VASECTOMY AND VASECTOMY REVERSAL

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On Sunday, March 28, 1976, the world's 4 billionth human being was born. In 1960 the world population was 3 billion; in 1850 it was only 1 billion.[1] Two thousand years ago the population of the world would require about 16 centuries to double, and yet today it is estimated to require only 30 years.[2] This staggering reality has created an urgent need for urologists and gynecologists to understand the effects of sterilization procedures and to be fully informed in their reversibility. It is generally conceded that vasectomy would be a much more appealing method of birth control if reasonable assurance of reversibility could be provided. As it is, vasectomy is one of the most popular operations performed in the United States today, yet there is a great deal of controversy about its effects. The clarification of this controversy will be of great assistance to world population planning and will be of great importance to the urologist who is confronted daily with the need doee sible approach toward vasectomy.

There are two major aspects of this problem. The first concerns techniques for obtaining a reliable reanastomosis of the vas deferens. With modern microsurgery, accurate reanastomosis of the vas deferens should be achievable in almost every case. Although stricture formation will occur, even this can possibly be overcome with a reoperation. These surgical techniques will be described in great detail, so that at least the anatomical barrier to reversibility can be bridged.

The second aspect of the problem relates to the effects of vasectomy itself on the male reproductive system which may make recovery of fertility impossible despite an accurate microscopic anastomosis. It is very clear that, despite

the most elegant microsurgical technique for reanastomosis, many patients still do not recover fertility; it must be assumed, therefore, that some kind of permanent damage occurs as a result of vasectomy. If these factors can be pinpointed then we could have an approach toward vasectomy that might make it potentially more reversible.

It would seem that interpreting the physiologic and pathologic effects of vasectomy would be a relatively simple and trivial matter. Yet the incredible array of contradictory findings in the literature on this subject makes such interpretation rather difficult. During the last 2 years of clinical investigation, we have come closer to understanding the factors which make recovery of fertility more likely after successful vas reanastomosis. This communication presents our own findings and correlates them with the literature on the effects of vasectomy. Although more work needs to be done, we are beginning to emerge from the confusion with a concept toward vasectomy that may avert some of the pathologic consequences that prevent some patients from regaining fertility despite an accurate vasovasostomy.

SPONTANEOUS RECANALIZATION

The most frustrating aspect of vasectomy reversal is that occasionally the two ends of the vas deferens reunite spontaneously without any effort on the part of the surgeon, and some patients may become again fertile. It appears to be Nature's way of mocking us, since we seem to have such difficulty in accomplishing the same end intentionally.[3, 4] With standard ligature techniques of vasectomy there is about a 1% risk that recanalization will occur. Recanalization may take place even after a section of the vas deferens is removed, the lumen is co-

agulated with diathermy, and the ends are ligated with silk after being turned back.[5] However, if the cautery technique alone is employed, it appears that recanalization is much less likely.[6]

Understanding the mechanism for a spontaneous reanastomosis is very important in explaining some of the poor results with conventional vasovasostomy techniques (i.e., no pregnancy despite the presence of sperm in the ejaculate). After vasectomy there is a buildup of pressure on the testicular side of the vas ligature; as the cuff of the vas deferens distal to the ligature necroses, there is a blowout and leakage of sperm. Sperm leak into the tissue between the two ends of the vas deferens and form a granuloma with multiple, interanastomosing, fistulous channels. Usually this granuloma scars down to the extent that there is no communication at all with the other side of the vas deferens, but occasionally a communication opens to the other side and sperm can meander through this incredible maze of interanastomosing channels to reach the other side; 1% of the time this communication will stay open and allow the patient to be fertile.

The majority of times this connection will not be adequate to allow proper passage of sperm, and the patient will be oligospermic with mostly nonmotile sperm. Eventually the granuloma will usually scar down completely so that the patient becomes aspermic again. Indeed, if one were simply to divide the vas deferens and put a single silk suture through both ends and tie it down to keep the ends in close proximity, it is very likely that some sperm would be recovered in the ejaculate. However, in most instances, patients would soon become infertile with poor sperm counts. Because of this earthworm-like capacity of the spermatazoa to grind their way through to the other side, it is extraordinarily easy to obtain sperm in the ejaculate after a vasovasostomy with almost any sort of technique. However, the incidence of fertility is likely to be low unless an adequate channel exists for proper passage of sperm.

Schmidt's cautery technique[6] essentially eliminates this concern of recanalization after vasectomy by sealing the vas so tightly that sperm leakage cannot occur and thus a sperm granuloma cannot form. There is a great deal of disagreement in various vasectomy series over the incidence and effect of a sperm granuloma. In this author's experience with vasovasostomy, over 30% of vasectomies are associated with

a sperm granuloma. It is rare that such a granuloma would be a source of discomfort to the patient. Indeed, for reasons which are discussed later, it appears that testicular discomfort after vasectomy is, if anything, more likely in patients who do not have sperm granuloma.

CONVENTIONAL APPROACHES TO VASECTOMY REVERSAL

The crudest attempt at reversing the effects of vasectomy was accomplished by Adler and Makris,[7] who actually took a portion of a vasectomized husband's testis, ground it up, and used it for artificially inseminating the patient's wife at ovulation time. A success was actually claimed with this technique, but apparently the authors were unable to convince any other patients to go along with this approach. This case is quite incredible since the sperm were unable to travel through the epididymis or go through the usual necessary maturation.

Most of the techniques for reanastomosis of the vas have involved the placement of a splint of either nylon or polyethylene tubing into the two ends of the vas deferens and suturing the muscularis together with three to eight stitches of 4-0 to 7-0 suture material. This kind of approach is generally crude and leads to sperm leakage, a sperm granuloma, and an inaccurate reconnection of the inner lumen of the vas.[8-15]

Of all of the series with conventional methodology reported to date, Phadke and Phadke[15] have had the best results, with an 83% incidence of sperm in the ejaculate and a 55% pregnancy rate. They noted that pregnancy tended to correlate with the quality and quantity of the sperm count and not with the sperm antibody titer. The majority of the patients in their study had had their vasectomies performed within 5 years of the reversal operation and most of them had sperm granulomas at the vasectomy site. The technique of Phadke and Phadke[15] was rather simple and the significance of their patient population in determining their high success rate was not apparent until very recently, and is discussed later in this article. Basically, most conventional techniques have yielded a 30% to 85% incidence of sperm in the ejaculate, with a 5% to 25% incidence of pregnancy.[16] However, from this vast literature, no solid information is available regarding the type of original vasectomy performed, the actual sperm counts at various intervals postvasovasostomy, or any characteristics of the patient that might have been

correlated later with good or bad results. Thus, it is impossible to figure easily from this array of poor results which factors would make success most likely.

Because of the awareness that most conventional surgical techniques for reanastomosis were inevitably crude, an effort was made toward developing reversible intravasal occlusive devices which could be used in the closed position when the patient wished to be infertile and in the open position when he wished to become fertile again.[17] The size of the inner diameter of these occlusive devices, or valves, was important in determining the quality and quantity of sperm in the ejaculate. When the inner diameter was too small it appeared to be inadequate for the normal passage of sperm.[17] These devices have caused many problems with plugging and leakage but have provided us with some interesting experimental data that document the importance of an adequate channel at the anastomotic site. The likelihood of requiring a good, relatively unstrictured, anastomosis was apparent also from the work of Freund and Davis,[18] who demonstrated that 60% to 70% of spermatozoa in the ejaculate come from the epididymis at the time of intercourse and do not slowly meander through the vas between ejaculations.

MICROSCOPIC TECHNIQUES

The advantage of using a microscope for anastomosis of the vas deferens was demonstrated in animals by several investigators, but only recently has an extremely reliable technique been available for clinical use.[19-22] Initial animal studies involved a one-layer anastomosis with a small number of ultrafine sutures. This approach seemed to work well in animals having no interval of time between vasectomy and vasectomy reversal, so that no damage had occurred to the epididymis or the testis (because of back pressure). In addition, no dilatation of the proximal side of the vas deferens had occurred, making a one-layer operation easier to perform with good mucosal approximation (and making a fertile result more likely even in the face of a less than adequate technical result). For the best mucosal approximation in the human situation where lumina are of different diameters, a two-layer approach is preferred by this author.

The details of the microscopic technique used in a series of 400 patients, which appears to provide as satisfactory an anastomosis as is presently possible, are discussed below. The success rates and our views on which factors other than a technically accurate reanastomosis influence the recovery of fertility are then discussed in detail.

Microscopic Two-Layer Anastomosis of the Vas Deferens (Figs. 1 to 3). Many of the details of this technique have been previously reported.[21-30] The anastomosis is performed under ×16 to ×25 magnification. The assistant grasps the anterior wall of the abdominal-side end of the vas deferens and the surgeon inserts his jeweler's forceps into the tiny opening and allows the forceps to open it. He then places the first mucosal suture anteriorly, making sure that the suture includes the elastic layer directly next to the mucosa. The suture is pulled through separately and then placed into the mucosa of the testicular-side lumen. It is then pulled through to near its end, an instrument tie is performed, and the suture is cut.

At this point visualization of the lumen may be difficult, so the assistant grasps the wall of the vas deferens again, only this time rotating it toward him. This procedure allows visualization of the inner mucosal lining, and again the surgeon inserts his jeweler's forceps into the lumen and places the next anterior suture adjoining the first one. After the first three mucosal sutures are placed anteriorly in such a fashion, the entire clamp is flipped around 180° and what was the posterior wall of the vas deferens is now visualized in the anterior position.

At this point one can easily view the anterior row of sutures from the inside to determine whether perfect mucosal alignment has been achieved. If extremely accurate mucosa-to-mucosa approximation has not been achieved, it is wise to
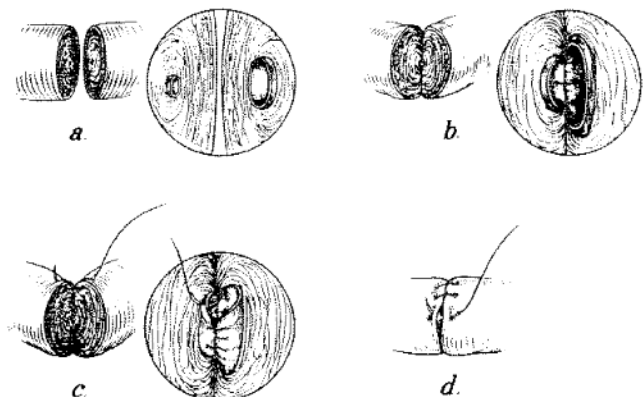

FIG. 1. Diagram of the steps in two-layer microscopic anastomosis of the vas deferens with 9-0 nylon suture. (Reprinted from reference 21.)
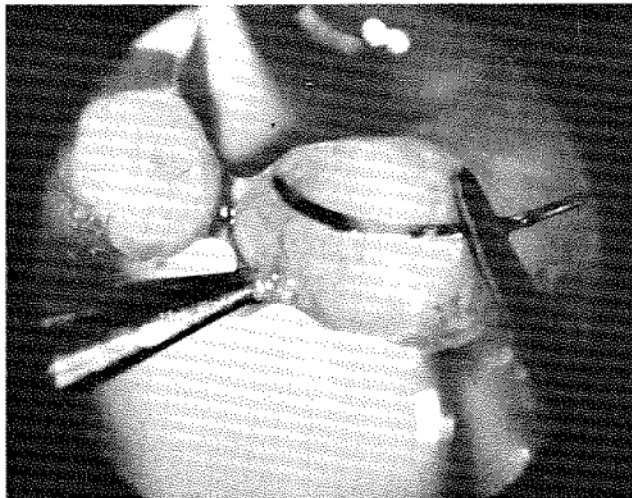
Fig. 2. The first mucosal stitch is placed.

replace the stitch. Unequal size lumina need to be matched, and if the sutures are properly spaced, it is possible to match the shrunken mucosa of the distal side with the dilated opening of the testicular side. The small lumen readily dilates to the diameter of the larger lumen. Thus, the sixth or seventh mucosal sutures usually close a tiny gap. There should be no tearing or inaccuracy in the lineup of these mucosal margins. When this is completed, a watertight and leakproof connection of the inner canal of the vas deferens should have been achieved, and the outer muscularis can be sutured separately.

Some surgeons, upon beginning to work with the microscope, have advocated simply doing a one-layer anastomosis. The major advantage of a two-layer technique is that a better mucosal approximation can be achieved with this ap-
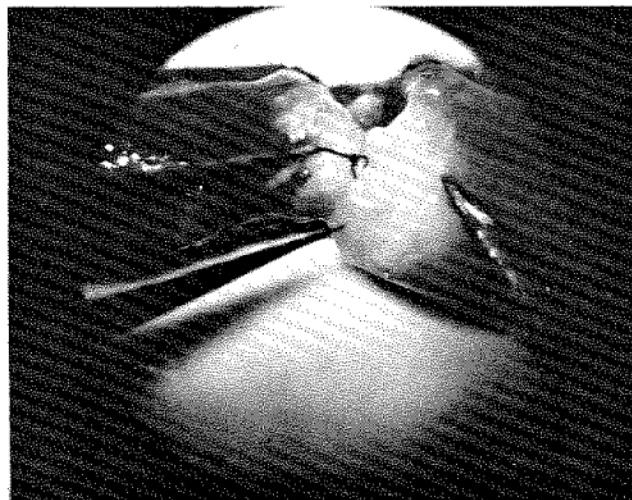

Fig. 3. After the first stitch is tied, the vas is rotated to expose the lumen for the second stitch.

proach. Contrary to one's initial impression, it is actually *easier* to perform an *accurate* anastomosis using two layers. If, instead of suturing the mucosal layer separately, one uses full-thickness stitches that traverse the muscularis and mucosa in one large bite, so much muscle is pulled into the anastomosis that the next stitch is very difficult to place accurately, and visualization of the mucosal edge of the lumen is very difficult for subsequent stitches. In addition, with a through-and-through stitch there is almost always a muscle bridge between the two mucosal edges which allows sperm leakage and granuloma formation. Finally, it is very difficult to match up the shrunken lumen to the dilated lumen with full-thickness stitches. A separate mucosal layer allows a very precise, more leakproof connection.

Accurate suturing of the muscularis ensures adequate strength and support to the anastomosis and allows normal conduction of peristalsis essential for the propulsion of sperm from the epididymis into the ejaculate. The muscularis closure should not be relied upon for making the anastomosis leakproof. This goal must be accomplished by the mucosal layer. If the muscularis is relied upon for this purpose and if the mucosal anastomosis is inadequate, then sperm will leak easily into this muscularis and create a granulomatous response with subsequent stricture formation. It is ironic that the same mechanism which allows even the crudest efforts at vasovasostomy to permit some sperm to flow into the ejaculate, namely a sperm granuloma, is often responsible for failure to obtain an adequate anastomosis.

Results with the Two-Layer Microscopic Technique. Approximately 400 patients have now been subjected to this technique and have been carefully studied both pre- and postoperatively in an effort to determine the factors which affect recovery of fertility.[33] The over-all pregnancy rate after 1½ years of follow-up of the first 42 unselected patients was 71%. Since very few patients become pregnant before 6 months have passed and most of the pregnancies begin to appear between 8 months and 1½ years, it is possible that the pregnancy rate will continue to increase in this initial group. Although some patients achieve normal sperm counts within the 1st month and impregnate their wives immediately, this is certainly the exception. In general, it is remarkable how long the full recovery of normal sperm counts requires. The sperm count

and motility tend to improve continually over the first 2 years of follow-up. Even patients who had impregnated their wives within 3 months continued to show gradual increases in sperm quantity and percentage motility with long-term follow-up.

PROSPECTIVE STUDIES ON FACTORS AFFECTING SUCCESSFUL RESULTS

Despite this high rate of success and our enthusiasm for this microscopic approach to vasectomy reversal, the long period of time sometimes required for recovery of fertility and the failure to achieve fertility in a significant number of patients led to our concern over what sort of permanent damage may have been created by the vasectomy and how this type of damage might be averted in future vasectomies. Most of the patients in this series have not been followed long enough to consider pregnancy results seriously, but since pregnancy in the early series correlated very well with the quality of the sperm count, we can at least derive some preliminary information from evaluating the recovery of normal sperm counts, motility, and morphology in the larger number of patients who have been operated upon more recently and who have been subjected to more carefully controlled observations both pre- and postoperatively.

Fifty-three patients had been operated upon previously by other accomplished urologists unsuccessfully, as evidenced by oligospermia or aspermia and failure to impregnate their spouses. Of these patients, 23 were originally considered surgical successes because of the presence of sperm in the ejaculate. Their failure to impregnate their wives was attributed to a variety of causes, most frequently sperm antibodies. Of those 23 patients, 13 had oligospermia with poor motility at the time of the second surgical procedure and 10 had changed from having sperm in the ejaculate postoperatively to being completely aspermic. In all of these cases severe obstruction was noted at the site of the former anastomosis. All 13 patients with oligospermia and poor motility recovered normal sperm counts with normal motility and morphology after microscopic reoperation using this technique. Of the 10 patients who were aspermic in this group, 8 developed normal sperm counts after reoperation and 2 have not given follow-up. Of the 51 patients in the group who gave follow-up, 41 recovered normal sperm counts after the

reanastomosis. Surgically, these were interesting cases because all involved the convoluted portion of the vas deferens and several involved the tail of the epididymis. Ten of the fifty-one patients failed to develop normal sperm counts after reoperation, but nine of these ten patients had no sperm whatsoever in their vas fluid on the testicular side of the obstruction at the time of the operation. By separating the 51 patients into those whose vasectomies originally had been performed less than 10 years previously and those whose vasectomies had been performed more than 10 years previously, we found that 91% developed normal sperm counts after reoperation if the original vasectomy had been performed within 10 years. Of those whose vasectomies had been performed more than 10 years previously, only 59% developed a normal count.

One hundred and twenty-one consecutive patients were followed for up to 8 months in order to relate the quality of the seminal fluid at the time of surgery to subsequent sperm counts. When the vasectomy was performed no more than 10 years previously, 91% developed a normal sperm count within 6 months and 94% had some sperm in the ejaculate. If the vasectomy had been performed more than 10 years previously, only 35% in this grouping obtained normal sperm counts within 6 months and only 47% had sperm in the ejaculate. When the vasectomy was performed within 2 years of the reversal operation, normal sperm counts occurred in every patient postoperatively. However, it is interesting that only 2 of the 56 patients whose vasectomy was within 5 years had no sperm in the vas fluid on either side at the time of the vasovasotomy. In the group whose vasectomies had been performed between 5 and 10 years previously, when there were sperm in the vas fluid at the time of surgery, 25 of 27 developed normal sperm counts. When no sperm were present in the vas fluid in this group, only 5 of 12 developed normal sperm counts and 6 had no sperm at all in the ejaculate. When the vasectomy was performed more than 10 years previously only 12 of 26 patients had any sperm in the vas fluid at the time of surgery. Furthermore, those whose vasectomies had been performed more than 10 years previously and who had no sperm in the vas fluid at the time of surgery did not show sperm in the ejaculate up to 6 months postoperatively. If sperm were present in the vas fluid, 75% developed normal

sperm counts even though the vasectomy had been performed more than 10 years previously.

This group of 121 consecutive patients demonstrated clearly the deleterious effect of a prolonged duration of obstruction on the successful return of fertility after reconstruction of the vas deferens. Any series of vasovasostomies weighted toward patients whose vasectomies have been performed more recently, no matter how crude the technique of surgery, will have a higher success rate than a series weighted toward patients whose vasectomies were performed longer than 10 years previously. One might surmise that nearly every anastomosis was patent, since the cases in which no sperm appeared postoperatively were those in which no sperm were present on the testicular side of the obstruction preoperatively. If sperm were present in the vas fluid preoperatively there was a 95% chance of developing a normal sperm count after surgery. Even if the initial sperm were degenerate and senescent with detached tails, these patients had a good prognosis.

The next 92 consecutive patients are probably the most fascinating and shed the most light on the whole mechanism for retaining fertility potential after vasectomy (Figs. 4 and 5). There appeared to be an improved quality of sperm in the vas fluid in patients who had minimal dilatation of the testicular-side lumen and in patients who had a sperm granuloma at the site of the vasectomy. In these 92 patients meticulous records were kept regarding the presence or absence and size of the sperm granuloma at the vasectomy site. The vas lumen diameter was measured on each side with a micromillimeter rule. The quality of sperm in the vas fluid was observed at the time of surgery. Records of postoperative sperm counts were kept.

Of the 184 vasa examined, a sperm granuloma was noted at the site of vasectomy in 59—an incidence of 32%. No particular symptoms of discomfort were related to the sperm granuloma. In this group, 92% had morphologically normal sperm in the vas fluid; the other 8% had morphologically normal sperm as well as some degenerate forms. In the group with sperm granulomas no vas failed to have good quality sperm in the fluid. Even when the vasectomy had been performed more than 10 years previously, none of the patients with sperm granulomas had poor quality sperm in the vas fluid. Thus, no matter how long ago the vasectomy had been performed, the presence of a sperm
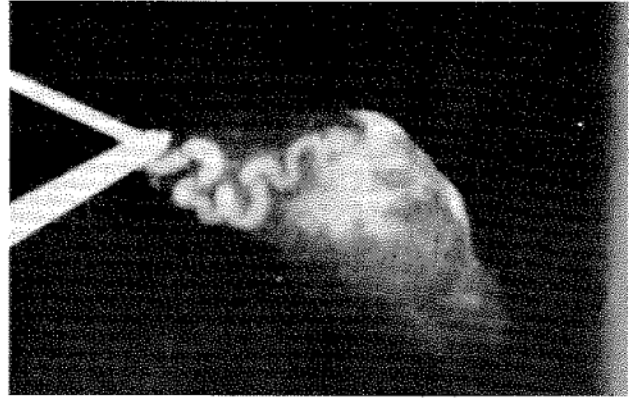

FIG. 4. Vasogram at the site of the sperm granuloma reveals extensive leakage into several fistulous tracts, allowing reabsorption of sperm and fluid.

granuloma resulted in a very high quality of sperm in the vas fluid at the time of surgery.

By contrast, only 7% of patients with no sperm granuloma had morphologically normal sperm in the vas fluid and 22% had morphologically normal sperm plus degenerate sperm. A total of 26% had no sperm in the vas fluid and 45% had only degenerated sperm heads. The internal diameter of the testicular-side lumen of the vas deferens was almost always 0.75 mm or less in vasa with sperm granulomas. In patients without sperm granulomas, the internal diameter of the testicular-side lumen was usually 1 mm or greater. Thus, the presence of a sperm granuloma was associated with less dilatation of the vas deferens on the testicular side of the obstruction.
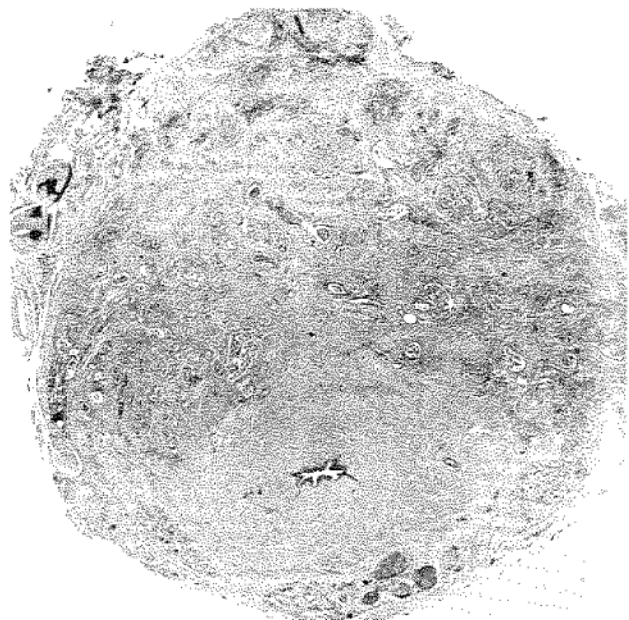

FIG. 5. Low-power view of a section of such a sperm granuloma near the terminal cut portion of the vas (hematoxylin and eosin stain).

The portion of vas deferens excised at the time of vasectomy and the area of vas deferens involved had no correlation whatsoever with sperm quality. Indeed, the majority of patients in this series had vasectomies extending to the convoluted portion and/or a very large segment of the vas deferens had been excised. This group was not weighted toward surgically favorable cases, but rather was weighted toward surgically unfavorable cases.

In patients who had unilateral sperm granulomas, the sperm quality was satisfactory on the side with the sperm granuloma but was of much poorer quality on the opposite side. Thus a dramatic benefit was conferred to the sperm output in the vas fluid on the side with a sperm granuloma that did not extend over to the side without a granuloma. These data favor the postulate that failure to recover fertility after an accurate anatomical reconnection of the vas deferens is due to the local effects of high pressure created by vasectomy. This intravasal pressure appears to be less in patients who have sperm granulomas. The presence of a sperm granuloma represents persistent leakage of sperm at the vasectomy site and modifies the deleterious effect of high intravasal and epididymal pressure after vasectomy (see Fig. 4).

The early follow-up of patients with sperm granulomas indicated that almost every patient developed a normal sperm count. Among those who did not have a sperm granuloma, 88% developed normal sperm counts if the vasectomy had been performed less than 10 years previously, but only 29% developed normal sperm counts if the vasectomy had been performed more than 10 years prior to surgery.

Thus the three most important factors that appeared to influence the return of fertility after vasovasostomy were (1) a meticulous microscopic technique for reconnection, (2) the duration of time the vas deferens had been subjected to obstruction, and (3) the presence or absence of a sperm granuloma at the site of vasectomy. The importance of an accurate microsurgical technique is underlined by previous failures in 53 men, the majority of whom recovered fertility after microscopic reanastomosis. The importance of the duration of time since the original vasectomy and the protective effect of a sperm granuloma demonstrate that the intravasal pressure created by the vasectomy is the major problem in restoration of fertility after accurate vasovasostomy. The epididymis can reabsorb fluid and thus withstand some of this increased intravasal pressure. However, the appearance of a sperm granuloma following vasectomy, venting this high pressure even further, seems to assure the recovery of a normal sperm count in most patients after a surgically accurate vasovasostomy. In the absence of such a sperm granuloma the duration of obstruction since vasectomy is extremely important.

In the majority of patients who do not have a sperm granuloma, the reabsorptive processes of the epididymis appear to be the major protective mechanism. Turner et al.[32] sampled fluid by micropuncture from four areas of the rat epididymis from the caput to distal cauda and documented a large water resorption from the epididymal lumen as the seminal fluid travels toward the vas from the testes. They did not note any significant sperm reabsorption and, in fact, noted a very significant increase in sperm concentration moving from the testes toward the tail of the epididymis.

EFFECTS OF VASECTOMY ON THE TESTIS: EXPERIMENTAL STUDIES

There is an incredible array of contradictory findings in animal experimentation. Different groups of investigators continue to produce opposite findings. Since many of the differences observed in experimental models may be related to species differences, the experimental data on the effects of vasectomy upon the testis are reviewed species by species.

Rats. The largest amount of work has probably been performed on the rat. In 1924, Van Wagenen[33] ligated the efferent ducts of rat testes and invariably noted degeneration of the germinal epithelium. At that time she stated that a similar degeneration could be brought about much more slowly by vas ligation. She postulated that the production of intratubular pressure might be a factor responsible for the degeneration. She felt that when the vas deferens was ligated, the sperm granuloma which gradually forms at the ligated end accepts the secretory products temporarily but no such outlet is available with efferent duct ligation.[34]

In 1962, Smith[35] performed similar experiments in the rat and noted that ligation of the vasa efferentia was followed by an increase in the diameter of the seminiferous tubules and increased testicular weight which peaked at 36 hours. Thereafter there was a progressive

shrinkage and atrophy of the seminiferous epithelium in the testes. The seminiferous epithelium was limited to a single row of cells by 28 days, and the weight of the operated testis was one-half that of the normal one.

On the other hand, vasectomy did not affect spermatogenesis. Vasectomy was followed by a temporary increase in the weight of the epididymis and by the inevitable formation of a sperm granuloma at the site of the vasectomy. At 6 days sperm granulomas appeared in the vasectomy site in most animals and subsequently became larger until reaching the maximal size at 40 days. The cauda epididymidis on the vasectomized side was visibly distended 40 days after the operation, but the distention eventually subsided, and at 60 days the difference between the two sides in the same animal was negligible. There were no histologic changes in the testes after vasectomy.

Smith[35] noted that sperm granulomas were much more likely to form in the rat than in the rabbit and guinea pig, thus explaining the much greater distention of the epididymis observed in the rabbit and the guinea pig than in the rat.

Neaves,[36] in 1973, observed that in rats with ligated ductuli efferentes, an immediate permeability of the blood-testis barrier at the Sertoli cell tight junctions was associated with rapid testicular weight gain, followed later by atrophy. He suggested that the tight junctions were sensitive to increased intratubular pressure and enforced retention of testicular secretions inside the seminiferous tubules. After vasectomy, however, the Sertoli cell tight junctions were unaffected and there was also no increase in testicular weight, supporting the view that blockage of testicular secretions distal to the epididymis was relatively innocuous. Neaves[37] noted no histologic changes in the testes and indeed no changes even in the weights of the epididymides on the ligated side and the non-ligated side after vasectomy. However, sperm granulomas formed at the site of the vasectomy in all animals.

Flickinger[38] studied the rat testis at intervals up to 9 months after vasectomy and noted that the fine structure of the rat testis remained completely normal after vasectomy. The Sertoli cells showed no evidence of phagocytosis, and Flickinger suggested that the main site of disposal of sperm after vasectomy lies distal to the seminiferous tubules. Twenty of twenty-one of

his rats developed sperm granulomas at the site of vasectomy despite all attempts to prevent them. He postulated that these sperm granulomas may permit the escape of sperm from the ductule system and may delay the development of potential changes in the male reproductive tract.

Segal[39] demonstrated that vasal ligation in young (14-day-old and 20-day-old) rats had no effect on spermatogenesis but did result in considerably swollen, dilated epididymides. Poynter[40] also demonstrated that vasectomy in rats followed for 20 days to 6 months caused no degeneration or deterioration of the germinal epithelium and no hypertrophy of interstitial cells. However, by 120 days postvasectomy every animal developed sperm granulomas on the testicular end of the severed vas deferens. Poynter[40] agreed with Oslund,[41] Moore and Oslund,[42] and Moore and Quick[43] that when degeneration of the seminiferous tubules was noted it was related to either an artifactual cryptorchidism created by the vasectomy or interference with the blood supply.

On the other hand, Rumke and Titus,[44] in studying the sperm antibody response to vasectomy in rats, noted in all animals which did not form a sperm granuloma (and oddly this was the majority) that the testis on the vasligated side showed signs of considerable histologic degeneration but the testis on the control side did not. The two animals which developed sperm granulomas had completely normal testes on the vasectomized side. This aspect of the findings of Rumke and Titus[44] was not emphasized, but may have significance.

Subsequent work has still not cleared the issue. Sackler et al.,[45] Plaut,[46] Rangam et al.,[47] Laumas and Uniyal,[48] and Altwein and Gittes[49] reported contradictory findings on the effect of vasectomy on the testes of rats.

Howards et al.,[50] using micropuncture techniques, demonstrated differences in sperm concentration in the seminiferous tubules in rats with sperm granulomas and without sperm granulomas. The vast majority had sperm granulomas after vasectomy despite great efforts to prevent them. Kwart and Coffey[51] considered sperm granulomas to be an adverse effect of vasectomy in rats, but noted "these granulomas contain massive accumulations of sperm which may account for a considerable portion of the testicular output of sperm. . . . This might suggest minimal reabsorption of sperm in the epididymis."

Thus, for rats the experimental literature would suggest that vasectomy does not result in permanent testicular damage except in the rare case where a spontaneous sperm granuloma does not form at the site of the vasectomy. However, experiments in other animals contradict this seemingly tidy explanation.

Dogs, Cats, and Mice. In dogs, Kothari and Mishra[52] noted that a vasectomy produced marked degeneration of the seminiferous tubules as well as some reduction in testicular volume. One of the real problems in this study, however, is that the testes were formalin-fixed and therefore the readability of the histology is in question. Kothari and Mishra speculated that testosterone secretion might actually be increased by vasectomy, as was originally suggested by Steinach[53] in the 1920s as a method for rejuvenation. In another series of dogs, Kothari and Mishra[54] again reported widespread degeneration of the seminiferous tissue, evident initially 1 week after vasectomy and continuing up to the 10th week with no evidence of regeneration. Despite the formalin fixation, their control testes appeared to be normal histologically.

Vare and Bansal[55] also demonstrated degenerative changes and atrophy in the seminiferous tubules during the first 4 months after vasectomy in dogs, but after this period regeneration took place in most of the tubules. By the end of 6 months the seminiferous tubules again appeared almost completely normal.

Grewal and Sachen[56] demonstrated degenerative changes beginning during the first few days after vasectomy with gradual regeneration over the next 6 months, so that at the end of 6 months all of the dogs had reattained normal histology of the seminiferous tubules. They noted neither dilatation nor changes in the epididymal tubule, which raises questions regarding their other observations. Joshi et al.[57] also demonstrated progressively less spermatogenesis in dogs over 6 to 8 weeks following vasectomy.

Only one study is available on vasectomy in the cat. Cunningham[58] in 1928 supported the work of Van Wagenen[34] in rats, demonstrating that vasectomy caused no damage to spermatogenesis. However, a ligature around the vasa efferentia was always followed by disorganization of the seminal epithelium and cessation of spermatogenesis.

In the mouse, Tamura and Crew[59] demonstrated that severe degeneration of the germinal epithelium of the testis invariably followed vasectomy or vasal ligation, but this did not become evident until a considerable period of time had elapsed. The greatest area of damage was around the region of the rete testis. Even at 150 to 250 days after the operation the testes revealed all stages of spermatogenesis, but the number of spermatozoa was reduced. The area of degeneration in the region of the rete testis was greatly dilated. Tamura and Crew[59] concluded that spermatogenesis is not completely arrested following vasectomy, but with long-term follow-up there are some degenerative changes.

Rabbits. In the rabbit, Swanson and Hafs[60] noted that vasal ligation depressed testicular sperm numbers by about 24% without altering testicular weight. They made no reference to sperm granuloma formation and did not perform histologic studies. However, vasoligation resulted in a significant decrease in testicular sperm concentration on the ligated side relative to that on the contralateral control side. In addition, vasoligation caused accumulation of sperm in the cauda epididymidis on the ligated side. The observations of Swanson and Hafs[60] "suggest that increased hydrostatic pressure within the ligated epididymis may partially inhibit spermatocytogenesis but not sperm transport from the testis to the epididymis."

Paufler and Foote,[61] also working with rabbits, noted that vasectomy did not appear to affect spermatogenesis. However, ligation of the middle of the corpus epididymidis had a severe effect, causing testicular swelling and subsequent atrophy of the seminiferous tubules.

Chiang and Cheng[62] noted reduction of spermatogenesis in three of seven rabbits, but their data were meager. MacMillan et al.[63] also noted significant reduction in testicular sperm numbers during the first 4 weeks after vasectomy in rabbits, with partial recovery by week 5. Testicular sperm numbers were not affected on the unoperated side or in sham-operated animals. Epididymal sperm numbers increased on the ligated side for the first 4 weeks and then declined by week 5.

Moore and Quick,[43] however, noted no degeneration of the seminiferous tubules, but there was a 2- to 3-fold increase in the size of the epididymis. No sperm granulomas were present in any of their animals. They noted that this massive increase in the epididymis may cause testicular displacement upward into the inguinal canal in experimental animals, and this artifactual cryptorchidism could account for the

degenerative changes some authors saw. There was no accumulation of sperm products in the seminiferous tubules, but rather they were transported against a pressure gradient to the epididymis, which increased massively to accommodate them.

Bulls. In dairy bulls Amann and Alqvist[64] noted that all vasectomized animals developed sperm granulomas. After 23 weeks some spermatozoa were found distal to the site of ligation in all of the nine bulls vasectomized. Amann and Alqvist[64] concluded that there was either increased sperm reabsorption in the epididymides of the vasectomized bulls or decreased sperm production. Their basic feeling was that vasectomy probably did not inhibit spermatogenesis and therefore there was an increased rate of sperm reabsorption.

Igboeli and Rakha[65] also noted that all bulls developed sperm granulomas after vasectomy. Vasectomy did not abolish spermatogenesis, and testis size was unaffected. Extragonadal sperm reserves in the corpus and cauda epididymides of the vasectomized bulls were significantly greater than in the control group. The increase in extragonadal sperm reserves in the vasectomized group could not account for the total testicular sperm output over the 5-year period, suggesting to Igboeli and Rakha a high rate of reabsorption. However, they did not pursue the question of how much of that reabsorption could have been accomplished by the sperm granuloma.

Guinea Pigs. Oslund[41] noted no effect of vasectomy on the testes of guinea pigs. However, Alexander,[66] working with guinea pigs, noted that vasectomy resulted in a disruption of spermatogenesis. In animals vasectomized 7 to 8 weeks earlier, spermatids were absent from most of the seminiferous tubules. Unilateral vasectomy resulted in impaired spermatogenesis on both the operated side and the contralateral unligated side, although the effect was more severe on the ligated side. In subsequent studies, however, this effect was not noted on the contralateral side, at least during the first 4 months post-vasectomy. The lesions appeared to progress with longer duration.

Primates. Alexander also noted in rhesus monkeys that spermatogenesis continued after vasectomy, but could not state whether daily sperm production decreased after vasectomy. At any rate, the continued production of spermatogenesis meant that there had to be some ac-

counting for what happens to the sperm that continue to be produced and yet have no outlet. Her work demonstrated that the rete testis is dilated after vasectomy and is a very reasonable place not only for fluids but for spermatozoa to be reabsorbed.

The evaluation of spermatogenesis in vasectomized humans is extremely meager and, although it is clear that spermatogenesis continues after vasectomy, there are some studies which weakly suggest that there may be either a temporary or partial suppression of spermatogenesis.[67-70]

Despite all of these studies there is still no clear answer to the question of the effect of vasectomy on the testis. However, it is apparent from cannulating the rete testis that a great deal of fluid is actually secreted by the testes and is normally reabsorbed by the head of the epididymis.[71] Thus, it is reasonable to suspect that any procedure which interferes with the flow and reabsorption of this fluid can result in pressure changes proximally. It is truly remarkable that this is one of the few organs the excurrent duct of which can be ligated with the expectation that total destruction will not occur, and subsequent fertility can result after reconnection. Without the capacity of the epididymides and efferent ducts to reabsorb fluid and perhaps to reabsorb at an increased rate after vasectomy, a great deal more damage would be produced by vasectomy.

EFFECT OF VASECTOMY ON THE EPIDIDYMIS AND SPERM TRANSPORT

It is clear that vasectomy results in a buildup of pressure on the testicular side of the obstruction with massive dilatation of the vas deferens and epididymal tubule. Whether or not this pressure is generated as far back as the seminiferous tubules is a subject of much debate. However, enough damage can occur to the epididymis and the entire sperm transport mechanism that this in itself may be one obstacle to the recovery of fertility after vasovasostomy. Again, the experimental literature on the subject is often contradictory and is reviewed animal by animal in order to avoid confusion because of species differences.

Rats. In rats, Lee[72] performed experimental studies in which he ligated the vas deferens in one group of animals and left the testicular-side stump unligated in another group. In the "open"

vasectomy group the epididymal end of the vas was not nearly as dilated as it was when the vas was tied off. In some of the open vasectomy groups, the lumen of the epididymis was found to be the same size as that in the control groups without any dilatation.

MacMillan[73] noted that, despite surgical interruption of sperm transport from the testis to the epididymis, the tubular system of the body of the epididymis emptied into the wider convolutions of the tail of the epididymis within 14 days. When completely isolated from the rest of the system, the final disposal of epididymal sperm appeared to be accomplished by dissolution in situ.

The tubular system of the body of the epididymis below the subcapital ligature began to empty toward the tail within 5 days. Fourteen days after surgery, the body of the epididymis was completely empty. Although by 127 days some of the tubules of the cauda epididymidis were devoid of sperm, most had sperm clumps and casts indicating dissolution of the non-ejaculated sperm which was not yet complete. Neither the speed of sperm dissolution nor its mechanism was significantly altered by the localized vasectomy.

Although the head of the epididymis was massively distended with spermatozoa, the vasa efferentia in the initial segment of the head remained characteristically empty. There appeared to be a rupture of the tubules of the head with an extravasation of their contents into the extratubular spaces and a subsequent encapsulation to form an artificial spermatocele. The spermatocele enlarged progressively until the time of sacrifice. Eventually the efferent ductules exhibited changes due to stasis of the sperm stream from the testis to the epididymis, and scattered groups seen in cross-section contained masses of fragmenting epithelial cells and degenerating spermatozoa. In some animals the efferent tubules were totally obstructed and in others there was a disorganization of the junctional region between the vasa efferentia and the initial segment of the head of the epididymis.

Within the seminiferous tubules, degenerating spermatozoal casts with complete destruction of the germinal epithelium were present in some of the centrally located tubules near the vasa efferentia. The remainder of the testes presented a normal histologic picture. Therefore, it may be important to recognize that portions of the

seminiferous tubules closest to the ductuli efferentes may show more severe histologic changes than those which normally are biopsied near the periphery. This rupture of the tubules of the head of the epididymis in this experimental model appears to allow decompression of the system. If stasis of the sperm stream results in efferent duct obstruction, a temporary testicular enlargement occurs followed by substantial testicular atrophy.

Again in the rat, Flickinger[74] noted sperm granulomas in practically every case of vasectomy. He recognized that granuloma formation may have had an effect on his results, perhaps by reducing pressure in the system. He speculated that, by permitting the escape of some sperm, sperm granulomas might delay the development of alterations in the male reproductive tract proximal to the point of ligation.

Alexander[75] also noted that in almost all cases in rats, a sperm granuloma formed at the site of ligation. Spermatozoa in the lumina of the ligated ducts began to disintegrate by 8 weeks. Whole spermatozoa were not ingested by epithelial cells, but spermatozoal remnants were absorbed.

Rabbits. In the rabbit, Gaddum[76] sampled sperm from the seminiferous tubules, the ductuli efferentes, and various levels of the epididymis to determine their intrinsic motility and fertilizing capability. Sperm from the seminiferous tubules and ductuli efferentes showed only weak, vibratory movements with no forward progress. In the distal portion of the head of the epididymis, sperm began to show a sudden increase in activity, with tight circular movements. As they traversed the corpus epididymidis, increasing numbers of sperm showed progressive forward movement with longitudinal rotation.

In order to determine whether this progressive increase in maturity of sperm was merely a function of time or was specifically dependent on passage through these various areas of the epididymis, Glover[77] ligated various portions of the epididymis and examined samples of spermatozoa from each portion. Ligation of the epididymis inevitably caused characteristic distention of the duct above the level of ligation with accumulation of spermatozoa and fluid. Epididymal sperm initially showed increased motility, but this was short-lived; by 3 weeks all of the spermatozoa were virtually nonmotile even when exposed to air. Glover believed that occlusion of the epididymis allowed the contained

spermatozoa to mature at any level of the epididymal duct, but then the abnormal environment so created eventually caused rapid deterioration of the spermatozoa.

In 1964 Gaddum and Glover[78] also ligated the distal end of the body of the epididymis and noted that the spermatozoa sampled from the distended ligated tubules exhibited very active motility even when withdrawn from as high as the head of the epididymis, but the changed environment resulting from the obstruction then resulted in their degeneration.[79]

Paufler and Foote[80] noted that vasectomy had very little effect on sperm transport from the caput to cauda epididymidis. Considerable motility and fertility were maintained for 12 weeks following the ligation, in contrast to a reduction in the fertility of sperm after 4 weeks in the group in which the cauda epididymidis was isolated by a ligation above and below. The fertility of sperm in the cauda epididymidis was thus maintained for up to 12 weeks when the cauda was not isolated, indicating that there was some mixing with younger spermatozoa being more freshly produced. Spermatozoa from the isolated cauda remained fertile for 4 weeks, but thereafter were infertile.

Jones[81] also studied rabbits vasoligated for up to 24 weeks and noted no sperm granuloma formation, massive dilatation of the epididymis, continued spermatogenesis, and continued passage of newly formed sperm into the cauda epididymidis.

Guinea Pigs. The fate of non-ejaculated spermatozoa is one of the major mysteries in this field and was studied in the guinea pig by Simeone and Young.[82] Their studies provided conclusions very similar to those observed in the human. It appears that spermatozoa that are not discharged during copulation undergo regressive changes which end in their death and subsequent liquefaction within the epididymis and within the vas deferens. The spermatozoa simply die of senescence and ultimately disappear by a process of liquefaction or dissolution in situ. Simeone and Young[82] suggested that "spermiophages" are simply degenerating germinal elements which have been sloughed off under abnormal conditions and carried into the lumen of the epididymis. No evidence of penetration of the epithelium by intact spermatozoa was noted. They searched for phagocytosis to account for the disappearance of spermatozoa, but could find no significant number of phagocytes for removal of sperm.

It is interesting that the data obtained by Simeone and Young[82] in 1931 appear to be similar to those found by Galle and Friend[83] more recently (in 1976), using more sophisticated electron microscopic techniques, again in the guinea pig. At intervals between 1 and 120 days after unilateral or bilateral vasectomy, epididymal and vas deferens segments were processed for thick and thin sectioning, freeze fracture, and cytochemical analysis by electron microscopy. No sperm granulomas had formed up to 120 days, but there was marked tubular distention of the epididymis and vas. No recognizable parts of spermatozoa were observed within or between epithelial cells or in the leukocytes. Besides normal spermatozoa, premature forms and spermatozoa with abnormal particulate clusters in the plasma membrane were conspicuous from 30 to 120 days postvasectomy. Intraluminal disintegration of sperm within the epididymis following vasectomy was suggested.

Primates. Alexander[84] examined the long-term effects of vasectomy in rhesus monkeys. She noted many morphologic and functional changes in the epididymis and ductuli efferentes. After vasectomy the ductuli efferentes were enlarged as much as 4 times their normal diameter, and spermatozoa were packed together in large numbers in the cauda portion of the epididymis. Spermatozoa became agglutinated in the efferent ductules and were ingested by macrophages. The ductuli efferentes of animals vasectomized for 2 or more years had a 2- to 4-fold increase in diameter and were packed with spermatozoa and numerous macrophages, some of which were ingesting sperm. The macrophages were not found in animals vasectomized only 1 to 3 months previously. Very few spermatozoa could be seen after 3 to 7 years in the cauda epididymidis. Alexander[84] concluded that there may have been some reduction in spermatogenesis but that most of the sperm which continued to be produced after vasectomy were probably reabsorbed in the ductuli efferentes.

Bedford[85] studied the long-term effects of vasectomy in a variety of animals, including the rabbit, hamster, rat, and rhesus monkey. Six months following bilateral vasectomy in the rabbit, there was enormous distention of the vas, although it did not extend to the corpus epididymidis. Testicular tissue histologically was normal, but the cauda epididymidis showed masses of solid

sperm and flattened epithelium. No infiltration by any type of leukocyte was observed unless rupture of the duct had occurred. Most of the sperm had lost their acrosomes, there was some separation of heads and tails, but no phagocytosis or leukocytic invasion was evident. By 8 months the corpus began to show signs of dilatation, and a series of lesions and ruptures could be seen as well as scars in the epididymis. In rats, epididymal lesions were also found and the tubules were full of sperm, but as in the rabbit no leukocytic infiltration was seen unless granulomas were present. Again in the hamster, no leukocytic infiltration was noted in the absence of sperm leakage and disruption of the tubules. Involvement of the caput in this animal resulted in depression of testicular activity.

Bedford[85] noted a far less marked response to vasectomy in rhesus monkeys. Some epididymal rigidity was found 3 to 4 weeks after operation, but this rigidity tended to decrease by 6 weeks. Discrete lesions of the cauda and the vas deferens could be demonstrated histologically 6 weeks after vasectomy, but they were too small for visual identification. In general, Bedford's data indicated that sperm were continually produced after vasectomy but that no reabsorption occurred until the epithelium ruptured, at which time leukocytic infiltration and invasion occurred. A significant effect on the testis itself appeared only in those cases in which duct distention by sperm reached the corpus.

Only a limited amount of work has been done on humans, but it is fairly well accepted at this point, owing to the excellent cinefluoroscopic studies of Mitsuya and the beautifully conceived studies of Freund and Davis, that at the time of intercourse there is a rapid series of purposeful and powerful peristaltic waves which propel sperm from the epididymis up through the vas deferens into the ejaculate. It appears that these purposeful contractions may be controlled by the local release of norepineprine stimulated by sympathetic nerve endings.[86-89] Therefore, successful peristaltic progression across the suture line after vasovasostomy may depend to some extent on adrenergic regeneration.[90-92]

deKretser[93] summarized a great deal of the confusion about the physiology or pathology of vasectomy by stating that, from the limited information available in vasectomized experimental animals, sperm production by the testes appears to continue and little specific damage occurs to the seminiferous tubules. No direct information is available regarding the seminiferous tubules in vasectomized men. However, ligation of the vas in most animals is followed by distention of the epididymal duct with rupture and granuloma formation which allows invasion of phagocytic cells responsible for the degradation of extruded spermatozoa.

Electron microscopic studies by Friend et al.[94] in humans subjected to vasovasostomy demonstrated that 3 months to 17 years after vasectomy, spermatozoa with normal membrane structure still form, they disintegrate in the lumen of the vas, and the epithelial cells ingest only the disintegrated products of these sperm. Junctional integrity is usually maintained, and leukocytes do not appear to be involved in the scavenging process. By 3 months after vasovasostomy, normal sperm appear in the ejaculate.

The ultimate conclusion of all these studies on changes in the epididymis and vas after vasectomy is that, if sperm maturation depends upon passage through a properly functioning epididymis, it is possible that normal sperm will not be recovered in the ejaculate—despite good testicular function—if the epididymis does not recover completely from the effects of the high pressure created by the vasectomy.[95]

SPERM ANTIBODIES

One of the earliest and most hopeful-appearing areas of research into the reversibility of vasectomy centered around the immunologic consequences. Many researchers have noted the formation of sperm autoantibodies after vasectomy, but most of the studies have not been able to demonstrate specifically the effect of sperm antibodies on the subsequent recovery of fertility.[2, 96-101] Some investigators have even failed to discern a significant rise in antibody titers, although they are in the minority.[102, 103]

More recently, Alexander[104] has correlated sperm-immobilizing antibody titers with failure to restore fertility in a group of 15 rhesus monkeys. Agglutinating antibodies, however, clearly had no effect. All 15 monkeys underwent vasovasostomy 6 months after the vasectomy and most of them had developed spontaneous sperm granulomas or sperm fistulas. Thirteen of the fifteen monkeys demonstrated fertility, and all had sperm in their ejaculates after vasovasostomy. Three of the thirteen fertile monkeys were actually subfertile. Only two of the six experimental animals with high levels of sperm-

immobilizing antibodies were completely fertile, and two were capable of impregnation but were classified as subfertile; two remained which were infertile. There were no infertile monkeys among the nine experimental animals which had no sustained antisperm antibody production. Only one of these nine animals was classified as subfertile. Thus there may be some correlation between the development of antisperm antibodies and subsequent infertility. However, it is not clear whether this is a cause-and-effect relationship, and the correlation is not very strong. The role of sperm autoimmunity in humans may become more clear from studies by Alexander and Silber that are in progress.

SUMMARY

It is clear that the effects of obstruction on the entire epididymal and testicular system are so vast that purely physical factors may affect the recovery of normal sperm production and maturation even after successful vasovasostomy. Anything which would tend to reduce the degree of vas pressure or the duration of that pressure would seem to make the subsequent recovery of fertility more likely after an accurate anastomosis. In this regard, the capacity for epididymal fluid reabsorption as demonstrated by Turner et al.[32] is probably a major source of protection after vasectomy. A sperm granuloma is another important source of protection in the patient who develops it. It is possible that the formation of a granuloma is not really a complication of vasectomy but a desirable result. Those without sperm granulomas at the vasectomy site are more likely to have sperm extravasation into the epididymis. A sperm granuloma at the vasectomy site represents a safety release valve which helps to alleviate the high buildup of pressure that otherwise would occur in the intravasal system proximal to the vasectomy site.

In studies by Alexander and Schmidt[105] the incidence of antisperm antibody levels appeared only slightly higher in men who had sperm granulomas than in those who did not have sperm granulomas. Thus it is difficult to predict whether the presence of a sperm granuloma in an individual patient is more likely to lead to the formation of sperm antibodies. However, it is clear from our clinical data that a sperm granuloma does confer remarkable protection from the pressure changes induced by vasectomy, which appear to be a major factor in preventing

the successful recovery of fertility after accurate vasovasostomy.

The confusing and often contradictory literature on the subject of vasectomy and vasectomy reversal has been reviewed. In our series the over-all pregnancy rate in an unselected group of early patients was 71%, but longer follow-up will be necessary to obtain firmer statistics. The recovery of fertility correlated with the return of normal sperm counts and with the quality of seminal fluid in the vas deferens on the testicular side of the obstruction at the time of vasovasostomy. The three most important factors influencing the return of fertility after vasovasostomy are (1) a meticulous microscopic technique for reconnection, (2) the duration of time the vas deferens has been obstructed, and (3) the presence or absence of a sperm granuloma at the site of the vasectomy. The presence of a sperm granuloma at the vasectomy site virtually ensures the presence of good quality sperm in the vas fluid at the time of vasovasostomy. If all three of these factors are favorable, vasectomy may indeed become reversible for most patients.

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