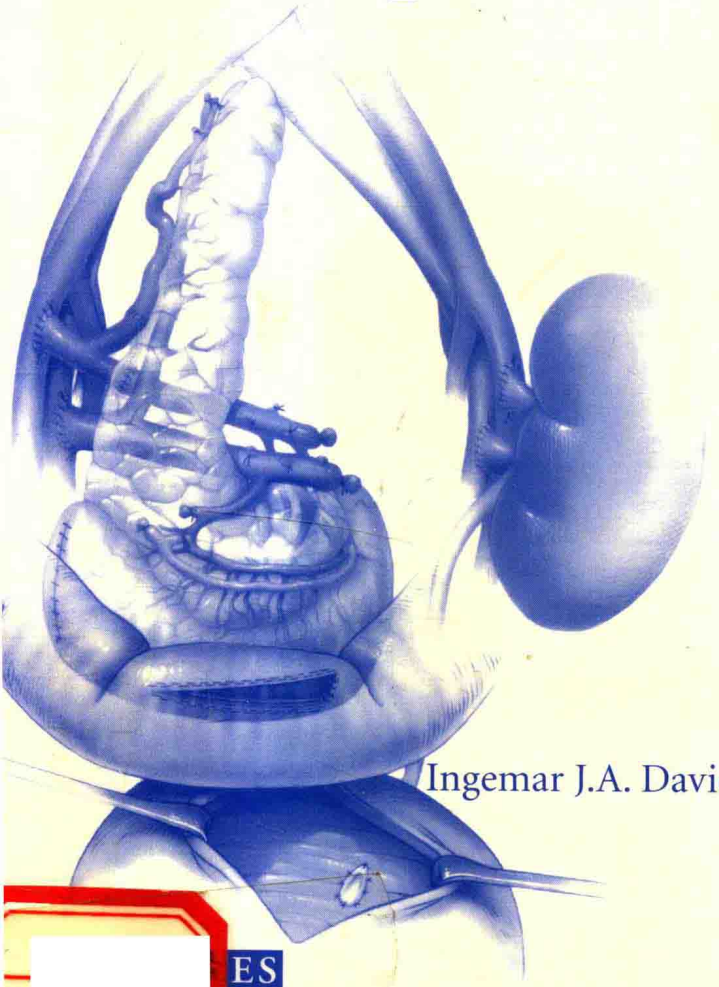
VADEMECUM

Handbook of

Kidney and Pancreas Transplantation



Ingemar J.A. Davidson

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Handbook of Kidney and Pancreas Transplantation

Detailed Surgical Procedures and Management Protocols

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Kidney/Pancreas Transplantation: General Considerations and Current Issues

Ingemar J.A. Davidson

UNITED NETWORK FOR ORGAN SHARING

The United Network for Organ Sharing (UNOS) was established in 1977 to operate the National Organ Procurement and Transplantation Network (OPTN) and the National Scientific Registry for Organ Transplantation. In this role, UNOS functions as a contractor for the federal government and as a private, nonprofit corporation. UNOS is unique in that it is a private corporation which sets policy for a sector of the medical community and is subject to review and final approval by the Department of Health and Human Services. The goal of UNOS is to ensure equitable and efficient organ allocation for transplantation. The current objectives of UNOS are to:

- Develop policies for equitable access to available organs by those in need of transplantation and for the equitable distribution of procured organs.
- Establish and maintain standards of quality in organ procurement, distribution and transportation, histocompatibility testing and data collection and assure that such standards are met.
- Collect, verify, store, analyze and publish data concerning human organ procurement and transplantation.
- Provide information, communication and transportation systems which enhance the successful utilization of available donor organs.
- Increase the number of organs available for transplantation by providing information, consultation and guidance to persons and organizations concerned with human organ transplantation.

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- Serve as a national resource regarding all aspects of organ procurement and transplantation.
- Provide administrative and logistical services which enhance the effectiveness of transplant professionals engaged in furthering transplantation.

UNOS includes every transplant center, organ procurement organization (organ bank) and transplant tissue typing laboratory in the United States. Members also include professional health organizations and voluntary members of the general public. UNOS is divided into 11 geographical regions with elected representatives or counselors from each. Various national committees of UNOS provide broad-based input into the 32 member UNOS board of directors which consists of 16 physicians and 16 lay persons. A national computerized waiting list for patients, linked to all organ procurement organizations and transplant centers, is maintained by UNOS. A point system has been established for the optimal distribution of organs. This system is based primarily on time on the waiting list, degree or quality of antigen matching and the panel reactivity antibody level, with pediatric recipients less than 11 years old assigned specific points. The point system may vary between UNOS regions and organ banks depending on local criteria.

Organs are first placed locally, then regionally and finally nationally. All blood type O kidneys are designated for blood type O recipients in order to avoid unfair distribution of O kidneys to non-O recipients. The final decision to accept a particular organ for transplantation will remain the prerogative of the transplant surgeon responsible for the care of the patient. There is mandatory national sharing for six antigen-matched kidneys, meaning that a patient identified through the UNOS computer as being ABO blood type compatible, with no HLA A, B or DR antigen mismatches for a specific organ, must be offered that donor kidney. The exception to this policy occurs when a kidney and a nonrenal organ (liver or pancreas) are to be transplanted simultaneously. Currently there is a "payback" rule for six antigen kidneys. UNOS maintains a scientific registry of data on all transplant recipients from the time of transplant through the loss of the graft or the death of the patient. The data includes immunosuppression drug use, first versus repeat transplant, recipient age, patient status and degree of histocompatibility at the time of transplant, organ preservation method and survival outcomes for graft and patient.

Shortage of Organs

Recent medical advances have increased the number of patients in need of transplantation to the point that the shortage of organs available for transplantation has reached alarming proportions. While the number of patients waiting for solid organs has increased in the United States in recent years, the number of organ donors has not. As of November 15, 1997, there were 55,994 patients on the UNOS waiting list for a solid organ transplant, the majority of whom (37,859) are waiting for a kidney transplant (Table 1.1). While the number of kidneys transplanted reflects organ availability, the increasing number of liver, pancreas, heart and lung transplants reflect improved medical technology, making these proce-

*Table 1.1. Solid organ waiting list as of November 15, 1997 and transplants performed in 1996**

	Wait List	Transplants 1996
Kidney	37,859	12,039
Liver	9,323	4,062
Pancreas alone	356	172
Kidney / Pancreas	1,596	850
Intestines	94	45
Heart	3,869	2,343
Heart / Lung	233	39
Lung	2,588	805
Total	55,994	20,354

* (UNOS Registry Data)

dures more feasible. This advancing technology is also reflected in the increasing number of patients on dialysis for end stage renal disease. In 1995, 68,870 new renal failure patients began dialysis in the United States, with more than 214,000 currently undergoing hemodialysis or peritoneal dialysis. In 1996, 1905 dialysis patients died on the waiting list.

THE END STAGE RENAL DISEASE (ESRD) TIMELINE

Many patients with increased creatinine are regularly seeing their primary physician or a nephrologist (Fig. 1.1, Phase 2). Interventions, such as aggressive blood pressure control, may delay or halt the development of progressive renal disease. As the creatinine rises to the 6-7 mg/dl range (GFR 10-15 ml/min) in nondiabetics, or 4-5 mg/dl in diabetic patients (GFR 15-25 ml/min) a vascular access should be placed since there is an impending need for dialysis (Fig. 1.1, Phase 3). Every effort should be made to allow 2 or more weeks before the use of a PTFE AV graft (i.e., GoreTex®, W.L. Gore, Flagstaff, AZ) and 4-6 weeks for a primary AV fistula to allow for maturation. However, about 75% of patients have no permanent vascular access by the time dialysis treatment becomes necessary (Fig. 1.1, Phase 4). Often, patients are referred too late and thus, require temporary central vein dual lumen catheters, with their inherent morbidity.

Depending on disease process and concomitant medical problems, many patients will remain on some form of dialysis treatment for the rest of their lives. Others are evaluated for a possible renal transplant and placed on kidney transplant waiting lists, where they may remain for varying periods of time depending on their blood type, preformed antibody levels, HLA matching, medical urgency and local organ bank efficiency (Fig. 1.1, Phase 4). The median waiting time to transplant for a blood type O patient is currently about 800 days (UNOS 1997). According to annual trends, of the more than 37,859 patients currently (11/97) on

the waiting list only about 12,000 will receive a kidney transplant per year (Table 1.1). The transplant procedure includes organ procurement, in which the kidney is part of a multi-organ procurement effort (Fig. 1.1 Phase 5). Typically, the organs are excised within 48 hours after a donor has been identified. Ideally, the kidney will be implanted and reperfused within 20 h of excision (the cold ischemia time). The transplant surgical procedure itself takes only 3-4 h (Fig. 1.1, Phase 6), followed by 5-10 days in a hospital setting (Fig. 1.1, Phase 7). The posttransplant close surgical surveillance period lasts for 90 days, which is the timespan Medicare has set as the global fee coverage for surgeons (Fig. 1.1, Phase 8). During this time, immunosuppression should be designed to prevent acute rejection episodes (see chapter 6, Tables 6.10, 6.11, 6.13 and Figs. 6.2, 6.3 and 6.6). After 3-6 months the patients typically revert to their referring physician for follow-up, which lasts for the duration of the graft or the patient's life (Fig. 1.1, Phase 9). Graft failure, for whatever reason, brings the patient back to Phase 2, either as a hemodialysis patient or back on the waiting list for a repeat transplant. Patients may be placed on the waiting list when the graft is failing and perhaps be transplanted before the imminent need for dialysis.

A SINGLE-ORGAN SHOCK MODEL

The cadaver renal transplant (CRT) procedure is a unique, clinical single-organ shock model. The short-term outcome depends on the status and management of the organ donor, the duration of ischemia time and the circumstances surrounding the recipient's surgery. In this respect, the transplant operation and procedural measures resemble those of shock and shock resuscitation. Long-term outcome is thought to be determined by immunological factors and also greatly influenced by perioperative factors including intraoperative fluid and drug management, surgical technique and early postoperative management. We and others have previously reported poor outcome after CRT with the occurrence of delayed onset of urine output and delayed function (defined as the need for hemodialysis treatments) after transplantation. Therefore, identification of perioperative factors associated with this occurrence and institution of measures to induce urine flow immediately after surgery are exceedingly important to avoid hemodialysis and improve long-term graft function. This was also a major finding in the 1990 UNOS scientific renal transplant registry.

Another purpose of this chapter is to further highlight several peritransplant factors that affect outcome. These include, but are not limited to, perioperative fluid and drug management, donor and recipient selection and management, and ischemia time. An early immunosuppression regimen designed to ameliorate acute rejection is the major factor leading to long-term graft survival (see chapter 6, Figs. 6.2 a,b, and 6.6).

During the last several years a number of developments have affected the results of renal and pancreas transplantation. The decline in posttransplant morbidity and mortality has continued despite the expansion of eligibility criteria for trans-

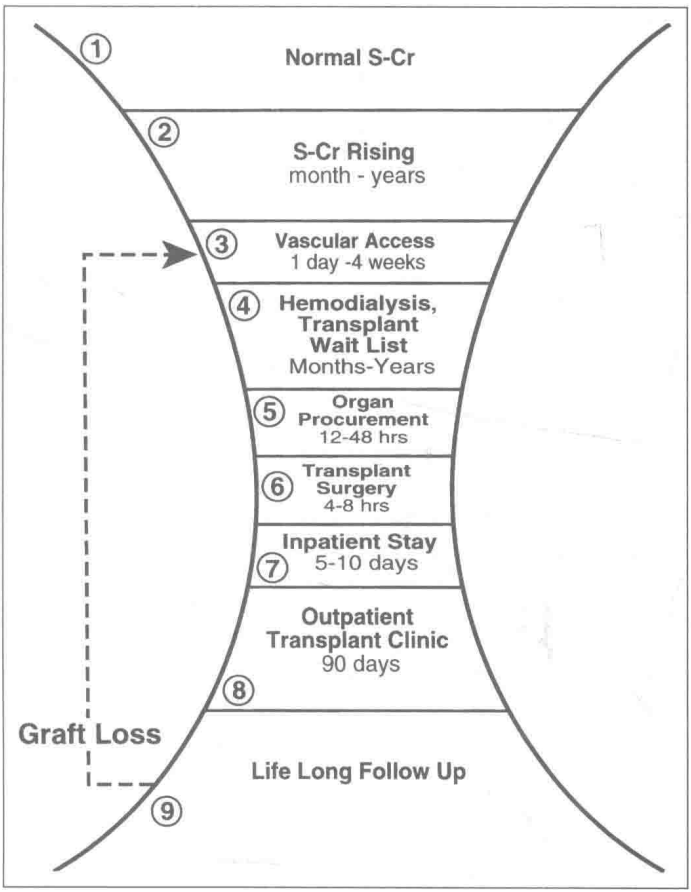

Fig. 1.1. The end stage renal disease (ESRD) time line as it pertains to renal transplantation. Patients with renal disease develop decreased renal function [2] and are followed early by their primary physicians and later usually by a nephrologist. As serum creatinine rises to 4-5 mg/dl in diabetics (GFR 15-20 ml/min) or 7-8 mg/dl in patients with no comorbidity (GFR 10-15 ml/min) permanent vascular access or peritoneal catheter is placed in anticipation of hemodialysis or continuous ambulatory peritoneal dialysis (CAPD) [3]. Patients may remain on hemodialysis for life or be evaluated for transplantation and placed on UNOS waiting list [4]. The transplant process involves donor maintenance and organ excision [5], recipient surgery [6], a short 5-10 day hospital stay [7], followed by close outpatient follow-up for 3-6 months [8], before reverting to their referring physician [9]. At any time patients may lose the organ to rejection or technical problems and revert to dialysis treatment.

plantation to include the higher risk recipients. Part of the increasingly successful outcome of transplantation is due to newer anti-rejection drugs. Specifically, the recent introduction of Mycophenolate mofetil (MMF) (Cellcept®, Hoffman-LaRoche, Inc., Nutley, NJ) has largely replaced azathioprine, and the new microemulsion formulation of cyclosporine A (CsA) (Neoral®, Sandoz Pharmaceuticals Co, East Hanover, NJ) with improved drug bio-availability resulting in less inter- and intrapatient variability, are likely to improve overall outcome. Perhaps of equal importance is the specific dose and combination of drugs over time, especially in the early days and weeks following transplantation. Consistently higher CsA blood levels of 300-400 ng/ml for up to 4 months (TDx/TDxFLx® cyclosporine Monoclonal Whole Blood Assay, Abbott Laboratories, Abbott Park, IL) has resulted in a predicted biopsy verified rejection rate of about 10% (see Fig. 6.7b, Table 6.15). The use of calcium antagonists, such as verapamil, induce higher CsA blood levels resulting in fewer acute rejections and partial protection from CsA induced nephrotoxicity. Our current drug protocols in the perioperative period are reported in detail in chapter 6 (Tables 6.3, 6.4, 6.5 and 6.10).

OUTCOME MEASURES OF KIDNEY TRANSPLANT

The outcome of transplantation is largely dependent on a number of system factors, as summarized in Table 1.2. Most outcome reports on renal organ transplantation are concerned with graft and patient survival, the most important factors from the patient's standpoint. The close relationship between early onset of urine output and improved outcome on each subsequent level cannot be overemphasized, and every effort should be made to institute early urine output. Immediate onset of urine production and large urine volumes are more beneficial than oliguria or no urine at all. Adequate renal function is physiologically more meaningful than just large urine volumes. Some renal function, even though not optimal but enough to avoid dialysis is preferable to delayed function necessitating hemodialysis in the early postsurgery phase. Delayed function offers a better prognosis for the patient than does a never functioning kidney, or graft loss, which is the worst scenario of the kidney transplant procedure short of loss of life. Clearly, from the patient's standpoint, these outcome variables are of increasing importance in the order that is listed in Table 1.2. From a study, research or statistical view the importance of variables is reversed. This is because the differences between study groups are more easily demonstrated for variables expressed by mean ± SD, such as urine volume and serum creatinine, than with variables described by percentages, such as graft and patient survival. This fact becomes obvious as survival variables exceed 90% and approach 100%, making it impractical or less meaningful to assess improved outcome measures.

A number of perioperative factors affect the outcome after renal transplantation (Table 1.3). The importance and application of these are reflected in protocol designs reported in chapters 5 and 6.

Table 1.2. Seven levels of outcome variables after kidney transplantation

1. Time of Urine Output Onset
2. Urine Volumes
3. Kidney Function
   serum creatinine
   glomerular filtration rate
4. Delayed Function
5. No Function
6. Graft Survival
7. Patient Survival

Table 1.3. System factors affecting transplant outcome

1. The effectiveness of national and local organ donor procurement program
2. Transplant program organizational structure and integrity
3. Perioperative fluid and drug protocols
4. Organ ischemia times
5. Immunosuppression drug protocols over time
6. Donor and recipient selection criteria

THE IMPORTANCE OF OUTCOME VARIABLE SELECTION

In the early days of transplantation, patient and graft survival outcome data were meaningful variables when survival percentages were in the 50-60% range. Currently, survival rates exceed 95% for patient and 90% for graft survival at one year. Therefore, these variables are less practical from a statistical standpoint to demonstrate improvement with a new treatment, i.e., an immunosuppressive drug. The incidence of rejection has also decreased in some centers to 20% or less within one year, making rejection a less practical method of measuring the outcome of transplantation. Therefore, renal function, including measurements of glomerular filtration rate and serum creatinine levels have become more important as outcome measures. Also, survival data has shifted emphasis from short- to long-term (5 and 10 year) survival. These changes in the way we assess transplant outcome are the result of tremendous progress made in the fields of immunology, drug development and surgical technique.

THE OPERATING ROOM

Anesthesia and Recovery

General anesthesia with endotracheal intubation is the standard for the transplant procedure. Measures should be taken to maintain body temperature, including warming blankets. The authors prefer a supplemental epidural catheter

placed for postoperative pain control over approximately 24-48 hours. A nasogastric tube is placed after anesthesia induction and removed at extubation. A percutaneous triple lumen venous central line is placed, preferably in the subclavian vein. An internal jugular line may be uncomfortable for the patient, since it will be in place for the duration of anti-thymocyte globulin (Atgam®, Pharmacia/Upjohn, Kalamazoo, MI) induction immunosuppression administration. The authors also use one of the lines for intraoperative central venous pressure measurements to guide blood volume expansion (see chapter 6, Tables 6.4 and 6.5). In programs where Atgam® is not part of the protocol, a central line may not be necessary. It is beyond the scope of this book to discuss detailed anesthetic methods and drugs to be used. However, the authors cannot stress enough the importance of communication between the anesthesiologist and surgical team before and during surgery as well as in the recovery room. There must be total cooperation and trust in the best interest of the patient, keeping in mind that short ischemia times mean better kidney function early after transplantation, as well as improved long-term graft survival. In this context, it should be emphasized that transplant patients, in addition to renal failure, often times have other significant comorbidity including diabetes, hypertension and heart disease. Therefore, the typical renal failure patient tolerates a lower dose of most drugs, especially sedatives. It is the authors' practice not to leave the patient until extubation has occurred and convincing, stable respiratory and hemodynamic situations are established after transplantation.

Instruments and Equipment

The authors cannot emphasize strongly enough the importance of being organized with regard to instruments and operating room equipment. When a transplant instrument cart was introduced the operating room time for simultaneous kidney/pancreas transplant was shortened by approximately 2 h, from about 7 to 5 h. An example of a unicell storage device (Starsys, InterMetro, Wilkes-Barre, PA) is pictured in Figure 1.2. This unit comes on wheels, is securely locked between cases and is continuously restocked. The contents of the unicell may vary based on basic instrument setup and the surgeon's personal preferences. The purpose is to improve OR efficiency, time and cost, to decrease traffic in and out of the room and to eliminate frustrating waiting time while specific items are located. In this context, the availability of computerized surgical instrument tracking systems, such as one designed by Dr. William Fry (Lynn, Ltd., 912 North Main #3, Ann Arbor, MI 48103 (313) 996-1777) should be encouraged. In such a system, the transplant unicell would be tracked by a simple code.

Back-table Work

The back-table work occurs in two stages, as described in chapter 2. The first stage is in the organ procurement operating room, immediately following organ excision, and the second is in the recipient operating room immediately prior to the transplant procedure. In both instances, optimal conditions should prevail. The surgeons must sit down, have good lighting, use magnifying glasses and opti-

Fig. 1.2. A transportable instrument and equipment storage unit such as the one depicted in the figure results in shortened OR time, less traffic in and out of the operating room and elimination of much frustration.

mal instrumentation. In the procurement operating room the purpose is only to prepare the organs for packaging and shipment. In the case of kidneys, this involves separation of the en bloc removed kidneys, determination and documentation of anatomy, and perhaps performance of a biopsy. This procedure is described in more detail in chapter 2, and Figures 2.1-2.5. No reconstructive surgery should be performed in the procurement operating room. The procurement team is tired, and optimal surgical circumstances may not exist due to high traffic created from several teams and organ procurement personnel. These are factors that may result

in sterility breaks. Furthermore, since the procurement surgeon may not be the transplant surgeon, he or she should not engage in any reconstructive surgeries which may not be in accord with practices of the transplant surgeon. Regardless of the circumstances, the procurement surgeon should not compromise on the quality of separating and assessing anatomy of the organs. Instruments for separating the kidneys should be easily available apart from those used for organ procurement. These must be kept sterile and moved from the main operating field to the back-table setting before contamination occurs.

The back-table work in the recipient OR may or may not require that the surgeon be seated. Often times the authors perform the final preparation with the kidney placed in a flat bowl of ice slush on top of the recipient's lower abdomen. This would be the case when the transplant surgeon also performed the procurement himself and does not expect any fine microvascular reconstructive surgery. However, when the kidney has been shipped in, or when reconstructive surgery is anticipated, a back-table setup should be in place. For pancreas transplantation, the back-table work is more elaborate, involving many steps and requiring microvascular instrumentation and special equipment (chapter 3, Tables 3.1-3.2, Figs. 3.1-3.4).

Special Surgical Considerations

The use of surgical magnifying lenses of at least 2.5X magnification is recommended. Technical errors are less likely to occur with proper magnification.

Micro-instruments

Several microsurgical instruments are highly recommended, available from companies such as Codman (Johnson & Johnson Professional, Raynham, MA) and Scanlan (Scanlan International, St. Paul, MN). For back-table work the authors prefer the nonlocking needle driver with a round handle that can be held as a pen and rolled in the surgeon's hand while suturing (Fig. 1.3a). The nonlocking needle driver allows continuous suturing without loss of eye contact with the operating field. Figure 1.3b shows a close-up view of the nonlocking needle driver used by the author for fine vascular surgery including backtable work and vascular access for hemodialysis. Needle holders with locking mechanisms often lead to loss of control while resetting the needle between each suture.

Along these lines the authors use micro-pickups of similar design depicted in Figure 1.4 a,b. As pointed out elsewhere in this publication, there must be no grabbing of blood vessels involving the intimal structures. Only pulling and pushing should suffice. Of course, perivascular adventitial fibrous tissue can be used to pull vessels.

The author recommends two types of micro-forceps. A small, indented "eye" improves the grip for vascular adventitial tissue. The sharp-tipped "Blue darter" forceps are especially useful for handling very small structures and for dilating vessels for corner suture placement (Fig. 1.4a,b).

For the transplant procedures themselves the same instrument principles prevail. However, the instruments must be longer to reach into the wound. Figure 1.5a

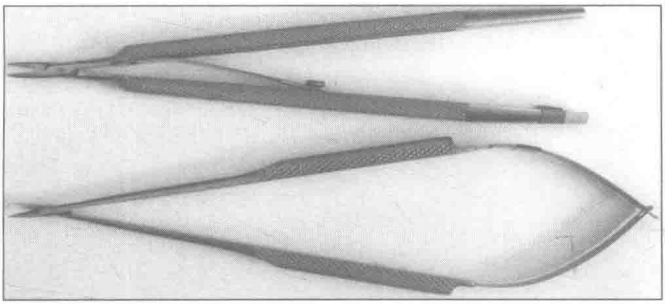

Fig. 1.3a. Examples of two types of micro-surgical instruments used for fine vascular reconstructions and back-table bench work.

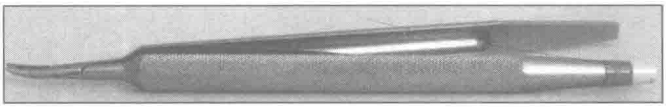

Fig. 1.3b depicts a nonlocking needle driver in more detail.

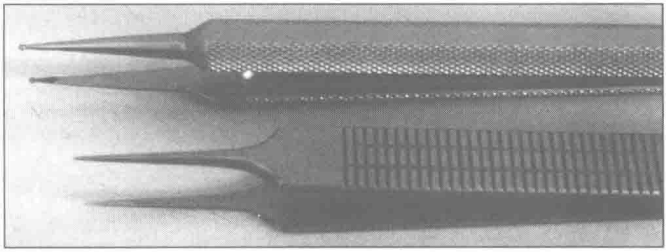

Fig. 1.4a. Example of micro-forceps, one with small indented eyes suitable to pick up small perivascular tissue and one with sharp pointed micro-forceps for very fine backtable work.

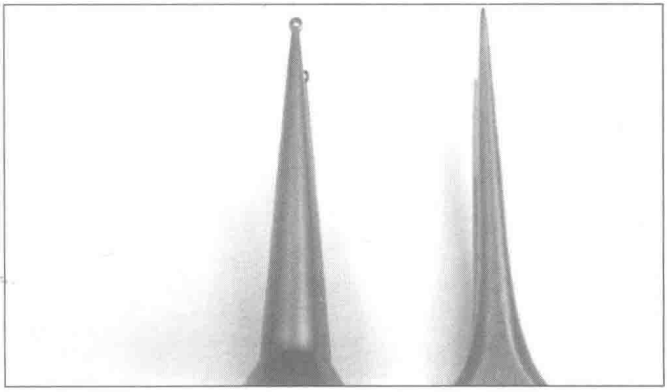

Fig. 1.4b depicts these two instruments in detail.