

# 3

## The Use of Chemical Agents in Female Sterilization

*RALPH M. RICHART*

Vasectomy is a simple technique that can readily be applied to large populations using an outpatient approach. Although it is a surgical procedure, male sterilization does not require entering the abdominal cavity and the incision and surgical manipulation are not associated with a high degree of risk. Because the procedure and the anatomy of the vas are relatively straightforward, paramedical technicians can be trained to perform vasectomies and significant numbers of male sterilizations have been performed by nonmedical teams in a number of countries.

In contrast, conventional female sterilization using any of the standard surgical approaches requires abdominal entry because the fallopian tubes are located within the abdominal cavity. A woman who is in the postpartum period or is thin and cooperative can be sterilized surgically through a relatively small incision, as with laparoscopic tubal sterilization. Even in highly favorable cases using state-of-the-art technology, however, a surgeon's skills are required in most settings because vital internal structures are close to the area being treated and may inadvertently be injured. The procedure is highly skill dependent and must be performed in a relatively protected environment.

Sterilization requires of the patient only a single motivation, following which it is, in demographic terms, the most effective family planning procedure in the cafeteria of contraceptive methods. As a surgical procedure, however, it is essentially unavailable to much of the developing world, owing to an inadequate number of physicians, particularly trained surgeons, in rural areas where most of the population lives; further, the surgically trained physicians who do practice in rural areas are overwhelmed with other problems, which to them are more pressing than elective sterilization. Even in the developed countries and even with the use of new technologies, female sterilization is an expensive procedure and absorbs a significant part of the available health funds.

Clearly a female sterilization procedure that is simple, inexpensive, non-morbid, and nonsurgical would be a useful adjunct to the delivery of family planning services, particularly in the rural areas of developing countries.

Investigators have made a number of attempts to develop a nonsurgical female sterilization technique using cryotherapy, electrocoagulation, mechanical plugs, the instillation of hot water, and chemical materials to produce local epithelial necrosis and fibrosis, and obliteration of the lumen through scarring. The physical methods, such as cryotherapy and silicone rubber in-

stillation, and certain chemical applications, are discussed elsewhere in this volume. It is the purpose of this chapter to review, principally from a historical perspective, the work with those agents not considered in more detail in other chapters.

STRONG CAUSTIC AGENTS

Strong caustic agents, including silver nitrate, zinc chloride, copper sulfate, and formaldehyde, were all studied extensively in animals, and with the exception of copper sulfate, each was also studied in humans (Table 3-1). All these agents produce significant local necrosis when applied topically to any epithelial surface with accompanying acute and chronic inflammation and edema. Their action is produced in part by protein coagulation, and the depth and extent of injury is dependent on the amount of material applied and the concentration of the active ion. The extent of the injury with these agents is difficult to control, and the tissue necrosis may be so extensive as to produce significant morbidity and even mortality in small animals.

In most of the animal experiments and in some of the human applications as well, massive tubal necrosis of the epithelium, the lamina propria, and even the muscularis, was described for silver nitrate, zinc chloride, and copper sulfate. Formaldehyde also produced necrosis but appeared to be more easily controlled. Despite extensive tubal damage, however, the common experience among investigators studying these potential tube-closing agents was that tubal regeneration was routine following a single acute application. It would appear that the acute insult left behind islands of epithelium that were capable of regenerating rapidly and recovering the luminal surfaces before they were

TABLE 3-1. Strong Caustic Agents

CHEMICAL	TYPE OF STUDY	SOURCE
Silver nitrate	Rabbit	Richart et al <sup>43</sup>
	Monkey	Omran & Hulka <sup>33</sup>
		Neuwirth et al <sup>32</sup>
	Pig	Omran & Hulka <sup>33</sup>
	Human	Richart et al <sup>41</sup>
Ringrose <sup>44</sup>		
Babcock <sup>2</sup>		
Zinc chloride	Rabbit	Richart et al <sup>43</sup>
	Monkey	Neuwirth et al <sup>32</sup>
	Rat	Zipper et al <sup>54</sup>
	Human	Babcock <sup>2</sup>
Copper sulfate	Rabbit	Schenker & Polishuk <sup>46</sup>
	Rat	Zipper et al <sup>49</sup>
Formaldehyde (alone or with ethanol)	Rat	Zipper et al <sup>51</sup>
	Rabbit	Schenker & Polishuk <sup>46</sup>
	Human	Davis (in men)*

TABLE 3-2. Clinical Trials With Ethanol-Formalin

SOURCE	NO. PATIENTS	NO. APPLICATIONS	CUMULATIVE BILATERAL CLOSURE RATE (%)*
Zipper et al (1972) <sup>51</sup>	8	1	0
	18	2	12
	21	3	35
	30	4	76
	12	5	93
	4	6	95
Total	93		

\*After 2 years' follow-up, 8.7% of patients who had a diagnosis of tubal closure had become pregnant.

scarred closed. Even when massive injuries using high concentrations of silver nitrate were produced, a significant proportion of the fallopian tubes remained open, despite major systemic reactions in the animals or humans treated with the substance. It became clear that chronicity was important in producing closure, even with highly active chemicals, and attempts were made to improve the closure rate either by multiple lavages, in the case of formaldehyde; by combining one of these agents with another agent, such as formaldehyde with ethanol; or by suspending an active agent in a vehicle that would prolong the release rate and the epithelial exposure.

In the case of formaldehyde, Zipper and his associates used the substance alone and with ethanol, with repeated applications, and reported a significant increase in the closure rates as the number of applications was increased (Table 3-2). The number of applications to produce a high degree of closure was unacceptable clinically, however, and despite the benign response of the patients to repeated doses of ethanol-formalin, the approach was eventually abandoned. Other investigators combined silver nitrate with a bland carrier and reported good closure rates in animals and in humans, but at higher concentrations there were significant clinical sequelae, including severe chemical pelvic peritonitis,<sup>44</sup> and the silver nitrate-dermabase cream combination was abandoned as not being appropriate for human use.

Our group continued to study silver nitrate because of its good tube-closing properties in a slow-release form and, in collaboration with Gregor and his colleagues,<sup>19</sup> devised a thixotropic silver acetate-alginate system that appeared to be promising. Experiments in primates, however, were unsatisfactory, since even in a slow-release vehicle, the silver acetate could not be controlled with sufficient precision to ensure a lack of unacceptable clinical side-effects.

## STRONG ACIDS AND BASES

Strong acids and bases produce an immediate acute inflammatory response and tissue necrosis, accompanied by severe inflammation and edema. Investigations of their use in animals and humans are listed in Table 3-3. The tissue response is similar to that found with other highly polar groups. As with strong caustic agents there is no specificity in the response to strong

TABLE 3-3. Strong Acids and Bases

CHEMICAL	TYPE OF STUDY	SOURCE
Sulfuric acid	Rabbit	Richart et al <sup>43</sup>
Salicylic acid	Rabbit	Richart et al <sup>43</sup>
Phenol	Rabbit	Richart et al <sup>43</sup>
	Human	Salgado <sup>45</sup> People's Republic of China <sup>39</sup>
Sodium hydroxide	Rabbit	Richart et al <sup>43</sup>

acids and bases and their application leads to widespread damage, which is dose related. Sodium hydroxide, sulfuric acid, and salicylic acid have not been applied to the human fallopian tubes, since the experience in animals was unsatisfactory. Although tubal damage could be produced, tubal closure was difficult to secure after an acute injury, the agents were difficult to control, and systemic effects and pelvic chemical peritonitis were common. In contrast, phenol has been used in a slow-release carrier by investigators from the People's Republic of China, who have reported good results. Their experience is detailed in Chapters 17 through 19.

### SCLEROSING AGENTS

Various sclerosing agents are used by vascular surgeons to produce venous thrombosis in the treatment of varicosities. Three representatives of this group of drugs-sodium morrhuate, sodium tetradecyl sulfate (Sotradecol), and sodium lauryl sulfate-have been applied to the fallopian tube, but as single agents they produce little or no effect on the tubal epithelium and they fail to produce tubal closure. Sodium morrhuate has been used in humans in association with tubal ligation but appears otherwise not to be clinically useful in producing tubal closure (Table 3-4).

### GRANULOMA-PRODUCING AGENTS

Many agents produce granulomas when placed subcutaneously in animals (Table 3-5). The beryllium compounds are particularly active in this regard and rapidly produce very large nodules when injected subcutaneously. Tal-

TABLE 3-4. Sclerosing Agents

CHEMICAL	TYPE OF STUDY	SOURCE
Sodium morrhuate	Rabbit	Richart et al <sup>43</sup>
	Human	Dieckmann & Harrod <sup>13</sup> Pitkin <sup>34</sup>
Sodium tetradecyl sulfate	Rabbit	Richart et al <sup>43</sup>
Sodium lauryl sulfate	Rabbit	Schenker & Polishuk <sup>46</sup>

TABLE 3-5. Granuloma-producing Agents\*

CHEMICAL	TYPE OF STUDY
Talc	Rabbit Human†
Asbestos	Rabbit Monkey
Cellobiose	Rabbit Monkey
Silica	Rabbit Monkey
Diatomaceous earth	Rabbit Monkey
Beryllium nitrate	Rabbit Monkey
Quartz	Monkey
Plant cells	Monkey

\*Richart RM, Taylor HC, Neuwirth RS: Experimental studies of fallopian tube occlusion. In Richart RM, Praeger D (eds): Human Sterilization, pp 360-367. Springfield, IL, Charles C Thomas, 1972.

†Ringrose C: Office tubal sterilization. *Obstet Gynecol* 42:151, 1973.

cum powder has produced granulomas in the peritoneal cavity, and asbestos is a classic granuloma-producing agent at any site. When these substances are infiltrated into the myometrium in the region of the interstitial fallopian tube, however, relatively small granulomas are produced, and they enlarge only slowly over a prolonged period. Even beryllium nitrate produces only microscopic granulomas after 9 months *in situ*. None of the granulomas produced by any agents reached sufficient size to close the interstitial fallopian tube mechanically. Except for Ring-rose's use of talc as a potentiating agent along with silver nitrate,<sup>22,44</sup> the granuloma-producing agents have not been applied chemically and appear to offer no potential for human use in producing tubal blockade.

## CYTOTOXIC AGENTS

A variety of cytotoxic agents exist and have been tested for their tube-closing abilities (Table 3-6). These include thioTEPA, colchicine, cadmium, podophyllin, and quinacrine. The use of quinacrine is discussed in detail in other portions of this volume. The other cytotoxic agents produce focal epithelial necrosis but not to a sufficient degree to ablate the epithelium. More importantly, they fail to produce fibrosis and tubal blockade and appear to have no potential for human use. In addition, most cytotoxic agents are mutagenic

TABLE 3-6. Cytotoxic Agents

CHEMICAL	TYPE OF STUDY	SOURCE
ThioTEPA	Rat	Zipper et al <sup>52</sup>
Quinacrine	Rat	Zipper et al <sup>53</sup>
	Rabbit	Zipper et al <sup>50</sup>
		Richart et al <sup>43</sup>
	Human	Zipper et al <sup>54</sup>
		Davidson & Wilkins <sup>7</sup>
		Benoit et al <sup>3</sup>
		Israngkun et al <sup>24</sup>
	Mehtaji et al <sup>26</sup>	
	Bhatt et al <sup>4</sup>	
	Alvarado et al <sup>1</sup>	
Colchicine	Rat	Zipper et al <sup>52</sup>
Cadmium	Rat	Zipper et al <sup>52</sup>
Podophyllin	Rat	Zipper et al <sup>52</sup>

and have distant cellular effects, even when applied locally, and thus would not be suitable for human use even if they closed tubes.

### TISSUE ADHESIVES

Tissue adhesives, principally from the cyanoacrylate series, have also been studied extensively and are treated in greater detail in other sections of this volume. Gelatin resorcinol formalin (GRF) was fabricated by Battelle Memorial Institute and was studied extensively in animals but was apparently difficult to control, was inconsistent in producing tubal closure, and was abandoned prior to instituting clinical trials (Table 3-i').

TABLE 3-7. Tissue Adhesives

CHEMICAL	TYPE OF STUDY	SOURCE
Methyl cyanoacrylate	Rabbit	Corfman et al <sup>5</sup>
		Richart et al <sup>43</sup>
	Monkey	Neuwirth et al <sup>32</sup>
	Pig	Omran & Hulka <sup>33</sup>
	Human	Stevenson & Taylor <sup>48</sup>
	Neuwirth et al <sup>31</sup>	
Ethyl cyanoacrylate	Rabbit	Richart et al <sup>43</sup>
	Monkey	Richart et al <sup>43</sup>
Isobutyl cyanoacrylate	Rabbit	Richart et al <sup>43</sup>
	Pig	Omran & Hulka <sup>32</sup>
Gelatin resorcinal formalin (GRF)	Rabbit	Grode et al <sup>21</sup>
		Falb et al <sup>17</sup>
	Mouse	Davis et al <sup>11</sup>

OTHER AGENTS

Silicone rubber instillation and intratubal devices have been used to mechanically block the fallopian tube of rabbits<sup>9,11,14,21</sup> and both have reached the stage of clinical trial.<sup>15,34-36</sup> Droegemueller and associates have used cryosurgery to occlude the fallopian tubes of baboons and also of women.<sup>13,18</sup>

Moulding and his collaborators have reported the use of hot water applied to the fallopian tubes of rabbits through a cannula to produce tubal necrosis and fibrosis,<sup>26-28</sup> but the method appears to be difficult to control and clinical trials have not been undertaken.

CLINICAL TRIALS

Clinical trials have been performed with silver nitrate (Table 3-8), ethanol-formalin (see Table 3-2), phenol-mucilage (Tables 3-9 and 3-10), methyl cyanoacrylate (MCA) (Table 3-1 1), and quinacrine. These trials have used a variety of delivery systems, ranging from simple lavage, to a hysteroscopically guided tubal cannulation,<sup>24,37</sup> to a blind delivery system using a soft rubber balloon as a piston to force the material into the fallopian tubes.<sup>42</sup>

In addition to these systems, Corfman and Taylor described a handheld cannula,<sup>6</sup> the Battelle group fashioned a tube-finding triangulation device,<sup>16</sup>

TABLE 3-8. Clinical Trials With Silver Nitrate (AgNO<sub>3</sub>) in Hydrophilic Cream

SOURCE	YEAR	NO. PATIENTS	CLOSURE RATE	PREGNANCIES	COMMENTS
Richart et al <sup>41</sup>	1971	14	100%	None	Culdoscopic delivery of 10% AgNO <sub>3</sub> . Pelvic tenderness and low-grade fever were noted.
Ringrose <sup>44</sup>	1973	100	50%	5	Blind cannula delivery of 10% AgNO <sub>3</sub> in dermabase cream.
		100	70%	1	Blind cannula delivery of 15% AgNO <sub>3</sub> in dermabase cream.
		60	Not stated	Not stated	Blind cannula delivery in 20% AgNO <sub>3</sub> in dermabase cream.  Patients suffered major complications particularly with higher doses, including two cases of paralytic ileus and other untoward effects. Talc was added to some preparations.

TABLE 3-9. Clinical Trials in 3940 Patients Treated With Phenol-Mucilage, 1979\*

% BILATERAL OCCLUSION	COMMENTS
Ranged from 77.6% to 93.5%	A series of compounds was used in which active agent was phenol. In some, salicylic acid was added. No data were given for composition of formulation in each of 7 series, but rate continued to improve until last series reached 93.5%.

\*Research Group of Tubal Occlusion by Drugs: Sterilization by occlusion of the fallopian tubes with mucilago phenol: A seven years' clinical observation. Chinese J Obstet Gynecol 14:79, 1979.

TABLE 3-10. Relationship Between Tubal Filling Length and Pregnancy Rate With Phenol-Mucilage

LENGTH OF FILLED TUBE (CM)	PREGNANCY RATE (%)
1-2	7.1
2-4	3.3
4	1.1
Ampulla	0.08
Fimbria	0.0

\*Adapted from data in Research Group of Tubal Occlusion by Drugs: Sterilization by occlusion of the fallopian tubes with mucilago phenol: A seven years' clinical observation. Chinese J Obstet Gynecol 14:79, 1979.

TABLE 3-11. Results of Clinical Trials With MCA

SOURCE	YEAR	NO. PATIENTS	BILATERAL CLOSURE (%)	COMMENTS
Stevenson & Taylor <sup>48</sup>	1972	12		Prehysterectomy application
Stevenson <sup>47</sup>	1976	34	66	Hysterosalpingography at 8 weeks
		11	90	Reapplication of MCA
Neuwirth et al <sup>31</sup>	1980	131	72	Closure rates of 54% to 78% in three series with various volumes of MCA (0.4-0.65)
		19	74	Reapplication of MCA
Richart & Neuwirth*	1981	180	80	0.6 ml MCA; modified FEMCEPT device
		19	98	Reapplication of MCA following patency detected by hysterosalpingography

\*Unpublished data.

and Moulding and associates attempted to isolate the cornua with a balloon to facilitate tubal injection.<sup>29</sup> These methods were largely unsuccessful.

There are a number of factors that constrain the design of a delivery system for caustic chemicals to the fallopian tubes. The principal one among these is that any substance toxic to the tubal epithelium will also be toxic to the peritoneal cavity. Thus, the system must reproducibly deliver the tubal sclerosing agent to the tubal lumen without producing an intraperitoneal spill. This constraint has been met in the FEMCEPT/MCA system by carefully controlling the volume and viscosity and by the precision of the blind delivery system. In the case of quinacrine, the drug appears not to produce significant side-effects when delivered to the peritoneal cavity, but the constraint has also been met by using delivery systems that diffuse the drug slowly into the fallopian tube, minimizing the quantity that reaches the peritoneal cavity. Other more caustic agents have been difficult to apply in a clinically acceptable fashion and have largely been abandoned. These considerations have been discussed in greater detail elsewhere.<sup>39</sup>

## DISCUSSION

Attempts to close the fallopian tubes by the use of caustic chemicals date back to 1849, when Froriep used a nitric acid-coated probe to cauterize the tubal lumen." Babcock also used a chemical contraceptive approach in 1924.<sup>2</sup> Other attempts at an outpatient-oriented sterilization approach used principally hot cautery until the early 1960s, when systematic studies directed toward a chemical cauterization technique were undertaken. Large numbers of chemical agents from virtually every class of compound that might be appropriate candidates for this procedure were screened, but most were found wanting.

At present, only three chemical agents are actively being pursued in clinical trials: quinacrine, phenol, and methyl cyanoacrylate. The efficacy of these three compounds is comparable, but they differ significantly in their modes of delivery. The phenol-based system apparently requires a high degree of skill in blindly placing a cannula at the tubal ostium. It is not clear to what degree this skill is transferable to large numbers of operators. The quinacrine investigators have yet to settle on a delivery mode, but the newer approaches to delivery, using IUD vectors or slow-release pellets, will provide great simplicity, if the experiments produce acceptable closure rates. The FEMCEPT system is more complex in its engineering and is a more expensive delivery system than a reusable cannula or an IUD vector, but it has produced increasingly satisfactory bilateral closure rates, and the delivery technique appears to be readily transferable, since most of the fourteen investigators who have used the system obtain comparable closure rates.

The nonchemical mechanical tubal blockade systems, including the intra-tubal devices and the silicone rubber technique, use hysteroscopy to identify the tubal ostia and to administer the tube-blocking device. Hysteroscopy is a highly sophisticated, mechanically complex technique that requires great skill for its application and service accessibility. It is not clear whether any system that uses a hysteroscope for delivery will be widely applicable, particularly in

the developing countries. Whether any or all of these outpatient-directed female sterilization techniques will gain widespread application must await the results of fertility trials under field use in a variety of settings.

The acceptability of one or more of these techniques depends, however, not only on the clinical results but on the context in which they are introduced and the context in which the data are compared with other family planning techniques. Surgical tubal ligation is a definitive procedure in which the tubes are physically identified and physically closed by coagulation, segmental excision, or application of a variety of occluding appliances. These techniques have an extremely low failure rate. However, they have significant morbidity and some mortality and are essentially unavailable to most of the world, owing to a lack of surgeons and operative support facilities. Intrauterine contraceptive devices, steroidal contraceptives, and barrier techniques all have a high failure rate and a high discontinuation rate, and the IUDs and steroidal contraceptives are associated with a variable degree of side-effects.

The outpatient female sterilization techniques should be thought of as lying someplace between the IUD and surgical sterilization in terms of acceptability to users. They will never achieve the high degree of reliability that has come to be associated with surgical sterilization, but they are nonoperative, they do not require extensive surgical support facilities, they do not require surgical skills, and they can readily be applied to large numbers of women. The FEM-CEPT/MCA system, for example, is applied with about the same ease as is an IUD insertion. There is clearly a trade-off between expensive, complex, highly available procedures on the one hand and inexpensive, simple, but less reliable procedures on the other. As long as a woman understands the trade-offs, then she should be free to choose among the techniques.

In areas in which surgical sterilization is, for all practical purposes, unavailable to the majority of the population, the introduction of these simple, rapid, inexpensive outpatient-oriented techniques should fill a significant gap in the armamentarium of family planning procedures. From a demographic point of view, the small number of failures should be unimportant in proportion to the high success rate, provided the women using these outpatient techniques are not led to believe that they are the equivalent of conventional surgical sterilization and also are not led to expect a 100% success rate.

Strategically, a variety of protocols can be constructed using an outpatient-oriented sterilization program, with the choice again representing a trade-off between expense and success rate. In some settings, for example, the choice may be to make a single application, to detect the failures as pregnancies, and to abort those women with failed procedures and then resterilize them using a second application or a conventional technique. In other settings it may be appropriate to treat each woman twice, thus lowering the failure rate but increasing the cost. In the most medically sophisticated areas, a single treatment followed by a hysterosalpingogram to identify the failures may be chosen.

Whichever route is chosen, there are sufficient data now to predict that these techniques can potentially be applied to large numbers of women in a short period of time with low morbidity and a high degree of demographic effectiveness. Whether they will in fact prove acceptable to the women who must use them must await field trials, but the results to date are encouraging.

## REFERENCES

1. ALVARADO A, QUINONES R, AZNAR R: Tubal instillation of quinacrine under hysteroscopic control. In Sciarra JJ, Butler JC Jr, Speidel JJ (eds): *Hysteroscopic Sterilization*, pp 85-94. New York, Intercontinental Book Corporation, 1974
2. BARCOCK WW: Chemical hysterectomy. *Am J Obstet Gynecol* 7:693-696, 1924
3. BENOIT A, MELANCON J, GAGNON M: Chemically-induced tubal occlusion in the human female using intrauterine instillation of quinacrine. *Contraception* 12:95, 1975
4. BHATT RV, PATHAK ND, CHAUHAN LN et al: A study of transcervical instillation of quinacrine before hysterectomy to test tubal blockage. Bombay, India Fertility Research Program, September 1977, p 171
5. CORFMAN PA, RICHART RM, TAYLOR HC: Response of the rabbit oviduct to a tissue adhesive. *Science* 148: 1348, 1965
6. CORFMAN PA, TAYLOR HC: An instrument for transcervical treatment of the oviducts and uterine cornua. *Obstet Gynecol* 27:800, 1966
7. DAVIDSON OW, WELKINS C: Chemically-induced tubal occlusion in the human female following a single instillation of quinacrine. *Contraception* 7:333, 1973
8. DAVIS JE: New methods of vas occlusion. In Zatuchni GI, Labbok MH, Sciarra JJ (eds): *Research Frontiers in Fertility Regulation*, pp 252-261. Hagerstown, Md, Harper & Row, 1980
9. DAVIS RH, ERB R, KYRIAZIS GA et al: Fallopian tube occlusion in rabbits with silicone rubber. *J Reprod Med* 14:56, 1975
10. DAVIS RH, MCDONALD J, KYRIAZES G et al: Effect on fertility of intrauterotubal injection of gelatin. *Obstet Gynecol* 42:446, 1973
11. DAVIS RH, MOONKA EK, PLATT HA et al: Chronic occlusion of the rabbit fallopian tube with silicone rubber. *Obstet Gynecol* 6:142, 1978
12. DIECKMANN WJ, HARROD JP JR: Tubal ligation (sterilization) by a modified Madlener method. *Am J Obstet Gynecol* 68:897-902, 1954
13. DROEGEMUELLER W, GREER BE, DAVIS JR et al: Cryocoagulation of the endometrium at the uterine cornua. *Am J Obstet Gynecol* 13 1: 1, 1978
14. ERB RA, DAVIS RH, KYRIAZES G et al: Device and technique for blocking the Fallopian tubes. *Contemp OB/GYN*, February 1974, p 92
15. ERB RA, REED TP: Hysteroscopic oviductal blocking with formed-in-place silicone rubber plugs: I. Method and apparatus. *J Reprod Med* 23:65-68, 1979
16. FALB RD, LOWER BR, CROWLEY JP et al: Transcervical fallopian tube blockage with gelatin-resorcinol-formaldehyde (GRF). In Sciarra JJ, Droegemueller W, Speidel JJ (eds): *Advances in Female Sterilization Techniques*, pp 208-215. Hagerstown, Md, Harper & Row, 1976
17. FRORIEP R: Zur vorbeugung der notwendigkeit des kaiserschnitts und der perforation. *Notizen Nat Neilkd* 211:9-10, 1849
18. GREER BE, DROEGEMUELLER W, BINGHAM PE et al: Uterine cryosurgery in baboons. In Sciarra JJ, Droegemueller W, Speidel JJ (eds): *Advances in Female Sterilization Techniques*, pp 231-238. Hagerstown, Md, Harper & Row, 1976
19. GREGOR HP, HSIA HT, PALEVSKY S et al: Fallopian tube cauterization by silver ion-polymer gels. In Paul DR, Harris FW (eds): *Controlled Release Polymeric Formulations*. New York, ACS Symposium Series #33, 1976
20. GRODE GA, PAVKOV KL, FALB RD: Feasibility study on the use of a tissue adhesive for the nonsurgical blocking of fallopian tubes. *Fertil Steril* 22:552, 1971
21. HEFNAMI F, FUCHS A-R, LAURENCE KA: Control of fertility by temporary occlusion of the oviduct. *Am J Obstet Gynecol* 99:42 1, 1967
22. IMLACH A: Edmonton gynecologist at legal odds with provincial college. *Can Med Assoc J* 112:1345-1355, 1975
23. ISRANGKUN C, PHAOSAVASDI S, NEUWIRTH RS et al: Clinical evaluation of quinacrine hydrochloride for sterilization of the human female. *Contraception* 14:75-80, 1976
24. LINDEMANN H-J, MOHR J: Review of clinical experience with hysteroscopic sterilization. In Sciarra JJ, Droegemueller W, Speidel JJ (eds): *Advances in Female Sterilization Techniques*, pp 153-161. Hagerstown, Md, Harper & Row, 1976
25. MEHTAJI S, JADMANI K, GOYAL V: Chemical sterilization with quinacrine. Fourth Transaction of Scientific Papers. Bombay, Indian Fertility Research Program, September 1977, p 167
26. MOULDING T, NORTON W, ORR W: Preliminary studies for achieving transcervical oviduct occlusion by hot water or low pressure steam. *Adv Plann Parent* 12:79-85, 1977

27. MOULDING T, SIROTTA P: Hot water as a tubal occluding agent. *Contraception* 19:433-442, 1979
28. MOULDING T, SIROTTA P: Hot water as a tubal occluding agent: Studies in detail. National Technical Information Service, PB293382
29. MOULDING T, STRAW W, THOMPSON H: The contrast pressure technique for female sterilization. *Contraception* 13:547-557, 1976
30. NEUWIRTH RS, RICHART RM, STEVENSON TC et al: An outpatient approach to female sterilization with methylcyanoacrylate. *Am J Obstet Gynecol* 136:95 1-956, 1980
31. NEUWIRTH RS, RICHART RM, TAYLOR HC: Chemical induction of tubal blockade in the monkey. *Obstet Gynecol* 38:5 1-54, 197 1
32. OMRAN KF, HULKA JF: Tubal occlusion: A comparative study. *Int J Fertil* 15:226, 1970
33. PITKIN RM: Sodium morrhuate for tubal sterilization. *Obstet Gynecol* 28:680, 1966
34. RAKSHIT B: Attempts at chemical blocking of the Fallopian tube for female sterilisation. *J Obstet Gynaecol India* 20:618, 1970
35. REED TP, ERB RA: Hysteroscopic oviductal blocking with formed-in-place silicone rubber plugs: II. Clinical studies. *J Reprod Med* 23:69-72, 1979
36. REED TP, ERB RA: Tubal occlusion with silicone rubber. *J Reprod Med* 25:25-28, 1980
37. REED TP, ERB RA, DEMAEYER J: Tubal occlusion with silicone rubber: An update. Presented at Lankenau Hospital, January 1980
38. Research Group of Tubal Occlusion by Drugs. Sterilization by occlusion of the Fallopian tubes with mucilago phenol: A seven years' clinical observation. *Chin J Obstet Gynecol* 14:79, 1979
39. RICHART RM: Female sterilization using chemical agents. In Zatuchni GI (ed): *Research Frontiers in Fertility Regulation*, vol 1, no 5, December 1981. Chicago, Program for Applied Research of Fertility Regulation
40. RICHART RM, GUTIERREZ-NAJAR AJ, NEUWIRTH RS: Transvaginal human sterilization: A preliminary report. *Am J Obstet Gynecol* 111: 108-110, 197 1
41. RICHART RM, NEUWIRTH RS: Unpublished data
42. RICHART RM, NEUWIRTH RS, BOLDUK L: Single application fertility regulating device: Description of a new instrument. *Am J Obstet Gynecol* 127:86-90, 1977
43. RICHART RM, TAYLOR HC, NEUWIRTH RS: Experimental studies of fallopian tube occlusion. In Richart RM, Prager D (eds): *Human Sterilization*, pp 360-367. Springfield, IL, Charles C Thomas, 1972
44. RINGROSE C: Office tubal sterilization. *Obstet Gynecol* 42: 15 1, 1973
45. SALGADO C: Sterilisation induced by intrauterine caustic injections. *An Brasil Genet*, June 1941
46. SCHENKER JG, POLISHUK JG: Regeneration of rabbit endometrium following intrauterine instillation of chemical agents. *Gynecol Invest* 4:1-13, 1973
47. STEVENSON TC: Methylcyanoacrylate (MCA) for tubal occlusion. In Sciarra JJ, Droegemueller W, Speidel JJ (eds): *Advances in Female Sterilization Techniques*, pp 2 16-224. Hagerstown, MD, Harper & Row, 1976
48. STEVENSON TC, TAYLOR DS: The effect of methylcyanoacrylate tissue adhesive on the human fallopian tube and endometrium. *J Obstet Gynecol* 79: 1028, 1972
49. ZIPPER J, MEDEL M: Human fertility control through the use of endouterine metal antagonisms of trace elements. In *Control of Human Fertility*. Nobel Symposium 15, Stockholm, Almqvist & Wiksell, 1970
50. ZIPPER J, INSUNZA S: Pharmacological agents that potentiate or inhibit the occlusive action of quinacrine in the rabbit tube and rat uterus. In Duncan GW, Falb RD, Speidel JJ (eds): *Female Sterilization: Prognosis for Simplified Outpatient Procedures*, pp 131-149. New York, Academic Press, 1972
51. ZIPPER J, MEDEL M, PASTENE L et al: Intrauterine instillation Of chemical cytotoxic agents for tubal sterilization and treatment of functional metrorrhagias. *Int J Fertil* 14:289, 1969
52. ZIPPER J, MEDEL M, PRAGER R: Alterations in fertility induced by unilateral intrauterine instillation of cytotoxic compounds in rats. *Am J Obstet Gynecol* 10 1:971, 1968
53. ZIPPER J, PRAGER R, MEDEL M: Biological changes induced by unilateral intrauterine instillations of quinacrine in the rat and their reversal by either estrogen or progesterone. *Fertil Steril* 24:48, 1973
54. ZIPPER JA, STACHETTI E, MEDEL M: Human fertility control by transvaginal application of quinacrine on the fallopian tube. *Fertil Steril* 21:581, 1970