Comparative Medicine
Copyright 2018
by the American Association for Laboratory Animal Science

Vol 68, No 2
April 2018
Pages 168–176

Case Study

Retrospective Review of Surgical Outcomes and Pair-housing Success in Vasectomized Rhesus Macaques (*Macaca mulatta)*

Dilrukshi K Ekanayake-Alper,[†] Steven R Wilson, and Jodi A Scholz[*,‡]

Providing social housing for adult male macaques can be challenging. One successful strategy for long-term social housing of adult male macaques is to pair them with adult females; however, unwanted breeding must be prevented by sterilization of the male or female. Vasectomy is a simple, highly effective, and minimally invasive method of contraception that is used at our institution to facilitate social housing. We performed a retrospective review to analyze the surgical outcomes and rate of postoperative complications after vasectomy of adult rhesus macaques at our research facility. In addition, we evaluated the success rate of pairing vasectomized macaques with female partners. Over 10 y, 16 macaques were vasectomized, of which 5 developed postoperative complications such as orchitis, epididymitis, or surgical site infection. These complications resolved completely and without incident after antibiotic and analgesic therapy; an additional male had postoperative incisional swelling that resolved quickly after NSAID treatment. This complication rate is consistent with that in humans by surgeons who perform open vasectomies relatively infrequently. In addition, 5 of the vasectomized macaques (31%) developed sperm granulomas, which are a common and generally benign complication in humans and have been reported to develop in 40% of macaques after vasectomy. Successful pair housing with a female partner was achieved for 13 of 16 (81%) of the vasectomized macaques. We conclude that surgical vasectomy is a safe and simple procedure that can be used as a highly effective method to facilitate social housing of adult male rhesus macaques in research facilities.

The Animal Welfare Act Regulations require institutions to develop an environmental enhancement plan to promote the psychologic wellbeing of NHP, which must include provisions to address the social needs of species that are known to be social in nature.[7] In addition, guidelines for the use of NHP in the laboratory environment emphasize that social interaction is one of the most important factors influencing the physiologic wellbeing of NHP.[37,48] The benefits of social housing macaques used in biomedical research have been extensively studied and reviewed.[13,14,29,30,33,34,56] Socially housed macaques are better able to cope with changes in the laboratory environment, engage in more species-typical behaviors, demonstrate an appropriate balance between aggression and passivity, and demonstrate fewer maladaptive behaviors and signs of chronic distress, compared with singly housed macaques.[29,48]

An extensive survey conducted in 2014 showed that 65% of indoor-housed NHP at research facilities were socially housed; for rhesus macaques specifically, 50% were socially housed.[12] Although these numbers are an improvement compared with the previous survey conducted in 2003,[15] a vast number of rhesus macaques in laboratory animal facilities remain singly housed. A variety of constraints to social housing were cited in the surveys, including cost, availability of housing, time or staff constraints, and interference with research protocols. In addition, both surveys indicated that lack of available compatible partners was a major constraint to pair housing.[12,15] Indeed, formation of isosexual pairs of adult macaques can be quite challenging, as evidenced by the numerous publications and discussions that address risks of social housing and various pair-forming strategies.[1,27,29,33,36,52-55] In particular, adult male macaques are often considered particularly difficult to pair because of their strong dominance-related behavior or aggression.[1,27,50] Although some institutions reliably form and maintain male–male adult pairs,[32,35,52] many struggle with success, and thus alternative strategies for pairing may be of particular value in maximizing social housing.

Consistent with previous reports, at our institution, one of the most successful long-term strategies for pairing adult male NHP is by housing with an adult female;[51,71] however, at least one of the animals must be sterilized to prevent unwanted breeding. A variety of reproductive sterilization options are available for both male and female NHP. In females, ovariectomy and ovariohysterectomy procedures are very effective but are surgically invasive and thus pose a risk of postoperative complications and a prolonged postoperative recovery phase. Hormonal contraception, such as administration of oral, injected, or implanted progestin or estrogen–progestin combination, is a potential noninvasive option for birth control. Many such regimens have been described, and although a full descriptive analysis of effectiveness is unavailable currently, failures (that is, pregnancy, implant removal) have been reported.[9] Another major consideration is that removal of ovaries or the administration of agents altering ovarian hormonal function can induce a state

Received: 24 Feb 2017. Revision requested: 04 Apr 2017. Accepted: 01 Jul 2017.
Department of Comparative Medicine, Yale School of Medicine, New Haven, Connecticut.

[*]Corresponding author. Email: scholz.jodi@mayo.edu

Current affiliations: [†]Columbia Center for Transplant Immunology and Institute of Comparative Medicine, Columbia University Medical Center, New York, New York; and [‡]Department of Comparative Medicine, Mayo Clinic, Rochester, Minnesota.

of osteoporosis. Although bone loss may not occur in NHP to the degree seen in postmenopausal women, it is a potential research variable, and bone integrity may be of particular concern in young females and active animals housed in large, complex enclosures.[38,39,67] Moreover, prolonged use of progestins such as medroxyprogesterone and melengestrol acetate have been associated with complications, including pyometra, reduced glucoregulatory function, and endometrial decidualization.[19,24,28,46,47,72]

Castration of male animals is an option that is routinely practiced in companion and production animal medicine, but it is not commonly performed in research NHP because it can cause marked behavioral and hormonal changes that might skew research data.[60,74] Indeed, the removal of sex organs in either male or female NHP may be undesirable, given the numerous behavioral, physiologic, and metabolic alterations that can occur in response to the presence or removal of sex hormones.[3,11,22,41,43,57,59] Therefore, the use of vasectomy, a method that preserves hormonal function, is an attractive option for the reproductive sterilization of adult male NHP in research facilities.

Vasectomy offers a relatively safe, effective, and permanent method of male contraception. In humans, vasectomy is the most common urologic procedure performed in the United States, with approximately 500,000 procedures performed annually.[17,31] The failure rate due to spontaneous recanalization is low, with reports typically ranging from 0% to 2%.[2,10,26,42,58,62,70] Vasectomy surgeries have been practiced in our research facility for more than 10 y to facilitate social housing of NHP. Here we present our experience with vasectomy in rhesus macaques, focusing on the technical feasibility of the procedure and postsurgical complications. We also discuss the use of this technique to enhance the pair-housing success in our rhesus macaque colony.

Materials and Methods

Animals. Over a 10-y period, potential candidates for vasectomy were identified during our ongoing social housing program evaluation or on request by the laboratory. These candidates were adult male rhesus macaques that had not been successfully housed in an isosexual pair or for whom no conspecifics other than potentially fertile females were available (for example, a younger male or infertile female). All vasectomies were performed specifically for the purpose of social housing.

Included in this report are all 16 male rhesus macaques that underwent vasectomy during this 10-y period. Their ages ranged from 5 y to 21 y at the time of surgery (Table 1). All macaques were enrolled in research protocols approved by the Yale University IACUC.

Husbandry and preventative medicine. Macaques were maintained in an AAALAC -accredited facility by using Animal Biosafety Level 2 practices. Physical exams were performed at least semiannually. Tuberculosis screening was performed through semiannual intradermal testing and annual serologic testing (for example, Primagam [Prionics AG, Schlieren-Zurich, Switzerland], PrimaTB Stat Pak [Chembio Diagnostic Systems, Medford, NY], or multiplex immunoassay [Intuitive Biosciences, Middleton, WI]). Viral screening was performed annually (Bio-Reliance, Rockville, MD, or Intuitive Biosciences, Middleton, WI) for simian retrovirus type D, simian T-cell leukemia virus, measles titer, and *Macacine herpesvirus 1*. Routine CBC and serum chemistries were performed annually. All macaques in this report were free of tuberculosis and were seronegative for simian retrovirus type D and simian T-cell leukemia virus. All animals except one (NHP 9 in Table 1) were seronegative for *Macacine herpesvirus 1*.

Macaques were fed a commercial standard primate diet (Teklad 8714, Envigo, Indianapolis, IN) supplemented daily with fresh fruits and vegetables. In addition, macaques were offered a wide variety of food enrichment (for example, peanuts, dried fruit, and commercially available primate treats) and an assortment of toys and foraging devices for enhancement of psychologic wellbeing. All animals were housed in stainless steel caging, and drinking water (either hyperchlorinated or tap water) was provided through an automatic watering system (Edstrom Industries, Waterford, WI). Room temperature and humidity were maintained at 72 ± 2 °F (22.2 ± 1.1 °C) and 50% ± 10%, respectively.

Anesthesia. All macaques selected for the study received presurgical evaluation on the day of surgery and had unremarkable preoperative CBC and chemistry panels. Macaques were fasted for 12 to 16 h prior to surgery. General anesthesia was established with ketamine (5 to 12 mg/kg IM) and atropine sulfate (and 0.02 to 0.05 mg/kg IM). In addition, 1 macaque received midazolam (1 mg/kg IM), and another received diazepam (1 mg/kg IM) due to previous experience with excessive muscle spasm or seizure activity under ketamine only. A third animal received a combination of ketamine (5.0 mg/kg IM) and dexmedetomidine (0.015 mg/kg IM) due to resistance to ketamine only. All macaques were maintained under general anesthesia with 2% to 3% isoflurane in 100% oxygen after endotracheal intubation by using standard technique.

Surgery. The typical surgical technique was as follows. Macaques were placed in dorsal recumbency, and the area around the ventral midline from the scrotum to the preputial area was clipped and prepared for aseptic surgery (Figure 1 A). In 4 animals, the incision was infiltrated with a solution of bupivacaine hydrochloride (0.25% to 0.5%) with epinephrine (1:200,000) for local anesthesia. Bilateral 2- to 3-cm prescrotal incisions were made over the easily palpable spermatic cord, by using a no. 10 blade (Figure 1 B). A combination of blunt and sharp dissection was used to access the vaginal tunic, which was incised by using sharp scissors or a scalpel. The spermatic cord was exteriorized from the incision by using a curved forceps positioned in a lateral-to-medial motion to visualize the vas deferens, which is generally medial to the testicular artery and pampiniform plexus (Figure 1 C). The vas was then isolated and dissected from the surrounding sheath and vessels by using a combination of sharp and blunt dissection (Figure 1 D and E). A 1- to 1.5-cm segment of vas deferens was excised after placement of a proximal and a distal 3-0 polydioxanone ligature. In 10 macaques, based on the surgeon's preference, the ends of the vas were cauterized by using a disposable thermal cautery pen (Figure 1 F). The vaginal tunic and subcutaneous layers were closed separately by using a simple interrupted or simple continuous suture pattern of an appropriate absorbable suture material, and the skin edges were apposed by using a buried subcuticular suture pattern (Figure 1 B). Histologic examination confirmed successful bilateral removal of the vas deferens in all cases.

Analgesia and postoperative care. Perioperative and postoperative analgesia regimens varied depending on the surgeon's preference. Twelve macaques received perioperative buprenorphine (0.01 to 0.03 mg/kg SC). All 16 macaques received NSAID treatment, either by using meloxicam (0.1 mg/kg SC) or carprofen (4.0 mg/kg SC), for 2 to 4 d to control postoperative pain and inflammation. Anesthetic induction and recovery were uneventful in all macaques. Anesthesia and analgesia regimens for each animal are summarized in Table 1.

Macaques were closely monitored during the postoperative period for signs of pain, such as lethargy, decreased appetite,

Table 1. Anesthesia, analgesia, postoperative complications, and social housing attempts after vasectomy in 16 rhesus macaques

NHP	Age (y)	Anesthesia	Cautery?	Local anesthetic?	Perioperative analgesia	Postoperative analgesia	Complication	Treatment	Outcome	Pairing after vasectomy
1	8	Ketamine–atropine, isoflurane	Yes	No	Buprenorphine Meloxicam	Meloxicam, 2 d	Sperm granuloma		Chronic sperm granuloma	Paired during 2nd attempt
2	12	Ketamine–atropine, isoflurane	No	No	Buprenorphine Meloxicam	Meloxicam, 2 d	Mild incisional swelling; sperm granuloma	Meloxicam	Swelling resolved; chronic sperm granuloma	Paired during 2nd attempt
3	9	Ketamine–atropine, isoflurane	Yes	No	Buprenorphine Meloxicam	Meloxicam, 4 d	Unilateral incisional abscess	Enrofloxacin Amoxicillin Meloxicam	Infection resolved	Paired during 3rd attempt
4	13	Ketamine–atropine, isoflurane	Yes	No	Buprenorphine Meloxicam	Meloxicam, 4 d	None			Paired during 2nd attempt
5	8	Ketamine–atropine, isoflurane	No	No	Meloxicam	Meloxicam, 3 d	Sperm granuloma		Chronic sperm granuloma	2 unsuccessful attempts
6	7	Ketamine–atropine, diazepam, isoflurane	No	No	Meloxicam	Meloxicam, 2 d	None			Paired during 3rd attempt
7	10	Ketamine–atropine, isoflurane	No	Yes	Meloxicam	Meloxicam, 2 d	None			Paired during 1st attempt
8	10	Ketamine–atropine, isoflurane	Yes	No	Buprenorphine Carprofen	Meloxicam, 3 d	None			Paired during 2nd attempt
9	21	Ketamine–atropine, isoflurane	Yes	No	Meloxicam	Meloxicam, 4 d	Testicular abscess	Enrofloxacin Ceftiofur Meloxicam	Infection resolved	Paired during 1st attempt
10	19	Ketamine–atropine, isoflurane	Yes	No	Buprenorphine Carprofen	Meloxicam, 3 d	None			Paired during 2nd attempt
11	13	Ketamine–atropine, midazolam, isoflurane	No	Yes	Buprenorphine Meloxicam	Meloxicam, 3 d	None			Paired during 4th attempt
12	6	Ketamine–atropine, isoflurane	No	Yes	Buprenorphine Meloxicam	Meloxicam, 4 d	None			Paired during 1st attempt
13	6	Ketamine–atropine, isoflurane	Yes	No	Buprenorphine Meloxicam	Meloxicam, 3 d	Bilateral epididymitis–orchitis; sperm granuloma	Ceftiofur Meloxicam Buprenorphine	Infection resolved; Chronic sperm granuloma	Paired during 1st attempt

Table 1. Continued

NHP	Age (y)	Anesthesia	Cautery?	Local anesthetic?	Perioperative analgesia	Postoperative analgesia	Complication	Treatment	Outcome	Pairing after vasectomy
14	7	Ketamine–atropine, isoflurane	Yes	Yes	Buprenorphine Meloxicam	Buprenorphine, 3 d Meloxicam, 1 d	Sperm granuloma		Chronic sperm granuloma	Paired during 1st attempt
15	6	Ketamine–atropine, dexmedetomidine, isoflurane	Yes	No	Buprenorphine Meloxicam	Buprenorphine, 3 d Meloxicam, 1 d	Bilateral epididymitis–orchitis	Enrofloxacin Meloxicam	Infection resolved	1 unsuccessful attempt
16	16	Ketamine–atropine, midazolam, isoflurane	Yes	No	Buprenorphine Meloxicam	Buprenorphine, 3 d Meloxicam, 1 d	Unilateral epididymitis–orchitis	Enrofloxacin Meloxicam	Infection resolved	2 unsuccessful attempts

and manipulation of the surgery area. The incision was closely monitored for evidence of swelling, infection, or dehiscence. After the incisions healed, animals were monitored daily by both the animal care staff and veterinary technical staff, and any abnormalities were reported to a veterinarian for assessment.

Formation of social pairs. Male and female macaques were paired by using a stepwise process, consistent with pairing procedures at the vast majority of facilities participating in the 2014 survey.[12] Prior to full-contact pairing, macaques were housed in adjacent cages that allowed visual access through a mesh panel or clear polycarbonate divider. The duration of the visual access depended on demonstration of affiliative or agonistic behaviors. Animals that demonstrated affiliative behaviors across the divider were paired relatively quickly (for example, the same day), whereas animals that demonstrated aggressive behaviors toward each other were not paired. If no clear affiliative or aggressive behaviors were noted, the macaques remained in adjacent cages for a longer period of time (for example, a few days), and as long as no aggressive behaviors were noted, a pairing attempt was made.

Retrospective review. We retrospectively reviewed all vasectomy surgeries that were performed over a 10-y period in rhesus macaques housed in our facilities (n = 16). For each animal, we reviewed age, anesthetic regimen, surgical technique, peri- and postoperative analgesics, complications and treatments, long-term clinical outcome, social housing attempts, and the success or failure of these attempts.

Results

Postsurgical complications. Complications are summarized by animal in Table 1. None of the vasectomized macaques developed postoperative hematomas, and none showed clinical signs consistent with postvasectomy pain syndrome, both of which are reported as relatively common complications in humans.[2,10,21,58] Six animals required veterinary care during the postoperative period. Macaque 2 developed mild incisional swelling 7 d postoperatively, which was treated and resolved with a single dose of meloxicam (0.1 mg/kg SC). Macaque 3 presented 2 wk after surgery with a swelling of the right vasectomy incision. The swelling was unresponsive to enrofloxacin (5 mg/kg IM) but resolved after a week of amoxicillin (10 mg/kg PO twice daily) and 3 d of meloxicam (0.1 mg/kg SC). Macaque 9 presented 10 d postoperatively for inappetence and bilateral scrotal swelling and erythema. Significant physical exam findings included pyrexia, orchitis, and epididymitis. Ultrasound examination of the area revealed thickened hypervascularized epididymides with a hypoechoic region. A fine-needle aspirate yielded purulent material from the hypoechoic region, and culture and sensitivity of the fluid grew *Staphylococcus aureus* that was sensitive to several antibiotics including enrofloxacin and cephalosporins. Intramuscular enrofloxacin (5 mg/kg once daily) treatment was initiated. A week of antibiotic therapy failed to achieve significant improvement on physical or ultrasound examination; ceftiofur (2.2 mg/kg SC once daily) was initiated, in conjunction with enrofloxacin. After 3 d of therapy, he regained his normal appetite and attitude. The swelling resolved and the incision healed uneventfully. Macaque 13 presented 15 d postoperatively with signs of a local infection and decreased appetite. Physical exam revealed bilateral, firm, enlarged testes that were warm to the touch. Ceftiofur sodium (2.2 mg/kg SC once daily) was administered for 10 d, meloxicam (0.1 mg/kg SC or PO once daily) for 5 d, and buprenorphine (0.005 mg/kg SC) twice on the first day; his condition resolved within a week. Macaque 15 presented 4 wk after surgery for mild preputial edema. Physical examination revealed bilaterally firm testicles that were warm to the touch. A 7-d course of enrofloxacin (5 mg/kg IM) and 3-d course of meloxicam (0.1 mg/kg SC or PO) resulted in a rapid resolution of the condition. Macaque 16 was noted to have a firm, warm testicle unilaterally during routine semiannual physical examination at 3 mo after surgery. The condition resolved after 18 d of enrofloxacin (5 mg/kg IM) and 7 d of meloxicam (0.1 mg/kg SC or PO).

Of the 16 animals undergoing vasectomy surgery, 5 (31%) developed sperm granulomas, all exhibiting a similar pattern of presentation. The granulomas developed within the first month after the surgery. Initially, they appeared as superficial swelling at or near the incision site and subsequently ruptured and drained. Microscopic examination of the exudates revealed spermatozoa along with numerous mononuclear phagocytic cells. The sperm granulomas typically healed spontaneously within 5 to 7 d after their initial appearance. We clinically observed that the granulomas commonly recurred, with a similar course of resolution within a week.

Vasectomized macaques and social housing. To minimize the chance of unwanted pregnancy, vasectomized macaques were given a 60-d rest period after surgery before they were paired with females.[61] All 16 vasectomized macaques underwent pairing attempts. Of these animals, 10 (62.5%) established a successful male–female relationship during the first or second pairing

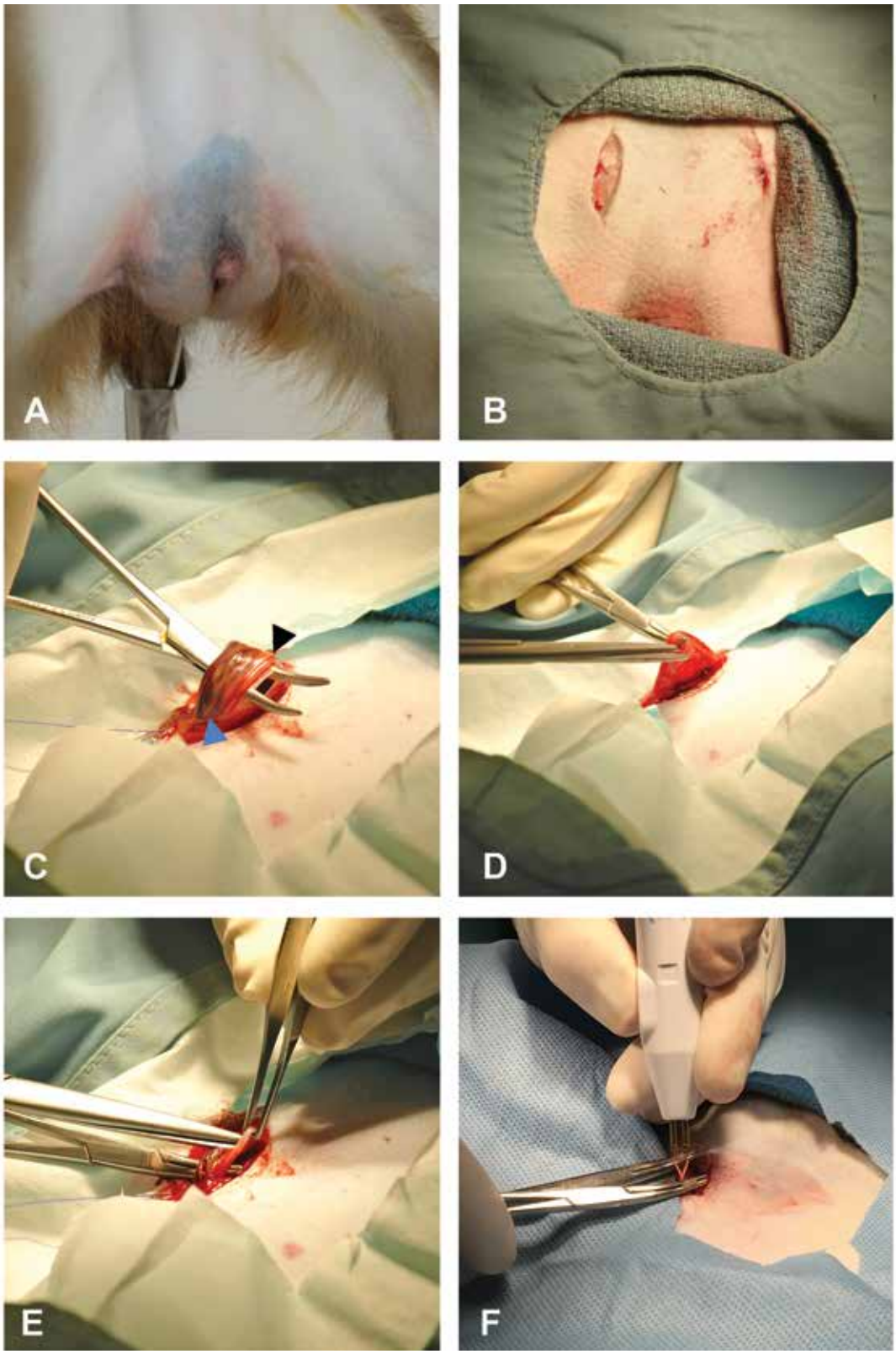

Figure 1. Surgical approach to the vas deferens. (A) The skin is aseptically prepared by shaving and use of appropriate surgical scrub. (B) The area is draped, and a 1- to 2-cm prescrotal incision is made directly over the spermatic cord. Here, the first incision site (left) has been closed by using a buried suture pattern, and the second incision has been made over the right spermatic cord. (C) The tunic (blue arrowhead) is incised, and the spermatic cord is elevated to identify the vas deferens (black arrowhead). (D) The vas deferens is isolated from the pampiniform plexus. (E) A 2- to 3-cm section of vas is isolated from the surrounding sheath and vessels. (F) A disposable electrocautery device is used cauterize the exposed ends of the vas deferens after the excised section is removed.

attempt, and 3 (18.8%) were paired with a female after 3 or 4 attempts. One of the vasectomized macaques (6.2%) was not paired due to severely aggressive behavior. The 2 macaques vasectomized most recently have undergone pairing attempts with 1 (n = 1) or 2 (n = 1) females but have not yet been paired successfully. Although the overall rate of successful pairing attempts was 43.3% (13 of 30 attempts), the overall success of establishing social pairs after vasectomy was 81.3% (13 of 16 males; Table 1).

Discussion

Vasectomy is a relatively safe method of contraception in many species, including NHP. Although not routinely practiced in veterinary medicine, vasectomy is the most common urologic procedure performed in humans.[8,58] It is typically an outpatient surgical procedure, generally performed under local anesthesia in a urology clinic setting.[2,8,58] Anesthesia for vasectomy in humans typically consists of local anesthesia at the site of incision as well as a vasal block using a local anesthetic.[4,8,44,58,66] For some patients, oral sedatives such as diazepam are given as an anxiolytic and for relaxation of scrotal musculature. In rare cases when patients do not tolerate local anesthesia alone or when the vas is difficult to isolate, intravenous sedation or general anesthesia is administered.[4,8,58] However, in NHP, general anesthesia is essential for the prevention of injuries to the veterinary staff and to reduce the stress of the animals.

The vasectomy surgical techniques currently used in humans vary widely. A systematic literature review performed by a panel of the American Urological Association on the topic of vasectomy resulted in a comprehensive set of guidelines that were published in 2012[64] and updated in 2015.[65] These guidelines describe the current accepted practice for performing vasectomies, which involves a minimally invasive technique. The 'no-scalpel' technique, originally developed in China in 1974 and described in detail in 1991,[45] involves the use of specialized surgical instruments and techniques to isolate, divide, and occlude the vas transcutaneously.[66] Briefly, a clamp is used to isolate the vas, the skin is pierced and retracted by using a vas dissector to make a small opening, and the vas is then elevated above the skin opening for division and occlusion.[45,65] Other minimally invasive techniques are also acceptable in humans, provided that the incision is shorter than 10 mm and that only minimal dissection of the vas and perivasal tissues is performed by using specific specialized instruments.[65] This technique has significantly reduced the operative time and postoperative complications compared with other conventional methods.[2,8,25,42,58]

After isolation, the vas deferens is resected, with or without excision of a section of vas. If excision is performed, the optimal length to excise in humans has not yet been determined; removal of larger sections may reduce the chances of recanalization but also results in increased tissue dissection. Common practice is to remove a 1-cm section.[8,58] In human medicine, submitting the resected vas for histologic evaluation is sometimes performed but is not considered necessary, because success is determined by postvasectomy semen analysis. Given that we do not perform this analysis for NHP in our facility, our standard practice is to remove an approximately 1 cm section of vas followed by histologic tissue confirmation.

The several methods of vas occlusion include suture ligation, use of surgical clips, fascial interposition, intraluminal cautery, and a combination of these techniques.[8,42,58,65] Cautery is accomplished through the use of electrical or thermal pulses applied intraluminally to seal the ends of the vas, with the intent to destroy only the mucous layer.[58] If cautery alone is used for vas occlusion, both the abdominal and testicular ends of the vas should be cauterized; when combined with fascial interposition, cauterizing just the abdominal end of the vas is acceptable.[18,49,58,65] Fascial interposition, a method in which a layer of the vas sheath is placed between the 2 cut ends of the vas, is an increasingly widespread vasectomy technique and is used to physically separate the ends of the vas to reduce the chances of recanalization.[58,69] When fascial interposition is used, it is combined with other methods.[58,64,69] Ligation with surgical clips or suture is another common method for vas occlusion, although recent studies have shown that failure rates are reduced when ligation is combined with another method, such as fascial interposition or cautery.[58,68,69] In the macaques we describe here, we used the conventional surgical method for all animals (bilateral incision, ligation, and removal of at least 1 cm of the vas), with cautery occlusion of the vas in the majority of cases.

The most common complications seen in humans undergoing vasectomy include hematoma, infection, failure of sterilization, sperm granuloma, acute postoperative pain, and chronic pain syndrome.[2,10,58] Hematoma formation is a common complication and is the primary cause for hospitalization after vasectomy.[2,40] The incidence of hematoma formation is approximately 2% but reportedly ranges up to 29%, with complication rates correlating with the experience of the surgeon.[10,40] We did not note postoperative hematoma formation in any of our vasectomized macaques.

The prevalence of surgical site infection after vasectomy in humans is approximately 3.5%, with reports ranging up to 38%.[10,49,50] The use of the no-scalpel technique is thought to be a major cause for recent reductions in infection rates.[2] Because of the low rate of infection after minimally invasive techniques, the use of prophylactic antibiotics is not indicated unless the patient is considered high-risk for the development of infection.[65] Five macaques in our report developed postoperative infections: 3 developed postsurgical epididymitis–orchitis; one had a testicular abscess; and the remaining macaque developed an incisional infection. All cases resolved after appropriate antibiotic therapy. The reason for the high incidence of postoperative complications in our NHP relative to humans may be due to several factors. In humans, the incision or access site is much smaller; in contrast, we used a traditional approach with bilateral incisions in our macaques, similar to what has been previously described.[5,16,35,63,73] This approach is technically easier for a surgeon who doesn't perform these procedures on a routine basis. Similarly, compared with some human physicians who typically perform this procedure frequently (that is, more than 50 times annually),[40] we perform this procedure on average once or twice each year. Therefore surgical time and tissue dissection is likely increased compared with a physician who performs this technique on a daily or weekly basis. Indeed, complication rates (including infections) are higher in humans when the surgeon is less experienced or performs relatively few vasectomies each year.[10,40] In addition, because our facility is a teaching institution, these surgeries are typically performed by a laboratory animal medicine resident in training under the supervision of a more experienced veterinarian. The instructional nature of the procedure typically adds to surgery time and potentially the degree of tissue dissection. Furthermore, unlike humans, who can comply with orders to rest and keep the incision clean and dry, activity and cleanliness are difficult to control in NHP. Cage size can be limited during the initial postoperative period, but the animal can still move around within the enclosure and is unlikely to rest as a human would. Lastly, NHP are notorious for picking at their incisions, potentially exposing the incision site to trauma

and bacterial contamination, which may contribute to secondary infection or incisional dehiscence. Providing vasectomized NHP with perioperative antibiotics is certainly an option to be considered, but this practice must be balanced with the goal of judicious use of antibiotics to prevent bacterial resistance.

Sperm granuloma was another common complication that occurred in 5 of our 16 vasectomized macaques. Sperm granulomas (that is, inflammatory reactions that occur in response to sperm leakage at the vasectomy site, epididymis, or rete testis) and microscopic granulomas have been reported to occur in 10% to 30% of human cases.[2,10] Granulomas may be microscopic or may result in a vasocutaneous fistula that periodically drains. In rhesus and cynomolgous macaques, the formation of vasocutaneous fistulas occurred in 40% of cases postvasectomy.[6] The rate of sperm granuloma formation in our macaques, as evidenced by the presence of vasocutaneous fistulae, was 31%. We have seen no evidence of pain, infection, or irritation associated with the granulomas, and we therefore consider them to be a benign complication.

Vasectomy traditionally has an overall failure rate of 1% to 2% in humans.[2,10,58,65] Failure can occur due to unprotected intercourse prior to confirmation of azoospermia or from recanalization. In humans, azoospermia is confirmed by performing sperm analysis, typically 8 to 16 wk postvasectomy.[65] Although collection of sperm via electroejaculation is an option in NHP, we have opted to use a combination of histologic confirmation of vas removal and a postvasectomy resting period of at least 60 d[61] to provide reasonable assurance of sterilization. Although our case numbers are relatively small at this point, there have been no failures as evidenced by unplanned pregnancies in our vasectomy program.

In some settings, the relative permanence of vasectomy may be considered a disadvantage (for example, zoos, research institutions with breeding colonies). Vasectomy reversal is an option that is performed in humans but is a microsurgical procedure that is technically demanding.[20] Reversible contraceptive methods may be on the horizon, such as intravas injection of polymers, but these products are not yet available on the market.[23] Therefore, at this point, vasectomy should generally be considered a permanent form of contraception.

All vasectomy surgeries in our macaque colony were performed to facilitate social housing, particularly with the goal of maximizing social housing for adult males. Although creating adult male–male macaque pairs has been successful in the past, our success rate is much higher in creating male–female pairs. This pattern is consistent with previous literature describing the relatively high success rate of forming male–female pairs in macaques.[51,71] In the males we report here, we observed an overall 81% success rate of pairing with females. A 2003 report noted a similar high rate of pairing success postvasectomy.[73] In that report, rhesus macaques were vasectomized to facilitate pairing with the goal of reducing self-injurious behavior in the males; all 6 vasectomized macaques were successfully housed with females on initial pairing for at least 1 mo.[73]

It is important to acknowledge that our report provides surgical technique details and outcomes at a single institution. The literature regarding vasectomy in NHP is relatively sparse, and no information regarding an established standard for surgical technique or an expected rate of complications is available currently. Future possible directions for follow-up to our report include prospective studies on various techniques (for example, effect of occlusion methods on the rate of postoperative complications) and international surveys of research and zoo facilities that perform vasectomies in NHP to gather information on common techniques and expected surgical outcomes. Other factors that would be useful to investigate include recovery time, best practices for postoperative care, duration of time before return to research performance, and postvasectomy behavioral changes that might affect research.

In conclusion, vasectomy of NHP can be a highly effective method for the creation of male–female pairs to maximize social housing options. We feel that the benefits of maximizing social housing for NHP far outweigh the risk of postoperative complications due to vasectomy. Moreover, these complications are generally minor and can be managed effectively. Therefore, vasectomy can be a valuable tool in an institution's social housing and enrichment plan.

Acknowledgments

We thank Drs Caroline Zeiss and Carmen Booth for histopathologic confirmation of excised vas deferens segments, Dr Pete Smith for image contributions, and Ms Molly Tarleton for providing pair-housing information. We also thank previous and current faculty and residents of the Yale Department of Comparative Medicine for providing surgical and perioperative care to the macaques described in this report.

References

1. **Abney DM, Weed JL.** 2006. Methods for successfully pair housing adult male rhesus macaques (*Macaca mulatta*). Am J Primatol **68 Suppl 1:**59. [(Abstract)].
2. **Adams CE, Wald M.** 2009. Risks and complications of vasectomy. Urol Clin North Am **36:**331–336.
3. **Adams MR, Kaplan JR, Manuck SB, Koritnik DR, Parks JS, Wolfe MS, Clarkson TB.** 1990. Inhibition of coronary artery atherosclerosis by 17β-estradiol in ovariectomized monkeys. Lack of an effect of added progesterone. Arteriosclerosis **10:**1051–1057.
4. **Aggarwal H, Chiou RK, Siref LE, Sloan SE.** 2009. Comparative analysis of pain during anesthesia and no-scalpel vasectomy procedure among 3 different local anesthetic techniques. Urology **74:**77–81.
5. **Alexander NJ.** 1977. Vasectomy and vasovasostomy in rhesus monkeys: the effect of circulating antisperm antibodies on fertility. Fertil Steril **28:**562–569.
6. **Alexander NJ.** 1981. Primates: their use in research on vasectomy. Am J Primatol **1:**167–173.
7. **Animal Welfare Regulations.** 2013. 9 CFR § 3.81.
8. **Art KS, Nangia AK.** 2009. Techniques of vasectomy. Urol Clin North Am **36:**307–316.
9. **Asa CS, Porton IJ, editors.** 2005. Wildlife contraception: issues, methods, and applications. Baltimore (MD): Johns Hopkins University Press.
10. **Awsare NS, Krishnan J, Boustead GB, Hanbury DC, McNicholas TA.** 2005. Complications of vasectomy. Ann R Coll Surg Engl **87:**406–410.
11. **Baker DG, Lipman NS.** 2015. Factors that can influence animal research, p 1441–1495. In: Fox JG, Anderson LC, Otto G, Pritchett-Corning KR, Whary MT, editors. Laboratory animal medicine. New York (NY): Academic Press.
12. **Baker KC.** 2016. Survey of 2014 behavioral management programs for laboratory primates in the United States. Am J Primatol **78:**780–796.
13. **Baker KC, Bloomsmith MA, Oettinger B, Neu K, Griffis C, Schoof V, Maloney M.** 2012. Benefits of pair housing are consistent across a diverse population of rhesus macaques. Appl Anim Behav Sci **137:**148–156.
14. **Baker KC, Bloomsmith MA, Oettinger B, Neu K, Griffis C, Schoof VAM.** 2013. Comparing options for pair housing rhesus macaques using behavioral welfare measures. Am J Primatol **76:** 30–42.
15. **Baker KC, Weed JL, Crockett CM, Bloomsmith MA.** 2007. Survey of environmental enhancement programs for laboratory primates. Am J Primatol **69:**377–394.

16. **Bansal N, Majumdar S, Ganguly NK, Chakravarti RN.** 1986. Long term effects of vasectomy on experimental atherosclerosis in rhesus monkeys. Aust J Exp Biol Med Sci **64:**527–533.
17. **Barone MA, Hutchinson PL, Johnson CH, Hsia J, Wheeler J.** 2006. Vasectomy in the United States, 2002. J Urol **176:**232–236.
18. **Barone MA, Irsula B, Chen-Mok M, Sokal DC, Investigator study group.** 2004. Effectiveness of vasectomy using cautery. BMC Urol **4:**1–9.
19. **Beck AP, Erdelyi I, Zeiss CJ.** 2014. Endometrial decidualization and deciduosis in aged rhesus macaques (*Macaca mulatta*). Comp Med **64:**148–156.
20. **Bernie AM, Osterberg EC, Stahl PJ, Ramasamy R, Goldstein M.** 2012. Vasectomy reversal in humans. Spermatogenesis **2:**273–278.
21. **Christiansen CG, Sandlow JI.** 2003. Testicular pain following vasectomy: a review of postvasectomy pain syndrome. J Androl **24:**293–298.
22. **Clark AS, Goldman-Rakic PS.** 1989. Gonadal hormones influence the emergence of cortical function in nonhuman primates. Behav Neurosci **103:**1287–1295.
23. **Colagross-Schouten A, Lemoy MJ, Keesler RI, Lissner E, Vande-Voort CA.** 2017. The contraceptive efficacy of intravas injection of Vasalgel for adult male rhesus monkeys. Basic Clin Androl **27:**1–7.
24. **Connolly MA, Trentalange M, Zeiss CJ.** 2016. Long-term clinical outcomes in diabetic rhesus macaques (*Macaca mulatta*) treated with medroxyprogesterone acetate for endometriosis. Comp Med **66:**343–348.
25. **Cook LA, Pun A, Gallo MF, Lopez LM, Van Vliet HA.** 2014. Scalpel versus no-scalpel incision for vasectomy. Cochrane Database Syst Rev **3:**CD004112.
26. **Cook LA, Van Vliet HA, Lopez LM, Pun A, Gallo MF.** 2014. Vasectomy occlusion techniques for male sterilization. Cochrane Database Syst Rev **3:**CD003991.
27. **Crockett CM, Bowers CL, Bowden DM, Sackett GP.** 1994. Sex differences in compatibility of pair-housed adult longtailed macaques. Am J Primatol **32:**73–94.
28. **Cruzen CL, Baum ST, Colman RJ.** 2011. Glucoregulatory function in adult rhesus macaques (*Macaca mulatta*) undergoing treatment with medroxyprogesterone acetate for endometriosis. J Am Assoc Lab Anim Sci **50:**921–925.
29. **DiVincenti L Jr, Wyatt JD.** 2011. Pair housing of macaques in research facilities: a science-based review of benefits and risks. J Am Assoc Lab Anim Sci **50:**856–863.
30. **Eaton GG, Kelley ST, Axthelm MK, Iliff-Sizemore SA, Shiigi SM.** 1994. Psychological wellbeing in paired adult female rhesus (*Macaca mulatta*). Am J Primatol **33:**89–99.
31. **Eisenberg ML, Lipshultz LI.** 2010. Estimating the number of vasectomies performed annually in the United States: data from the National Survey of Family Growth. J Urol **184:**2068–2072.
32. **Gilbert MH, Baker KC.** 2010. Social buffering in adult male rhesus macaques (*Macaca mulatta*): effects of stressful events in single vs pair housing. J Med Primatol **40:**71–78.
33. **Goosen C, Van der Gulden W, Rozemond H, Balner H, Bertens A, Boot R, Brinkert J, Dienske H, Janssen G, Lammerss A, Timmermans P.** 1984. Recommendations for the housing of macaque monkeys. Lab Anim **18:**99–102.
34. **Hannibal DL, Bliss-Moreau E, Vandeleest J, McCowan B, Capitanio J.** 2016. Laboratory rhesus macaque social housing and social changes: implications for research. Am J Primatol **79:**1–14.
35. **Harrison RM, Domingue GJ, Heidger PM Jr, Roberts JA, Schlegel JU.** 1977. Vasectomy in rhesus monkeys. I. Surgical techniques and gross observations. Urology **9:**639–644.
36. **Hartner M, Hall J, Penderghest J, Clark LP.** 2001. Group-housing subadult male cynomolgus macaques in a pharmaceutical environment. Lab Anim (NY) **30:**53–57.
37. **Institute for Laboratory Animal Research.** 2011. Guide for the care and use of laboratory animals, 8th ed. Washington (DC): National Academies Press.
38. **Jerome CP, Peterson PE.** 2001. Nonhuman primate models in skeletal research. Bone **29:**1–6.
39. **Jerome CP, Turner CH, Lees CJ.** 1997. Decreased bone mass and strength in ovariectomized cynomolgus monkeys (*Macaca fascicularis*). Calcif Tissue Int **60:**265–270.
40. **Kendrick JS, Gonzales B, Huber DH, Grubb GS, Rubin GL.** 1987. Complications of vasectomies in the United States. J Fam Pract **25:**245–248.
41. **Kessler MJ, Wang Q, Cerroni AM, Grynpas MD, Gonzalez Velez OD, Rawlins RG, Ethun KF, Wimsatt JH, Kensler TB, Pritzker KP.** 2015. Long-term effects of castration on the skeleton of male rhesus monkeys (*Macaca mulatta*). Am J Primatol **78:** 152–166.
42. **Labrecque M, Dufresne C, Barone MA, St-Hilaire K.** 2004. Vasectomy surgical techniques: a systematic review. BMC Med **2:**1–12.
43. **Lacreuse A.** 2006. Effects of ovarian hormones on cognitive function in nonhuman primates. Neuroscience **138:**859–867.
44. **Li PS, Li SQ, Schlegel PN, Goldstein M.** 1992. External spermatic sheath injection for vasal nerve block. Urology **39:**173–176.
45. **Li SQ, Goldstein M, Zhu J, Huber D.** 1991. The no-scalpel vasectomy. J Urol **145:**341–344.
46. **McCarthy TJ, Beluhan FZ, Bardawil WA, Bennett BT.** 1989. Pyometra in a rhesus monkey secondary to prolonged therapy with medroxyprogesterone acetate. Lab Anim Sci **39:**71–72.
47. **Murnane RD, Zdziarski JM, Walsh TF, Kinsel MJ, Meehan TP, Kovarik P, Briggs M, Raverty SA, Phillips LG.** 1996. Melengestrol acetate-induced exuberant endometrial decidualization in Goeldi's marmosets (*Callimico goeldii*) and squirrel monkeys (*Saimiri sciureus*). J Zoo Wildl Med **27:**315–324.
48. **National Research Council.** 1998. The psychological wellbeing of nonhuman primates. Washington (DC): National Academies Press.
49. **Philp T, Guillebaud J, Budd D.** 1984. Complications of vasectomy: review of 16,000 patients. Br J Urol **56:**745–748.
50. **Randall PE, Ganguli L, Marcuson RW.** 1983. Wound infection following vasectomy. Br J Urol **55:**564–567.
51. **Rehrig A, DiVincenti L Jr, Schery LA.** 2014. Social housing of nonhuman primates in a research facility: socialisation across macaque species and sexes. Anim Welf **23:**387–389.
52. **Reinhardt V.** 1989. Behavioral responses of unrelated adult male rhesus monkeys familiarized and paired for the purpose of environmental enrichment. Am J Primatol **17:**243–248.
53. **Reinhardt V.** 1994. Pair-housing rather than single-housing for laboratory rhesus macaques. J Med Primatol **23:**426–431.
54. **Reinhardt V.** 1994. Safe pair formation technique for previously single-caged rhesus macaques. Washington (DC): Animal Welfare Institute.
55. **Reinhardt V.** 1995. Arguments for single-caging of rhesus macaques: are they justified? Animal Welfare Information Center newsletter **6:**1–8.
56. **Reinhardt V, Reinhardt A.** 2000. Social enhancement for adult nonhuman primates in research laboratories: a review. Lab Anim **29:**34–41.
57. **Rettberg JR, Yao J, Brinton RD.** 2014. Estrogen: a master regulator of bioenergetic systems in the brain and body. Front Neuroendocrinol **35:**8–30.
58. **Rogers MD, Kolettis PN.** 2013. Vasectomy. Urol Clin North Am **40:**559–568.
59. **Roselli CE, Resko JA.** 2001. Cytochrome P450 aromatase (CYP19) in the nonhuman primate brain: distribution, regulation, and functional significance. J Steroid Biochem Mol Biol **79:**247–253.
60. **Schenck PE, Slob AK.** 1986. Castration, sex steroids, and heterosexual behavior in adult male laboratory-housed stumptailed macaques (*Macaca arctoides*). Horm Behav **20:**336–353.
61. **Schexnider JM, Baker DG, Hasselschwert DL.** 2007. Semen evaluation for verification of azoospermia after vasectomy in chimpanzees (*Pan troglodytes*). J Am Assoc Lab Anim Sci **46:**46–49.
62. **Schwingl PJ, Guess HA.** 2000. Safety and effectiveness of vasectomy. Fertil Steril **73:**923–936.
63. **Seppan P, Krishnaswamy K.** 2014. Long-term study of vasectomy in *Macaca radiata*—histological and ultrasonographic analysis of testis and duct system. Syst Biol Reprod Med **60:**151–160.
64. **Sharlip ID, Belker AM, Honig S, Labrecque M, Marmar JL, Ross LS, Sandlow JI, Sokal DC, American Urological Association.** 2012. Vasectomy: AUA guideline. J Urol **188:**2482–2491.
65. **Sharlip ID, Belker AM, Honig S, Labrecque M, Marmar JL, Ross LS, Sandlow JI, Sokal DC, American Urological Association.** 2015. Vasectomy: AUA guideline, amended.[Cited 21 February

2018]. Available at: www.auanet.org/guidelines/vasectomy-(2012-amended-2015).

66. **Shih G, Njoya M, Lessard M, Labrecque M.** 2010. Minimizing pain during vasectomy: the mini-needle anesthetic technique. J Urol **183:**1959–1963.
67. **Smith SY, Jolette J, Turner CH.** 2009. Skeletal health: primate model of postmenopausal osteoporosis. Am J Primatol **71:** 752–765.
68. **Sokal D, Irsula B, Chen-Mok M, Labrecque M, Barone MA.** 2004. A comparison of vas occlusion techniques: cautery more effective than ligation and excision with fascial interposition. BMC Urol **4:**1–8.
69. **Sokal D, Irsula B, Hays M, Chen-Mok M, Barone MA, Investigator Study Group.** 2004. Vasectomy by ligation and excision, with or without fascial interposition: a randomized controlled trial. [[ISRCTN77781689]] BMC Med **2:**1–11.
70. **Sokal DC, Labrecque M.** 2009. Effectiveness of vasectomy techniques. Urol Clin North Am **36:**317–329.
71. **Truelove MA, Martin AL, Perlman JE, Wood JS, Bloomsmith MA.** 2015. Pair housing of macaques: a review of partner selection, introduction techniques, monitoring for compatibility, and methods for long-term maintenance of pairs. Am J Primatol **79:**1–15.
72. **Usborne AL, Bolton IB, Slukvin I.** 2002. Stromal decidualization of endometriosis in the rhesus macaque (*Macaca mulatta*): a case report. Comp Med **52:**167–170.
73. **Weed JL, Wagner PO, Byrum R, Parrish S, Knezevich M, Powell DA.** 2003. Treatment of persistent self-injurious behavior in rhesus monkeys through socialization: a preliminary report. Contemp Top Lab Anim Sci **42:**21–23.
74. **Wilson AP, Vessey SH.** 1968. Behavior of free-ranging castrated rhesus monkeys. Folia Primatol (Basel) **9:**1–14.