of RBCs and WBCs. Note bacterium at arrow. Bar = 15μm
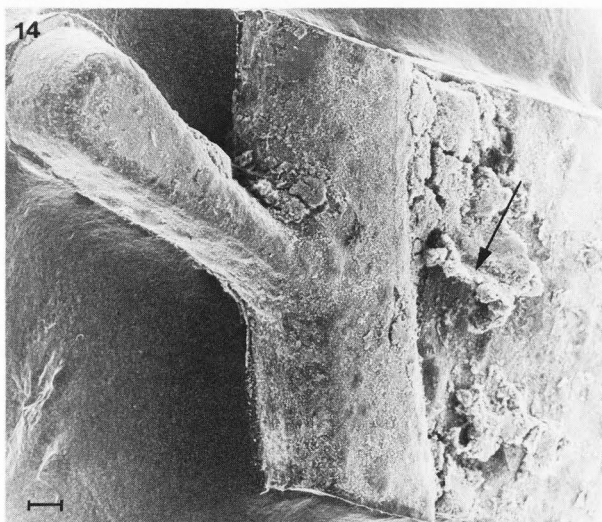
Fig. 14: Portion of a Dalkon shield IUD. There is an obvious coating on the surface of the IUD; this coating is elevated in the region of the arrow. The entire surface of the IUD is coated. Bar = 20μm
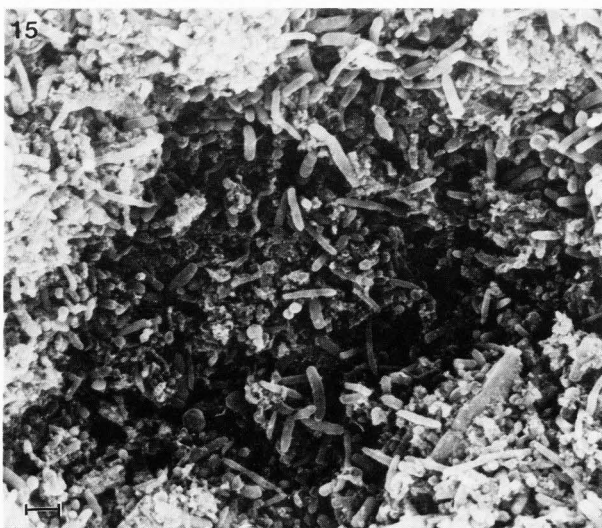
Fig. 15: Detail view of the coating of the IUD seen in Fig. 12. This IUD came from a woman with actinomycotic infection of the female reproductive system; she had worn the IUD for more than three years. The coating is formed of many bacterial organisms. Bar = 2μm

bacteria and fungi, are usually intimately associated with the crusts (Figs. 8 & 15). We have not encountered acid fast stained bacteria but believe this relates to technical difficulties when using this stain with paraffin embedded material. The crusts from the two index case IUDs with severe PID provided definite Ca and P peaks on XRMA (Figs. 16 & 17).
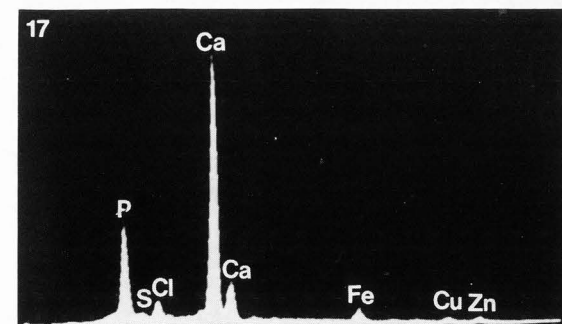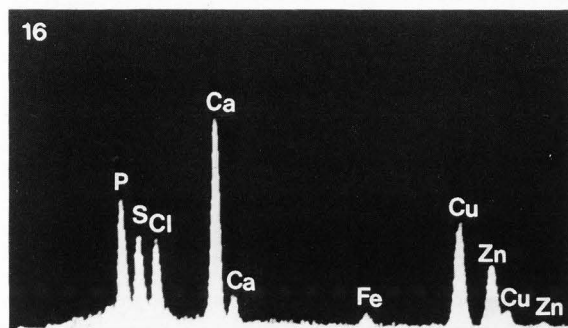
Fig. 16: Microanalysis of an IUD from one of the two index cases with severe PID following long-term (greater than 3 years) constant IUD use. There are Ca, S, P, and Cl peaks contributed by the surface deposits; the Cu and Zn peaks represent components of the IUD itself.

Fig. 17: Microanalysis of the string from another patient with PID. Strong Ca and P peaks are present. There were obvious deposits upon the surface of the string in the region where this spectrum was obtained.

Discussion

It is important to exclude the possibility of bias introduced by acquisition of only certain types of IUDs; both collection and population biases in our collection are minimized by the wide spectrum of medical practices from which these IUDs originated and the diversity of IUDs obtained. Our studies are based upon a collection which contains the same proportion of IUD types seen in common usage patterns in the US (29). The types of IUDs collected during 1985 are generally the same as the 1977-1986 collection, although fewer older style IUDs are represented in the later group. All 42 IUDs representing the index cases remain in use today.

From the 93 cases we have studied and those described in the established literature it is possible to recognize common pathologic mechanisms operative in a variety of IUD-related diseases and to establish general conclusions.

It is apparent that early diagnosis of IUD-related disease requires morphologic analysis of IUDs, associated tissues or CV smears. Specimens submitted for analysis must be accompanied by appropriate clinical information. Without these clinical data the pathologist is bereft of appropriate perspective and must necessarily limit the interpretation of the findings present. The IUD and any associated material should be carefully examined and the latter must be examined microscopically. In most of the cases (65%) we have presented in this paper the tissues associated with the IUDs were abnormal. In our experience, examination of the IUD itself generally lends little understanding to the condition of the IUD-bearer while examination of the associated tissue does. Conjoint examination of both the IUD and the host tissues and correlation with clinical details is the most productive. From our experience we conclude that:

1. IUDs are altered while in utero. The alterations occur as a surface phenomenon which affects the IUD, any attached materials, such as metal coils, and the string. Calcification is the most common alteration found. The process of Ca salt deposition appears to be time dependent; IUDs in place for longer than two years commonly have such deposits.

2. IUD surface depositions are associated with a variety of microbial organisms, especially in those instances where PID is clinically apparent. The microorganisms are usually intimately related to the surface deposit. Severe IUD-related inflammatory disease is virtually always associated with prominent IUD surface deposits, but prominent surface deposits are not always associated with severe inflammation or disease.

3. Inflammatory changes in the endometrium are common with IUD use. These changes are most severe in those instances where the woman is symptomatic. The severity of the endometrial changes appears synchronous with and directly proportional to the extent of IUD surface alteration.

4. IUD-related disease tends to affect certain kinds of patients. These women often have multiple sexual partners and usually have worn their IUD for three or more years.

5. Minor IUD-related disease is usually not related to alterations of the IUD itself or to histopathologic changes in the endometrium.

6. Major IUD-related disease is related to IUD usage, to the time the IUD has been in situ without replacement, to the severity of alterations of the IUD surface and is virtually always inflammatory or infectious in nature.

We have encountered fewer cases of serious IUD-related infectious and inflammatory disease amongst the 51 cases collected in 1985 compared to the 42 index cases which were collected earlier because our clinical colleagues now regularly remove or change IUDs after two years of use.

Physiologic Effects of IUDs

Numerous studies have explored the biologic effects of IUDs (Table 5). Multiple physiologic parameters have been analyzed without identifying either the mechanism of action of IUDs or the origin of IUD-related disease. The most important conclusion from the physiologically oriented studies may be found in the second FDA report on IUDs (74):

"It is not yet completely understood how any particular IUD prevents pregnancy. It is currently believed that the numerous cellular and biochemical alterations induced in the endometrium by the presence of the device are responsible. The various devices may actually have several different mechanisms of action, one perhaps being more important with a particular device than others. However, in all species studied, there is one common thread of similarity, i.e., the development of a local endometrial reaction as evidenced by a specific type of leukocytic infiltration. This reaction seems to interfere in some manner with the implantation of the fertilized ovum in the uterine cavity and is currently believed to represent the primary mode of action of the IUD".

The physiologic studies of IUD bearers have documented that a host response occurs to the IUD and that this response may be IUD-specific. Characteristics of the host response have been clarified by morphologic and microanalytic studies. These studies reveal greater detail about the nature of the host/IUD interaction and the changes which occur to the host and IUD. They also shed considerable light upon the mechanisms involved in IUD-related disease. Such studies have involved cytologic, histologic, TEM, SEM and microanalytic methods.

Host Response to IUDs

Initial cytologic studies performed during the 1970s detected IUD-induced host responses which affected both the host tissues and the IUD. Sagiroglu and Sagiroglu showed that smears of IUDs removed after being in place from five hours to 39 months had a surface accumulation of host cells but that bacteria were associated with the IUD only transiently for the first five days (59). In 1971, Highman reported on the

TABLE 5

BIOLOGIC EFFECT OF IUDS

Physiologic Studies

	Year	IUD/Agent	Effect
1.	1974	Cu-T200	Serum progesterone 1-2 days late; earlier onset of menses (25).
2.	1979	Cu-7	Endometrial estradiol-17-β-dehydrogenase unaffected (69).
3.	1980	Cu-T200	No changes in serum copper or urinary copper excretion (54).
4.	1980	Cu-SC	Elevated copper in cervical mucus (55).
5.	1980	Cu-IUDs	Decreased serum iron and transferrin saturation; hemaglobin constant (15).
6.	1980	Cu-T	Ovarian function unaffected; ovarian-endometrial asynchrony (12).
7.	1981	Cu-T200	No changes in coagulation factors (41).
8.	1981	Cu^{+2}ion	Caused dose dependent increase in myometrial contractility (43).
9.	1981	ns*	Lower uterine fluid fibrinolytic activity. Increased serum proteinase inhibitors in uterine fluid. Increased urokinase in uterine fluid (4,6,7,41).
10.	1982	Cu-T	Lower daily levels of hPRL (1).
11.	1983	M.spiral	Elevated endometrial tissue PGF but not PGE (74).
12.	1965	ns*	Severe infection or increased tubal transport rate.
13.	1970s	ns*	Inflammatory response (74). Increased lysosomal hydrolases, protein, non-protein nitrogen and urea. Increased AlPase, AcPase, glycogenesis, phospholipids, oxygen consumption, total proteins, RNA/DNA ratio (74). Asynchronous endometrial development. Elevated serum C-reactive protein (74).

*ns: IUD type not specified

association of calcific bodies with IUD use (27). In that same year, Gupta et al. discussed the changes which occur on the surface of the IUD and suggested that the host is capable of degrading the IUD (23). The studies of Fornari demonstrated that IUD use unequivocally results in tissue changes, which affect both the endometrium and the endocervix, appear in diagnostic CV smears (13). They showed these changes, which may mimic neoplastic alterations, were inflammatory in origin.

By 1979 it was apparent that IUDs were associated with a pronounced host response and that deposits occurred on the surface of IUDs. Trebichavsky and Nyklicek showed in a TEM study directed at the cellular response of the host to the IUD that the entire IUD was covered by host cells by 48 hours after insertion (68). Over time the cellular covering changed from PMNs to macrophages. Eventually the IUD became covered by a variety of cellular types and debris and 47% of IUDs worn for three or more years had bacteria on their surface even though 35% of these were sterile by culture methods.

In 1981 two important papers defined the nature of the host cellular response to supposedly biologically inert IUDs. Casslen et al. compared the cellular composition of uterine fluids from 75 otherwise healthy Cu-T200 IUD users with similar fluid obtained from 48 non-users and found significant differences (5). The IUD-user uterine fluids demonstrated little or no change in the number or nature of endometrial cells and showed a modest increase in the numbers of mast cells and eosinophils. Marked changes were seen in the numbers of

lymphocytes, phagocytes and granulocytes of the uterine fluids of IUD users. There was a thirty-fold increase in the number of lymphocytes and phagocytes, the latter of which also accounted for roughly one-third of the total cells in the fluid. PMNs accounted for almost two-thirds of the cells in the uterine fluid and showed a 300 fold increase in number.

A similar study by Kobayashi et al. in Japan confirmed the host cellular inflammatory response to the IUD (39). They studied 26 healthy women who had used the Ota ring for one to five years duration and quantified the cells obtained from the IUDs at removal. They found an IUD cellular 'coating' composed of 49% macrophages, 42.7% PMNs, 4% endometrial cells, 1.3% mast cells and 3% assorted other cells. On the average there were 65.5x10(4) cells/IUD; the range was 1.3-280x10(4) cells/IUD. They also identified inhomogeneity in the host response to the IUD and divided their patients into two groups based on more or less than 5x10(5) cells/IUD. In the former category there were 10 women with an average of 144.3+79.2x10(4) cells/IUD while in the latter group 16 women had an average of 18.3+3.3x10(4) cells/IUD. This variation in host response documented at the cellular level previously has been seen histologically. In the histopathologic studies, however, the variability of the host response seems to be related to the type of IUD used and its duration of use. The first histologic study by Willson et al. in 1965 examined endometrial changes in 292 women wearing polyethylene Margulies spiral IUDs (72). They found the endometrium responded to the ovarian cycle

(although there seemed to be some delay in the endometrial response), congestion of the superficial vascular sinuses of the endometrium and increased edema formation. They also demonstrated a 19% incidence of chronic endometritis in those women who had worn their IUD for 4 - 25 months.

The role of inflammation in IUD-associated histologic changes of the endometrium has been confirmed upon multiple occasions. In 1968, Ober et al. reported on 200 endometrial biopsies from women who had worn various kinds of IUDs (52). This group of patients included 107 symptomatic and 93 asymptomatic women. In the endometrial biopsies from these women they identified the following as minor lesions: lymphocytosis, granulation tissue, focal gland loss and asynchrony. Among major lesions they included acute and chronic endometritis. The biopsies from the 107 symptomatic women revealed 25.2% of women with major lesions and 45.8% of women with minor lesions. Amongst the asymptomatic women only 9.7% had major lesions seen in their endometrial biopsies while 50.5% had minor lesions.

With some notable exceptions to be discussed below, the endometrial inflammatory response associated with IUD use does not necessarily seem to be IUD specific. Moyer and Mishell studied the endometrial response to Lippes loop IUDs which had been placed preoperatively in 167 women scheduled for hysterectomy (46). The specimens were examined at various times after insertion, the range being a few hours to as long as five years. All specimens demonstrated inflammatory responses composed of PMNs, plasma cells, and mononuclears; the mononuclear infiltrates persisted for years. An elevation of endometrial cavity fluid protein content was also characteristic of women wearing IUDs.

The nature and intensity of the pervasive endometrial inflammatory response, particularly in the case of polyethylene IUDs, seem to be related to the time the IUD had been in situ. Moyer et al. studied 75 patients who had Lippes loop IUDs placed prior to hysterectomy (47). They found a transient, post-insertion contamination of the endometrial cavity with low virulence bacteria, a contamination which was spontaneously resolved in all cases within 48 hours after insertion. Those endometria which contained the IUDs for up to six days before hysterectomy demonstrated a stromal inflammatory infiltrate composed of PMNs, lymphocytes and monocytes. When the IUDs had been in place for 7-49 days the inflammatory infiltrate was composed of neutrophils, plasma cells and increasing numbers of monocytes and there were also focal ulcerations of the endometrial surface. The inflammatory infiltrates persisted in those women who wore their IUDs for several months before hysterectomy. Similarly, Hayashi et al. found in 145 women who had used a variety of IUDs, that the extent of endometrial inflammation was greater in those who had worn their IUDs for more than two years (26).

Ober et al. studied in greater detail the temporal relationship of inflammation and symptomatology in 393 women who used a Lippes loop IUD for 18 months or longer (51). Among the 60% who remained asymptomatic for 3 or more years there was a 2.5% incidence of endometritis. The 20% of women who became symptomatic during the first 3 years had a 20% incidence of endometritis and the 20% of women who became symptomatic after more than 3 years of continuous IUD use had a 40% incidence of endometritis. In all the women the symptomatology was menometrorrhagia and pelvic pain.

In some instances, the type of IUD does, however, influence the host response. Mestranol loaded spring coil silastic IUDs, for instance, are associated initially with endometrial hyperplasia and later with endometrial atrophy (11). Whether simultaneous drug delivery ameliorates the inflammatory response is not clear in this study because the IUDs were worn no longer than 12 weeks. Similar problems plague interpretation of tissue responses to progesterone loaded IUDs which are designed to be used for no longer than 12-24 months. The addition of elemental copper to the IUD does increase the inflammatory response (10,53) and it has been shown that intrauterine metallic copper results in PMN infiltrates in the endometria of animals (10).

It is now apparent that polyethylene, polyethylene plus metal and metallic IUDs all are associated with endometritis (49). In fact, the inflammatory process involves the Fallopian tubes as well. In 1984, Collins et al. (8) demonstrated, in a population of 73 women (20 IUD users, 25 OCP users and 28 barrier method users) an excess of Fallopian tubal inflammatory changes in those who used IUDs. Others (49) have also shown that IUD use is associated with both endometritis and salpingitis.

A characteristic example of IUD-type specific endometrial inflammatory response is provided by the Majzlin spring IUD. Ober et al. studied 69 endometrial biopsies from women with this stainless steel IUD (50). These biopsies came from 68 patients, 12 of whom were asymptomatic. The asymptomatic patients had worn their IUDs for 2 to 10 months and significant inflammatory changes were seen in 16.6% of their endometrial biopsies. Amongst the 56 symptomatic women, who had worn their IUD for 0.5 to 15 months, 78.6% of the biopsies had significant inflammatory changes. In 36.3% of all the biopsies there were bacteria demonstrated by Brown-Brenn staining of paraffin sections. In the case of the Majzlin spring IUD, which was composed of iron, chromium, nickle, and to a lesser degree manganese, silicon, sulfur, carbon and phosphorus, the endometritis seems to have been metallo-chemical in origin. Chromium and nickle are particularly suspect as primary irritants; the bacteria were not thought to be the primary cause of the inflammatory process.

Electron microscopic studies have revealed exciting details about the relationship between the host and the IUD. The IUD itself, regardless of type, produces fundamental changes in the cellular architecture of the reproductive

tract epithelium irrespective of the inflammatory process. In 1984, Wollen et al. found a change in Fallopian tube epithelial cell populations of 12 healthy, non-pregnant women using a variety of IUDs (73). They demonstrated a decrease of ciliated endosalpingeal cells from 40% to 20%.

Other studies have examined in greater detail the ultrastructural changes associated with IUD use. In 1976, Hsu et al. studied endometrial tissues obtained from 7 patients who ranged from 39-51 years of age and who had Cu-T or Cu-7 IUDs placed from 2 to 54 days prior to hysterectomy (28). By LM they found an inflammatory response which was present in the lumen, glands and stroma and which was greatest at the IUD sites. By TEM, there were superficial endometrial erosions at the IUD contact site, intraepithelial lymphocytes and neutrophils, giant lysosomes evidencing cellular damage short of cell death, loss of cilia and an absence of the nucleolar channel system where such a channel system should be found. On SEM examination they found endometrial surface epithelial cell microvillar changes, a prominent mucoid inflammatory response, erosions of the surface epithelium and RBCs and WBCs scattered over the endometrial surface. Using energy dispersive microanalysis they were unable to detect copper in the specimens, their limit of resolution being $5 \times 10(-18)$g/200μm diameter. The absence of detectable Cu in the tissues is curious since the element is clearly a stimulant of the endometrial inflammatory process (10,53). Absence of Cu also was shown by Gonzalez-Angulo and Aznar-Ramos who studied endometrial tissues from 12 women who wore Cu-T200 IUDs for 6-12 months (18). In their study they were unable to demonstrate tissue Cu using the rubeanic acid histochemical technique and energy dispersive XRMA. They also demonstrated evidence of cellular injury on TEM by noting mitochondrial matrix vacuolization, myelin figures and increased numbers of lysosomes.

Sheppard and Bonnar concentrated upon microvascular changes in IUD exposed endometria as demonstrated by TEM studies (63). They studied endometria from 15 patients who had worn a variety of IUDs for various periods of time ranging from 4 to 48 months. The majority of tissue changes were associated with the actual sites of IUD contact although similar but lesser changes were seen in adjacent endometrium. The alterations were associated directly with the Cu content of the IUD, the proximity of the IUD to the endometrium and the area of the IUD/endometrial interface. The pathologic features observed included microthrombi, platelet/fibrin aggregates in endothelial gaps of the superficial stromal capillaries under the IUDs, an associated stromal hemorrhage and superficial erosions of the endometrial surface.

IUD/String Alterations

IUD-associated histologic responses are accompanied by changes which involve the IUD itself. These IUD alterations may be categorized under the concept of IUD biotransformation. IUD biotransformation is a biphasic process comprised of: 1. biodegradation of the IUD and/or the string, and 2. biodeposition on the IUD and/or the string (61). Table 6 summarizes major contributions to the concept of IUD biotransformation.

The first observations of IUD biotransformation were published by Gupta et al. (23) who demonstrated encrustation and disintegration of Lippes loop IUDs using incident LM. Johnson et al. studied IUD encrustation in greater detail using incident LM and x-ray diffraction quantitative analysis (30). They demonstrated calcium salt deposition on various kinds of IUDs, considered calcium carbonate to be the major component of such calcification and suggested that Ca deposition tended to increase with the duration the IUD was used. Biale et al. (3), using SEM, chemical and stress analysis of Lippes loop IUDs, found calcium carbonate upon and corrosion of the surface and increased rigidity the longer the IUD was in place. Rosenfeld et al. (58), using SEM and XRMA, demonstrated similar Ca salt deposition on the Cu wire of Cu-7 IUDs. Keith et al. (34), also using SEM and XRMA, performed a detailed study of IUD crystalline surface deposits on various IUDs. They revealed apatite as the major crystal of the calcification and specifically identified an euhedral crystal rosette composed of $[Ca_5(PO_3)_3(F,Cl,OH)]$.

Disintegration of the IUD, its string or both has been repeatedly observed; this is the process which we prefer to name biodegradation. Changes in metallic components of IUDs, particularly Cu wires, are not altogether surprising since the metal is placed in an electrolyte solution for prolonged periods of time. Larsson et al. studied wire weights of coiled Cu wire IUDs and demonstrated a decrease in wire weight over time (42). The change was minimal and did not appear to affect contraceptive efficacy. Kosonen and Thiery, using LM, similarly demonstrated wire corrosion and fracture of IUDs with coiled Cu wire (40). Similar results have been obtained in animal studies using wires made from a variety of metals. Using XRMA and metallographic techniques Gonen et al. (17) demonstrated fragmentation of and deposition on the surface of wires composed of pure Au, Pt, Cu and alloys of these three metals. The deposits on the outer surface of these wires revealed elemental Ca, Cl, and S by XRMA.

Destruction of the plastic IUD or its string seems at first glance unlikely. In fact, IUDs were reintroduced early in the 1960s because plastics were available and because they appeared to be biologically inert; it was suggested that the body essentially ignored the IUDs made of polyethylene. The host reaction to the IUD involves not only a cellular response but includes the capacity to degrade synthetic materials previously thought impervious to biologic action. Biologic degradation of both nylon materials and Vicryl and Dexon sutures, the latter two being composed of copolymeric glycolide and lactide and copolymeric glycolic acid respectively, has been demonstrated

TABLE 6

IUD BIOTRANSFORMATION

Reference	Year	Study Type	Conclusions*
(24)	1971	Incident LM	Encrustation (Lippes loop).
(66)	1975	Incident LM, TEM, bacteriologic	Disintegration of and bacterial colonization within string (Dalkon shield).
(67)	1975	Incident LM, TEM, bacteriologic	Wicking effect of structurally unique tail (Dalkon shield).
(30)	1976	Incident LM, X-ray diffraction, quant. analysis	Ca salt deposit on IUD surface (various types); Calcium carbonate, the major crystalline component, tends to increase w/ duration in situ.
(14)	1976	SEM	Surface alterations and depositions (Dalkon shield).
(3)	1978	SEM, chemical analysis, stress analysis	Calcium carbonate deposition, surface corrosion, increased rigidity (Lippes loop).
(63)	1980	SEM, TEM, XRMA	Bio-material: cells, fibrin. Inorganic material: calcium deposits. Tendency to increasing calcium deposits with time (Lippes loop, Saf-T-Coil, Dalkon shield, Cu-7, Progestasert™).
(17)	1981	XRMA metallography	Au, Pt, Cu and duplex wires; rats. Ca, Cu, Cl, S formed deposits with inner and outer layers; fragmentation.
(58)	1981	SEM, XRMA	Ca deposits on Cu wire (Cu-7).
(42)	1981	Wire weights	Minimal decrease in wire weight over time; not related to contraceptive effectiveness (Cu devices).
(40)	1983	LM	Corrosion and breaking of wires (Cu devices).
(2)	1983	SEM	Bacteria on and in Dalkon shield tail; tail provides niche and acts as wick.
(57)	1984	SEM	Deterioration of Dalkon shield tail.
(35)	1985	SEM, XRMA	Detailed study of crystalline surface deposits; various IUDs; apatite, euhedral crystal rosette seen [$Ca_5(PO4)_3$ (F,Cl,OH)] on 15 year in situ Lippes loop.
(36)	1985	SEM, XRMA, X-ray diffraction	Cellular and acellular crust on various IUDs; Ca salts present (phosphates?); crust/fibrillar-amorphous layer/IUD interface seen suggests sequential crust formation.

*see text references for detailed citations

previously (16,56,64).

The Dalkon shield IUD is a classic example of biotransformation resulting in IUD-related disease. Gaudoin et al. used SEM to show that the Dalkon shield was altered in situ and that both surface depositions and alterations were produced (14). Roberts et al. (57) revealed, with SEM, that the Dalkon shield IUD tail have demonstrated bacteria on and in the Dalkon shield tail. Tatum et al. (66,67), using incident LM, TEM and bacteriologic studies, demonstrated disintegration of the Dalkon shield

IUD and bacterial colonization of the string.

Tatum et al. also demonstrated that the structural design of the Dalkon shield IUD tail permitted a "wicking effect" whereby bacteria continually gained access to the endometrial cavity (67). The Dalkon shield IUD tail has a polyfilamentous nylon core surrounded by a nylon sheath. During manufacture the nylon sheath was damaged at points where knots were tied and at these sites biologic degradation of the nylon was greatest. The knots were tied at the distal end of the tail and also at the point where the

tail attached to the IUD, the latter knot being within the cavum uteri when the IUD was in place. Using correlated in vivo and in vitro studies, Tatum et al. (67) demonstrated that motile bacteria, pathogens included, could gain access to the inner core of the string. The organisms enter either through the open end in the vagina or via mechanically induced or hydrolyzed breaks in the distal knot, travel up the string and gain access via the proximal knot site where the string is attached to the tail. In the case of the Dalkon shield a combination of poor architectural design and inadvertent poor choice in materials conspired to place the users of these IUDs at high risk for inflammatory and infectious disease.

The material deposited upon the surface of the IUD, the biodeposit, is not composed solely of inorganic Ca salts. Using SEM, TEM and XRMA, Sheppard and Bonnar studied deposits on the surface of a variety of IUDs (Lippes loop, Saf-T-Coil, Dalkon shield, Cu-7 and Progestasert™) and found Ca bearing materials which tended to increase in amount with the time the IUD was in situ (63). They also found cells and fibrin deposits as integral parts of the biodeposit material. In the most recent study, Khan and Wilkinson, using SEM, TEM, XRMA and x-ray diffraction, studied the surface deposits on a variety of IUDs (36,37). Their data indicated that most of the Ca salts present were carbonates in the form of calcite. These Ca salts seemed to be intimately intermixed and associated with cellular and non-cellular materials to produce a complex crust. Their studies revealed the structural organization of the biodeposit: the layer closest to the IUD was fibrillar and rather amorphous and the outer crust contained crystalline materials. These results suggested a definite sequence in crust formation, findings entirely consonant with the frequent observation that the formation of IUD biodeposit is time dependent.

IUD Related Disease

These well documented changes which involve the IUD, the host and the host-IUD interface may be operative in the genesis of IUD-related disease and demand interpretation in that context. To do so it is important to place IUD-related disease in perspective. The studies cited above demonstrate that changes of the IUD and of the host tissues are both time related, as is the generation of IUD-related disease. Prolonged duration of the IUD in utero is not, however, synonomous with IUD-related disease. Kaye et al. have shown in their patient population that long term use of IUDs is not associated with increased morbidity or mortality (33). They studied 200 women who used a variety of IUDs (Lippes loops-A, -C and -D; Dalkon shield; Saf-T-Coil; Cu-T200). In this population there were 670 insertions of IUDs and they experienced as complications up to 8% pregnancies and 3.2% infections, none of the latter being serious. These women had worn IUDs continuously for at least 10 years; during this time period there had been numerous reinsertions of 'fresh' IUDs.

Nonetheless, IUD use is associated with disease. Kahn and Tyler, in a six month study of 7900 IUD-related hospitalizations during 1973, derived an estimated morbidity rate of 3-10 hospitalizations/1,000 woman-years of IUD use and an estimated death rate of 1.0-7.3 deaths/1,000,000 women-years of IUD use (31,32). Thus, there seems to be a category of patients, perhaps different from the private practice, well motivated, middle class women in the study of Kaye et al. (33), who are at risk for serious disease and even death as a result of IUD use. The relationship between socioeconomic status, sexual practices and IUD-related disease are thoroughly discussed elsewhere (35,66).

Some insight may be obtained by examining the type of IUD-related disease and relationship of those diseases to the type of IUD used as shown in Tables 7 and 8 respectively. From Table 7 it is apparent that minor IUD-related disease is rare to uncommon and is associated with physiologic alterations. These physiologic alterations usually occur so soon after IUD insertion that the processes of biotransformation do not seem likely causes of the minor IUD-related diseases. The major IUD-related diseases, on the other hand, are temporally concordant with the appearance of host tissue changes and IUD biotransformation processes. Amongst the variety of mechanisms known or thought to be at the root of serious IUD-related disease, inflammation and infection are those which occur most commonly. Similarly, when IUD-related disease is classified according to type of IUD used (Table 8), it is apparent that infectious/inflammatory disease is the most common type of disease process and is also most commonly associated with the more serious complications of IUD-related disease, reproductive failure and death.

We propose that serious IUD related disease is caused by or is a direct consequence of biotransformation processes and that most of the induced diseases are mediated by inflammation and infection operating either separately or in tandem (61). We propose that inflammation/infection is the paradigm of serious IUD-related disease, the interaction of these processes being demonstrated in Fig. 18. As proof of the central role of biotransformation processes in the initiation of IUD-related disease we invoke the multitude of morphologic and microanalytic studies cited above; among these reports the results by Khan et al. are typical.

The observation by Khan and Wilkinson (36) that there is an amorphous layer immediately adjacent to the IUD upon which the proteocalcareous deposit forms is important and suggests that the first step in IUD biodeposition is the formation of a proteinaceous surface coating similar to the salivary pellicle which precedes dental plaque formation (48). Because IUDs, except for those which are medicated, do not interfere with the menstrual process the IUD is exposed during menses to a wide variety of proteins ordinarily confined to the stroma by the endometrial epithelium. These proteins may add to the surface coating of the IUD. Amongst

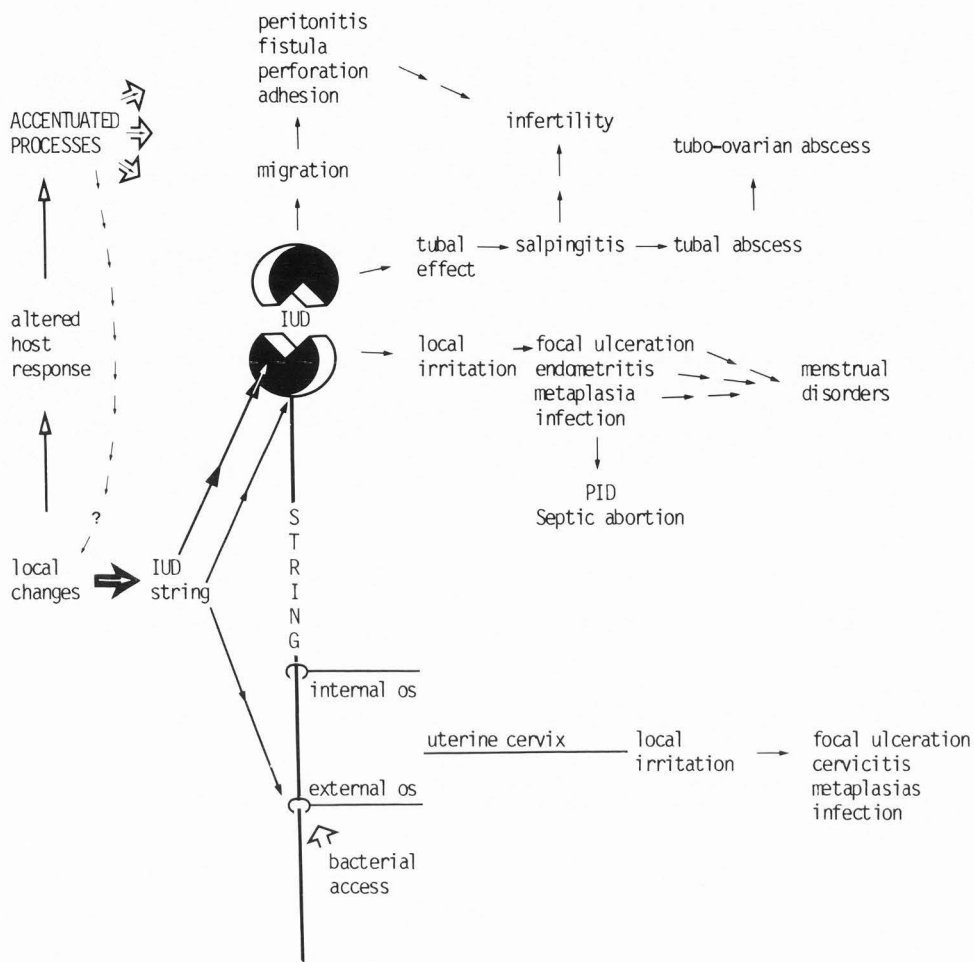## INFLAMMATION/INFECTION AS THE PARADIGM
OF IUD-RELATED DISEASE

peritonitis
fistula
perforation
adhesion

ACCENTUATED
PROCESSES

infertility

tubo-ovarian abscess

migration

tubal → salpingitis → tubal abscess
effect

altered
host
response

IUD

local → focal ulceration
irritation endometritis →→ menstrual
             metaplasia →→ disorders
             infection

PID
Septic abortion

?

local
changes

IUD
string

S
T
R
I
N
G

internal os

uterine cervix _____ local   focal ulceration
                         irritation → cervicitis
                                       metaplasias
external os   infection

bacterial
access

Fig. 18: Cartoon characterization of the proposed paradigm for serious IUD-related disease. The
          presence of the IUD induces changes in the host tissues and a host reaction which alters
          the IUD. These alterations of the IUD result in accentuation of the host responses. Changes
          in the host tissues acting in concert with the altered host/IUD milieu result in the
          inflammatory and infectious diseases which constitute the majority of serious IUD-related
          disease.

these stromal proteins are the ubiquitous extra-cellular matrix proteins, laminin, fibronectin and collagen IV.

It is important to note that fibronectin binds non-covalently to gram-positive and gram-negative bacteria and yeasts and that laminin receptors have been identified on invasive strains of S. aureus (44,70). Vercellotti et al. have shown that some gram-positive bacteria bind to and may be aggregated by fibronectin, laminin and collagen IV; in this study the authors concluded that, "These adhesion molecules play a role in the normal colonization of sites by microorganisms and in invasion during pathogenesis" (71). Others have shown that all the epithelia of the reproductive tract, including the endometrium, have a prominent glycocalyx. In the vagina it is thought that, "The

adherence of many types of bacteria to the vaginal epithelial cells appears to be effected by the interaction of polyanionic components on the surface of both the bacterial and epithelial cells" (38). Such adhesion mechanisms apparently play a role in Fallopian tube infections (9) and may be similarly operative in the colonization of biotransformed IUDs by pathogens.

Further supporting evidence for these adhesion mechanisms may be found in SEM studies of osteomyelitis in which infecting bacteria grow on the dead bone, essentially a foreign body, in coherent microcolonies found within an adherent biofilm (19). The biofilm of osteomyelitis has a fibrous matrix and contains host cells and bacteria surrounded by matrix. The bacteria are further enveloped by an exopolysaccharide polymer, which stains with ruthenium red. The

TABLE 7

CLASSIFICATION OF IUD-RELATED DISEASES AND COMPLICATIONS

Classification	Type	Frequency	Time Frame	Mechanism(s)
I. Minor	1. Syncope	Unusual-rare	Immediate insertion	Vagal bradycardia, hypotension
	2. Perforation	$\leq$8.7/1,000	Insertion and later	Faulty insertion, design failure, etc.
	3. Expulsion	0.7-19.3/1,000	First month	Poor size match
	4. Cramping & bleeding	4.0-14.7/1,000	Early and late	Size, shape and position of IUD
	5. Fe-deficiency anemia	?	Later	Menorrhagia
	6. Pregnancy	Rare	Not specific	Not defined
II. Major	1. Chronic salpingitis	Up to 47%	Increases after 2 years	Not defined
	2. Infertility	Increased	Not specified	Not defined; inflammation/infection
	3. Ectopic pregnancy	"5%"	Not specific	Unknown; salpingitis?
	4. Septic abortion	?	?	Design failure
	5. PID	1.3-8%	Increases after 2 years	Not defined
	6. Fetal loss	10-50X[a]	Second trimester	Septic abortion
	7. GI perforation	Rare	-	Puerperal perforation and migration
	8. Medication	Rare	-	Anticoagulant associated hemorrhage
	9. Death	1.0-7.3/ 1,000,000 women years	1 month - 2 years	Usually infection

? = no precise data available.
- = no data available.
a = increase over spontaneous incidence in absence of IUD.

TABLE 9

RECOMMENDATIONS REGARDING PATIENT CARE

1. Change IUDs regularly, perhaps every two years, and interrupt the biotransformation process.

2. Carefully counsel patients about complications, not only what can happen but also which alterations in normal patterns are warning signs.

3. Evaluate and observe with great care those women who are symptomatic no matter how protean their symptoms. Consider removing the IUD and using an alternative means of contraception.

4. Examine carefully the removed IUD and adherent material, no matter how small the fragments may be.

5. Follow carefully those women using IUDs.

authors of the osteomyelitis studies conclude that, "The adherent mode of growth may reduce the susceptibility of these organisms to host clearance mechanisms and antibiotic therapy and thus may be a fundamental factor in acute and chronic osteomyelitis". Such mechanisms of escape from host defenses may permit growth of pathogens within IUD biodeposits and the attainment of sufficient numbers to establish an infectious disease process.

The model which we propose for IUD-related diseases is shown in Figure 19. The model is concordant with our present understanding of the types of disease processes associated with IUDs, the types of IUDs associated with disease and with the multitude of structural and microanalytic studies of IUDs. The construction of the model has been entirely dependent upon data from morphologic and microanalytic studies. Our understanding of IUD-induced alterations in host tissues, the alterations on and of the IUD and the apparent interactions between these forces to produce IUD-related disease, in fact, have come as a result of morphologic analysis, thorough microanalytic probing and careful correlation of clinical and pathological observations.

TABLE 8

CLASSIFICATION OF IUD-RELATED DISEASE BY IUD TYPE

| TYPE | DISEASE | PATHOGENESIS | PROGNOSIS | | |
			LIMITED INCAPACITY	REPRODUCTIVE FAILURE	DEATH
1. Diamond +Au	Infections	Non-inert devices	±	+	+
2. Silkworm gut	"	"	±	+	+
3. Silkworm gut and Ag	"	"	±	+	+
4. Nylon	Device failure	Fragmentation by body systems	+	-	-
5. Stainless steel	Infection, perforation, menorrhagia	Chemical irritation	+	+	±?
6. Plastics:					
Saf-T-Coil	Minor diseases	Not apparent	+	±	-
Birnberg bow	Major diseases	?Inflammation/ infection	+	+	±?
Lippes loop	Minor diseases, Major diseases,	Not apparent Inflammation/ infection	+	±	-
	Infertility		+	-	-
	PID		±	+	±
Dalkon shield	Mid-trimester Abortion	Design failure Inflammation/ infection	-	+	+
	PID	"	+	+	
Cu devices	Minor diseases, Major diseases,	Not apparent	+	-	-
	Infertility	Inflammation/	+	+	-
	PID	infection	+	+	±
Medicated	Minor diseases, Major diseases,	Hormonally related	+	-	-
	Ectopic pregnancy	Unknown	+	±	±

Epilogue

IUDs returned to use at a time permissive to the introduction of new devices, permissive to a fault, in fact. It is difficult to conceive how such devices could be introduced today without studies more thorough than were performed in the 1960s, recognizing that at that time bioengineering and materials science were fledgling areas. Today the truly inert IUD remains as elusive as ever and although IUD-related disease persists the IUD continues to be used by millions of women. Even though two major manufacturers of IUDs have withdrawn from the market there remain others and the IUD, as noted above, remains a popular contraceptive device. Those IUDs still in use are not exempt from the types of changes or proposed mechanisms of disease listed above. It is important, therefore, that patient care and observation be modulated by our current understanding. Table 9 lists recommendations regarding care of patients with IUDs.

It also seems unwise to ignore the efficacy and popularity of IUDs as a contraceptive device. Rather, we should capitalize upon our experience to date, continue to carefully observe those IUDs which remain in use and design IUDs which are both safer and effective. When possible future trends in IUD design and evaluation are considered (Table 10) it is apparent that morphologic and microanalytic studies must be continued by multidisciplinary teams.
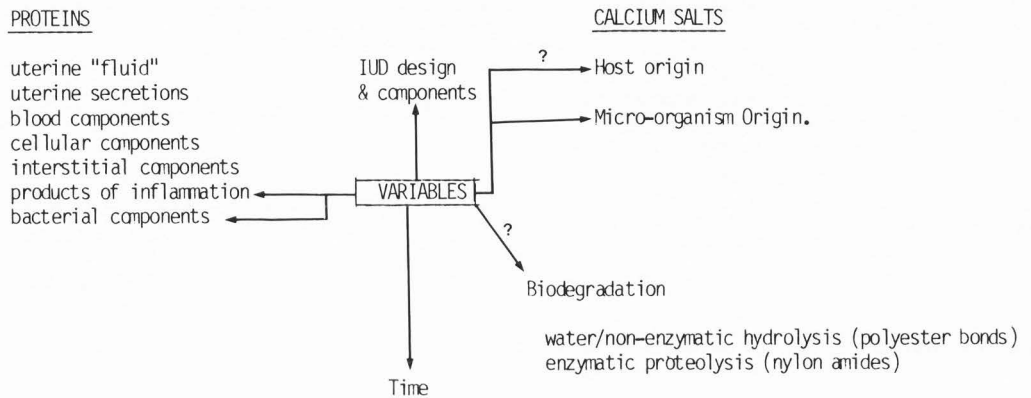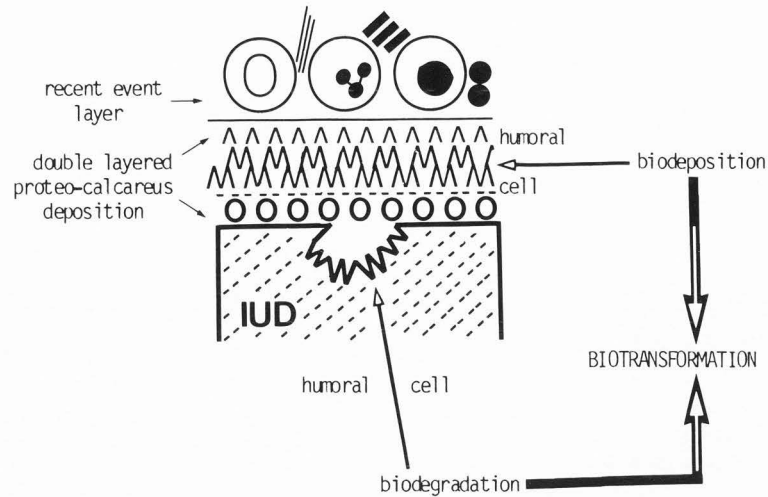
Fig. 19: Details of the biotransformation processes which contribute to the genesis and progress of serious IUD-related disease. a. a cartoon view of the IUD surface, seen on cross section. The proteo-calcareous deposition is formed from both cellular and humoral components. Under this layer there are changes which affect the physical structure of the IUD; these changes may involve dissolution of or changes in the mechanical properties of the IUD and its string. The outer layer of the biodeposit represents the "recent event layer" within which may be found RBCs, WBCs, protein strands, crystalline material and bacteria of various kinds. b. the variables which contribute to the two major components of the biodeposit are shown. The major variables seem to be proteins of various kinds, the nature of the materials of which the IUD is made, Ca salts, biodegradation processes and time in situ.

List of Abbreviations

AcPase	Acid phosphatase	OCPs	Oral contraceptive pills
AlPase	Alkaline phosphatase	P	Phosphorus
ARS	Alizarin red S	PAS	Periodic acid-Schiff
Au	Gold	PGE	Prostaglandin E
Ca	Calcium	PGF	Prostaglandin F
Cl	Chlorine	PID	Pelvic inflammatory disease
Cu	Copper	PMNs	Polymorphonuclear neutrophils
CV	Cervicovaginal	Pt	Platinum
FDA	Food and Drug Administration	RBCs	Red blood cells
GMS	Gomori-methenamine silver	S	Sulfur
H&E	Hematoxylin and eosin	SEM	Scanning electron microscopy
hPRL	Human prolactin	TEM	Transmission electron microscopy
IUD	Intrauterine device	US	United States
LM	Light microscopy	WBCs	White blood cells
MoB	Bunting's molybdenum blue	XRMA	x-ray microanalysis
		Zn	Zinc

TABLE 10

FUTURE TRENDS IN IUD DESIGN AND EVALUATION

1. Continue to explore the application of new materials, such as polyether urethane.

2. Continue to explore the role of metals in terms of their capacity to promote contraception, inflammation and bacteriostasis.

3. Continue to explore the role of the IUD as a means of delivering pharmacologic agents which may influence contraception, the host response, biotransformation and control of micro-organisms.

4. Continue to explore the nature of biotransformation, its consequences, the molecules which participate in the phenomenon and the control mechanisms involved.

5. Design and fund these studies to allow long-term follow-up of no less than 5 years, utilizing multidisciplinary teams of materials scientists, reproductive biologists, obstetrician/gynecologists and reproductive pathologists.

6. Include in such studies a wide range of patients of diverse races, socioeconomic levels, sexual behaviors and marital and reproductive status.

7. Use the full range of clinical studies and basic science examinations which have proven so useful in providing our current fund of knowledge of IUD-related disease.

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Discussion with Reviewers

S. R. Khan: Knowing what we know now, would you recommend use of the IUD as a contraceptive device?
Authors: This is a difficult question; its answer must be addressed at two levels. The literature which we have reviewed and multiple other articles which we have not cited attest to the usefulness of the IUD as a means of contraception. In addition, this collective experience clearly identifies the conditions under which IUD use is likely to be safe and those conditions in which serious disease may be encountered as a direct result of using an IUD. Unfortunately, there is no guarantee that significant IUD-related morbidity will not be encountered under the best circumstances. The inability to predict which women are at risk for serious IUD-related disease leads to threatening medico-legal liability. In the US, the IUD-related litigation risk is well understood by medical and legal professionals and the women who use IUDs. Georgia Dullea's article in the New York Times (Liability Crisis Complicates Contraception; Style, B8, Monday, May 19, 1986) is perhaps a fitting public summary; she quotes therein the comments of one gynecologists: "No sane physician would dare give an IUD today, except to his wife".

Reviewer V: Why were the IUDs collected in 1985 sent to you?
Authors: It is the practice in our institution to send all IUDs which are removed to the pathology laboratory for examination. This allows the attending physician to explore the possibility of clinically silent but serious IUD-related disease when the results of the pathologist's examination suggests such a possibility. Examples of suggestive findings include: Gupta bodies on CV smears obtained coincident with IUD removal, purulent and malodorous deposits on the IUD and string, and significant histopathological alterations in tissues attached to the IUD and string.

Reviewer V: What is a major IUD-related disease and what is a minor one?
Authors: In the course of our extensive literature review we perceived the need to distinguish amongst the wide variety of IUD-related complications. As noted by Reviewer V, "IUD associated complications occur most frequently during the first 12 weeks of insertion ----." These complications are, for the most part, minor occurrences and transient situations which

had to be distinguished from long-term or life threatening morbidity subsequent to IUD use. It is our perception that the mechanisms operative in the former are distinctly different than those functioning in the latter. Our definitions of these two broad categories of IUD-associated complications are:

MINOR IUD-RELATED DISEASE
conditions which do not -
    threaten or destroy reproductive
      capacity
    seriously impair or permanently
      destroy work capacity
    require more than ambulatory care
most are physiologic reactions or
    limited excesses or normal physiologic
    functions (ie, cramping and expulsion
    of the IUD)
are usually treated easily, inexpensively and do not need extensive follow-up

MAJOR IUD-RELATED DISEASES
conditions which -
    are life threatening or fatal
    threaten, impair significantly or
      destroy reproductive capacity
    seriously impair or permanently destroy
      work capacity
    require in-patient care and extensive
      follow-up
    often require surgical intervention

Reviewer V: Why don't you get oral abscesses and infections with prolonged dental fillings? Should IUDs be made of similar materials?
Authors: There is an instance in which intraoral dental 'crust' formation is associated with a disease process similar to serious infections related to IUD use. The formation of dental plaque, particularly where that plaque extends into the gingivo-dental sulcus, is related to periodontal disease and tissue destruction. In both settings it appears that the crust and micro-organisms play a synergistic role. There is much merit to the suggestion that exploration of a wider range of materials might produce a safer IUD.