HISTORY OF THE TRANSURETHRAL RESECTION SYNDROME

GEORGE F. STEINHARDT, M.D.
RALPH R. LANDES, M.D.

Dr. Steinhardt is with the Danville Urologic Clinic in Danville, Virginia, and is Clinical Assistant Professor, Department of Surgery/Division of Urology at the University of North Carolina, Chapel Hill.

Dr. Landes is with the Danville Urologic Clinic in Danville, Virginia, and is Clinical Professor, Department of Surgery/Division of Urology at the University of North Carolina, Chapel Hill.

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The transurethral resection (TUR) syndrome is characterized by the sudden development of apprehension and irritability during or shortly after a transurethral resection of the prostate. Emesis, cyanosis, fasciculations, lower abdominal pain and convulsions can accompany the initial symptoms. Although hypertension and bradycardia are frequently present at first, shock may soon develop. Anemia (out of proportion to blood lost at the time of surgery), oliguria and uremia sometimes precede the fatal outcome.[1]

This symptom complex was first described clearly in 1946 by Creevy and Webb.[2] In their report they discuss a patient who developed restlessness following resection of 58 Gm of prostatic tissue. The patient's serum was found to have a dark red discoloration on the day of surgery. Although no quantitative analysis was performed, the dark red color was attributed to free hemoglobin. The serum cleared on the first postoperative day, but the patient developed progressive oliguria and uremia. In spite of peritoneal dialysis, the patient died of pulmonary edema on the tenth postoperative day. A postmortem examination showed that the renal tubules were filled with hemoglobin casts. The critical observations in this patient were the discoloration of the serum and the subsequent postmortem demonstration of lower nephron disruption attributed to the heme pigment deposition in the renal tubules.

In a letter from Dr. Baxter Smith in 1946, we obtain some intimate background information on the most dramatic events leading up to unraveling the riddle of many previously inexplicable deaths associated with TURs. The story begins at the Old Town & Country Club in St. Paul, Minnesota, where the Twin Cities Urologic Society held its meetings. Dr. Smith, then a partner of Drs. Creevy and Webb, describes a conversation he held during a cocktail hour in the spring of that year with Richard Kennedy of Eau Clair, Wisconsin, and John Emmett of the Mayo Clinic:

"[We] were discussing the clinical picture later named the transurethral syndrome, and we agreed it seemed to be associated with blood loss, but not necessarily related to the size of the resected gland; Dr. Emmett said that he had seen it following resection for bladder tumor. Later, when Dr. Kennedy and I were continuing the discussion he said that Dr. F.E.B. Foley had noted bloody ureteral spurts during a resection when the patient had not been bleeding prior to the resection. To me this seemed that it had to be due to hemolysis and I mentioned this to Drs. Creevy and Webb.

"Shortly thereafter in May of 1946, I was resecting the prostate of a physician's father at St. Barnabas Hospital when Dr. Creevy called for me to help him with a difficult nephrectomy with which he was having trouble. Dr. Webb took over the resection. On the way home that evening I stopped to see the patient who looked sick, as patients with the TUR syndrome do. I drew some blood and let it clot and following the clotting the serum looked about as red as did the clot proving the presence of hemolysis as we had predicted. The patient went on with the typical picture of transurethral syndrome. We treated him with our rather crude peritoneal lavage. He expired probably of pulmonary edema although we didn't know anything about the dynamics of the syndrome at that time. Autopsy showed lower nephron nephrosis with hemoglobin casts."

Dr. Creevy told one of us (Dr. Landes) a slightly different version of this story many years after the event and shortly before he died. According to Dr. Creevy, the birth of the idea occurred at the above-mentioned meeting when Dr. Foley mentioned that he had observed translucent bloody efflux from both ureters during a TUR on a patient whose urine had been clear preoperatively. Dr. Creevy suggested that this was probably due to hemolysis which might explain the TUR syndrome.

Drs. Creevy and Webb subsequently wrote up their case for publication. Their bibliography is remarkable for its lack of urologic notations. Of 38 references, only three were urologic and two of them were personal communications. It is astounding that a major cause of mortality from an innovative operative procedure could go unrecognized, or at least unreported, for 15 years *after* the procedure had been generally accepted. But it seems to be the case for the transurethral resection syndrome.

Although Dr. Creevy was the first to report the reaction, he gave credit in his paper to William McLaughlin, then a special fellow at the Mayo Clinic, for first suggesting the idea. Later, at the Hitchcock Clinic, Dr. McLaughlin wrote two papers on the subject,[3,4] in which he described the absorption of irrigating fluid (water) into the prostatic veins with resultant hemolysis and renal damage. In trying to obtain credit where he no doubt thought credit was due, Dr. McLaughlin wrote, "Although this concept was independently arrived at by one of us (W.L.M.), others have come to similar conclusions."[3] It is unlikely that McLaughlin was the first resident to see his ideas in print, penned by a mentor, nor is he likely to be the last.

Just before the publication of Dr. Creevy's paper, W.E.M. Wardill in England reported to the Medical Society of London on his experience with transurethral resection.[5] He described in detail the case of a 64-year-old man who developed oliguria postresection and was found to have "transfusion nephrosis" despite the fact that he had received no blood. No conclusions were drawn from the case, but one wonders how many other clinicians had similar experiences but, lacking an explanation, dismissed their observations and quickly resumed resecting.

Shortly after the publication of Dr. Creevy's paper, a flurry of reports appeared on the topic. What had gone unnoticed for 15 years was now an everyday occurrence. M. Griffin even estimated that the incidence of the TUR syndrome was 2.5% of all resections, and he noted that a patient with a small prostate gland seemed to be more at risk for its development.[6] One of the more important papers appearing at this time was written by Landsteiner and Finch.[7] They observed that absorbed hypotonic fluid could result in hemolysis and then uremic death. They also measured the amount of free hemoglobin in the sera of 15 patients undergoing resection. Ten of these patients were noted to have significant hemolysis, but none of them incurred any untoward sequelae. To test further the hypothesis that the hemolysis was due to absorption of water by way of the periprostatic veins, the authors ingenuously added 1 Gm of sodium salicylate per liter of irrigating solution. Then they measured the postoperative sera for salicylate and calculated the amount of water that had to be absorbed to produce the observed concentration of salicylate. They estimated that as much as 1000 ml of irrigating fluid could be absorbed through the venous channels opened during the operation. Much larger volumes of irrigating fluid were documented by others. It is probable that the observations of Landsteiner and Finch were made independently of Creevy and Webb, for they did not refer to any other work except their own.

Although Creevy and Webb, McLaughlin, and Landsteiner were the first to identify absorption of hypotonic irrigating fluids as a problem, earlier urologists recognized that the transurethral resection had its hazards. G.R. Livermore in 1936 noted that uremia "occurs far more frequently than is reported . . . [and] usually causes death."[8] No explanation for the uremia was presented, but we assume that at least a few of the uremic deaths were due to the TUR syndrome. Extravasation during resection was also recognized as a potential complication by urologists in the 1930s and, retrospectively, we can understand that absorption of fluid was inevitable with these occurrences. In 1935 D.R. Rudnick presented five cases of detached trigone during resection.[9] Regarding one patient he wrote, "Transurethral resection was carried out under nitrous-oxide anesthesia. The resection had proceeded with the removal of a large quantity of tissue, estimated at between 4 and 5 grams, when difficulties were met with. The visual field suddenly became obscured and could not be cleared up with irrigation. . . . "

In the conclusion of his paper, Dr. Rudnick wrote prophetically: "The only plausible explanation [for shock and death] is that a toxic irrigating fluid, such as boric acid or tap water enters open veins." No urologist can help but feel a wave of compassion for the early resectionist who tried in vain to see through the persistent bloody ooze of opened venous sinuses. Although the problem was not recognized, many patients must have died in the early years of resection as a result of fluid absorption since the mortality rate for transurethral resection was astonishingly high. At Cook County Hospital in Chicago, 283 patients underwent resections between 1933 and 1935. Of these, 51 (18.5%) died.[10] In a personal conversation, Dr. Rolnick told one of us (Dr. Landes) that 25 of the first 50 patients died. G.J. Thompson and H. Buchtel felt that, for the patient, the "nervous strain, the lithotomy position for prolonged periods, the long continued instrumentation with resultant trauma of the perineum and pelvis had a very deleterious effect."[11] Despite the nervous strain, it is more likely that fluid absorption was a more significant factor in the death of many of these patients.

It is interesting that early resectionists recognized that it was not necessarily large glands that led to complications. Glands without intravesical extension were believed to be the most difficult to resect.[12] This fact is understandable in view of the poor optics of the time and the proximity of the periprostatic veins to the bladder neck. As with any procedure, greater experience led to improved survival statistics, and the severity of the complications was found everywhere to be in proportion to the experience of the operator.[13] Resectionists learned empirically to stay within the surgical capsule of the prostate; by so doing, morbidity was minimized. We note that the mortality for a TUR had been reduced to around 1.5% when Drs. Creevy and Webb first described the TUR syndrome.

The relationship between the TUR syndrome and hemolysis due to intravascular infusion of hypotonic irrigating solutions led to intense activity in developing safer irrigation solutions. In 1938 Carl Ebert, with the aid of a biochemist, Lucien Bavetta, was the first to use a 5.4% glucose solution as an irrigant.[14,15] This came as a result of insights he gained following the uremic death of a resected patient who had incurred much extravasation. Although Dr. Ebert did not report his experience, he used this isosmotic and nonelectrolyte solution for many years. The glucose solution produced massive hyperglycemia if a significant amount was absorbed, thus unmasking the huge quantity of fluid that was entering the bloodstream. The glucose solution became quite sticky when dry, and the instruments and gloves used in

VIGNETTES AND GOSSIP SURROUNDING THE EARLY DAYS OF TUR

Adrian W. Zorgniotti, M.D.

My first exposure to transurethral surgery came when I was a third-year medical student assigned to the Long Island College Hospital in Brooklyn — fourteen years after the Stern-McCarthy resectoscope had been introduced. The surgeon was John J. Bottone, a man with a gruff voice and a heart of gold. The operation was, as it is today, a one-man procedure with the notable exception that an obedient, compliant and wide awake assistant was an absolute necessity, as we shall see.

Maximilian Stern (1877-1945), the true father of the modern resectoscope.

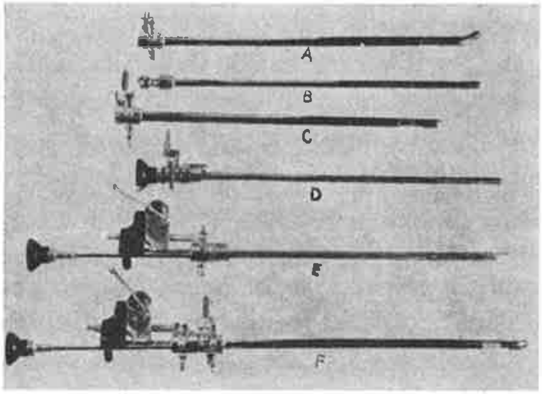
The resection was performed in the "cysto room" on a table whose positions were set by turning several wheels with protruding handles. The instrument was the latest Stern-McCarthy, with a 68A foroblique lens tipped with the tiniest light bulb I had ever seen. The sheath was of yellowish brown Bakelite with a Timberlake obturator, and Dr. Bottone went to some length to point out areas on the lower part of the fenestrum that had been scorched by previous careless operators who had failed to release the foot switch as the loop entered the sheath and disappeared from view. This lack of eye-foot coordination was inexcusable.

The Bovie unit, the miracle that permitted cutting and coagulating under water, was also a masterpiece of the cabinetmaker's art, having been fashioned of finely grained woods, its black controls standing out against a varnished brown wood background. This electric wonder had one serious defect in everyone's eyes — it had only one foot control. An assistant had to stand by the operator with a small strainer in one hand to catch the pieces of prostate that eddied out of the sheath while the other hand was firmly poised on the machine's current-changing switch ready to respond to Dr. Bottone's hoarse commands of "cut," "burn," "cut," "burn," etc. It was rough being a medical student in those bygone days!

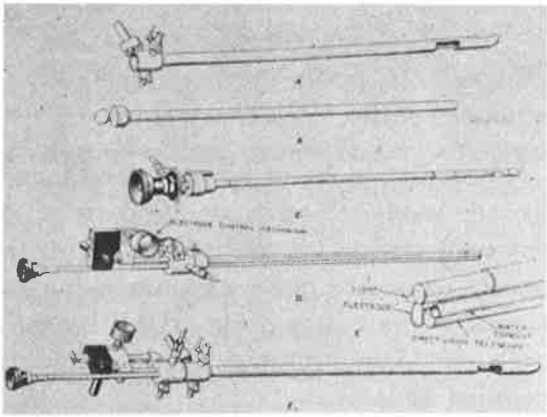
Two Pioneers of TUR

The Ferdinand C. Valentine Medal of the Section on Urology of The New York Academy of Medicine has been awarded to two pioneers in transurethral surgery: Theodore M. Davis (1966) and Reed M. Nesbit (1976). Both men spoke about their early experiences with TUR and both evening discourses were delightful experiences for those lucky enough to be present.

Dr. Davis was one of the first to realize the importance of Maximilian Stern's instrument, which was introduced in 1926. Davis's first problem was to obtain a "resectoscope," as Stern had named it. The Wappler Electric Company, Inc. (later called ACMI), would not sell him one without Stern's approval — a situation reminiscent of the early days of a more recent technique, prostatic cryosurgery. A loophole in Stern's agreement with Wappler was found, however, whereby a resectoscope could be "loaned" without breach of contract. Thus Davis got his instrument.



Theodore M. Davis's improvement of the Stern resectoscope was the forerunner of the Stern-McCarthy instrument: (A) original Stern sheath with long beak and 5/8-inch fenestrum; (B) obturator; (C) Davis's sheath with short straight beak and 7/8-inch fenestrum with a depth 3/5 that of the sheath; (D) observation right-angled telescope; (E) working parts; (F) assembled instrument.



The Stern resectoscope, an instrument that had all of the essentials of today's models: (A) sheath; (B) obturator; (C) examining telescope; (D) direct vision telescope, water conduit, light carrier and cutting loop; (E) end of working parts enlarged; (F) assembled instrument (loop may be seen in fenestrum).

The Stern resectoscope had a telescope and movable loop as does the present-day instrument. However, when Davis used it with the existing cutting-current generator, he encountered considerable hemorrhage in the patient which had not been expected. Davis's next step was to try passing a hemostatic current through the loop from a different generator, but this resulted in destruction of the loop. Undaunted but worried, he managed to halt the bleeding with a Bugbee electrode passed through a cystoscope. Davis then set about to improve the resectoscope loop so that it could stand the hemostatic current without shorting out. Thus was born the Stern-Davis resectoscope (1931).

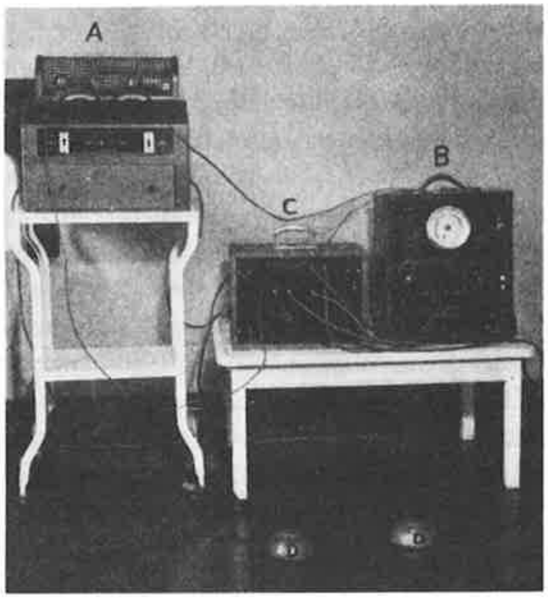
Davis also worked with Wappler and, later, W. T. Bovie of Harvard in perfecting current generators that worked under water and produced separate currents for cutting and hemostasis.

Dr. Davis became highly skilled at the TUR and made other contributions to the development of the instrument and the operation's technique. Nesbit, in his 1976 Valentine presentation, said "Davis made the operation look easy" and attributed to him a big surge in demand for instruments of "panic proportions." Urologists quickly learned of the difficulties. Articles began to appear with titles such as: "Prostatic Resection Without the Moonlight and Roses" (1933) and "Second Thoughts on Prostatic Resection" (1934). The growing pains had begun.

Two "signs of the times" in Davis's talk are worth recounting. Most of his resections were done on Sundays when local demand for electricity was at a minimum and so the current generators could be counted on to perform reasonably well. The second interesting bit of information was the fact that in those early days the operation was performed in Davis's office after which the patient was transferred to the hospital for postoperative care!

Dr. Nesbit's discourse in 1976 was similarly entertaining and informative. He reviewed the entire history of resection. His most important points were that the development of the Stern-McCarthy resectoscope was "fundamental" and "has stood the test of time."

The McCarthy instrument used an open fenestrum and beak as we know it today. The sheath was of Bakelite, which was first used by Kenneth Walker for transurethral electrosurgery. The lens system was the superb ACMI foroblique telescope. The electrical system was integrated into a smooth, well-insulated rack and pinion working element. This instrument remained the standard for many years.



Davis also made contributions in the area of current generators for both cutting and coagulation: (A) early generator; (B) spark gap diathermy unit; (C) electromagnetic switch; (D) foot switches.

Nesbit also spoke of his own contribution, the one-handed Nesbit modification of the McCarthy device. He told of how ACMI had initially refused to make a prototype but that later, after some convincing, ACMI agreed to make one. This prototype was subsequently modified by Iglesias.

Nesbit ended his talk with a quotation from Bigelow who, though speaking of litholapaxy, could just as well have been making a prophecy for TUR:

> "I know of no other surgical operation in which a little want of skill or of care is so insidiously liable to fatal accident. The skill here is of a peculiar kind: and though a surgeon may use the knife well, it does not follow that he also uses the lithotrite [resectoscope] well."

resection developed a gummy feeling. Therefore, Ebert changed the solution from glucose to urea. A 1.8% urea solution resulted in some hemolysis, and so he finally settled on a 0.9% urea solution, but this irrigant never became popular.

Other solutions were investigated. R.M. Nesbit and S.I. Glickman found glycine to be a satisfactory irrigant.[16] In a study published in 1951, Drs. Goodwin, Cason and Scott[17] suggested that a 3% mannitol solution was an ideal irrigant. In addition to its nonhemolytic and nonelectrolytic properties, mannitol was inexpensive, nontoxic, a diuretic, and did not clog up the instruments. Using the 3% mannitol solution, they found no hemolysis in more than 250 resections and, justifiably, concluded that postoperative hemoglobinemia could be eliminated by using improved irrigating solutions. They also observed that hypertension was an early sign of the impending TUR syndrome and attributed this to the hypervolemia produced by the intravascular infusion of the irrigant as first suggested by Dr. Landes.

Although there was widespread recognition of the need for an isotonic irrigant, some controversy developed over the exact pathogenesis of the TUR syndrome. It was confirmed that some patients had typical post-TUR resection reactions, even though isotonic solutions had been utilized and there was no hemolysis.[18,19] Failure to recognize hemolysis was usually due to a delay in drawing blood, since hemoglobin is rapidly cleared from the blood by the spleen and liver. On the other hand, it was shown that water could be a safe irrigant. In one series, 428 consecutive patients were treated without a single reaction.[20] Hemolysis was noted in 27 patients, but the effects were inconsequential. The absence of problems in this particular series is probably more of a tribute to the author's ability to stay within the confines of the prostatic surgical capsule and avoid overdistention of the bladder than a testimonial for the safety of water and the harmless nature of hemolysis.

The champions of isotonic irrigants accused the untroubled advocates of distilled water of staying out of trouble by leaving a large layer of adenoma behind (*i.e.,* doing an incomplete resection). However, experimentalists repeatedly demonstrated that the relatively low levels of hemoglobinemia seen clinically at the end of a TUR rarely caused renal failure. Only when massive volumes of water were infused would hemolysis develop to the degree that renal failure ensued.[21] Hemoglobinemia was soon discounted as the sole cause of oliguria and uremia following TUR of the prostate. There was no doubt that hemolysis did occur, but the researchers began to doubt that the levels of free hemoglobin that resulted were sufficient to cause problems. To support this, they pointed to the early work of inquisitive investigators who unashamedly injected hemoglobin into patients while investigating such things as black water fever and transfusion reactions. D.R. Gilligan and coworkers, for example, injected 1 to 16 Gm of hemoglobin into 12 patients to produce serum hemoglobin levels of 40 to 380 mg% with "no febrile or other untoward reactions."[22]

What, if not hemolysis, is the cause of the TUR syndrome? Certainly the reaction itself is real enough, as any urologist who performs transurethral resections knows. As with many clinical problems, the answer is multifaceted. Studies have shown conclusively that as an isotonic irrigant solution is absorbed into the periprostatic veins, the total amount of body water increases. This may produce signs of water intoxication that resemble the TUR syndrome in many ways. The rise in total body water leads to dilutional hyponatremia and a decrease in extracellular osmolarity,[23] cerebral and pulmonary edema with resultant confusion, nausea, hypoxemia and cyanosis. Combined blood loss and hemolysis produce anemia and shock[24] — an ideal setting for acute tubular necrosis. Certainly hemolysis potentiates the renal damage, but hemolysis can be prevented by using isotonic solutions.[25] Lastly, bacteremia at the time of surgery may contribute substantially to the development of postoperative hypotension, oliguria, and uremia, especially if the periprostatic venous plexus is opened prematurely and bacteria have direct access to the bloodstream for prolonged periods.

The story of the transurethral resection reaction constitutes an interesting chapter in the history of urology. Early resectionists were aware that the "undesirable sequelae that may follow transurethral surgery are of such frequency and gravity that our utmost consideration is demanded."[26] However, at that time, most urologists were too preoccupied with achieving personal mastery over the unforgiving and demanding technique of transurethral resection to recognize just what factors contributed to the "undesirable sequelae."

Pioneers in the TUR technique slowly learned that complications could be minimized by restricting the resection to the confines of the surgical capsule of the prostate. Avoiding the periprostatic veins has led to an acceptable mortality rate. Widespread utilization of isotonic nonelectrolytic irrigating solutions has further decreased the incidence of the TUR syndrome to less than 1%.[27] Reducing the operating time to one hour or less has dramatically lowered the frequency of reactions. Treating hyponatremia by administering 5% NaCl and hypervolemia by administering appropriate diuretics has been of great value.

Transurethral prostatic surgery has thus emerged as the hallmark of the truly educated and skilled urologist.

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