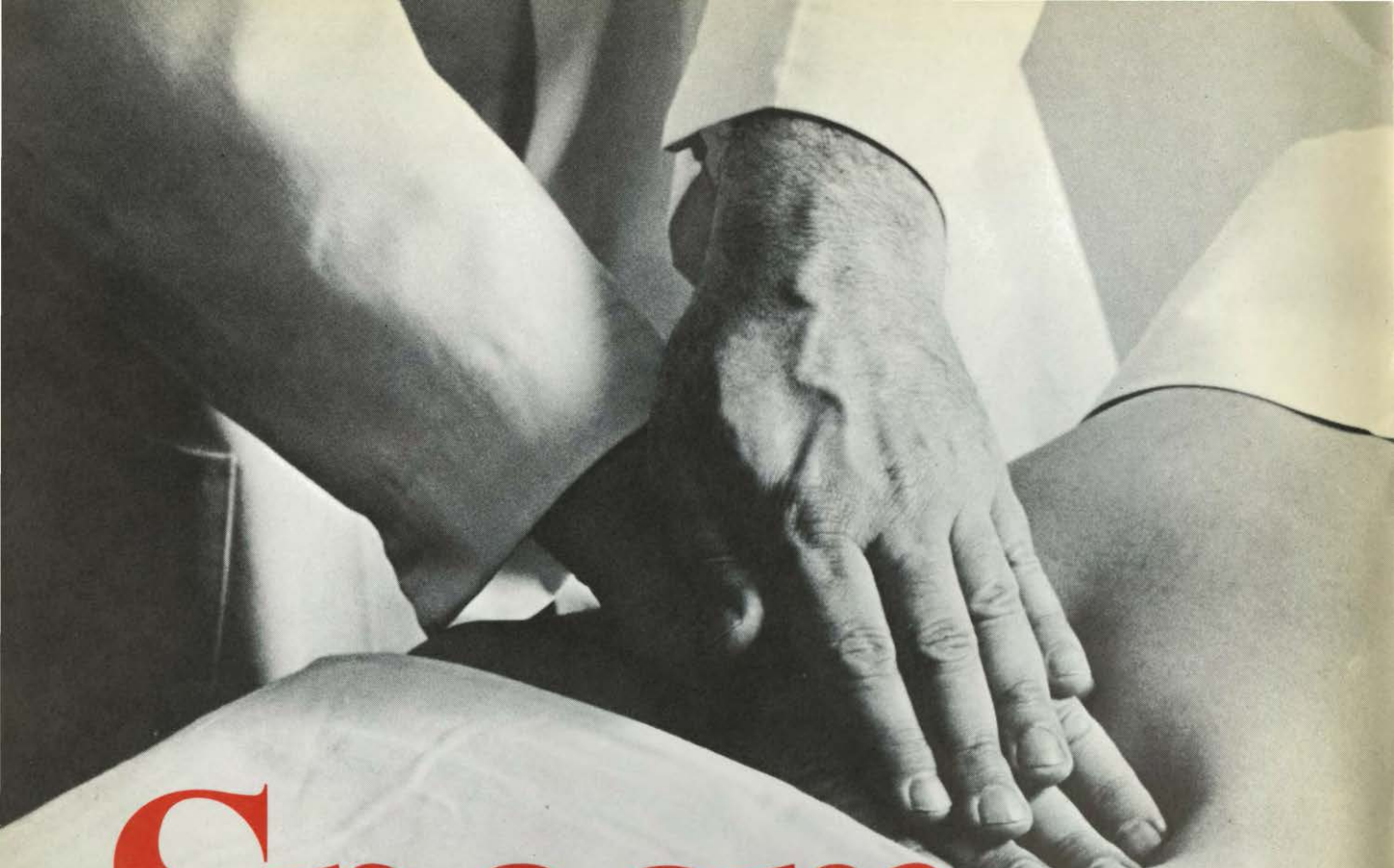


# MCV/Q

MEDICAL COLLEGE OF VIRGINIA QUARTERLY  
VOLUME NINE • NUMBER THREE • 1973





# Spasm reactor?

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atropine sulfate	0.0194 mg.	0.0194 mg.	0.0582 mg.
hyoscine hydrobromide	0.0065 mg.	0.0065 mg.	0.0195 mg.
phenobarbital	( $\frac{1}{4}$ gr.) 16.2 mg.	( $\frac{1}{2}$ gr.) 32.4 mg.	( $\frac{3}{4}$ gr.) 48.6 mg.

(warning: may be habit forming)

**Brief summary.** Adverse Reactions: Blurring of vision, dry mouth, difficult urination, and flushing or dryness of the skin may occur on higher dosage levels, rarely on usual dosage. Contraindications: Glaucoma; renal or hepatic disease; obstructive uropathy (for example, bladder neck obstruction due to prostatic hypertrophy); or hypersensitivity to any of the ingredients.

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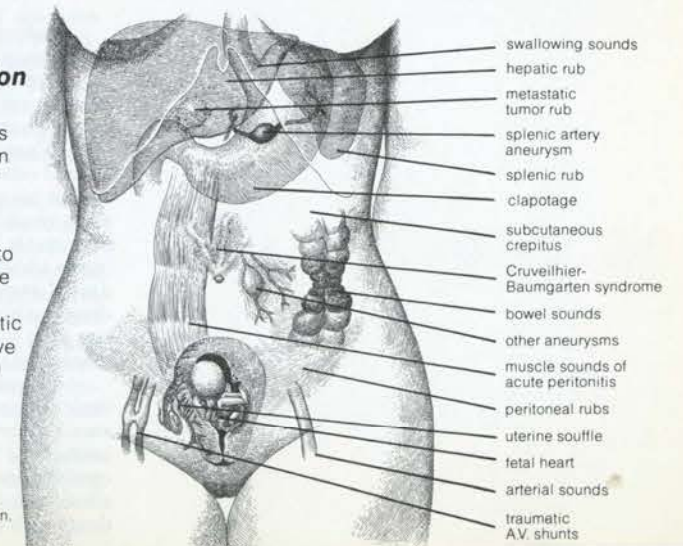
on physical examination of the abdomen:

### Pointers on auscultation

"It is fair to say that the stethoscope is as important as any instrument for examination of the gastrointestinal tract."\*

Sources of diagnostic noises to be considered during a routine abdominal auscultation. In addition to visceral-peristaltic activity, these sounds may have their origin in visceral-parietal friction as well as in vascular and muscular activities.

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\*Palmer, E.D.: Clinical Gastroenterology, ed. 2, New York, Hoeber Medical Division, Harper & Row, Publishers, 1973



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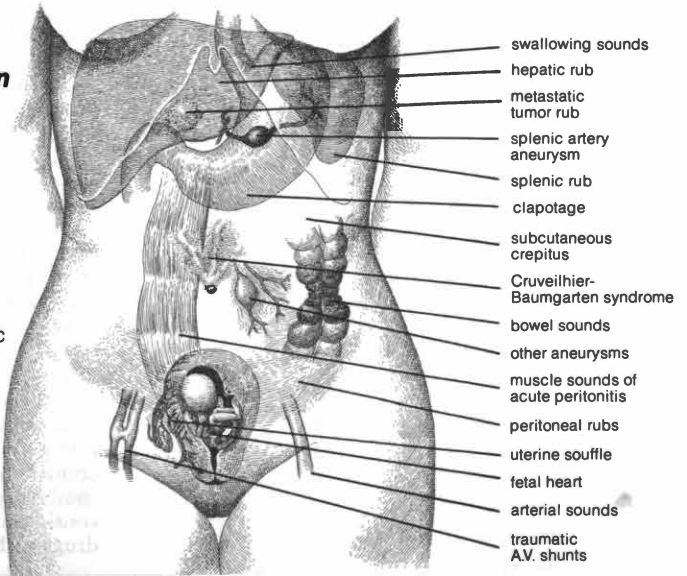
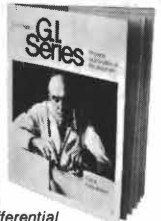
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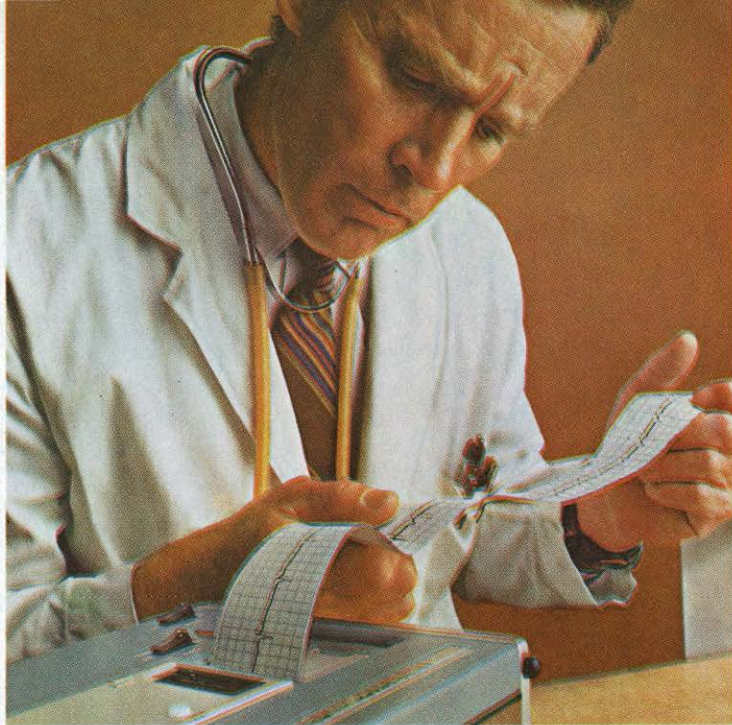
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in presence of impaired renal or hepatic function. Paradoxical reactions (*e.g.*, excitement, stimulation and acute rage) have been reported in psychiatric patients and hyperactive aggressive children. Employ usual precautions in treatment of anxiety states with evidence of impending depression; suicidal tendencies may be present and protective measures necessary. Variable effects on blood coagulation have been reported very rarely in patients receiving the drug and oral anticoagulants; causal relationship has not been established clinically.

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MEDICAL COLLEGE OF VIRGINIA QUARTERLY

*A Scientific Publication of the School of Medicine  
Health Sciences Division of Virginia Commonwealth University*

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## INTRODUCTION

The Annual Stoneburner Lecture series this year has been devoted to clinical adult and pediatric urology. The purpose of the papers presented was to give the urologist and the primary care physician an overview of the problems and the latest developments and advances in technique. We were fortunate to have as the Stoneburner Lecturer, Dr. John K. Lattimer, Professor of Urology and Chairman of the Department of Urology at the Columbia-Presbyterian Hospital in New York. Dr. Lattimer's talks on "The Optimum Treatment of the Undescended Testis" and "Carcinoma of the Prostate: The Great Widow-Maker" were extremely timely. This series of lectures was co-sponsored by the Mid-Atlantic Section of the American Urological Association.

Included in this group of papers is the First Annual Carl Bunts Lecture in Urology. Dr. Bunts retired as Chief of the Urological Service at the McGuire Veterans Administration Hospital in June of 1972 and was a pioneer in the management of the urinary tract of the spinal cord injury patient. Dr. John Hutch was the first Carl Bunts Lecturer and was the fourth resident whom Dr. Bunts trained in urology. Dr. Hutch was born in the State of Iowa where he attended the University of Iowa undergraduate school and the School of Medicine. Following an internship at Salt Lake County General Hospital, he completed a residency in Urology at the Veterans Administration Hospital in Richmond. After returning to Iowa for one year, he then became associated with the University of California at San Francisco where he was Associate Professor of Urology. He was a pioneer in ureteral antireflux surgery and was a world authority on the anatomy and physiology of the lower urinary tract, urinary control and urinary incontinence. Dr. Hutch met an untimely death on September 14, 1972. This paper is unique in that it is an expression of the experience of a pioneer through the development of a surgical procedure which has been a real contribution to the management of the patient with urinary tract infections.

Warren W. Koontz, Jr., M.D.  
Professor and Chairman  
Division of Urology  
Medical College of Virginia  
Virginia Commonwealth University

# A Twenty-Year Experience with Surgery for Ureteral Reflux\*

JOHN HUTCH, M.D.

It is a real honor to be asked to return to Richmond, particularly for a Northern boy, to give the first R. Carl Bunts Lecture. Many in the audience will wonder why all this fuss about the retirement of the head of a small department in a VA Hospital in Richmond. Those who wonder only do so because they did not have the privilege of knowing Bunts well. I could say that Bunts was a great leader, a great scientist, and a great physician. I could say that Bunts had no children and that he and his lovely wife, Dori, have made Bunts' residents their lives and family. While all these things are true, they fall woefully short of the mark in describing or attempting to explain why there is all this fuss about Carl Bunts. Bunts is being honored because he is a rare human being, the kind of person that most of us meet only once or twice in a lifetime. I had the honor of being Bunts' fourth resident from 1948 to 1951. He cast his spell over me then, and as I have met the other residents through the '50's and through the '60's and now into the '70's, I sense in talking to them that he has done the same thing to them now that he did to me and to my contemporaries 25 years ago. Maybe it is magic, maybe Bunts has congenital charisma, maybe Bunts has a quality that our young people strive to achieve, namely, being a warm human being.

With this introduction, I will move on to the scientific part of the presentation which deals with 22 years of experience in vesicoureteral reflux, most of which, of course, started right here in Bunts' department.

When I began my residency in Richmond, Vir-

ginia in 1948, urologists were aware of vesicoureteral reflux as an entity. It was known to occur in patients with badly distorted urinary tracts, particularly those with obstruction at or below the bladder neck, and those with urinary tract tuberculosis or neurogenic bladders. No one sought out reflux *per se*, and if it was found, it was not considered to be causative but rather the result of the distorted urinary tract. Certainly, no one thought of treating reflux *per se* but rather in treating the disease that was causing the reflux. This apathy towards reflux is reflected in the fact that during the five-year period from 1943 to 1948 no articles on reflux appeared in the *Journal of Urology*. Since our hospital in Richmond was a paraplegic center, we were more aware of reflux than most urologic departments throughout the country. We were doing two-film cystograms on all of our paraplegic patients when I arrived there in June, 1948, and we had been doing this for some years. We felt great concern about the progressive dilatation of the upper urinary tract that we were observing in some paraplegic patients. The theory was that these urinary tracts were dilating because of an obstruction at the ureterovesical junction, and our therapy was aimed at cutting out this obstructive segment and reimplanting the ureter into the bladder in such a way that the obstruction could not occur. We used the same technique in paraplegics that we used in patients with bladder tumors in whom we did a partial cystectomy with ureteral reimplantation into the bladder. We kept groping for a better method of performing ureteral reimplantation. We used the fish-mouth technique; we also tried the direct mucosal-to-mucosal type of anastomosis that Cordonnier was then popularizing in ureteral sigmoid anastomosis. We made some abortive attempts at tunnel formation by passing the ureters through the bladder wall obliquely, but it must be remembered that we were operating to overcome obstruction and that

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\* This is a transcription, edited by Dr. Warren W. Koontz, Jr., of a lecture presented by Dr. Hutch at the First Annual R. Carl Bunts Lecture in Urology, May 25, 1972. Dr. Hutch met an untimely death on September 14, 1972.

our main effort was to secure the ureter in its new location in an unobstructed manner. The results of these operations were disappointing. Improvement was rarely demonstrated either clinically or by x-ray. Early in my residency, we performed five consecutive operations based on these principles. In three patients, all function was lost from the involved kidney, and in two, function was preserved only by nephrostomy drainage. We now know that these operations failed because they did not stop the reflux, but this was not appreciated then. At this time, the prevailing feeling among urologists was that operation for megaloureter at the ureterovesical junction was contraindicated because the results were often so disastrous.

Dr. Bunts suggested that I attempt to find out what was happening to the urinary tracts of patients with neurogenic bladders with the passage of time. We had a wealth of material to draw from, including the records and x-rays of several hundred paraplegics taken since the founding of the department in 1945. These x-rays were mostly IVP's, some retrogrades, and a large number of cystograms. Reviewing this material case by case, I became aware that some of the paraplegic patients were developing a specialized type of saccule or diverticulum that was located at the point where the ureter was entering the bladder. Certainly these bladders contained many saccules and diverticula, but there was something different in the appearance about this particular saccule and its consistent location. I set aside a number of cystograms demonstrating this saccule and showed them to Dr. Bunts. After reviewing these x-rays, we arranged to cystoscope these patients to determine whether there was any connection between the saccule and the ureteral orifice. Cystoscopy proved that the saccule was always above and lateral to the trigone; the ureter always ran down the floor of the saccule. In each case the catheter passed through this segment with no obstruction, and there was no thickening of the intravesical ureter to account for obstruction of any type. From these observations it was apparent that the ureteral hiatus was dilating. In the process of dilation, the intravesical ureter was falling into the saccule that resulted and was losing the support of the bladder muscle behind it. It seemed that the logical method to correct this was to excise the saccule surgically and to push the ureter into the bladder and then to close the bladder behind the ureter.

We knew that we had to repair the bladder

muscle behind the saccule, but we did not know what to do with the mucosa. At that time, I felt that was not very important. We decided to sew the mucosa under the ureter. Unfortunately, this proved to be a mistake and was the technical defect that caused some of the early operations to obstruct. The simple logic involved was appealing, and since our efforts to correct the dilated upper urinary tract of the paraplegic had produced such poor results, Dr. Bunts was more than willing to try this new operation. Therefore, on May 17, 1950, with Dr. Bunts as my assistant, we did a left ureterovesicoplasty on a 28-year-old paraplegic patient with left reflux. We believe that this was the first time any person was ever operated on specifically to correct reflux. To our joy and amazement, three-week and six-week postoperative cystograms showed no reflux, and the postoperative intravenous pyelogram looked better than the preoperative one. Encouraged by our success, we performed our second operation on June 23, 1950. It, too, was successful. Our first bilateral ureteral vesicoplasty was done on August 31, 1950. By April 1951, we had operated on 9 patients and 11 ureters and had successfully stopped the reflux in 8 of the ureters and had encountered no obstruction.

Dr. Austin Dodson, our consultant, had been watching our series develop, and he suggested that it be presented to the prize essay contest sponsored by the American Urological Association, rather than submitting it to the *Journal of Urology* through regular channels. This essay was awarded first prize and was presented before the American Urologic Association in Chicago in June 1951. This resulted in the elimination of Dr. Bunts' name as co-author since he was not eligible under the rules of the essay contest. If the paper had been submitted to the *Journal of Urology* through regular channels, Dr. Bunts would have been a co-author, and the operation would have been the Hutch-Bunts operation from the first. While this did not seem particularly important at the time, it resulted in the fact that many urologists do not appreciate the vital role played by Dr. Bunts in the development of the original ureteral vesicoplasty.

Dr. Ruben Flocks then asked me to spend a year at my alma mater, the University of Iowa, and to try the operation on some of his patients with meningomyeloceles and primary reflux. It was at Iowa City that I became aware of the tremendous difference in reflux in children with primary reflux

and in paraplegics. The children with primary reflux had none of the gross changes in the bladder wall that were so characteristic of the paraplegic patients, nor could I find saccules at the ureterovesical junction. This was distressing because my explanation of the etiology of reflux in paraplegics was that the changes in the bladder wall created a sacculum at the ureterovesical junction which damaged the valve mechanism resulting in reflux. This theory could be extended to include reflux in patients with true infravesical obstruction such as prostatic hypertrophy, urethral strictures or urethral valves because these patients, like the paraplegic, had vesical trabeculation and sacculum formation, but it could not possibly explain the most common type of reflux (primary reflux). Cystoscopically, these children had normal appearing bladders. The only positive cystoscopic finding was golf-hole orifices which we could not explain satisfactorily at that time. The results of our surgical experience in Iowa City were published in the *Journal of Urology* by Dr. Raymond G. Bunge, Dr. Ruben Flocks, and me and reported the first series of antireflux surgery in nonparaplegics. This series contained several brilliant successes, but our enthusiasm was dampened somewhat by the appearance of the most feared complication: obstruction at the operative site. In looking back on this series, we got our good results in the patients with primary reflux and our failures in the meningo-myelocele group. During the next five years antireflux surgery gained some advocates. Eugene St. Martin and his group published reports of a favorable nature. Dr. Bunts, on the East Coast, and I, on the West Coast, continued to use the operation, but its acceptance was impeded by fear of obstruction at the operative site. Dr. Bunts and I felt a personal responsibility for this operation and polled the members of the American Urologic Association who had used the operation to determine the results they had obtained. During this period, many of the operative failures were sent to me for a second operation. Actually, this proved to be a blessing in disguise, because it was in re-operating on the patients that I realized that the basic defect in the original operation was sewing the mucosa under the transplant.

The first modification of the original operation came in 1958. This was by Dr. Wyland Leadbetter and Dr. Victor Politano. It included all the features of the original operation and did so without a suture line under the transplant. It also handled the mucosa

correctly by passing the ureter through a submucosal tunnel. The second operation or modification was presented by Dr. Al Paquin. Here the ureter was cut off outside the bladder and brought through a new opening high up in the bladder wall and down through a submucosal tunnel. The Paquin operation originally incorporated a Vest nipple to prevent stenosis of the cut end of the ureter. This operation was highly successful and is widely used today with a number of modifications. I believe at the time of Dr. Paquin's untimely death, he felt that the nipple was no longer necessary.

It is my belief that when we successfully stop the reflux, we stop all further attacks of acute pyelonephritis, and we make the patients clinically well. On the other hand, the pyelonephritic changes on the IVP preoperatively never change; they will remain forever. Any hydroureter or hydronephrosis present preoperatively, however, will slowly return to normal. When we stop the reflux, we stop any further progression of the renal deterioration. We are converting active pyelonephritis into healed pyelonephritis. No function loss prior to surgery can ever be regained. Successful antireflux surgery does not assure that the bacteriuria will not recur. I believe that the source of the bacteriuria is the urethra flora and that when the reflux is present those bacteria have immediate access to the kidney. Following successful antireflux surgery, the bacteria still have easy access to the bladder urine, but if there is no longer any reflux the infection will be limited to the bladder.

To evaluate antireflux surgery fairly, we must discuss three different time periods. The first time period runs from 1950 to 1958. The second period runs from 1958 to 1968, and the third period runs from 1968 to the present. The reported results in the 1950 to 1958 period, when the *Hutch I* was the only operation available, were about 80% completely satisfactory (defining completely satisfactory as stopping the reflux without causing obstruction at the operative site). During the second period, due to the efforts of many urologists working to improve the operation, 90% were completely successful. During the last five years over 95% were completely successful. Fortunately, from the first, antireflux surgery has been evaluated against solid x-ray criteria; by this I mean preoperative IVP's and cystograms and postoperative IVP's and cystograms. This has given a validity to the reported results in the antireflux surgery not present in many types of surgery.

During the last 15 years, we have lived through what I like to call the cystogram explosion. During my residency we rarely did cystograms on anyone. Then all of a sudden we did many cystograms, and we learned a lot about the role of reflux in all types of urinary disease. If we do an IVP we get a lot of information, but the IVP alone is not enough to be certain that a serious urological disease is present. We also get a lot of information from the cystogram, but the cystogram alone is not enough to give urologic clearance. I have the feeling that if we have the combination of a normal IVP and a normal cystogram in a patient with urinary tract infection that this patient has almost no chance of going on to uremia from pyelonephritis. If we could screen everyone in the United States with urinary tract infections with an IVP and cystogram, we could eliminate those patients in whom both studies were negative. Almost all of the patients in whom the possibility of progressive pyelonephritis exists will have a positive cystogram or a positive IVP, or both, on the initial screening examination. All of us have been giving urologic clearance on the basis of a negative pyelogram and a negative cystogram, and it is very rare that a patient whose first work-up shows a negative cystogram and negative pyelogram will ever get into serious trouble subsequently. These patients may have more attacks of urinary tract infections, but they will be limited to the bladder.

Any patient with a proven urinary tract infection should be worked up and classified as in Table 1. A careful history should be obtained, and if the urinary tract infections are occurring without fever, the history is classified as cystitis. If the infections are occurring in the presence of fever, the history is classified as pyelonephritis. The cystogram is read as showing or not showing reflux, and the pyelogram is read as showing or not showing the changes of pyelonephritis. A patient classified in this manner falls into one of five groups. The overwhelming ma-

jority will be in the cystitic group. They will have a cystitis history, a negative cystogram, and a negative pyelogram. A smaller group of patients will have a history of pyelonephritis, yet their x-ray work-up is negative. This is classified as Grade I pyelonephritis. Patients with Grade II pyelonephritis have a positive cystogram, yet the pyelogram is still normal. In Grade III pyelonephritis, the cystogram shows no reflux, but the pyelogram shows pyelonephritis. In Grade IV pyelonephritis, both the cystogram and the pyelogram are positive.

Once your patient has been properly classified, a logical plan of management is easy. The patient who has cystitis and Grade I pyelonephritis has in common a negative pyelogram and negative cystogram. This is the group of annoying but basically harmless urinary tract infections. This type of patient can be given intermittent antibacterial therapy with confidence that the patient does not have a serious urological disease. Patients with Grade II pyelonephritis may be treated with constant antibacterial therapy or with antireflux surgery. Patients with Grade III pyelonephritis have a positive IVP but no reflux. Most of them are adults, and most of them got their pyelonephritis because they had reflux when they were children. I have pointed out that changes of pyelonephritis stay in the kidneys forever. Fortunately, most of the Grade III pyelonephritis represents a healed pyelonephritis and no treatment is warranted. However, there are some sleepers in this group. These are patients in whom the initial cystogram shows no reflux, not because the reflux has actually disappeared but because it has become intermittent. When this possibility is suspected you must repeat the cystogram until the reflux is found. The classification then changes to those patients with Grade IV pyelonephritis. Patients with Grade IV pyelonephritis have a pyelonephritic history, pyelonephritis on the pyelogram, and reflux on the cystogram. I believe that all of these patients should have antireflux surgery.

#### PANEL DISCUSSION

**Dr. Paul Langlois:** Dr. Hutch, you did not mention the adult female with symptoms only of cystitis, without chills or fever, without high back pain, flank pain and so forth, who does have reflux.

**Dr. Hutch:** This would be a patient with a cystitic history who has reflux on the work-up. We studied patients who had a cystitic history and found normal pyelograms and cystograms in all but seven. It is

TABLE 1

CLASSIFICATION	HISTORY	REFLUX	PYELONEPHRITIC CHANGES
Cystitis	Cystitis	No	No
Pyelonephritis			
Grade I	Pyelonephritis	No	No
Grade II	Pyelonephritis	Yes	No
Grade III	Pyelonephritis	No	Yes
Grade IV	Pyelonephritis	Yes	Yes

very rare to have a cystitic history and a positive finding on either the cystogram or the pyelogram. When this does happen, the patient should be graded not according to the history but according to the x-ray findings, so that your patient in spite of her cystitic history should be Grade II pyelonephritis.

**Dr. Joseph Fiveash:** The child with the golf-hole ureter is no problem in management nor is the child with the wisp of reflux who has no changes in the upper tracts. Do you still believe in the maturation of the intravesical ureter, and if so, do you have any hints to tell us which child will mature the ureter and which will not?

**Dr. Hutch:** We have all had many patients who outgrow their reflux due to some process of maturation. We all have our own criteria. In patients with Grade II pyelonephritis where we have normal kidneys and proven reflux, we have two courses—1) constant antibacterial therapy or 2) antireflux surgery. We

all develop our own methods to determine which ones we are going to follow. We have to individualize these cases and each patient is so different.

**Questioner:** I would like to ask you if you go along with Lyons urethral ring?

**Dr. Hutch:** Yes, I think that it is the urogenital diaphragm.

**Questioner:** Are there cystoscopy changes in patients with primary reflux.

**Dr. Hutch:** There is no question that in primary reflux there are two things that are actual facts; one is that the trigones are very large. This means that the orifice is abnormally lateral, and they also have golf-hole orifices. Thus, any theory that is going to explain primary reflux has to explain the golf-hole, and it also has to explain the megatrigone and the gradations that Dr. Lyons and Dr. Tanagho talk about which are excellent in bringing this information into an organized form.



# Medical Management of Stone Disease\*

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The purpose of this review is to try to take a practical approach toward the management of patients with renal calculous disease. This will be a personal approach; I will, however, try to avoid injecting my prejudices and research interests. I want to show that proper management can be achieved even in the most unsophisticated environment.

**Clinical Evaluation.** It is often true that the first evaluation is the most important in giving a clue to underlying cause. Therefore, every effort must be made to avoid failure and thus discourage both clinician and patient. Patients with renal stones generally seek help when they are experiencing symptoms which may be due to partial obstruction with loss of appetite and perhaps partial dehydration. This is not the time to investigate one's patient as the underlying metabolic disorder may be completely obscured. Thus, delay until the patient has resumed his normal state is important.

I do not believe that it is worthwhile in this area to submit a patient to an evaluation who has passed and/or made a single stone. We live in a stone belt. In this area, 80% of the patients who have made only one stone will not make another. In the remaining percentage of patients who have made one stone, there is nearly an 80% chance that they will make another within a year. As yet we have no test available to us that will allow us to distinguish the true stone former.

A careful history must probe for previous episodes and associated conditions such as urinary infections, excessive dehydration, diarrhea, fractures with prolonged immobilization, high alkali, Vitamin D or milk intake. Certain drugs, for example Diamox® and steroids, are associated with stone

formation. A family history of calculi is often present and may be so prominent, as in cystinuria or oxaluria, that the patient already knows the diagnosis.

A careful urinalysis with recording of the pH, crystal content, and presence of bacteria is still the best single test in the management of these patients.

The following laboratory evaluations are important and can be done while in the hospital or as an out-patient:

- 1) Urine for culture and sensitivity.
- 2) Urine for cyanide-nitroprusside test (screening for cystine).
- 3) Teach the patient to test the pH of every voided specimen of urine with nitrazine paper (Lilly Company).
- 4) Three determinations of serum calcium, phosphorus, uric acid, and creatinine and additional routine determinations of total protein, albumin, alkaline phosphatase, and electrolytes.
- 5) Three 24-hour urines for calcium, phosphorus, magnesium, uric acid, and creatinine.
- 6) Analysis of stones should include x-ray diffraction or crystallographic analysis which is readily available. This is very important because, at this time, medical management is directed toward the crystalline components.
- 7) Plain film of the abdomen with an intravenous pyelogram. The roentgenographic appearance of calculi with particular attention to the position in the parenchyma or collecting system and also evidence of layering of calcium over a possibly radiolucent nidus are most important in arriving at the diagnosis for a specific cause of a stone and thus planning the therapy. It goes without saying that it is necessary to exclude all forms of obstruction, and at-

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tention should be paid to whether there is parenchymal calcification which can take various forms. A peppering of small calculi outlining the renal papilla often suggests renal tubular acidosis; however, if this is confined to only one papilla then one would think more of a medullary sponge kidney. If there is evidence of infection of the urinary tract, then I believe that a voiding cystourethrogram should always be carried out to detect the presence of vesicoureteral reflux.

### Calculi.

*Uric Acid Calculi.* In this area, uric acid calculi make up 15% of all calculi seen. They are the only truly radiolucent stones and are not necessarily associated with hyperuricemia and hyperuricosuria. They are most often associated with excretion of unusually acid urine and repeated bouts of dehydration. One may see these types of stones in patients with chronic diarrhea. Certain cytotoxic drugs, particularly those used in the treatment of lymphomas and leukemia, the thiazides, salicylates, and steroids will cause uricosuria, and in the presence of low urinary pH, uric acid stones can form.

Patients will respond very rapidly to a program of high urinary output and alkalization. The patient must continually check his urine, particularly the morning specimen, and adjust the dosage of bicarbonate so that the pH is above 6.0.

In some patients it may be necessary to add allopurinol to the regimen, and the dosage will vary from 100–800 mg daily. This potent enzyme inhibitor will prevent further uric acid calculi formation, but there is the theoretical possibility of xanthine stone formation so alkalization must be continued to prevent this possibility.

At present, it is possible to completely prevent uric acid calculi. Surgery should play a minimal part in the management of these patients even when stones are present in the urinary tract. It has long been known that high output of alkaline urine will sometimes dissolve these stones. The introduction of allopurinol to the armamentarium has provided some dramatic cures. I have five patients in whom uric acid staghorns have completely disappeared after an average of six months.

*Cystine Calculi.* The diagnosis of this familial disease will usually follow from the routine testing noted above and the finding of hexagonal crystals

in acid urine. One should stress again that these stones are radio-opaque because of their 27% content of sulphur and that they have a typical ground glass appearance.

At the Medical College of Virginia, we have an unusually high incidence of cystine stones because of the presence of this inherited metabolic disease in the Chickahominy Indians. Usually, the incidence is only 0.5–1% of all stones.

Therapy is directed toward maintaining the urinary volume in excess of 2,500 ml per day, including an intake of at least 500 ml of fluids in the mid-sleep hours. The urine is maintained alkaline, and the patient is instructed to check his urine and adjust the dosage of his alkalizing medication in order to keep the pH of the urine above 6.5. If the patient follows such a regimen conscientiously, the solubility of cystine in urine will increase and further stone formation may not occur. This can readily be checked by routine urinalysis. Patients who are unsuccessful in such therapy may require the addition of D-penicillamine to the treatment program. This drug is given in dosages of 1–4 g per day guided by the screening tests for cystine (nitroprusside tests).

D-Penicillamine is not completely without its complications; a rash may occur but can be abated by stopping the medication for two weeks and then resuming it by gradually increasing it from 250 mg per day to the required daily dose. Nephrotic syndrome has occurred and requires cessation of the therapy along with prolonged medical observation. There is an increasing number of reports of patients losing their sense of taste while on this drug.

Reappearance of the stones or failure of the stones to dissolve might imply failure of therapy. On several occasions, however, we have found that this was due to the production of stones of other chemical makeup; therefore, these patients must be very carefully followed and watched in case such an event occurs.

It is extremely important when treating these patients with penicillamine to keep the dose as low as possible, that is, to keep the urinary cystine level below 250 mg per day by the minimum dose of D-penicillamine possible. It is conceivable, and we have seen it here on two occasions, that prolonged high doses of penicillamine will interfere with collagen maturation and thus give rise to bruising and striae formation; great care must be exercised in the management of these patients.

**Calcium Calculi.** The stones that contain calcium are found in a wide spectrum of conditions that can be broken down into individual management problems once the proper diagnosis has been made. The principal breakdown is into those patients with or without infection. One should not lose sight of the fact that many so-called infectious stones may have had as a nucleus an uninfected stone so one should adjust the therapeutic attack accordingly.

**Triple Phosphate Calculi.** Stones associated with infection imply the presence of stones containing varying amounts of calcium magnesium ammonium phosphate. Their roentgen appearance is variable as they may have a high content of so-called matrix. Therapy is directed toward eliminating the infection. It is essential to correct obstruction, diabetes and hyperparathyroidism, and to remove all foreign bodies; otherwise, any therapy directed toward the infection will be doomed to failure.

Appropriate antibiotic therapy must be intensive and often prolonged until the urine is sterile and stays that way. Acidification of the urine is certainly very helpful. A regimen using methenamine and ascorbic acid is helpful. We have found that in some patients methylene blue will lower the urinary pH, and it seems to prevent organization of the matrix and prevents it from binding the calcium ions.

Oral use of magnesium or phosphates is contraindicated. If one can lower the urinary phosphorus by use of a low phosphorus-containing diet and Basaljel®, then success has been achieved. It is often extremely difficult to insure that patients remain on this regimen, however, and I no longer use it except with very compulsive patients.

I believe it can rarely be said that a stone is purely secondary to infection.

**Calcium Oxalate and Calcium Phosphate.** Prior to discussion of the management of these common stones, a few general observations should be made. Pure calcium phosphate stones are most commonly found in association with metabolic diseases; for example, hyperparathyroidism, renal tubular acidosis, immobilization syndrome, and stones associated with the hypercalcemia of malignant disease and sarcoïdosis; a more intensive investigation by a metabolic unit is indicated. Many patients will alternate calcium oxalate and phosphate stones, presumably due to the variation in urinary pH, as calcium phosphate precipitates at high urinary pH. Hyperoxaluria should be suspected in children or young patients with recurrent stone formation.

Calcium oxalate and/or phosphate calculi represent a disease complex which has many factors associated with it, and therefore, it seems that one should direct attention and therapy toward the most prominent biochemical abnormality that the preliminary investigation turns up; always remember that continuous monitoring and flexibility are essential.

**Hypercalciuria.** There is still considerable controversy as to the best therapy for this common problem. The following therapies are recommended:

**Thiazides.** If given in a dosage of 500 mg twice daily, they will reduce the urinary calcium and elevate the magnesium. There are certain side effects, however, which may be potentially harmful. Metabolic acidosis and potassium deficiency have been reported. Citrate excretion is practically abolished and hyperuricemia may occur. Rarely, this will cause hypercalcemia unmasking that group of people who exhibit normocalcemic hyperparathyroidism. All of these patients must be warned to keep their sodium intake low, or the effect of the thiazides will be nullified. It is questionable whether this form of therapy should be combined with the phosphate type as there exists the potential of exacerbating the renal damage that can occur from phosphate ingestion.

**Neutral Orthophosphate.** In 1958 and 1959, Drs. Howard and Thomas made a crucial observation concerning "evil urine" and its ability to calcify rachitic rat cartilage while good urine would not do this. This led to the discovery that neutral orthophosphate taken orally will consistently lower urinary calcium and convert evil to good urine. Subsequent work by others in the field has confirmed that a dosage of 1.3–1.5 g per day is sufficient to stop stone formation. Unfortunately, this dosage is sometimes limited by the diarrhea which may occur.

**Uricosuria.** There is a group of patients whose only detectable metabolic abnormality was a relative uricemia and uricosuria. Interestingly, these patients often belong to the so-called "young executive stone former." It has been possible to control their oxalate stone formation with a low dosage of allopurinol (50 mg) and alkalization.

**Calcium/Magnesium Ratio.** There is a group of stone formers who have a ratio of these ions to each other greater than three and who appear to benefit from magnesium oxide therapy usually administered as Milk of Magnesia® tablets. I should stress that some workers have not been able to demonstrate these differences so that if one uses

this therapy, very careful monitoring and study is essential.

**Lack of Detectable Abnormality.** There is a group of people in whom there is no detectable abnormality on the biochemical survey. A variety of therapeutic approaches is currently under study.

Dr. Prien is presently conducting a study on the effect of magnesium oxide (300 mg per day) and pyridoxine (10 mg per day) in the management of recurrent stone formers. He will provide the protocol and therapy in return for follow-up results.

Studies on methylene blue by Boyce and by Smith have been reported previously. At this time, methylene blue (65 mg three times a day) would seem to be effective in preventing the formation of stones in uninfected calcium oxalate stone formers. I admit that it may also be helpful in "urine watchers" in that they will tend to keep up an adequate fluid intake.

**Discredited Therapy.** Aspirin, hyaluronidases, and cranberry juice have fallen into disrepute as forms of therapy.

**General Measures.** As has been indicated, each patient will require individualized therapy. It is extremely important to be prepared to evaluate patients continually as to their response to a particular therapy and, if necessary, to shift to another.

Dietary therapy is not emphasized; however, all patients are instructed in a simple low calcium diet. There are a few people who can remain on diets and successfully reduce the urinary calcium levels.

All patients are taught to measure their urine volume and to aim to maintain an output above 100 ml in one hour. It is probably wise to advise patients to avoid excessive consumption of soft drinks, since a carbohydrate load has been shown to induce hypercalciuria of frightening proportions. I believe the intelligent participation by a patient in his medical management is probably the single most important facet in the management of recurrent urinary calculi.

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# Some Important Factors in a Community Dialysis Program\*

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The purpose of this paper is to acquaint physicians who are not nephrologists with the experience of one of their colleagues in the operation of a hemodialysis service as a part-time endeavor. My intention is not to present detailed or advanced scientific data on dialysis techniques or on the care of chronic renal failure but to discuss how and under what circumstances the urologist, internist, or general physician might significantly augment the present treatment care system for end-stage chronic renal disease. I will attempt to describe a mode and philosophy of operation applicable to the community hospital and private practice setting which is derived from our experience in providing care for acute and chronic renal failure in a city of 50,000 with a service area of 300,000 people located more than one hour from the nearest large medical center. Our unit started with one machine and one patient five years ago and now has seven dialyzers serving an average case load of 13 patients.

The need for increased personnel and facilities for the care of patients with end-stage renal disease is well established. It is generally estimated that each year 40-60,000 patients die from chronic renal disease; 8,000 might benefit from chronic dialysis and/or renal homotransplantation.

The January 1973 report of the National Dialysis Registry showed 7,498 patients on dialysis at 424 centers in the United States in contrast to 100 patients at 25 centers in 1964. The statistics indicate a fairly rapid development of facilities for dialytic therapy in the United States, but obviously the system cannot provide treatment to many more than 25% of the patients who might offer

themselves for care. Historically, of course, most of our dialysis centers have been established at our university hospitals. Because of shortages of space and funds at these institutions, however, in addition to their limited geographic distribution, it is not reasonable to expect that the very substantial increase in facilities needed can occur at these centers. The university hospital can, however, be of great assistance in training patients for home dialysis and in the direct or indirect technical support of smaller units in other communities. It certainly is reasonable to expect that community dialysis centers, their costs lessened by more freely available space, decreased transportation expenses and greater flexibility in personnel, might provide a significant opportunity for expansion of our treatment capability. In our smaller cities the case material may not be sufficient to support a full-time nephrologic practice where the urologist or other interested physician might consider establishing a dialysis unit. The decision must be predicated on a number of factors; the first is the need in a general geographic area. It is generally estimated that there are about 38 patients per 1,000,000 persons per year who will benefit from chronic dialysis or transplantation. A small part-time service can probably be justified by an influx of four patients per year considering that some patients may be on chronic dialysis without consideration for transplantation, and even those registered for cadaveric transplants in a very active organ exchange program will usually have waiting periods of about six months before a transplant. We will discuss cost factors of importance in determining the practicability of small dialysis units in some detail later.

Another factor that must be considered, of course, is the distance patients must travel to existing facilities. If a patient must travel more than two hours

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round trip for a dialysis, the actual cash cost of dialysis to the patient may be increased as much as \$2,000 to \$3,000 per year and, more importantly, the burden on him and his family in terms of fatigue and time lost from work can be prohibitive. If such a situation exists in your community it might provide further encouragement to attempt to establish dialysis facilities locally. Another factor to be considered is the availability of space suitable for dialysis. The physical requirements of a unit are not elaborate, requiring only electricity and hot and cold running water. It should be convenient to the director and his staff and, ideally, adjacent to the physician's office so that his staff might relieve each other for lunch or assist in the event of mechanical or clinical difficulties. The natural tendency is, of course, to consider using hospital space for a unit. With current hospital

construction costs of \$55–75.00 per square foot, however, the general shortage of space in our hospitals, and the fact that empty space that might be used for patient care is a potential source of income of \$25–40,000.00 per bed per year, it may not take long before either the hospital wishes to use some of the allocated space for other purposes or one finds that space needed to expand the dialysis unit is not available. In our experience, the undeveloped basement of our offices provided, with relatively minor alterations at a cost of \$8,000, a satisfactory facility to dialyze seven patients at a time with room to expand easily to nine, and at a negligible fixed overhead (fig. 1). Similar flexible low cost facilities might be established in empty apartments, stores, or in unused portions of medical offices.

An additional factor to consider is the coverage



Fig. 1

available when the director is away on holiday or at medical meetings. This is generally not as great a problem as it sounds because a technician with six months of fairly active experience can deal with all but true medical emergencies and another physician can usually be found who will take at least a peripheral interest in one's unit. The most important medical support necessary is advice at a distance from an experienced nephrologist, preferably from an institution with an active dialysis and transplantation program. It is unlikely that the urologist or other general physician by virtue of his training will share all the knowledge of a nephrologist, and contact from time to time is most helpful. I have shared patients with the renal and transplantation units at the University of Virginia Hospital, Medical College of Virginia, and Duke University Medical Center and found without exception that they were most enthusiastic about having another facility in their general geographic area and anxious to be of assistance. In fact, half of our new patients in the last two years were referred from these hospitals for treatment. The other advantage of close liaison is that it is important for a fair proportion of patients in a small dialysis unit to be registered in an active transplant unit. It is obvious that unless patients are transplanted with some regularity and with an attrition rate of about 10% per year on dialysis, one's unit will rapidly fill and have no room for next year's patients.

Lastly, the most important factor to consider is your own enthusiasm and the firmness of your commitment. Supervising a dialysis unit can be a most satisfying avocation. Yet, it requires a rather substantial and permanent commitment, and certainly, it is not the sort of thing that one would choose in making the transition between flying lessons and finger painting. If one would anticipate that the day to day supervision of dialytic therapy would probably become a tedious matter, it is probably best not to start. There are few other fields, however, which can provide the personal satisfaction of supplying a vitally needed medical service. In all our offices from time to time, we feel progressively estranged from our patients by the demands of third party payers, the Columbia Broadcasting Company, and ever increasing case loads. Chronic dialysis is one field in which the doctor-patient relationship is closer and more direct than in almost any other area in medical practice, and this itself can be most rewarding.

Having decided to commit oneself to starting a

unit, there are two further pitfalls to avoid. The first is the tendency to start too elaborately. I know of at least two instances in Virginia where hospitals considered establishing a dialysis unit involving plans calling for major remodeling with complex central dialysate delivery systems and quite a large number of dialyzers. The cost estimates ran into six figures and the institutions abandoned their plans before getting started. While I am sure that central delivery systems and other refinements in the physical plant can be of distinct economic benefit in large established units, their cost and the loss of flexibility incurred by having a substantial initial capital investment are distinct disadvantages in starting a small unit. At the present time, it is possible to purchase an entirely adequate new dialyzer for as little as \$1,800 and sufficient supplies to dialyze a patient for six weeks with an additional \$330. This general type of equipment is rather portable, requiring only a water source and drain and a grounded electrical supply, thus giving one the opportunity to move the unit at will if larger and otherwise more suitable quarters become available. Additionally, a prudently used dialyzer can be sold much in the manner of a used car if the physician involved becomes disenchanted. The point is that there is no need to make a large and fixed real estate or equipment investment with the sort of commercial equipment that is available from a number of sources. Another reason for starting small is that an area not previously serviced by a hemodialysis unit will not be oriented toward referring patients for care of chronic renal failure. The number of new patients in the first year or two may be smaller than one might anticipate. As time goes on, even drawing from the same geographic area, the number of new patients seems to increase each year as internists, family physicians, and pediatricians become oriented toward optimum treatment of those afflicted with chronic renal failure. We had three new patients in our first year of operation and seven new patients in our fifth year.

The second detour to avoid is to start with the idea that one will do acute or emergency dialyses and avoid taking care of chronically ill patients. As a practical matter, it is virtually impossible to maintain equipment and achieve a standard of excellence in the performance of technicians unless they are dialyzing regularly. Quite a large number of community and university hospitals, having attempted to start in this manner, almost invariably have found it necessary to begin at least some chronic dialyses

to avoid loss of their equipment or having it fall into disrepair and the personnel need continual practice to maintain their competence. The primary reason for this is that the patients requiring emergency dialysis are relatively few and in most instances are best treated by peritoneal dialysis. The indications for acute dialysis might be simply summarized as follows:

- 1) Temporary dysfunction or hypofunction of the kidneys because of acute and potentially reversible renal disease.
- 2) Correction of intractable edema or severe electrolyte disturbances.
- 3) Removal of potentially toxic substances.

In the first two categories above, peritoneal dialysis is generally preferred in the absence of a relative contraindication to that procedure, such as abdominal wall sepsis, advanced pregnancy, bleeding diathesis and so forth. Patients in category 3 are usually best treated by hemodialysis. A considerable body of evidence is emerging, however, that dialysis is of little benefit in intoxications particularly when due to lipid soluble or protein bound agents and is generally not indicated except in the gravest circumstances. To illustrate this point, in the past three years we have performed approximately 2,400 chronic hemodialyses and only 34 acute hemodialyses on 14 patients; the types of cases encountered in these 14 patients were as follows:

- 1) Intractable edema, two (one died).
- 2) Thrombotic thrombocytopenic purpura, three (one died).
- 3) Glutethimide intoxication, two (one died).
- 4) Interstitial nephritis secondary to ampicillin, one patient.
- 5) Acute tubular necrosis post surgery, five (four died).
- 6) Polyarteritis nodosa, one patient.

While one might gather that some of the most rewarding experiences were found in the group treated with acute hemodialysis, the need to perform this procedure is rather infrequently encountered and would probably not, in our context, permit the effective functioning of a dialysis team. In performing chronic dialysis regularly, the maintenance of our staff's skill and equipment permits us to begin an emergency hemodialysis within 25 minutes providing adequate vascular access is attained. Interestingly enough, the more active a chronic service becomes, the greater becomes the skill and confidence of the paramedical personnel, and the directing physician is

less burdened with the technical aspects of dialysis. Our experience is that it requires less time to supervise the care of thirteen patients now than it took to supervise four patients three years ago.

The choice of patients to be offered care is obviously a matter which must be faced. Many institutions maintain dialysis selection committees, often including laymen, to determine which patients are to be treated. In my experience there are a number of disadvantages to this approach. First, it is contrary to the basic traditions of our civilization to try to place a relative value on a given patient's continued existence, and as a practical matter, there is no one, neither physician nor layman, who is very accurate in determining who will be a cooperative and conscientious chronic dialysis patient. Two of the very best patients I have been privileged to look after were turned down at other centers, one because of lower than average intelligence and the other because of a criminal record some years before. Finally, since many chronic renal failure patients appear rather suddenly and in dire straits, it is often difficult to learn much about them socially and psychologically before one has to make the medical decision as to the desirability of chronic maintenance. Our policy is to offer chronic dialysis to all patients who do not have other medical conditions which preclude rehabilitation. When selecting by medical criteria alone, one will find a somewhat higher attrition rate than in highly selective centers because a number of patients will opt out either voluntarily or involuntarily as they find they are unable to conform to the rather rigorous discipline which is part of the daily life of a successful chronic dialysis patient. This mode of operation is bound to lead to some disappointments, but in most circumstances it is vastly preferable to leave the nonmedical decisions to the patient and his Maker than to another human being who is really ill-equipped to decide.

The next problem that faces the small unit director is the establishment of satisfactory vascular access for once- or twice-weekly treatment. Historically, of course, chronic dialysis emerged as a practical treatment system with the development of the Scribner-Quinton teflon-silastic shunt in the early 1960's, and many chronic dialysis patients still use these devices. They provide ease and rapidity of connection to the dialyzer and rather predictable flows; effective care generally requires average flows in excess of 200 ml per minute. However, they are subject to disruption and the possibility of exsangui-



nation. They are also susceptible to infection and clotting and require a substantial inventory of expensive tubes and tools. Many large centers and most home dialysis patients use shunts, but in small dialysis units such as ours, the internal A-V fistula as developed by Brescia may be the preferred method for providing access. Although starting a dialysis on a patient with a fistula is slightly slower and requires a higher level of training, fistulas are rather free of clotting and infection and require only needles or cannulas as ancillary equipment. In our unit, fistula flows have been comparable to those of shunts once the fistula has been established for a month or two. A third technique, percutaneous puncture of the femoral vein as developed by Shaldon, has been used very effectively in chronic patients in other units and in ours as a temporary measure while awaiting maturation of a fistula. The venipuncture required is more difficult than in a fistula and is less easily relegated to one's staff in our experience.

As far as dialysis is concerned, I have referred above to the desirability of having a small self-contained unit. We started using the recirculating single pass twin coil unit such as is available commercially through Travenol Laboratories. The merits of various dialysis apparatus are a subject for hours of debate and beyond the scope of this discussion. The versatility of the Travenol unit, however, is advantageous for a small program because it is able to remove both excess metabolites and fluid, has a single source for all components and technical assistance and has ease of assembly and disassembly, thus reducing training time and, of course, cost of operation. There are, certainly, many other effective commercial dialyzers available with very competent support for the small unit. Our last two dialyzers are made up of Life Med control equipment and Dow capillary kidneys for which we have fine outside support and which provide some technical advantages with certain patients. One of the factors that might influence the final choice of equipment is the kind of hardware in use at the nearest large center. If one is going to have his personnel trained at or exchange patients with a nearby center it might be beneficial to use similar equipment as both staff and patients will profit. At any rate, I think one can anticipate a great deal of help from any of the major equipment sources.

One matter that must be considered is the financial support of your patient's care. Each health insurance company and state has its own policy. In general, even in states with conservative fiscal tra-

ditions, however, patients who are totally disabled from chronic renal failure will find at least partial support from Medicaid or the Vocational Rehabilitation Departments. Cost control is of prime importance. The three factors most amenable to control are personnel, disposable equipment, and physical overhead. I have previously stressed the advisability of having dialysis technicians with a variety of skills as being of great importance for a small unit. Experience has indicated that the optimum cost-effective and clinically efficient patient-to-technician ratio is three or four to one. Therefore, since dialyzers *per se* are rather inexpensive, in a three- or four-patient service, it is usually less costly to dialyze four persons twice per week than two persons four times per week, assuming your technicians can work elsewhere as office nurses or in some other capacity on the remaining days. The critical factor is flexibility in personnel and a constant evaluation of the most cost-effective way to organize their activities from time to time as the patient load of one's unit varies.

With respect to disposable equipment, the single largest element in cost is the coils. There has been a progressive decrease in the cost of commercial coils from \$22 to \$15 each over the past two years, and further decreases to just over \$10 per coil are anticipated in the next few years. To parallel this, there has been considerable interest in reusing coils, and there are a variety of techniques described in the literature for cleansing and preserving them for reuse. Our experience would indicate that often in small units, the personnel costs involved in preserving coils do not permit highly significant savings.

The third area where cost reduction may be effected is in decreasing the actual physical overhead of dialysis as I mentioned previously. The detailed cost analyses are available in the literature, the best one of which, in my opinion, indicates a cost of \$130 per dialysis for hospital units and \$69 and \$46 for satellite and home dialysis, respectively. These reductions reflect, of course, lowered physical overhead and travel expenses and, in the case of home dialysis, lowered personnel costs. While there is considerable enthusiasm for home dialysis in many quarters, I doubt that home therapy will be the method used to bring dialysis to the majority of patients who need it. While it is highly effective in selected patients, there are simply large numbers of patients or patients' families who either by virtue of their timidity or

limited background cannot perform dialysis at home. Also, there are still significant numbers of patients in rural areas and in lower class urban America whose living quarters simply do not permit the installation of a dialyzer. At one time, we surveyed our service of ten patients and found that three had no indoor plumbing in their living quarters; an additional two did not have hot water and one other patient was illiterate. Of the two chosen for training for home dialysis, one refused the opportunity and the other, after a considerable amount of training, requested that he be allowed to continue coming to our unit. One factor that must be faced is that many rural counties in the southeast have adult populations with an educational level of less than seven years, and this places a substantial limitation on the number of people who can be trained efficiently to care for themselves. One cannot help but be impressed with the results of our colleagues in the state of Washington who are training large numbers of patients for home dialysis. It is obvious, however, that they are working in a different social milieu and are able to commit rather large amounts of money to evaluate special techniques for training large numbers of home dialysis patients. Additionally, while all dialysis patients are subject to depression and other rather serious psychiatric problems, home dialysis patients and families seem to have very high rates of divorce, suicide, and secondary spouses. In any event, two-thirds of all dialysis patients in the United States are in centers as opposed to home dialysis programs, thus indicating that the latter may not be as universally applied as has been indicated in some quarters.

If one's unit continues to grow in size, the point will be reached where its demands will exceed the skill and energy of a part-time director. In our case, that point was reached 12 months ago, at which time we had grown to eight patients being dialyzed on four machines. We were able at that time to add a highly qualified nephrologist to our group. Our unit has since grown to 13 patients and seven machines, and we are presently performing 100 dialyses per month. Five of our patients had cadaveric transplants this past year through the Southeastern Regional Donor Program; three of them retained kidneys at this time. The development of our dialysis service to the level where a nephrologist was required has, of course, resulted in the addition of considerable expertise in the management of renal disease and hypertension in our community.

In closing, I hope I have imparted some valua-

ble information not easily available in the literature based on our own practical experience in the operation of a small part-time dialysis unit. I think I can assure interested physicians that as one's knowledge and skill develop in this area, the operation of such a unit will be a progressively rewarding and stimulating experience.

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# Surgery of the Adrenal Glands\*

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This paper is a surgical overview of adrenal gland disorders and emphasizes new developments in diagnosis and management. Adrenal disorders are relatively rare but clinically, they are very important. If they go undetected, they can produce severe metabolic disturbances which may be fatal.

## Indications for Adrenal Surgery. (Table 1)

**Metastatic Breast Cancer.** Today, the most common indication for adrenal surgery is metastatic breast cancer. At our institution 10–15 bilateral adrenalectomies are performed each year for this reason. Breast cancer is the number one cancer in women. There are approximately 70,000 new cases each year; unfortunately, 60% of these cases, or 42,000, will develop metastases at some time and will become candidates for palliative treatment. Some of these tumors are estrogen dependent, and this is the rationale for removing the two main sources of estrogen—the ovaries and the adrenals. If the ovaries are still present at the time of the adrenalectomy, they are removed. This procedure is not performed if the patient has hepatic or pulmonary insufficiency or advanced brain metastases. Forty percent of the patients with metastatic breast cancer experience a clear-cut response with a decrease in the size of all lesions and no new disease. This status has been maintained for at least six months. Five percent have an arrest of their tumors and the remaining 55% have had no response. In the responder group, 55% are still alive two years after adrenalectomy. In the non-responder group, almost all of the patients have died; only 4% have survived for two years.

**Metastatic Prostatic Cancer.** In metastatic prostatic cancer, bilateral adrenalectomy never gained

wide acceptance by urologists, and it is rarely performed today. Its effectiveness is difficult to assess since there are only a few widely scattered reports in the literature. Although this operation was used occasionally as a primary form of treatment in patients with advanced prostatic cancer, it was usually employed in those patients who relapsed after an initial favorable response to orchidectomy-estrogen treatment. In these proven androgen-dependent tumors, it was hoped that a further lowering of androgen production might produce a second clinical remission. This hope was never realized, but it is reported that more than one-half of those patients treated with adrenalectomy experienced a transient response, usually relief of bone pain.

**Adrenal Cysts.** The most common type of adrenal cyst seen clinically is the pseudocyst due to a hemorrhage into a normal adrenal gland or into an adrenal tumor. One interesting form of this cyst, for which one should be on the lookout, is calcified adrenal hemorrhage in the newborn. These newborns are found to have a mass above one or both kidneys often outlined by a rim of calcification. Usually, there is no evidence of adrenal insufficiency or excessive blood loss. The etiology is thought to be trauma since most of these babies are the product of a difficult breech delivery. If the diagnosis is secure, surgery is not necessary.

**Pheochromocytoma.** Pheochromocytoma, a neural crest tumor, is the best defined cause of curable hypertension today and accounts for about 0.5% of all cases of hypertension. At the present time, we have the capability of diagnosing 100% of these tumors with relatively simple, safe and inexpensive biochemical tests. Despite the ability to diagnose these tumors, however, an estimated 1,000 persons die each year in the United States from complications of unrecognized pheochromocytoma. Surgery is particularly hazardous in patients with unsuspected

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TABLE 1.

## INDICATIONS FOR ADRENAL SURGERY

1. Palliation of hormonally dependent tumors
  - A. Metastatic breast cancer
  - B. Metastatic prostatic cancer
2. Adrenal cysts
3. Hyperfunction of the adrenal cortex due to
  - hyperplasia
  - adenoma
  - carcinoma
4. Tumors of the adrenal medulla
  - A. Benign—pheochromocytoma, ganglioneuroma
  - B. Malignant—neuroblastoma

pheochromocytoma, and the death rate in one such series was 50%. Before the availability of adrenergic drugs, elective removal of a pheochromocytoma carried a mortality rate of 25%. Today, with careful management, the mortality rate is around 1%.

*Conditions Requiring Chemical Screening for Pheochromocytoma.* Table 2 shows the chemical tests that are now used as screening tests. These tests are replacing the pharmacologic tests, regitine and histamine, that were used regularly until just a few years ago.

Most patients have intermittent rather than persistent symptoms, and these so-called "spells" or

TABLE 2.

## CONDITIONS REQUIRING CHEMICAL SCREENING FOR PHEOCHROMOCYTOMA

1. Hypertension—sustained or paroxysmal
2. Sudden attacks or spells precipitated by physical exertion or excitement
  - A. Symptoms accompanying attacks—headaches, perspiration, pallor or flushing, nausea or vomiting, dizziness, fainting
3. Hyper- or hypotension associated with trauma, anesthesia, or parturition
4. Hypermetabolic state
5. Relative with proven pheochromocytoma
6. Neurocutaneous syndrome (von Hippel Lindau's or von Recklinghausen's)

attacks have certain characteristics. They appear suddenly and usually last less than an hour, often for only 15–30 minutes. Usually two or more symptoms are experienced together, and each spell tends to be a carbon copy of the previous one. The most common symptoms are headache, perspiration, pallor and pallor. The frequency of these attacks is quite variable, and about one-quarter of the patients will have one or more each day and about two-thirds will have one or more each week.

With the chronic outpouring of catecholamines causing a hypermetabolic state, these patients may be hiding under the diagnosis of hyperthyroidism or diabetes mellitus. The hypermetabolic state results in many of these patients being on the thin side in marked contrast to the majority of patients with essential hypertension who are overweight.

This disease is frequently familial and in our somewhat atypical series about one-half are of this type. One family in particular, the McCoys, has been particularly productive with 10 of 28 members having pheochromocytoma. The famous Hatfield-McCoy feud was probably fueled by the high incidence of this tumor in the combatants.

The association of this tumor with neurocutaneous diseases and with other tumors of neuroectodermal origin, such as thyroid and parathyroid, is well established and probably results from their common embryological origin.

*Diagnosis.* The diagnosis of pheochromocytoma today hinges on biochemical confirmation of the overproduction of catecholamines. Urine normally contains small quantities of the free catecholamines and their metabolites—the metanephrines and 3-methoxy-4-hydroxy-mendelic acid (VMA). The excretion of all three of these compounds is persistently high in almost every patient with pheochromocytoma, even those with paroxysmal hypertension. Each test is more than 90% accurate, with the free catechol determination being the most accurate, around 99%; metanephrine is 97% accurate, and VMA is 90% accurate. There are no reported cases of pheochromocytoma with negative tests for all three determinations. At the University of Virginia, we rely on free catechols and VMA.

Pharmacological tests are not recommended because they are more hazardous, more expensive, and less accurate than urinary assays. In a series of patients from the National Institute of Health, 25% of the patients with proven pheochromocytoma had negative pharmacological tests. Since the diagnosis

of pheochromocytoma depends upon the accuracy of biochemical tests, it is important to take a careful drug history, for all three determinations are subject to error if certain drugs have been taken.

*Location of Tumor.* The pheochromocytoma is known as the 10% tumor—10% multiple, 10% extra-adrenal, and 10% malignant. Multiple tumors are more apt to occur in children and in familial pheochromocytoma with reported incidences of 20–50%.

*Extra-Adrenal Chromaffin Tumors.* The chest is the most common site of the tumors, except for the abdomen, and accounts for 1–2% of them. These tumors usually present as posterior, mediastinal, paravertebral masses readily detected by appropriate chest x-rays. The rare tumors in the neck are palpable. Bladder pheochromocytomas are of particular interest. Patients often complain of headache with or after voiding. Fifty percent of the patients with bladder pheochromocytomas have hematuria. These tumors are usually not visible on cystoendoscopy, since they are located in the muscle wall.

*Localization of the Tumor.* Once the diagnosis of pheochromocytoma is established by chemical means, we do not make a special effort to localize the site of the tumor. There are two reasons for this approach: 1) At surgery, we always examine both the adrenal glands and the para-aortic and pelvic regions, the usual sites for intra-abdominal pheochromocytomas, 2) All of our efforts are directed at avoiding stimulation of the tumor with catecholamine release, and diagnostic procedures such as angiography and retroperitoneal gas insufflation often stimulate the tumor and have caused some deaths.

Our radiological work-up consists of chest x-rays to rule out the 1–2% intrathoracic tumors, and a double dose IVP with tomography to look for depression and flattening of the upper pole of the kidney. We do not perform arteriography, venography, or gas studies. If arteriography is planned, be sure your patient is on protective pharmacologic blockade with alpha blocker phenoxybenzamine (dibenzylamine) and have an i.v. in place with both alpha and beta blockers available in the x-ray suite.

We get some help in localization from our urinary catechol determinations. If the urine contains increased amounts of epinephrine, as well as norepinephrine (NE), 90% will be found in the adrenal gland, 10% in the organs of the Zuckerkandl, those tiny chromaffin bodies near the origin of the inferior mesenteric artery. If the urine contains increased

TABLE 3.

## MANAGEMENT OF PATIENTS WITH PHEOCHROMOCYTOMA

## Preoperatively

1. Pharmacologic blockade
  - A. Partial alpha adrenergic blockade using long-acting phenoxybenzamine (dibenzylamine)
    - 1) Blood pressure is lowered to normal or near normal levels.
    - 2) Symptoms are lessened.
    - 3) Plasma volume is expanded with resultant drop in hematocrit of 5–10%.
    - 4) Surgical course is smoother and less hazardous.
  - B. Beta adrenergic blockade is used *only in selected cases.*
    - 1) Persistent tachycardia or arrhythmia despite adequate alpha adrenergic blockade
2. Transfusion of packed RBC's as indicated by the fall in hematocrit

TABLE 4.

## MANAGEMENT OF PATIENTS WITH PHEOCHROMOCYTOMA

## Surgery

1. Continuous monitoring of blood pressure, central venous pressure and cardiac activity is established *prior to induction.*
  - A. Arterial pressure—*intra-arterial catheter for a continuous readout and recording when desired*
  - B. Central venous pressure—*catheter is inserted in the external jugular vein.*
  - C. Cardiac activity—*continuous ECG observation*
2. Minimize or avoid stimuli known to cause tumor to release catecholamines.
  - A. Positioning of the patient
  - B. Muscle twitching
  - C. Hypercarbia or hypoxia
  - D. Intubation
  - E. Drugs—*curare, cyclopropane*
3. Premedication
  - A. Drying agent—*atropine or scopolamine*
  - B. Narcotic—*morphine*
  - C. Tranquilizer—*Valium®*
4. Anesthetic technique
  - A. General anesthesia rather than block
  - B. Induction—*thiopental (Sodium Pentothal®)*
  - C. Intubation—*succinylcholine following small dose of pancuronium to avoid muscle fasciculations*
  - D. Agent of choice—*halothane*
  - E. Maintenance of relaxation during surgery—*pancuronium*

amounts of NE only, however, be prepared for a more extensive search of the abdomen, for only 60–70% of these tumors reside in the adrenal gland. This reflects the fact that extra-adrenal chromaffin tissue elaborates NE almost exclusively. Plasma catechol determinations via vena cava sampling at different levels are reserved for those patients requiring a *second* surgical exploration for pheochromocytoma—either for recurrent tumor or for a previously missed tumor.

*Management of Patients with Pheochromocytoma—Preoperative.* (Table 3) The primary aim of the preoperative preparation and the anesthetic management is to minimize stimuli to the pheochromocytoma to prevent sudden and dangerous alterations in heart rate, rhythm, and arterial pressure. The key point of preoperative preparation is *partial* alpha adrenergic blockade. This usually takes four-to-five days to accomplish, but it is well worth the effort primarily because it takes most of the risk out of surgery. I emphasize the word *partial*, for if you had total blockade, you would lose two very helpful diagnostic signs—a rise in blood pressure on manipulation of the tumor and a drop in blood pressure after the removal of the tumor. Sometimes extra-adrenal tumors are difficult to locate, and it is very helpful to be able to gently palpate the para-aortic and pelvic areas seeking a blood pressure response. Beta blockade is not useful for preoperative preparation.

*Management of Patients with Pheochromocytoma—Surgery.* (Table 4) Surgery is our current way of handling pheochromocytoma patients, but I would like to emphasize that there is no single anesthetic agent or technique which is the *sine qua non* of anesthesia for pheochromocytoma. It is important to establish your monitoring prior to induction, for this is almost as tumor-stimulating as manipulation of the tumor itself during surgery.

We have been happy with halothane. It elicits no sympathoadrenal activity and it decreases the peripheral vasculature response to NE. There is some evidence that it may make the heart more irritable and more prone to cardiac arrhythmia, but this has not been our experience. Methoxyflurane was touted as the anesthetic agent of choice for several years, but it is infrequently used nowadays because of some reports that it caused high output renal failure.

I think the use of pancuronium during intubation is an excellent example of the very careful

anesthetic technique required. Commonly during intubation with succinylcholine, there are transient muscle fasciculations which may stimulate the tumor, so to avoid this possibility, pancuronium is given ahead of time.

We always use a subcostal incision in these patients, inspecting and palpating the pelvic and para-aortic region and both adrenal glands. We try to manipulate the tumor as little as possible. The single adrenal vein is ligated first if feasible. If only one adrenal is involved, the entire adrenal gland is removed. If this is the only tumor, there is generally a significant drop in arterial pressure which is usually corrected by volume replacement. If arterial pressure does not drop or if, after a short period of hypotension, it bounces back up to supernormal levels, you had better look around for a second tumor. Remember that 10% of patients will have more than one tumor, and if your patient is a child or has familial pheochromocytoma, the probability of a second tumor increases to 20–50%.

*Management of Patients with Pheochromocytoma—Problems in the Operating Room.* (Table 5) When manipulation of the tumor causes arterial pressure to shoot up to levels of 250/150 or higher, the surgeon's catechol level is not far behind. We rely primarily on phentolamine drip in this situation, but if we are at all worried, we do not hesitate to

TABLE 5.

## MANAGEMENT OF PATIENTS WITH PHEOCHROMOCYTOMA

## Cardiovascular Problems During Surgery

1. Hypertension
  - A. Phentolamine drip—short-acting alpha adrenergic blocker
  - B. Sodium nitroprusside—direct smooth muscle relaxant
  - C. Deepen anesthesia with halothane.
2. Hypotension after removal of the tumor
  - A. Volume expansion with blood, plasma, albumin and lactated Ringer's solution
  - B. Neo-syneprine<sup>®</sup> or norepinephrine drip—alpha adrenergic stimulators
3. Arrhythmias
  - A. Lidocaine intravenously, bolus or drip
  - B. Propranolol intravenously, bolus or drip—beta adrenergic blocker
  - C. Reduce halothane concentration.
  - D. Check blood gases to rule out hypercarbia and/or hypoxia.

use nitroprusside. Sodium nitroprusside effectively lowers arterial pressure by *direct action* on smooth muscle allowing you to titrate the pressure down to the level you desire.

Hypotension is not the problem it used to be thanks to preoperative alpha adrenergic blockade. In most cases, volume expansion, usually with albumin and Ringer's lactate, corrects the hypotension.

Cardiac arrhythmias worry me a lot more than hyper- or hypotension. We reduce the halothane concentration and give lidocaine initially and if this solves the problem—fine. Lidocaine, though, is really a minor league drug in this situation and if the arrhythmia does not respond fairly promptly to lidocaine plus the decreased halothane concentration, 1–2 mg of the beta blocker, propranolol, often gives dramatic relief.

**Primary Aldosteronism.** This interesting syndrome, first identified by Conn in 1954, is another cause of curable hypertension, probably accounting for 2–3% of all hypertension. Unlike the hypertension seen with pheochromocytoma, it is always sustained and usually benign with diastolic pressures usually less than 130 mm.

**Physiology  $Na^+K^+H^+$ .** The phenomenon of renal escape is important because of its clinical implications. Aldosterone acts primarily on the distal renal tubule causing retention of  $Na^+$  and  $H_2O$  while enhancing the excretion of  $K^+$  and  $H^+$ . If this ion exchange continued unchecked, the retention of  $Na^+$  and  $H_2O$  would necessarily result in massive edema, but this does not take place. Patients with primary aldosteronism do not have edema. After two-to-three days of aldosterone, the kidneys escape from the  $Na^+$  retaining effect but they do not escape from the  $K^+$  losing effect of the hormone. Initially, salt and  $H_2O$  retention take place, the ECF compartment is expanded, and the patient gains around 2 kg. At this point, however, three-to-five days after administration of aldosterone, renal escape is complete and urinary  $Na^+$  levels, initially low, go back up to normal and  $Na^+$  equilibrium is established at a higher level. The exact mechanism of renal escape has not been clarified. Aldosterone does *not* lose its  $Na^+$  retaining effect on the distal tubule but there is decreased reabsorption of  $Na^+$  by the proximal tubule, probably secondary to the action of volume sensitive salt-losing hormone referred to as the third factor. The decreased reabsorption of  $Na^+$  by the proximal tubule throws an added load on the distal tubule, and this added load balances out the en-

hanced  $Na^+$  reabsorption due to aldosterone. The net result is normal urinary  $Na^+$ .

Aldosterone is an unusually potent hormone. Each day, only 0.1 mg is produced, and chronic production of as little as 0.2 mg per day, only two times the usual output, can cause primary aldosteronism. This amount can be produced by a tiny adenoma less than 2 mm in size. Because of the hormone's potency, most adenomas found at surgery are small. Whereas the average size of a pheochromocytoma is around 100 g, 85% of these adenomas are less than 10 g and 75% are less than 3 cm in diameter.

**Renal-Adrenal Interaction.** There are only three direct stimuli to aldosterone production, adrenocorticotrophic hormone (ACTH),  $K^+$ , and angiotensin II. ACTH is of little importance in the day-to-day aldosterone output, since it stimulates aldosterone release only in emergency or acute situations and for only a short period of time. In normal man, the renin-angiotensin system and  $K^+$  regulate aldosterone secretion through negative feedback loops. If hyperkalemia is present, the increased aldosterone production enhances the urinary excretion of  $K^+$ , returning plasma  $K^+$  levels toward normal, thereby removing the stimulus. When the effective blood volume is reduced, the renin-angiotensin system increases aldosterone production and the resultant retention of  $Na^+$  and  $H_2O$  returns the blood volume toward normal and shuts off the renin-angiotensin system.

In patients with malignant hypertension or in other disorders associated with *chronic underperfusion* of the kidneys, renin, angiotensin II, and aldosterone levels are chronically high and the induced aldosteronism is unable to shut off the renin mechanism. This is called secondary aldosteronism.

**Classification of Aldosteronism.** (Table 6) Until fairly recently, primary aldosteronism was a pretty clear-cut syndrome. The patients, more commonly women 30–50 years old, had longstanding hypertension with associated hypokalemia and muscle weakness. Surgical removal of a small adenoma almost invariably corrected the hypertension and the hypokalemia.

The first cloud on the horizon was the report of many patients with normokalemic primary aldosteronism. Some of these represent milder forms of the syndrome, but many times these patients remain normokalemic because they have been placed on a low salt diet. The magnitude of the  $K^+/Na^+$  exchange is directly related to the number of  $Na^+$  reaching the



TABLE 6.  
CLASSIFICATION OF ALDOSTERONISM

Primary Aldosteronism

1. Benign adrenocortical adenoma—75%
2. Adrenocortical hyperplasia or hyperfunction—25%
  - A. Idiopathic
  - B. DOCA—remediable
  - C. Glucocorticoid—remediable
3. Adrenocortical carcinoma

Secondary Aldosteronism

1. Physiologic via three known direct stimuli
  - angiostensin II
  - potassium
  - ACTH
  - A. Renin-angiotensin system
    - 1) Reduced plasma volume—hemorrhage, dehydration, low salt diet, upright posture
  - B. Potassium
    - 1) High potassium diet
  - C. ACTH
    - 1) Stress—surgery, trauma, anxiety
2. Pathologic
  - A. With hypertension
    - 1) Malignant hypertension
    - 2) Renal vascular hypertension
    - 3) Oral contraceptive hypertension
  - B. Without hypertension
    - 1) Juxtaglomerular hyperplasia
    - 2) Cirrhosis with ascites
    - 3) Nephrosis

distal tubule. A low salt diet would limit this ion exchange and blunt or obscure the clinical picture. Many of these normokalemic patients exhibit hypokalemia after several weeks on a high salt diet.

In the last few years, it has become apparent that hyperplasia is responsible for many cases of primary aldosteronism, and current estimates suggest that 25% are due to hyperplasia or hyperfunction, and the final figure may go even higher. This relatively high incidence of hyperplasia is very important, for these patients are treated medically, not surgically. If bilateral adrenalectomy is performed on these patients, the hypokalemia is corrected but the hypertension is not.

At present, the idiopathic and DOCA remediable forms of hyperplasia are treated with spironolactone, an aldosterone antagonist which blocks aldosterone at the renal tubule. The gluco-corticoid remediable form, or A-G syndrome, is treated with dexamethasone.

In the secondary forms of aldosteronism, either physiologic or pathologic, the aldosterone is elevated because the renin-angiotensin system is in high gear. As a result, patients with this condition have higher levels of renin, angiotensin II, and aldosterone.

*Diagnostic Studies.* (Table 7) Before performing the screening test, the patient should be off all medication, particularly the thiazide diuretics, for a minimum of two weeks.

A high salt diet is used for two reasons. In normal people, a high salt diet expands the ECF volume, thereby suppressing the renin-angiotensin mechanism and decreasing the secretion of aldosterone. With low secretion rates of aldosterone, urinary  $K^+$  levels are low and plasma  $K^+$  levels remain unchanged. In patients with primary aldosteronism, the autonomous production of aldosterone is not suppressed by the high salt diet, and the availability of plenty of  $Na^+$  permits the aldosterone present to exert its maximal effects. With the  $K^+/Na^+$  exchange operating maximally, the resultant high urinary excretion of  $K^+$  causes hypokalemia.

The first step in making the definitive diagnosis is to prove that the patient has excess aldosterone in the urine. To widen the gap between normal patients and those with primary aldosteronism, this determination is performed while the patient is on a high salt diet. Once you have established that the patient is overproducing aldosterone, you then must separate primary from secondary forms. The high aldosterone

TABLE 7.

STUDIES TO DETECT PRIMARY ALDOSTERONISM

1. Screening Test
  - A. Determine plasma potassium concentration after two weeks on a high salt, moderate potassium diet.
    - 1) If plasma potassium is  $<3.5$  mEq/L, patient may have aldosteronism.
    - 2) If plasma potassium is  $>3.5$  mEq/L, patient does not have aldosteronism.
2. Diagnosis
  - A. Nonmalignant hypertension
  - B. Overproduction of aldosterone
    - 1) Failure to suppress abnormal aldosterone production with a high salt diet
  - C. Underproduction of renin
    - 1) Failure to stimulate renin production with a low salt diet and upright position

levels seen in secondary aldosteronism are due to overactivity of the renin-angiotensin system, so that these patients all have *abnormally high* levels of renin. In patients with primary aldosteronism, the chronic overexpansion of the ECF suppresses the renin-angiotensin mechanism and renin levels are low. To widen the gap between normal and primary aldosteronism, this determination is performed while the patient is on a low salt diet and after three-to-four hours in the upright position. These two maneuvers double and triple the output of renin in normal individuals but have little or no effect on patients with primary aldosteronism.

*Diagnostic Studies.* Since the majority of these tumors are small and relatively hypovascular, they are not detectable by the usual techniques—IVP, nephrotomography, arteriography, or retroperitoneal pneumography. It is important to prove the presence of an adenoma, since surgery is not the treatment of choice for hyperplasia-induced primary aldosteronism.

There are three special techniques available for lateralization. Adrenal venography successfully outlines the adenoma in around 85% of the cases. Adrenal venous blood is sampled at the time of venography, and if you detect high levels of aldosterone on the side of the lesion, with close to peripheral levels on the unaffected side, the accuracy of diagnosis approaches 100%.

A recently introduced scanning test, presently expensive and unavailable except at a few selected medical centers, may become the best diagnostic tool of the future. Its obvious appeal is its complete safety. Photo scanning is performed after administration of 19-iodocholesterol labeled with radioactive iodine I<sup>131</sup>. Lugols is given ahead of time to block

the uptake of iodine by the thyroid. The kidney areas are localized with Hg chlormerodrin scan. Five-to-six and eight-to-ten days after administration of radioactive material, scanning of both adrenals is accomplished using a computer-assisted Anger gamma camera.

*Surgery.* Preoperative preparation is aimed at correcting the hypokalemia. Hypokalemia increases the irritability of the heart so that surgery might cause ventricular fibrillation or other arrhythmia. Hypokalemia also weakens the muscles, increasing the danger of respiratory insufficiency if curare-like agents are used.

Hypokalemia may be corrected in two ways. Spironolactone, aldosterone blocker, reverses the effects of aldosterone and returns plasma K<sup>+</sup> levels to normal in three-to-four days. Low salt-high K<sup>+</sup> diet also returns the plasma K<sup>+</sup> to the normal range but this takes a little longer, usually seven-to-eight days. We prefer the dietary approach since it is more predictable.

We prefer the transabdominal approach because it allows us to examine carefully both adrenal glands before making any decision. These tumors occur *only* in the adrenal glands and 94% are unilateral. If aldosterone tumor is clearly visualized on one side, it would be feasible to perform a unilateral adrenalectomy via the flank approach since less than 6% are bilateral. Because these tumors are so small, you have to free the gland sufficiently to permit inspection and palpation of the entire gland. As the lateralization techniques—venography and adrenal scanning—become more usable, a flank approach might be preferred. Unlike other forms of curable hypertension, the blood pressure usually takes weeks-to-months in returning to normal levels.

# Urinary Incontinence: A Problem to Hold On To\*

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**Introduction.** In this presentation attention will be focused on the problem of urinary incontinence. We will look briefly at the various types and causes for this distressing disorder (Table 1). Mention will also be made as to treatment with particular emphasis on the surgical correction (or attempts at correction) of the postoperative urine leakage such as one sees following prostatectomy or trauma.

Before we talk about incontinence, it would be helpful to look at the normal mechanisms which allow us to contain urine for long periods of time and at the appropriate and socially acceptable time, to eliminate our liquid waste products with minimum effort and exertion. In the female there is no distinct urethral sphincter or muscle which can be identified as such. The entire urethra acts as a valve mechanism. The resistance to outflow through the urethra increases as one proceeds from the bladder neck, reaching a maximum resistance in the midportion, and then gradually lessening again as the meatus is approached. Theoretically, the longer the urethra, the more effective the sphincter action. Indeed, it is this lengthening principle which is often utilized during treatment of some forms of female incontinence.

The male is much better endowed for here we have two distinct mechanisms, and definite musculature can be identified as sphincter. In the event of damage to one or the other sphincters, the other one will serve quite as well as a competent mechanism. Definite circular fibers can be identified at the level of the bladder neck which are adequate to contain all of the liquids within the bladder during the resting state. This is the sphincter that is routinely destroyed or damaged in some way at the time of a

prostatectomy. Providing the external sphincter is intact, this will not make the patient incontinent. Distal to the prostatic urethra and at the level of the urogenital diaphragm, sphincter muscles are identified; all are limited to an area of several millimeters in length. These can very easily be seen on cystoscopy as one withdraws the cystoscope. Beyond the level of the veru the sphincter muscle closes down the urethra. During the act of voiding both sphincters relax, the bladder detrusor muscle then contracts, and the urine is passed.

**Urge Incontinence.** This results from a primary abnormality of the bladder, rather than damaged or incompetent sphincters. This is not true incontinence in that the patient is not continually wet. The patient will suddenly have an uncontrollable urge to void, and a small quantity of urine escapes before an appropriate facility can be located. There is an abnormal stimulus acting upon the detrusor muscle, causing bladder contractions, and overriding the sphincter. This is seen in irritated bladders, such as during an episode of cystitis or following extensive radiation to the bladder wall. A similar mechanism is in operation when "bladder spasms" are experienced with an indwelling Foley catheter. Here the bladder surface, in particular the sensitive area around the trigone, is mechanically stimulated by the catheter balloon. If this spasm or detrusor contraction is great enough, urine will be forced out of the bladder and around the catheter. When this urine leakage occurs, one is inclined to replace the catheter with a larger one to totally occlude the urethra. This serves only to increase the stimulation, and thus the bladder spasms and urine leakage are worsened. Actually, a smaller, less irritating catheter should be used in conjunction with some agent to decrease bladder tone such as Pro-Banthin® or

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Valium®. In the case of urge incontinence associated with cystitis, attention should be directed to resolving the bladder inflammation which in turn should improve bladder control.

**Paradoxical (or Overflow) Incontinence.** When the bladder is unable to empty due to obstruction it continues to fill until such point as the intravesical pressure is increased beyond the sphincter pressure, resulting in urine leakage. This usually produces a weak dribbling type of urine flow. This can occasionally be seen secondary to a cerebrovascular accident when the bladder innervation is impaired and bladder muscle tone is decreased. Often, the patient with paradoxical incontinence will give a history of satisfactory urine control during the day when he exerts greater effort to remain dry but wets himself at night when more relaxed and the sphincter pressure is less, thus producing the "elderly bed-wetter." Generally, if untreated the problem gets worse and eventually the dribbling begins to occur both day and night. Initial management requires drainage and decompression of the bladder with use of a catheter. In addition to a decompensated thin-walled bladder, the problem of post-obstructive diuresis must be expected and treated accordingly with fluid replacement and supportive measures. After the patient is stabilized, the etiology of the original obstruction must be determined and relieved. If bladder impairment is not reparable, long-term urine drainage will be required.

**Stress Incontinence.** As mentioned earlier, in the female the sphincter is poorly defined, and the entire length of urethra acts as a control mechanism. When relaxation of the pelvic floor occurs, such as after multiple pregnancies, there is shortening of the urethra as well as prolapse of the bladder base and urethra. Green has shown that as this relaxation occurs, the relationship of the bladder base to the urethra is critical to urine control in the female. This vesicourethral angle can be accurately measured on a cystourethrogram and is helpful in planning corrective surgery. These patients are normally dry during normal activity, and the voiding pattern is unremarkable. The urethral sphincter, however, is just borderline with normal vesical pressures; the sphincter resistance is adequate to control urine. When intravesical pressure is slightly increased, however, such as when coughing or laughing, the integrity of the sphincter is overcome and urine leakage occurs. In general, treatment requires surgical correction to

TABLE 1  
TYPES OF URINARY INCONTINENCE

1. Urge Incontinence
2. Paradoxical (or Overflow) Incontinence
3. Stress Incontinence
4. Enuresis
5. Structural Defects
6. Acquired Sphincter Damage

provide adequate support to the bladder and urethra as well as to lengthen the urethra. This can be done through the anterior vaginal wall by reinforcing the urethra with adjacent tissue. The most commonly used procedure is the Kelly Plication. The correction can also be made from above by tacking the urethra and anterior bladder to the undersurface of the symphysis and rectus sheath, as in the Marshall-Marchetti-Krantz procedure.

**Enuresis.** The word enuresis is of Greek origin meaning urine leakage, but by common usage over the years it has been limited to wetting during the hours of sleep. Except for the paradoxical incontinence seen in the elderly, enuresis is a problem of the younger patient.

**Other Structural Defects.** Anatomical defects of the lower urinary tract may result in urinary incontinence even in the presence of a normal urethral sphincter mechanism. These can be both congenital or acquired in origin. In the former group one sees patients with extrophy of the bladder or with a severe degree of epispadias. Likewise, one sees patients with fistulous communications such as occur between the urethra or bladder and the perineum as is found in certain types of imperforate anus. In the female, an ectopic ureter may exit beyond the urethral sphincter or in the vagina producing incontinence. Urinary incontinence can result from abnormal or absent innervation to the bladder and sphincter which is secondary to spinal cord defects as occurs in those patients with congenitally absent sacrum and myelomeningoceles. Acquired defects, especially in the female, may be the result of gynecological surgery or traumatic deliveries resulting in urethral or vesicle fistulae. Radiation therapy for malignant disease may produce fistulae between the urinary tract and some other organ system with its associated urine leakage. Treatment for these conditions should be aimed at closure of the structural defects such as repair of the fistula and excision or

relocation of the ectopic ureters. If closure of the defect is not surgically possible some form of urinary diversion may be necessary.

**Acquired Urinary Incontinence.** The problem of acquired urinary incontinence is a result of direct damage to the sphincter mechanisms such as one sees following prostatectomy. An entire spectrum of urinary leakage can be seen depending on the degree of sphincter integrity remaining. If the fibers have been weakened but some circumferential fibers remain, the patient may have typical stress incontinence with adequate control at rest with low intravesical pressures; however, when coughing or straining the intravesical pressure exceeds the sphincter resistance and urine is on its way. When sphincter damage is more extensive, such as when a cut or tear extends through the entire membranous urethra, the patient will have a continuous dribble. In fact, it is probable he may not be able to void at all if urine runs out freely and there is no accumulation in the bladder. This is indeed a distressing problem, both for the patient and the doctor. Since most of the other forms of urinary incontinence are "acts of God," and the surgeon is not directly responsible for the patient's dilemma, there is not the overwhelming motivation one sees at attempts to correct the postoperative incontinence. With one act of commission the surgeon has unleashed untold woe upon himself and his unfortunate damp patient.

All of the techniques and approaches to prostatectomy can result in postoperative incontinence. In some types of prostatectomy, however, this complication is much more common. The likelihood of this problem occurring is greater when a total or radical prostatectomy is done for malignancy. In looking at the multitude of techniques, apparatus and corrective operations, it is clear that variety and enthusiasm have more than compensated for what has been

meager in success (Table 2). Suggestions to resolve this problem range from the extreme of suicide on the part of the patient to having the doctor leave town and set up practice elsewhere. In most cases, neither of these two recommendations is very useful. If some portion of the sphincter is intact, it is possible to strengthen these fibers by use of perineal or urethral sphincter exercises. The patient is instructed to "cut-off" his stream several times during each voiding and to remember to "pucker up" his perineum when straining and assuming the upright position. If the patient is totally incontinent, which, according to Dr. Kauffman, occurs in a "small but vocal percentage of postprostatectomy patients," the problem is far more serious and difficult to treat. If one simply throws up his hands and admits defeat, some type of external appliance or device will be needed. This includes wearing a pad, rubber pants, or graduating to a penile clamp such as a Cunningham clamp. At a more sophisticated level, one could advance to the use of a urosheath; the McGuire urosheath of Richmond origin is probably the best known.

Numerous surgical procedures have been advocated for returning the patient to continence. In the early 1920's, the late Dr. Hugh Young suggested excising a portion of the bladder neck to narrow the bladder outlets. This was based on the theory that by excising the scar tissue and lengthening the urethra, control would return. I have not been able to obtain any data on the success rate other than to say this procedure is not generally popular among current practicing urologists. Dr. Thompson suggested suspending the bladder and prostatic urethra from the anterior abdominal wall and undersurface of the symphysis pubis. This is similar to the procedure reported by Drs. Marshall, Marchetti and Krantz for correcting stress incontinence in the female. Further attempts have been made to compress the urethral lumen by external pressure. Dr. Foley devised a fascinating pneumatic compression clamp which surrounds the urethra. Initially, a segment of the urethra was isolated from the penile shaft and provided with a skin covering to form a type of "bucket handle" to the urethra. The activating device for the pressure cuff was kept in the patient's pants pocket. A mere push of the button and the pressure was on. It was said to be good for taking long automobile or bus rides, but because of the need for an external appliance, it never became very popular. Using a more physiological approach, at-

TABLE 2  
METHODS FOR CONTROL

1. Suicide
2. Urologist Leave Town
3. Social Ostracism
4. Wearable Urinal
5. Retention Catheter
6. "Texas" Catheter
7. Cunningham Incontinence Clamp
8. Attempt Surgical Correction

tempts were made to provide the external compression by some portion of the patient's own musculature. A strip of gracilis muscle or rectus muscle could be freed up and looped around the urethra, similar to a cowboy's lasso. Fascial strips were also used with some degree of success. The failure with this method is probably related to the use of voluntary muscles and fascia which are not able to provide the constant contraction which is essential to the muscle tone found in naturally occurring sphincter muscles. To counter this problem, investigators very cleverly chose to use a portion of the anal sphincter to provide continence to both the urethra and anus. Two methods are available. One means is to cut a strip of anal sphincter which has been freed and loop it around the urethra. This is then sutured back to its original attachment. More recently, Dr. Mathison has suggested that a strip of anal sphincter be freed but left intact at both of its ends. The urethra is then cut and pulled through the sphincter loop and then reanastomosed. A number of our patients have undergone this latter procedure. The first one, who was totally incontinent of urine prior to the operation, had a perfect result; he was delighted. Since then our patients have not been as fortunate. Not only has the incontinence continued, but there have been subsequent problems with stricture formation at the urethral anastomosis site.

A new twist was added to the story of urinary incontinence therapy in 1956, when Dr. Beneventi reported his approach to the problem. He exposed the urethra through the perineum after marking the urethra with two stay sutures. The urethra was transected between the sutures. The cut ends were then rotated, one 180° to the right and the other 180° to the left, and reanastomosed into the new position, giving a 360° twist to the new urethra.

Various materials have been utilized to squeeze off the urethral lumen. In the early 1960's, Dr. Berry achieved some success in establishing urinary continence by inserting a small rectangular acrylic prosthesis between the bulbous urethra and the overlying musculature. The prosthesis was held in place by suturing it to adjacent muscles or directly to the bony ischial and/or pubic rami after drilling holes for suture placement. Interest for this prosthesis faded when patients complained of perineal pain or the prosthesis became infected and required removal.

Using much the same approach, Dr. Hinmann

suggested using a piece of a rib rather than the acrylic prosthesis to compress the urethral lumen. The delicate balance, however, between enough compression to establish continence and yet not obstruct urine outflow was rarely achieved.

More recently, Dr. Kauffman has advocated a more pliable form of compression of the urethra by crossing the crura over the bulbous urethra and suturing them in place. Because of failure, this has been modified several times. The crura were sutured directly over the urethra, and eventually the use of a "wad of marlex" tucked under the crura was suggested. This uses foreign material for support, and we are again troubled with the infection and fistulae formation. One of our patients treated with this marlex support actually eroded the prosthetic material directly into the urethral lumen. A recent report from the University of Minnesota has described the use of a new silastic urethral compression cuff which is entirely buried beneath the skin. It is somewhat reminiscent of Dr. Foley's old pneumatic cuff. The squeeze bulbs, however, are recessed into the scrotum, one valve into each compartment with the pressure reservoir hidden beneath the rectal muscles. It appears to be rather complicated, and while its use is thus far quite limited because of the previous problems with such devices, one would question how practical it will be clinically.

In conclusion, it may be said that the problem of urinary incontinence has not been solved. With regard to the various plastic operations proposed for correction of the paralyzed sphincter with complete permanent incontinence, it would be as true today as it was in 1939 for Dr. Herman to say: "The results, with few exceptions, are unsatisfactory."

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# Prostatic Acid Phosphatase: A Potpourri\*

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In 1938, Gutman *et al.* (6) described increased levels of acid phosphatase in metastatic carcinoma of the prostate. Since then, when most of us hear the term "acid phosphatase" we immediately think of prostatic cancer, and justifiably so. The link, however, between the test and the diagnosis is not as clear and simple as many of us would like to believe.

I would first like to discuss this enzyme, reviewing some of its chemistry, its clinical value and the pitfalls and problems associated with the routine tests. Then I would like to tell about some work in which we have been involved that we hope will increase the diagnostic value of this enzyme and perhaps point the way to advances in clinical enzymology in other areas.

**Chemical Assays.** First let us remember that the term "acid phosphatase" simply means an enzyme which, at pH below 7.0, hydrolyzes phosphate esters liberating the phosphate ion and replacing it with an -OH group. Prostatic acid phosphatase is only one of many enzymes in this category. The organic portion of the phosphate ester involved is not specifically defined by the term acid phosphatase, and this brings up our first problem. We do not know the natural physiological substrate of prostatic acid phosphatase. Indeed we know very little about the biological function of this enzyme. Consequently, we must measure its activity using synthetic phosphate esters which are, as far as we know, completely unrelated to prostatic physiology and reproduction. Each new substrate gives rise to a new assay, a new set of units, new degrees of specificity and sensitivity and new problems of interpretation.

As previously mentioned, there are many forms

of this enzyme which are not derived from the prostate. Indeed, it is present to some degree in virtually all tissues as a lysosomal enzyme. In blood chemistry, however, the most common source of non-prostatic acid phosphatase is the red blood cell. For this reason several clinical assays have been developed which readily differentiate between prostatic and erythrocytic acid phosphatase. Table 1 lists the methods and substrates commonly employed in the clinical laboratory. The Bodansky (4) and Babson-Read (2) as well as the newer thymolphthalein phosphate method described by Roy, Brower, and Hayden (14) will not detect red cell acid phosphatase. The King-Armstrong (7) and Bessey-Lowry (3) methods will detect the red cell enzyme, however, and employ an inhibitor, usually L(+) tartrate, to differentiate prostatic and erythrocytic acid phosphatase. Table 2 lists inhibitors which can be used for this purpose. Although selective substrates and inhibitors can make this distinction, it should be emphasized that they do not provide a truly specific test for prostatic acid phosphatase. Indeed,  $\beta$ -glycerophosphate and  $\alpha$ -naphthyl phosphate are histochemical substrates (7) commonly employed for staining acid phosphatase in a variety of tissues.

For tissue analysis and for occasional pathological sera, inhibitors and substrate selectivity do not clearly distinguish between prostatic and non-prostatic acid phosphatase. Table 3 lists some of the nonprostatic diseases which have been reported to cause elevations in serum acid phosphatase and while they rarely present a problem of differential diagnosis in carcinoma of the prostate, we should not ignore their existence.

A far more common problem is the interpretation of serum acid phosphatase levels where the enzyme is of prostatic origin and where we are concerned with the diagnosis and staging of prostatic

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TABLE 1.

METHOD	SUBSTRATE	PROSTATE	RBC
Bodansky	$\beta$ -Glycerophosphate	$\Delta$	
King-Armstrong	Phenylphosphate	$\Delta$	$\Delta$
Bessey-Lowry	<i>p</i> -Nitrophenylphosphate	$\Delta$	$\Delta$
Babson-Read	$\alpha$ -Naphthyl phosphate	$\Delta$	
Roy-Brower-Hayden	Thymolphthalein phosphate	$\Delta$	

TABLE 3.

## NON-PROSTATIC CAUSES OF ELEVATED ACID PHOSPHATASE

Gaucher's disease  
Osteitis deformans  
Thrombocythemia  
Lipid histiocytosis  
Hemorrhagic shock  
Lymphoblastic leukemia  
Nonprostatic carcinoma

cancer. Most prostatic carcinomas produce this enzyme, and low serum levels in the face of apparent widespread diseases are usually the result of heat denaturation at neutral or alkaline pH as this enzyme rapidly loses its activity if the serum sample is not acidified and refrigerated.

An elevated serum prostatic acid phosphatase in general suggests prostatic cancer which has extended beyond the prostate; however, prostatic surgery, diagnostic palpation, and prostatic infarction may cause transient enzyme elevations. Careful attention to the time when the sample is drawn and to specimen handling will greatly improve the reliability of routine serum assays.

**Immunology.** In order to provide a highly specific means of diagnosing prostatic cancer, we began investigating the antigenicity of prostatic tissue and secretions first in dogs (8) and later in man (10, 11). Using antisera raised in rabbits immunized with dog prostatic fluid or human sperm-free ejaculate we could demonstrate an immunological organ specificity of prostatic acid phosphatase. This specificity had also been observed by Shulman and his co-workers (15) and has been confirmed by several other investigators (12, 13). Our methods of demonstrating antiprostatic acid phosphatase involved reacting the antisera with prostatic homogenate in an Ouchterlony agar gel immunodiffusion system. After precipitin lines formed, the gel was washed and stained histochemically for acid phosphatase (14).

TABLE 2.

INHIBITOR	PROSTATE	RBC
Ethyl alcohol 40% . . . . .	(+)	(-)
L (+) tartaric acid 0.02 M . . . . .	(+)	(-)
Formaldehyde 2% . . . . .	(-)	(+)
Cupric ion 0.001 M . . . . .	(-)	(+)

Extensive absorption of the antisera with non-prostatic tissues confirmed the tissue specificity of both dog and human prostatic acid phosphatase. Antihuman prostatic acid phosphatase was then raised against a partially purified enzyme preparation. Human sperm-free ejaculate was passed through an ion-exchange column packed with DEAE Sephadex (A-50) equilibrated with 0.1 M Tris-HCl pH 8.0. Acid phosphatase was trapped in the column while most other seminal proteins passed through freely. The enzyme was then eluted with a sodium chloride molarity gradient, concentrated by ultrafiltration and used with complete Freund's adjuvant to immunize New Zealand White rabbits (15). This antiserum was also checked by Ouchterlony immunodiffusion together with a diazo coupling stain for acid phosphatase as described previously (15). The serum was tested against prostate, liver, spleen, kidney, pancreas, salivary gland, gastric mucosa, large and small bowel, breast, lung, muscle, lymph node, heart and freshly prepared packed platelets. The only positive reaction was with prostatic acid phosphatase. Antiserum of this quality can be used to specifically identify and quantitate the prostatic enzyme.

The sensitivity of gel diffusion tests is too low to detect normal or moderately elevated serum acid phosphatase; however, these simple, inexpensive tests can be used to identify prostatic cancer since the tissue itself is usually quite rich in the enzyme.

**Clinical Study.** A logical application of such a test would seem to be the identification of prostatic carcinoma in bone marrow as the tumor characteristically spreads to bone and the presence of bony metastases is a critical factor in staging the disease. In order to compare the concentration of prostatic acid phosphatase in bone marrow with that in serum, quantitative radial immunodiffusion plates were prepared by incorporating the antiserum in 1.5% agar

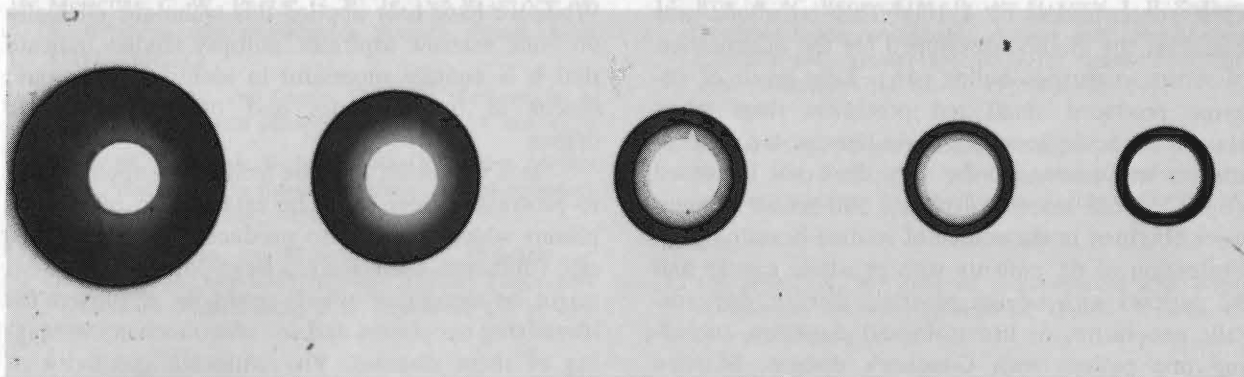


Fig. 1—Serial dilution of prostatic acid phosphatase showing reduction of precipitive ring with decreasing enzyme concentration.



Fig. 2—Comparative immunodiffusion results. M = marrow well, S = serum well.

A. Negative reaction in control patient with hematological disorder.

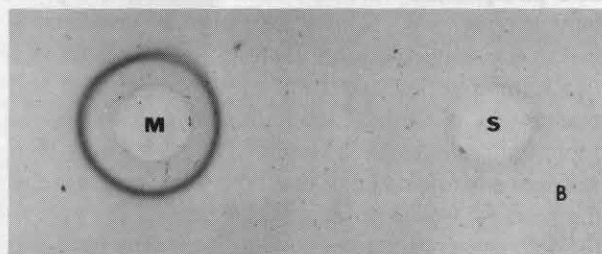


Fig 2—B. Positive reaction in metastatic prostatic cancer and slightly elevated serum acid phosphatase. No precipitive ring has formed around the serum well.

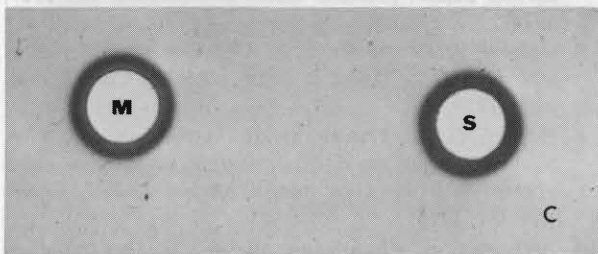


Fig. 2—C. Negative reaction in patient with metastatic prostatic cancer and marked elevation in serum acid phosphatase. The rings are of equal size and do not prove the presence of tumor in the marrow.

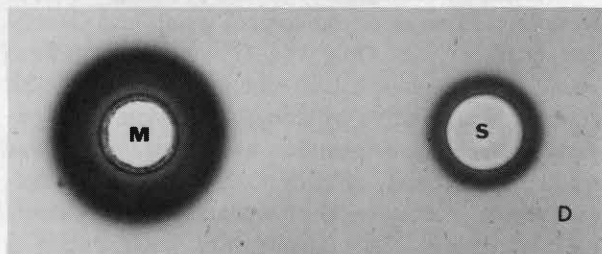


Fig. 2—D. Positive reaction in patient with metastatic prostatic cancer and very high serum acid phosphatase. The much larger marrow ring proves tumor in the marrow.



Fig. 2—E. Negative reaction in the patient with benign prostatic hyperplasia and elevated serum acid phosphatase following transurethral resection. No precipitive ring is formed around the marrow well.

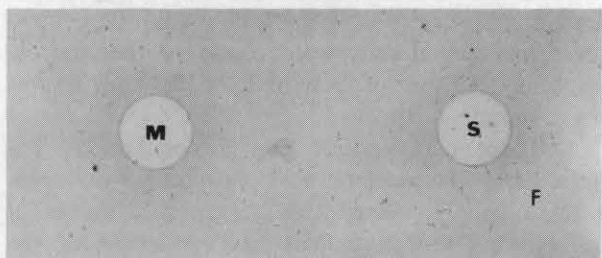


Fig. 2—F. Negative reaction in patient with Gaucher's disease, elevated serum acid phosphatase and Gaucher's cells in the marrow sample. The antiserum does not precipitate nonprostatic acid phosphatase.

at a concentration of 1:100. This technique was based on the method developed for the quantitation of serum immunoglobulins (16). Low levels of enzyme produced small red precipitin rings when stained for acid phosphatase. As the enzyme concentration was increased the ring diameter increased (fig. 1). Bone marrow aspirates and serum samples were obtained in the course of routine hematological evaluation of 61 patients with prostatic cancer and 32 patients with benign prostatic disease, nonprostatic neoplasms, or hematological disorders, including one patient with Gaucher's disease. Marrow smears were stained with Wright-Giemsa and screened for tumor cells. Paired smears stained for acid phosphatase were also used to screen for prostatic cancer cells. Comparative radial immunodiffusion was carried out on quantitative gel plates with two sample wells. Serum was placed in one well and marrow in the other and diffusion carried out at room temperature for 24 hours. The plates were then washed and stained. If the precipitin ring around the marrow well was larger than that of the serum, the test was considered positive. If no ring occurred around the marrow well or if serum and marrow produced rings of equal diameter, the test was considered negative for bony metastases (fig. 2A-F).

**Results of Bony Marrow Study.** Malignant cells were seen in three of the control group and Gaucher's cells in one. Only the Gaucher's cells were stained by the phosphatase reaction. None of the 32 controls was positive by immunodiffusion. One patient with benign prostatic hyperplasia who was studied immediately after cystoscopy showed detectable serum prostatic acid phosphatase but no detectable enzyme in the marrow, thus documenting a serum elevation due to prostatic manipulation. Among the 61 patients with prostatic cancer, 12 had malignant cells in their marrow and gave a positive immunodiffusion test. Four other cases of prostatic carcinoma were positive by immunodiffusion; however, no tumor cells were found in the marrow aspirates. All four of these patients had bony lesions by x-ray.

These data suggest that a comparative immunoassay for prostatic acid phosphatase may provide a simple, inexpensive yet specific means of establishing that a patient has carcinoma of the prostate in an advanced stage. In two cases, we have obtained positive immunodiffusion tests on men with carcinoma of undetermined primary. Both of these were subsequently proven to have prostatic cancer.

While we have only applied this technique clinically on bone marrow aspirates, autopsy studies indicate that it is equally successful in identifying prostatic cancer in lymph nodes and other nonprostatic organs.

It is our belief that the techniques applied here to prostatic cancer could be extended to other neoplasms which continue to produce some tissue specific substance. Ultimately, a large battery of antisera might be developed which could be employed for identifying neoplasms and for immunochemical staging of these diseases. The antigenic specificity of enzymes and other cellular products provides a new parameter for clinical laboratory testing which should lead to improved diagnostic procedures in both neoplastic and non-neoplastic diseases.

*Author's note:* The immunological studies described in the above article were accomplished in a cooperative study carried out by Drs. Charles L. Johnston, Jr., M. J. V. Smith, Warren W. Koontz, Jr. and the author.

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# Carcinoma of the Prostate: The Great Widow-Maker\*

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The percentage of urological cancers is considerable. Of all of the cancer deaths in our country, 10% are urological; in men alone, 18% are urological. It is immediately obvious that a very important aspect of this specialty is the treatment of cancer.

Of the 18% urological deaths among males, more than half are due to cancers of the prostate. When a patient is seen with evidence of a metastasizing cancer and a search is made for the primary site or source, there is always a hope that it will be cancer of the prostate, because we can do a great deal for this cancer that cannot be done in many other cancers.

A comparison of the various urological cancer deaths will show that cancer of the prostate is the most frequent. Second is carcinoma of the bladder, followed by kidney tumors. In comparing cancer of the prostate with other cancers in older men (men over 75), prostatic carcinoma is the most common cause of cancer deaths. If figures for cancer of the colon, rectum and stomach are combined, the resulting figure is slightly in excess of that for prostatic tumors. The impressive fact is that cancer of the prostate is the most significant cause, makes the most widows, of all the cancers among older males. With every passing decade, the number of cancers that one finds in any autopsy series of older people increases steadily. It does not increase among the people with cirrhosis, perhaps because of the increased circulating estrogens in older people who have hepatic cirrhosis. If men were to live for an indefinite period of time, practically all of them would die of cancer of the prostate. The secret weapon is the rectal examination to detect the prostatic nodule before it has developed to a more advanced stage.

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\* This is a transcription, edited by Dr. Warren W. Koontz, Jr., of a lecture presented by Dr. Lattimer at the 26th Annual Stoneburner Lecture Series, February 22, 1973, at the Medical College of Virginia, Richmond.

Dr. Charles Huggins' classic cross sections of the prostate (4) showed that the cancerous, dark area is almost always in the posterior lamella against the rectum where the rectal finger can easily palpate the nodule. It is universally recognized that rectal palpation of the nodule will disclose cancer in only 50% of the cases. Nevertheless, in the 50% where cancer exists, the extent of the cancer is usually more than one would suspect from what one can feel. Recently, I have had it brought to my attention very forcefully that an asymmetry of the prostate without any particular increase in firmness may be worthy of great attention. I have had several patients who related that their internist had detected an asymmetry two or three years prior to biopsy and diagnosis. The instrument we use for biopsies is one developed by Dr. Ralph Veenema.

This instrument can be used with local anesthesia, but it is much easier with pentothal anesthesia. We prefer the Veenema instrument, however, since it gives a substantial fragment of tissue as compared to the Silverman or Vim-Silverman needle biopsies. Inadequate specimens may prevent the pathologist from rendering a diagnosis. We also want larger fragments because we grow the biopsies in tissue culture. This gives not only a dimension of additional size, but also gives an opportunity to experiment with that patient's cancer to see what medications act best against it and to see how it might differ from others.

Of the prostate tumors biopsied, 11% were confined to the prostate. Bone scans, bone surveys, and marrow acid phosphatases have shown that 55% of the prostate cancers have extended locally. There is still another substantial group that has extended beyond the confines of the pelvis. The treatment varies in these different groups. It is the first group that is amenable to radical excision; the second group may be amenable to radiotherapy plus hormone therapy. For the third group, one must

depend upon hormone therapy and hopefully, in the next few years, immunotherapy.

Only 13% of patients with prostatic cancer were detected at an operable stage. The periodic rectal examination is a campaign which we must all wage. It affords the greatest chance of success for making a contribution in preventive medicine. The executive physical examinations that many companies sponsor is one of the best programs in the area of prevention. Occasionally, we find cancer in the chips from a transurethral prostatectomy which we did not suspect from rectal palpation. Then we have the dilemma of whether cancer has been left in the capsule, and we may resect a little more after a while to see whether we have chips. A few patients have undergone radical prostatectomy. Since radical prostatectomy is difficult technically following transurethral prostatectomy, we resort to radiotherapy plus hormones or just hormones alone. Following radical prostatectomy, we administer antiandrogen treatment in the form of castration and estrogens for every patient who will take what we consider to be our best advice. We have a substantial number of cases treated in this way and are awaiting the 20-year follow-up to compare with surgery alone.

When suprapubic or retropubic enucleation reveals cancer, we are better able to determine whether all of the tumor has been removed. If so, there is no need to go back and do a radical procedure. Frequently, when the patient has been through a big operation, he is not anxious to undergo further operative therapy. We are building some experience with radiotherapy after enucleation. One of our worries was that strictures might be more common and indeed be a bad feature of this type of therapy, but this has not turned out to be true.

We prefer the radical retropubic prostatectomy. We do not perform radical perineal prostatectomies except for instructional purposes or for a particular case where it seems to be indicated. With the radical perineal prostatectomy, there is no opportunity to investigate for nodal metastasis.

The first and classical study that Nesbit and his group (5) compiled indicated that stilbestrol increased the five-year survival of patients with prostatic cancer. Orchidectomy was a little better and the combination was better than either one alone. The Veterans Administration report (2) has indicted stilbestrol therapy as a cause of coronary artery disease, phlebitis, and perhaps cerebral artery disease. In the wave of shock and enthusiasm on

their part they have gone overboard and have discouraged a number of physicians from using stilbestrol.

Castration, however, is a more certain way of obtaining an antiandrogenic effect and has none of the drawbacks that stilbestrol itself might have. We combine hormone therapy, or antiandrogens with castration. Castration is not of great importance to most of our patients. Their sex life has almost ended by the time we see them for their cancers, and they do not mind trading a better life expectancy for castration. Bony metastases of considerable extent will clear remarkably with antiandrogen treatment, and likewise, pulmonary metastases have cleared.

Drawing on Dr. Huggins' experience (3), we have an interesting bit of information. A patient with metastases from a cancer of the prostate, proven by biopsy, was given stilbestrol by Dr. Huggins. He was left with just one or two metastases. Dr. Huggins then performed an orchidectomy and the nodules disappeared. Thus we have two different modes of action with these two agents. A combination will be more effective than either one alone. It is not just an additive but it is a different action.

A patient with cancer of the prostate which had obstructed the ureter was benefited by radiotherapy in shrinking the prostate. He was given 6,000 r of radiotherapy to the prostate area and the obstruction was relieved. The enthusiasts for this particular method of therapy, and particularly Dr. Malcolm Bagshaw (1), have put together a very large number of patients treated more or less with radiotherapy alone. Their success rate has been so good that they tell us that radiotherapy is curative. Raimey (6), however, has produced at least a dozen cases where he has biopsied the prostate after radiotherapy and the cancer appeared exactly as before radiotherapy. He argues that the cancer is not cured. Bagshaw replies that it looks like cancer but is not cancer and will not grow. Time will tell whether radiotherapy is really effective. Supervoltage therapy and perhaps larger doses and better targeting are improving results and the question is whether radiotherapy is as good as radical prostatectomy.

The Veterans Administration study suggests that conservative therapy is as good as radical surgery, but my view, after reviewing all of the studies, is that we do not yet know whether radiotherapy is indeed as good.

The next question concerns combining radiotherapy with antiandrogen therapy. Will that be as

good as a radical operation? At this moment, we do not know. We do know that if we remove the tumor, at least we are rid of the major part of the focus. The question remains, what about the cells that are spilled or that have migrated away? In reply to that question, one can demonstrate various experiments where a large mass of cancer treated by any modality has no great chance of shrinking. If the large tumor mass is removed and you leave behind only a few cells, then you may indeed kill those few cells by whatever supplementary means you use. We must look in the future to taking out the mass of cancer and then successfully treating what is left behind by immunological, hormonal means or by x-ray. We must think in terms of combination, and in my mind it is not entirely clear whether the radiation therapy plus hormone treatment is as good as surgery alone or surgery plus hormone treatment.

Occasionally, there will be a massive cancer and the resectoscope will be necessary to tunnel an opening through it. This can be done and supplemented by other treatments. Another modality for this problem is freezing the prostate. We insert a cryoprobe much in the same location as the resectoscope sheath. The temperature is dropped to minus 170° F and the mass of prostate freezes completely solid. It looks like a ball of ice, and literally, it is a ball of ice. Over the course of the next few weeks, the prostate will then slough. A catheter may have to remain in place for quite a long time while the gelatinous slough is removed. Later, there will be a very satisfactory tunnel through the middle of the prostate, whether it is benign or malignant.

There has been some suggestion that the very act of freezing will set up an immune reaction in the body wherein the body will attempt to reject, not only the frozen prostate, but also perhaps the metastases. There is some encouraging evidence of this, and we have research going on presently in this field. We have been freezing the prostate three times, a so-called triple-freeze, and this is alleged to improve the immunological response and is a new dimension that is worth testing. It is not certain that it will be as good as we would like but, nevertheless, bone pain does diminish.

If the prostate tumor appears to be resectable, we prefer to use the suprapubic approach. Our operation involves dividing the urethra just beyond the apex, dividing the vasa, dissecting the seminal vesicles down to their tips and dividing the vessels. We take the fascia around the seminal vesicles pur-

posely because we have found that this is the first route of extension of the disease outside of the prostate. We also remove a cuff of bladder.

We take pieces of tissue from a benign area and pieces from the cancerous area and grow them in a medium that is laced with radioactive food in the form of thymidine and cytidine. We then make a radioautograph of this and determine the DNA and RNA synthesis rates in these various areas. We find a very clear picture of benign activity in the benign areas and a very clear picture of greater activity (five or six times as much mitosis) in the cancerous area. Dr. Myron Tannenbaum, one of our researchers, has found that the area surrounding the cancer was as active as the cancerous area. This surprised him, and he then subjected the cells from this area to a higher magnification and discovered some very interesting material in what we refer to as the demilitarized zone, just outside the cancer.

The cancers of the prostate are histologically so much like cancers of the breast that we run a lot of parallel work in the two fields. Dr. Tannenbaum looked at cancers of the breast and found the same virus-like material in them. Turned on edge, the rods of the material look more target-like. Looking at the cancers themselves in both the breast and in the prostate, he found the virus-like material in the lumen of the prostate and the breast. A different kind of virus-like particle, the so-called "C" particle has been found in the milk of a mouse with breast cancer as well as in the semen of her mate. A similar "C" particle has been found in the semen of one of our patients with cancer of the prostate. We are now heavily involved in antibody testing of all of our patients and their wives to see if there is any possible relationship between cancers of the prostate in men and cancer of the breast or genitalia in their wives. We studied 5,000 men and found 186 men with cancer of the prostate, where the wife had been living and having intercourse with him for at least two years before the diagnosis of cancer of the prostate was made. We found 8-9% of the wives of those patients had cancer of the breast. When one compares this with the expected incidence of such a group, it is 500 times more. From this very carefully controlled group, it was found that the controls had an incidence of less than 1%—a finding of more than just passing interest. From this work we now advise that all of the wives of patients with cancer of the prostate have a very careful breast examination, cervical Pap smear and ovarian examination at least every six

months. We have been cautious about stirring up a lot of anxiety where it might be unfounded, but knowing these facts and saying nothing would not be right either. We consider it advisable to be cautious in the campaign of encouraging the wives of men with cancer of the prostate to be examined more carefully and conscientiously than wives in the general population.

It is possible to take a time-lapse picture of a cancer cell and see what happens as it begins to divide. First, a refractive outer coat appears as the cell goes from the resting configuration to the stage where it is about to divide. The chromosomal material begins to shape into a spindle and starts to divide. Then the spindle forms very decidedly and some minutes later, there are two sets of chromosomes, divided and beginning to pull apart. They pull apart further, and two cells begin to form, now having a configuration more like the resting phase. If you know how many frames per second or per minute are involved in these changes, you can time the intervals between each of these phases. We usually take two-to-four frames per minute. The cancer cells take longer to divide than the normal cells, but the cancer cells go through this procedure much more often than the normal cells. An eye dropper can be used to add various anticancer medications to the culture to see how the course of events can be influenced. If the mitotic process stops, one can see in what phase it stops. The anticancer agents can be labeled and observed as they go into the cell. If the particles are fine enough and are hooked up to an immunological apparatus, it is possible to discover where they went in the cell. The technical aspects of this procedure pertain to the fact that some drugs go into the cell wall, some into the mitochondria, some into the nucleus, and other drugs act on the nucleolus. If one is using multiple drugs, it is helpful to have different modes of action. We have done this with the Wilms' tumor drugs and have sorted them to determine the actions of the different medications and have been able to obtain some information about the different modes of action and the most effective combinations. In spite of this technical apparatus, we still find the most important single case-finding factor influencing the successful treatment of this prostate cancer to be the periodic rectal examination.

Another aspect of scientific advancement is the fact that the cancers have caused the development of various immunological changes in the blood stream. Sometimes various antigens and antibodies

are present. There has been a rekindling of enthusiasm about this. Certain carcinomas of the bowel and certain embryological pieces of bowel give off antigens into the blood that can be measured quite easily. We have discovered that in various urological cancers this same antigen, called a cancer-associated antigen or a carcinoma embryonic antigen, is detectable. We have demonstrated that in various samples of prostate from various samples of the patient population, we would find an increased and measurable amount of tumor-associated antigen that would not be of any value as a screening test because it was not always positive. Yet it did have value as a test of failure of treatment. If one surgically removed the prostate in a cancer patient and the test became negative, that was a good sign. If the test remained positive following surgery, one would know that all of the tumor had not been removed. Therefore, one might be more vigorous with the antiandrogenic or irradiation treatments. We have used it as an index of failure in radiotherapy cases where the first portal was mapped out and treatment included the prostate only. If the test remained positive, then we knew we had failed to kill all of the cancer and we then irradiated to a larger field. Thus the test does have some usefulness even in its present crude form. The obvious implications are that we may be able to develop an antigenic test specifically for the prostate. This is what we are working on and I am sure others are investigating it also. This field is of considerable importance and interest.

We have used the same tumor-associated antigen, hooking it onto a bridging-type of enzyme substance, onto which can be hung a color, namely a reddish-brown color. If the tumor is positive with this antigen, we can treat the patient with this material and the cancerous areas will turn a very distinctive color. In a lymph node where the cancer is not obvious and where, by ordinary investigation, that is light microscopy, it may not be possible to tell that these areas are cancerous, this test will show that the node is very specifically cancerous.

The same technique might be applied to the Pap smear to ascertain whether there are cancerous cells in tissues. With the electron microscope, one can tell for sure, but you cannot scan wall-to-wall with the electron microscope. With the antigen, it would be possible to pinpoint the areas that turned red and go directly to them with the electron microscope. We may be able to apply our greater scientific capability to the clinical staging of the cancer and thus



bring about a more specific and accurate staging and treatment. The implications of this are considerable.

Our only protection against cancer of the prostate and its rapid growth is the annual physical examination. We know that various cancers divide at different rates. We do not know the reasons for all of the differences. We do not even know why one person develops a prostatic cancer and the next does not. The fact that it is endocrinologically dependent, the fact that it is possible to survey what goes on in great detail through the capabilities that we have makes the urological specialty very valuable in the cancer area.

We are able to study the rate of growth, regression or improvement of solid tumors of the kidney through pyelography, aortography and angiography better than other fields. Epithelial tumors of the bladder can be observed with the cystoscope and biopsied periodically to follow the efficacy of treatment or to get specimens for study. Hormone-dependent therapy in cancer of the prostate gives us more leverage and opportunity to study the activity of cancer. The advances that have been accomplished, in fact some of the great success stories of cancer, have been urological. I think the prostate was certainly the bellwether of all the demonstrations that a hormone-dependent cancer could be influenced. I think it is part of our responsibility as urologists to

realize that we have this opportunity. I know that all of you share with me this enthusiasm to do everything we can and to be in a position for contributing more than any other specialty to the study of cancer.

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# Psychiatric Problems in Urology\*

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The emotional charge invested in the genitalia far exceeds that of any other part of the human anatomy. Both the conscious and the unconscious feelings about the genitalia are subject to gross distortions which do not respond readily to logic or to intellect. This means that the complete urologist must view the emotional aspect of his area of work from two angles:

- 1) Illnesses, injuries, and manipulations of the genitalia, regardless of etiology or need, may produce major emotional upsets in susceptible people.
- 2) Symptoms involving the genitalia may be the first and most prominent expression of an emotional disturbance.

An example of an emotional disturbance which was precipitated by (you will note that I do not say "caused" by) genital manipulation occurred with a 45-year-old aide at a Veterans Administration teaching hospital. Hematuria had been discovered in the aide's urine upon a routine physical examination. The cause could not be determined readily, and he was admitted to the hospital for a cystoscopy which was done by the chief resident in urology. The procedure did not yield a diagnosis, and the aide was discharged with instructions to be readmitted in three days for a more complete work-up. He returned to his ward work but adamantly refused to have any further procedures even though the cause of his urinary bleeding was still undetermined. His nursing supervisor asked me to see him in consultation when he was heard making threats toward the cystoscopist.

The aide spoke freely and convincingly of what the urological resident had done to him. He was perfectly accurate in his details, except that he

quite irrationally misinterpreted the entire procedure. He had not been able to get an erection since the cystoscopy, and it represented to him a gross homosexual assault which had deprived him of his "manhood." He was so enraged that he was determined to kill the urological resident. The aide was not psychotic nor out of contact with reality in any other sphere.

Two one-hour sessions with the aide resulted in detaching some of his rage from the urological resident and in getting him to see that there might be other causes for his impotence. He remained quite suspicious, however, and would not agree to more urological examinations. Before his next appointment a few days later, a perfect stranger jostled him on the street as he was entering a neighborhood bar. Unfortunately, he had been hunting rabbits that morning and he had a shotgun in his nearby car. He quickly took the shotgun from the car and literally blew the head off the man who had accidentally bumped him. He had displaced his rage from its original object, the cystoscopist, but it obviously was still there.

This anecdote represents a type of paranoid reaction which is not uncommon after genital manipulation or injury, but fortunately most are not so severe and do not end so tragically. The operating urologist had not communicated fully to the patient; he did not make certain that the patient had a complete understanding of the procedure, and he did not work with the patient after the procedure to make certain that there were no overt or covert misunderstandings.

Janis (2) stressed that surgical procedures about genitalia produce an inordinately high level of anxiety in most patients and that it may be catastrophic in some susceptible individuals.

An example of the genitalia becoming symptomatic as an expression of an emotional reaction occurred in a young housewife who presented herself

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to her family doctor for dysuria. The physician found nothing of note and referred her to a urologist. He found no reason for the painful urination, and the patient did not return. However, over the next one and one-half years, the patient visited many urological clinics throughout the country and spent several thousands of dollars. The symptoms persisted despite innumerable urethral dilations, the installations of many medications, and several ineffective prescriptions for urinary tract sedatives and antibiotics.

She came to the attention of a urologist in a teaching center who was interested in the emotional aspects of his patient. He took a very careful history which included a detailed account of her sexual life and of her feelings about it, and he discovered that the dysuria had originated under the following circumstances: The lady and her husband had been to the country club one evening and had had more than their usual number of martinis. In some sexual play at home her husband titillated her clitoris with his tongue, and she had the first orgasm of her life. A few days later they repeated the act after several martinis, and again she had a gratifying orgasm. The next day, however, she began to have pain and burning upon urination.

The final urologist allowed her to vent her feelings of guilt and allowed her to express the fact that she felt that this act had made her some sort of a "pervert." (Like many superficially sophisticated people, she also was very fundamental and conservative in her basic beliefs.) During these brief sessions he was able to communicate to her that she was in no way abnormal but that she might need a bit of work concerning the fact that she had been unable to have orgasm by other methods. The dysuria stopped on approximately the fifth visit and had not recurred at a two year follow-up.

Sexual problems in the female frequently are expressed as urinary dysfunction. The intimate anatomical and neurophysiological connection between the lower urinary tract and the sexual apparatus is obvious, but many times it is not so obvious that the female uses this part of her anatomy, especially the urethra, to express conflicts in the area of sexuality and hostility (4). The symptoms may vary from urinary retention to dysuria, frequency and incontinency. There does not appear to be a one-to-one relationship between the symptomatology and a specific sexual conflict, but some degree of anger, frustration and/or general hostility frequently

is seen. Some of our vernacular statements, such as "Piss on you," indicate an unconscious awareness that the urinary functions can be related to strong emotions, frequently hostile. There can be no substitute for a full sexual and marital history as a part of the diagnostic work-up in every patient with complaints involving the genitourinary tract, even when they are of obvious organic etiology.

Another group of patients, those with a diagnosable mental illness, frequently present with complaints involving the genitalia. For example, the conviction that there is a urinary tract infection, frequently a venereal disease, is quite common in severely depressed and in schizophrenic patients. One young man, a 25-year-old farmer with borderline schizophrenia, went to his family physician with the conviction that he had gonorrhoea. No infection was discovered, and the patient was dismissed. This did not change his conviction, of course, so he visited a urologist in a nearby larger town and was given the same information. The urologist had done a good diagnostic work-up, but he had ignored the possibility of a deeply fixed delusion which, in fact, existed. The young man went home and put a .38 caliber bullet in his head. The physician's responsibility is not finished simply because there are no positive physical findings to explain the complaint.

Many mildly disturbed adolescents are convinced that they have an undersized penis or distorted testicles and present to the physician with this complaint. Undue examinations or manipulations do nothing to ameliorate the deep anxiety and may serve to fix the idea more firmly. The complaint usually represents grave doubts of sexual identity and/or of general adequacy and should be viewed as a warning sign. Simple reassurance by an authority figure may be sufficient, but the adolescent should be encouraged to voice his deeper feelings.

No discussion of the psychological aspects of urology can ignore impotence. The ability to achieve and maintain an erection suitable for sexual activity is one of the prime measures of manhood in Western society. Earlier, and perhaps more thoughtful societies, included religious ceremonies and frequently had specific deities to insure man's continued potency. The Egyptians, in keeping with their extremely compulsive attention to all details, took pains to insure that this part of man's existence would continue in the after-life by mummifying the penis in the erect position. Judeo-Christian religions solved the problem by completely doing away with

any form of sexuality in the life hereafter. In order to accomplish this, it was necessary to classify sex as a sinful thing to be avoided except for procreation. Thankfully for those of us who came after them, they were not able to succeed entirely, but they did leave us a legacy of problems which still plague us.

Differentiation of psychogenic impotency from that of organic etiology usually presents no great problem. Impotency of organic etiology is rarely selective in nature, but the reverse is true for that of psychogenic origin. The physician determines whether or not the man achieves erections during dreams, upon arising in the morning, during masturbatory attempts, with daytime fantasies, or with one woman and not another. A positive response to any of these areas goes a long way toward ruling out organically produced impotency. A major exception to this is the impotency which accompanies severe depression. The impotency of depression may cover all areas of sexuality, but the crucial point here is that the desire will be just as absent as the ability. The lack of potency will be of little or no concern to the patient who is truly depressed; whereas, it usually creates great anxiety in non-depressed males.

Whether or not the urologist chooses to treat male impotence, he cannot avoid his diagnostic responsibilities and the need to counsel the patient about possible treatment. Many patients respond to a type of superficial educational counseling quite within the ability of any physician, but all will appreciate the opportunity to talk to an interested and knowledgeable authority and to receive guidance toward the proper treatment.

Time does not permit discussion of all the many urological entities that have a major psychiatric component. In general, we have said that all genital manipulation should be considered from this viewpoint, but obviously some have a greater significance than others. The manipulations involving children are always of extreme importance, and the urologist who treats children must have an understanding of the developmental phases of childhood and what they mean to future emotional adjustment. In general, such procedures should not be done unless absolutely essential, and if the child's history indicates that emotional problems already exist, then a consultation with a child psychiatrist is mandatory.

It is equally important for the urologist involved with procedures such as kidney transplants to know that both the patient and the donor frequently have

rather severe emotional reactions. Most of these reactions appear to be preventable if adequate concern is given to them before surgery. Donors, for example, frequently develop feelings of anger and rejection (1). They seldom are given the sort of credit and adulation which they think their major sacrifice warrants, and reactions of passive-aggression and depression are not uncommon.

There have been equally important reactions in those receiving kidney transplants (3). One center, for example, has noted that a recipient who is still living in excellent physical health after more than ten years has failed to function at even the most rudimentary level since receiving his new lease on life. While this may be considered a surgical success, it is by no means all that could be desired. Marked attention to this aspect must be considered just as significant as the more technical problems.

The crux of this aspect of urology is that in no other medical speciality is a complete emotional history so important. Patients will not volunteer much of the significant material unless asked. For example, a 44-year-old professor of engineering had a routine, elective hemorrhoidectomy. He was seen in consultation by a urologist when he was unable to void spontaneously by the sixth postoperative day. Nothing was effective and eventually some operative procedure was done transurethrally. The patient still could not urinate when the catheter was out. Another procedure, a bladder neck resection, was performed with no results, and after several weeks, a psychiatrically oriented urology resident sat down with the patient and took a complete history as follows:

The man was unmarried, lived alone with his mother, had never had a sexual life beyond masturbation, and had not even had a girlfriend. He had never been able to urinate in any public place without being totally alone and while sitting on a toilet seat. Even at home he had trouble starting a stream while standing and had never in his life urinated while another person was in the room with him.

This history should have alerted the original surgeon and certainly would have warned the urologist to avoid surgery if at all possible. If not possible, he would have done as little as possible while working with the patient's emotional problems or asking for psychiatric consultation.

Major diagnostic problems with, or genital surgery upon one member of a marriage should always include the partner. Valuable information may be obtained by interviewing the partner, and many

false beliefs may be corrected with a beneficial effect upon the patient. For example, the wife of a man scheduled to have a prostatectomy of any type has many fantasies of what will happen to his sexual abilities. She should be encouraged to express her thoughts; then she should be given the facts as the urologist sees them. This is equally true of any form of genital manipulation.

The urologist may wish to consider himself primarily a surgeon and wish to avoid the role of sexual consultant or marriage counselor. That is hardly possible for one whose field of work is the genitourinary system. Patients expect the urologist and the gynecologist to be experts in all areas of sexuality, and perhaps they have a right to do so. The well-read patients of today expect the urologist to explore the sexual and marital aspects of their conditions and to counsel them accordingly. This means that the complete urologist needs expertise in the techniques of interviewing as well as in the techniques of surgery.

In summary, the urologist cannot escape from a major responsibility for his patients' emotional com-

ponents. The very area of his work is highly charged with emotional potential, primarily of a sexual nature. A careful sexual history is essential to the full understanding of the symptoms of many urological complaints and is equally necessary for the prevention of emotional complications to genital surgery.

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# The Urologist and the Law\*

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The basic concepts of the law as they pertain to urology are no different from any other part of the law which pertains to the medical profession. I shall not spend a lot of time going over that, except to say that you owe the same duty that any other physician owes to a patient, and that is to exercise that degree of care which the average urologist would exercise under the same or similar circumstances. The courts generally say further, "in the same or similar communities," and then qualify it still further by saying, "regard being had for the state of medical science at the time." It narrows down to the fact that you do not have to be the best, but you cannot be the worst. If you conform to this standard, you have a reasonably good chance of staying out of trouble as far as the law is concerned.

Now let's go into two or three areas which have arisen recently and which should give all of the medical profession some concern. I am sure you have heard the term "informed consent." Basically, the term "consent" itself implies that if you do a procedure upon a patient without the patient's permission, you have committed a battery on that patient, and the patient is entitled to recover for any damages done. No expert testimony is required, and you can be liable for punitive damages which your malpractice insurance carrier will not pay. This is a very narrow field because very seldom do physicians today do procedures without some type of permission or consent.

But the area of "informed" consent is a much more complex proposition, and the problems are steadily increasing, both medically and legally. The underlying concept to this whole proposition is fundamental to American jurisprudence; that is, that every human being of adult years and of sound mind

has a right to determine what shall be done to his own body. There are numerous examples of this. One of the classic examples is that of the Jehovah's Witnesses who, because of their convictions, will not accept blood transfusions. The courts, all the way to the Supreme Court of the United States, have uniformly held that a person has such a right of refusal even if it means his death, and you have no right to intervene. When you get down to the basic premise that each individual should be allowed to determine what happens to him, no one can question the validity of the principle. It's good and it's sound. There are ramifications, though, when the patient has given consent but where a complication or risk develops. If the patient has not been told about the risk, he may bring a suit contending that he was not adequately informed and had he been, he would not have consented. This is not a battery, although in some places this has been attempted in order to get punitive damages. The courts uniformly recognize that this is no more than a breach of duty, the duty that you have to treat your patient properly. There is a duty to inform the patient of what you are going to attempt to do and the possible complications and risks, and a failure to do so amounts only to a breach of that duty. It is treated in the same category as any other negligence action.

From this, then, let us consider the two basic principles which must be kept in mind. First of all, the patient has a right of self-determination, and this imposes upon you the duty to make a disclosure to him. Second, the amount of the disclosure is to be measured in terms of "reasonable." Basically, that is what the courts have said, and that is what the duty is based upon. These principles are generally recognized, although I must say they are not recognized in all places, and have been treated rather casually in some places. The majority rule among the states today is that in determining how much is to be disclosed to a patient, the same rule is followed

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as determines the standard of care in treating the patient, namely, what the standard is within the medical community. This is generally followed and has been a reasonably good defense up until now. I might say, for those of you who are from Virginia, the question has not arisen here, and I do not anticipate any great problems.

There are two recent cases, however, which throw a shadow over the whole question of consent and disclosure. They do not set forth any specific rules to be followed, but they do establish that the duty goes much further than anyone had ever contemplated. The first was a case from the Court of Appeals of the District of Columbia handed down in May 1972. To summarize briefly, a nineteen-year-old male had only a back pain. He was seen by a series of physicians and finally by a neurosurgeon who recommended that he have a laminectomy. He was not told that about 1% of the laminectomies end up with some sort of paralysis. He agreed to the operation, and unfortunately, after a chain of varying events, he became paralyzed. The District Court which heard the case ruled, as a matter of law, in favor of the physicians, both on the question of malpractice and negligence in the way the operation was performed and also on the failure to inform the patient of all the risks involved. The Court of Appeals reversed the case on all issues and sent it back for trial on the merits. Some of the statements made by the court are general statements which apply across the board:

Due care demands that the physician warn the patient of any risks to his well-being by the contemplated therapy. The patient must have some understanding and familiarity with the therapeutic alternatives and their hazards. The physician must disclose the choices and the dangers inherently and potentially involved.

Those are rather broad, sweeping admonitions. The court said that the standard is "what is reasonable under the circumstances and that this is not to be determined solely by the physician." The court went on to say that this is a matter in which laymen have knowledge and are in a position to express an opinion or view. It is not in the same category as the type of treatment that should be rendered for a particular condition. All of the risks which potentially affect the decision to be made by the patient must be revealed. The court defines this by saying,

"A risk is thus material when a reasonable person, in what the physician knows or should know to be the patient's position, would be likely to attach significance to the risk or cluster of risks in deciding whether or not to forego the proposed therapy." That is a way of saying that you must put yourself in the patient's position, so to speak, in prospect and not in retrospect. If a reasonable person, knowing what the risk is, might forego the procedure, you must tell him what the risk is. The court has gone further and said, "A very small chance of death or serious disability may well be significant; a potential disability which dramatically outweighs the potential benefit of the therapy or the detriments of the existing malady may summon discussion with the patient."

Whenever nondisclosure or particular risk information is open to debate by reasonable-minded men—laymen, not physicians—the issue is for the finder of the fact, the jury. What in effect the court has said is that the question of whether or not the patient should have been told about certain risks is going to be a jury issue in every case. No matter how many times the court may instruct the jury that they are not to view the case in retrospect, it is impossible for them not to do so. They cannot get out of their minds what has already happened.

The second case came up even more recently than the first—in October 1972 in California. In this particular instance, the surgery was for the treatment of a duodenal ulcer, a very small duodenal ulcer that had been very difficult to diagnose, even by x-ray. The surgeon explained that there were certain risks in the general anesthesia. He explained the nature of the operation, but none of the inherent risks, one of which is that in a certain percentage of the cases—I think about 5%—there may be some injury to the spleen or its adjoining structures. The patient did have injury to the spleen because one of the arteries broke loose, and he almost bled to death internally. Neither did the physician explain that the evolution of a new ulcer might occur; he got one of those. The patient had several other complications and he sued the doctors and the hospital. This court came to the same general principle as the court in the District of Columbia, holding that, as to the duty to disclose available choices of therapy and dangers inherently and potentially involved, the physician must comply. The right of self-decision by the patient is the measure of the defendant's duty to reveal.

Now, both of these cases recognize two general exceptions which you should keep in mind. One is in the case of an emergency or where the patient is incapable of making a decision because of mental incompetency or infancy. If the treatment is immediately necessary, you can proceed without any type of consent. If the patient is incapable of making any type of decision because of infancy, the parents can certainly be fully advised and the consent obtained from them, if there is no emergency situation. The second refers again to the majority rule and there the court says that where the welfare of the patient dictates that he should not be told, there is reason not to tell him, but the burden of proving this is on the physician, not on the patient. In other words, this is an excuse or a reason for nondisclosure. The burden is on the plaintiff to prove he was not told, and if he was not, it is up to you to justify not having told him. The court pointed out that the fact that the patient may decide not to have therapy is not reason for not telling him.

One court pointed out that nondisclosure is justified only where the reaction to the risk information, as reasonably seen by the physician, is menacing, almost life threatening to the patient. That is almost the only instance in which you would be justified in not telling the patient. In this regard, I should warn you that you must have expert testimony to back up your decision. In the case in the District of Columbia, the surgeon testified that it was not in the best interest of the patient to tell him that he might be paralyzed from this laminectomy. The court paid no attention to that statement whatsoever, saying that it was for the jury to decide, since the physician was the only one who said this, and he had not given any background or any medical reason why it would have been harmful to the patient. There was no reason to believe that he was emotionally unstable or anything of that kind. I realize full well the restraints this places upon the medical profession, but I do not think we can ignore the fact that to some extent a person does have a right to determine what is going to happen to him.

Both of these cases attempted to set forth certain types of things that a patient should or should not be told and little can be derived from reviewing these, because they do not make that much sense. One of the cases, for instance, referred to minor procedures and complicated procedures, and what you do in one case and what you do in the other. Of course, you can imagine what's going

to happen when someone says, "Well, it wasn't minor, after all; it was complicated."

There is another type of situation you encounter in "informed consent" cases. A patient was to have an arteriogram performed. There was no emergency; it was not necessary at the time that it be done; it was an optional procedure. The surgeon did not tell him that there was a risk of paralysis inherent, and he became paralyzed. The plaintiff recovered—that is, a verdict against the doctor.

In another case, a patient of oriental descent developed hypopigmentation—I believe it was during pregnancy. She consulted a dermatologist, who recommended dermabrasion, but he did not tell her that it was only 50% effective and that the condition might even be worse after he finished. It was worse, and she sued him. There was no question in that case. The court said that he had failed to conform to the duty imposed upon him to advise the patient fully of the successful nature of the operation if performed, and also of its chances of failure.

The courts have said, in effect, that if there is a serious risk of death or danger of death, even if the percentage is very small—down to 1% in one of the cases—the physician must so advise the patient. Also, he should explain any alternative methods of treatment. Frequently, this is omitted. I have found this to be true in any number of cases in which I have been involved. The physician has not told the patient that there were other methods of treating the condition, and he has left the patient with the impression that the one recommended by him was the only one. What it boils down to is this: If the patient doesn't want to take the chance, on what basis can the medical profession justify forcing him to do so? If you can answer that question, then you have solved the problem, because then you can omit anything you want to.

Some simple "do's" and "don't's": You must or should disclose the general procedure and generally what you expect to do, and what the patient should expect from the procedure. Also, you should identify the surgeon who is going to perform the surgery, and whether or not others will assist, particularly residents. In several of the teaching institutions, I have found that they do not tell a patient ahead of time that the surgery may be performed by residents. The risk of serious harm or death, where applicable, should be disclosed. This would be true in any major case, or certainly where any general anesthetic will be used. The peculiar risks of the



procedure involved should be explained to the patient. There's a greater duty to disclose if the procedure is experimental, new or novel, ultrahazardous, if there is a possibility of altering the sexual capacity or fertility of the patient, if it is purely for cosmetic purposes or if it is an optional procedure.

The "don't's" that you might add to this include: Do not say that any procedure is simple, under any circumstances. Do not ever tell a patient that no complication can occur. Do not just answer the patient's questions and expect that to fulfill your obligation to fully inform the patient. Do not expect others to make a disclosure for you, such as the anesthesiologist who may come to see the patient, or any of the house staff. Do not minimize any part of the procedure or make a guarantee of any kind or any statement that resembles a guarantee or an assurance that you or the procedure will cure the patient.

There is one exception, of course, and that is if the patient specifically does not want to be informed, you do not have to do so. Some people may not want to be informed of what can happen to them. If they do not want to, you should not burden them with it, but you should certainly document the circumstances very amply and very completely in the chart.

I point out these two cases because they are a sharp departure from what has been the rule. How many states will proceed to follow this I have no idea. But a word of caution is always in order: If you adequately protect yourself in this regard, you are certainly on the safe side. As I understand it, it is always better to overtreat than to undertreat.

With respect to infants, I would mention that the consent should come from the parents; also, that now in most of the states 18, not 21, is the age of majority. Suppose an eighteen- or nineteen-year-old college student comes into your office needing treatment. He has no means of support, and you are concerned about who is going to pay your bill. You get in touch with the parents and ask them by long-distance telephone if they will take care of the bill. They tell you that they will. Suppose a long series of treatment is undertaken, and the bill mounts into the thousands of dollars. The parents do not want to pay the bill, and they do not have to. At least in Virginia, and in most other states, the promise to pay the debt of another has to be in writing to be enforceable. This is the so-called statute of frauds. All you have to do is get the parents to write you a letter and tell you that they are

responsible for the care and treatment of their child.

Another thing to keep in mind is the value of a good set of records. One of the primary problems that I have run into is the inadequacy of some of the records kept by some of your colleagues, but I am sure none of you would neglect these. It is customary not to write down negative findings, but it is very easy to write down "otherwise negative" after you have made an examination. At least give some notation there, since the chart has to be your only means of remembering several years later that you did make other examinations. If there is a particular area of the patient's body that was being treated or was injured at one time and has cleared up, a notation of this should be made in the chart to back up the fact that you did an examination.

I spent eight days recently in a case where one of the main contentions was that a neurological examination had not been performed upon a patient from the day he was admitted to the hospital to the day he was discharged. The physician said that he had, but there was nothing in the chart to prove it. We were able to get out of it all right, but it was a difficult proposition. It is easy to correct. Any time the patient refuses treatment, this fact should be put into the chart. If you have a discussion with the patient with regard to the type of treatment, the alternatives, the risks, and so forth, this should also be put in the chart.

It is my recommendation that, if you are going to perform planned surgery on a patient, you should take his consent in your office before the patient goes into the hospital. Then he cannot complain that he was under sedation, or that he was upset, or any number of other things that might influence his making a wise and full decision.

A chart should contain, at each instance, the complaints of the patient, the history, the type of examination made, the treatment, the medication, if any, and any instructions which you gave the patient. Also, if the patient fails to keep an appointment, you should have your office staff thoroughly instructed to document this on the chart and then in the appointment book, and do not throw the appointment books away. There have been several instances where this information was deemed crucial, and we were able to go back into the records and prove that a patient had failed to keep an appointment, after the patient had testified that he was never told to come back.

I need not emphasize that any treatment which

may in any way affect the sexual ability of the patient is particularly sensitive, apparently for everyone and should be well documented. This should be thoroughly explained to the patient; even the remote possibilities should be thoroughly explained. If there is any question about it, it would not hurt to obtain written consent. There have been several cases recently where physicians who have performed vasectomies have been sued because the operations were not effective. There have been cases where people have been allowed a recovery of damages for the cost of rearing a perfectly normal child who was unwanted, after the husband or the wife had supposedly been sterilized. This is becoming a very sensitive situation, and it is a place where many of your colleagues have gotten into trouble. In one case which I read, no tests were run after the vasectomy was performed to determine whether there were any sperm. Others have given assurances to the patients that if they let the physicians perform the operation they would not have any more children. That is what I mean by not giving any guarantees. Do not say anything that can be construed as a guarantee. Be sure that the consent form you use spells this out clearly and simply, that there is no assurance that the operation will be effective, and that there is no guarantee of any kind.

With respect to the treatment of infants, I should say that the courts will intervene on behalf of an infant in a case where treatment is necessary or where the lack of treatment will be detrimental to the infant. Cases in point are where courts have ordered transfusions for Jehovah's Witnesses. In one case, the court ordered a T/A because the child needed it and the parents objected.

There are two cases in particular which I have seen recently where the court approved kidney transplants. One was where the donor was about 27 years old and mentally incompetent. He had the only really good matching kidney, and the court gave its approval for the use of the kidney from the incompetent to help his brother. They had psychiatrists who came in and testified that this would be of benefit to the incompetent because he was emotionally and psychologically dependent upon the well-being of his brother. Another case was that of twins about nine years old. The court said there again, based upon medical testimony, that it would be detrimental to the surviving infant if he knew that he could possibly have saved the life of his twin but was not given the opportunity to do so.

There is one last area of which we should be aware. That is alienation of affection by doctors on patients or spouses of patients. The significant thing is not only the conduct of the physician but the liability of his partners in his conduct. In one case, involving the pediatrician of a group practice the husband went to the senior partner, who was the managing partner, and complained about the pediatrician's conduct toward his wife. The managing partner did not do anything about it. He did not even discuss it with his partner, and after it was over, the court said it was up to the jury to decide whether this amounted to consent to the conduct of his partner. If it did, then the partnership, as well as the man who was involved personally, could be held liable, and this was true even though it did not involve partnership time.

There was a recent case where a patient and her husband recovered from a physician—I understand it was a psychiatrist—\$30,000 in compensatory damages and \$120,000 in punitive damages for alienation of affection. I do not know how long this had been going on, but it went on long enough for the jury to decide to punish someone. You should be aware of the fact that malpractice insurance does not cover punitive damages. Even if there is coverage for compensatory damages—and it is questionable whether there is, in that kind of case—there certainly would not be for the punitive damages. You would have to pay that out of your own pocket.

In this regard, never examine any female patient without your nurse being present. It has almost reached the point where you should not even talk to her without your nurse being present.

Some of the matters I have referred to may seem unusual or unlikely and thus may not be long remembered. Let me reiterate, however, the importance of two items in particular. If nothing else remains long in your minds, do not forget that complete and adequate records are essential, both in the hospital and in the office. Nothing else will take their place when they are needed. Finally, keep in mind always the significance of informed consent. It is a rapidly changing principle and one which touches literally every field of medicine. It may be difficult to accept in all its aspects. You may not, probably do not, agree with much of it, but it is here to stay. It is an established legal concept, and it is far better to recognize it as such and learn to live with it rather than be caught by it. Good luck!

# Renal Hypertension\*

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The advances in our knowledge of renal hypertension over the last 75 years represents outstanding accomplishments in experimental and clinical medicine. A review of the highlights of this important investigation in hypertension should begin with Tigerstedt and Bergman's work in Scandinavia which demonstrated in 1898, that extracts of kidney possessed a hypertensive action. They gave the name "renin" to the impure substance which produced this effect. For the next 30 years much work was done on the vasoconstrictor action of extracts of the adrenal medulla, the nervous system and the kidney.

At the height of the depression, Harry Goldblatt, with a few hundred dollars, began his investigations on the production of hypertension. His classical report in 1934 gave investigators an easy method of producing permanent renal hypertension. He used a tiny adjustable silver clip on the renal artery of dogs to produce partial or incomplete ischemia of the kidney. His work was confirmed promptly by many others.

In 1938, Fasciolo, Houssay and Taquini in Argentina, by cross-venous techniques, demonstrated that the ischemic kidney produced a hypertensive substance, renin. In 1939, Braun Menendez and his group in Argentina extracted a substance which they called hypertensin, produced by the incubation of renin with plasma globulin or hypertensinogen. Page and Helmer, almost simultaneously in the United States, reached similar conclusions but used different terminology, renin plus renin activator produces angiotonin.

Over the next 15 years much work was done on these extracts and enzymes. Finally, a decapeptide substance was identified. In 1956, Skeggs showed that a converting enzyme made the substance an

active vasopressor material by splitting off two amino acids.

A year later, Bumpus in the United States and Rittel in Switzerland synthesized angiotonin or hypertensin, depending on which group was involved. A year later, Page and Braun Menendez got together and came up with the bastard term—angiotensin. Levels of renin activity in patients were determined by the bioassay technique perfected by Gunnels until 1969, when Haber described a practical radioimmune assay for angiotensin which has gained wide acceptance by the medical profession.

On the clinical side, Butler in 1937, published the first report of nephrectomy for unilateral pyelonephritis with relief of hypertension. This began the era of nephrectomy for all sorts of diseases with the hope of relieving hypertension. In 1939, Blackman examined at time of autopsy renal arteries of 50 patients with so-called hypertension. A high percentage of arteries (87%) had arteriosclerotic plaques and 54% were found to have severe stenosis. This report was not accepted at the time by the profession. In 1944, Yuile classified renal artery obstruction occlusive disease into extrinsic and intrinsic types. Finally in 1948, after many years of indiscriminate renal sacrifice, Homer Smith laid down the criteria for cure of hypertension, 145/90, and this closed the era of imprecise diagnosis of renal hypertension.

In 1950, Parke Smith and Arthur Evans in Cincinnati published a large series of translumbar aortograms with a low incidence of complications, resulting in a wave of popularity for aortography by urologists and later vascular surgeons. Up to that time, it had not been widely accepted by the medical profession in the United States. In 1952, at the Cleveland Clinic, we began to apply aortography in hypertensive patients. In 1954, Freeman and his associates reported the first case of endarterectomy of the renal artery with relief of hypertension. In 1954, Howard and his colleagues at Johns Hopkins

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published their classical report of cure of hypertension by nephrectomy. They called attention to the importance of careful scrutiny of the intravenous pyelogram for renal atrophy and to the fact that urine from the affected kidney had a lower sodium concentration and lower urine volume.

In 1957, the first report on the use of homografts for correcting fibromuscular hyperplasia of the renal artery appeared. Since then many techniques have evolved for the correction of all kinds of renal artery disease.

Renin is a proteolytic enzyme with a molecular weight of about 40,000. Its only known activity is to break a specific leucine-leucine bond on renin substrate produced in the liver. Renin originates in the granular cells surrounding afferent arterioles adjacent to renal glomeruli. These juxtaglomerular cells, along with a few specialized distal tubular cells (*macula densa*) in the same region, form the juxtaglomerular apparatus. This structure may be considered a combination baroreceptor and sodium sensor.

After renin acts on the substrate, angiotensin I is formed. As it passes through the circulation, it is acted on by the converting enzyme to form angiotensin II, the vasoconstrictor material causing arterial constriction and hypertension. Angiotensin II is also a major stimulus for aldosterone secretion

by the adrenal gland, providing a feedback mechanism and completing the cycle initiated by renin release. Renin is inactivated in the liver, and angiotensin II is probably inactivated at its receptive sites. This is a dynamic, rapidly responding circuit. Renin is released within a few minutes after appropriate stimulation. Decline is equally rapid. Among recent discoveries, plasma and tissue enzymes have been found to exist which are capable of degrading angiotensin I and II to form a heptapeptide which exerts a powerful influence on the adrenal cortex to secrete aldosterone and preserve sodium.

We have used Haber's radio-immune assay technique for the last two and one-half years in Dr. Wan's biochemical laboratory at Norfolk General Hospital. This is a specific assay for angiotensin I generation rate, which in most situations provides a correct measurement of renin activity. Nearly 400 measurements of plasma renin activity were made between August 1970 and December 1971; over 900 determinations, which included 56 bilateral renal vein determinations, were done in 1972. Approximately 20 patients were selected for operation in 1972. In the first two months of 1973, we have operated on nine patients who have had this investigation recently at Norfolk General Hospital, reflecting in part the increased interest in renal hypertension since the use of renin assays on a wide scale.

# Urological Care of the Paralyzed Patient\*

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The paraplegic injured during World War I had only a 10% chance of surviving the first year. Only 20% of the American paraplegics could even be evacuated. A great majority of the deaths were caused by urinary tract sepsis. Starting in the mid and late 1940's, however, with the discovery of broad spectrum antibiotics, many of the early complications were eliminated and the survival rate greatly improved. Since 1946, over 2,000 patients have been admitted to the McGuire Veterans Administration Hospital. This spinal cord injury service receives approximately 400-500 admissions per year with about 70 being new patients.

**Mortality.** The general mortality figures dealing with longer surviving time point to the greatly improved overall care. We recently reported the mortality figures on 170 World War II paraplegics followed for 25 years and 100 Korean War paraplegics followed for 20 years (2). The overall survival was 40% and 74%, respectively. However, the survival rate greatly increased if the patient had a good neurogenic bladder (Table 1). The distinction between a good neurogenic bladder and a poor bladder will be discussed subsequently. Also, of those living at 25 and 20 years, respectively, the incidence of pyelonephritis and caliectasis was significantly higher in the patient with a poor bladder.

The main cause of death remains renal failure. The poor bladder group had a much higher incidence of renal deaths; whereas, most of the good bladder patients succumbed from non-renal causes. The great majority of the nonrenal deaths were of cardiovascular origin. It was interesting that if the kidneys were essentially normal after 12-15 years

of cord injury life, whether the patient had a good or poor neurogenic bladder, he would succumb just as often from nonrenal causes.

**Definitions.** A good neurogenic bladder will fulfill these criteria:

- 1) A bladder with sufficient capacity to act as a reservoir, and this with consistency.
- 2) Residual urine, less than one-third of the bladder capacity or less than 100 cc.
- 3) Establishment of urethral voiding, although defective control dictates the use of an external appliance.
- 4) No permanent vesicoureteral reflux.

If these objectives cannot be accomplished, then the bladder must be treated with continuous Foley catheter drainage. The patient is then classified as having a poor or unbalanced bladder. There seems to be no question that the poor bladder patient saddled with long-term catheter drainage with its problems of constant urethral and bladder infections, increased incidence of small, contracted, spastic bladders leading to vesicoureteral reflux, hydronephrosis, chronic pyelonephritis, and amyloidosis has a very poor prognosis. Most of these patients will eventually succumb to renal failure.

We use a simple classification for neurogenic bladder when dealing with spinal cord injury (Table 2). If the spinal cord injury is above the sacral reflex arc (S-2, S-3, S-4), then the lesion is of an upper motor neuron type. Most upper motor neuron lesions will develop a good reflex contraction. A small percentage never develop a detrusor contraction, however, and must remain on intraurethral catheter drainage. These patients are classified as having a poor nonreflex bladder. The true lower motor neuron lesions, because of the disruption of the sacral reflex arc, will also have a nonreflex bladder. Many of the patients can remain catheter-

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free, however, because of their ability to credé as well as increase their intra-abdominal pressure.

**Acute Spinal Shock Phase.** During spinal shock, the bladder is atonic and must be decompressed either by continual catheter drainage or by intermittent catheterization. Suprapubic diversion, whether by suprapubic cystostomy or cutaneous vesicostomy, should not be instituted, for there is a high incidence of developing a small, contracted, spastic bladder. If urethral complications occur, then diversion may be implemented by way of the perineal route. A #16 Foley catheter is used for continuous drainage, and the bladder is irrigated twice daily with an antiseptic solution. The Foley is taped over the lower abdomen to prevent any lower tract complications. If urethral sepsis develops, a three-way multi-hole Bunts catheter is used in order that the urethra itself can be irrigated with Clorpectin® or other antiseptic solutions.

The results of intermittent catheterization, as recently reported in the literature, have been impressive (3). At our paraplegic center, we have been unable to institute this program due to lack of personnel. There are approximately 30 patients in spinal shock at all times, and this would require about 150 catheterizations daily under strict aseptic techniques.

**Chronic Phase of Spinal Cord Injury.** Approximately 65% of our patients spontaneously developed a good reflex neurogenic bladder following spinal shock. A small percentage of these patients will have bladder decompensation manifested by high residual urine. Excessive spasticity of the external sphincter causes the detrusor contraction to be ineffective, and thereby the patient continues to maintain a high residual. It has been demonstrated in many reports that the site of greatest urethral resistance is in the prostatomembranous urethra (7). We have just recently reported the results of external sphincterotomy in 150 patients (8). The best results were achieved when the cystometrogram demonstrated a reflex bladder and the sphincterogram demonstrated a hypertonic, spastic external sphincter. Following external sphincterotomy in the reflex bladder group, there was an average decrease in retrograde urethral pressures of 19 mm of mercury. The results of 110 patients with a reflex bladder were impressive in that the success rate was 86%. Theoretically, if we consider these results and the fact the 65% will become catheter free spontaneously, then approximately 90% of all upper motor neuron lesions will have a reflex bladder and should

TABLE 1  
PERCENT SURVIVAL

	Over- all	Good Bladder	Poor Bladder
World War II (25 yrs.) 170 patients	40%	50%	20%
Korean War (20 yrs.) 100 patients	74%	83%	60%

develop a catheter-free state. This figure will never be reached due to lower tract complications, small penis, allergy to the condom external appliance, and the fact that some of these patients like the convenience of continuous intraurethral drainage. Naturally, the patients with a nonreflex bladder must remain on Foley catheter. Recently, in some patients with external sphincterotomy, we have been resecting the anterior part of the lateral lobes of the prostate (5). Several of our external sphincterotomy failures were corrected by this maneuver.

**Complications.** The most common causes of renal failure in the cord injury patients are:

- 1) Pyelonephritis
- 2) Renal amyloidosis
- 3) Hydronephrosis without vesicoureteral reflux
- 4) Permanent vesicoureteral reflux

**Pyelonephritis.** Pyelonephritis of some degree is present in most paraplegics. Uncomplicated pyelonephritis (not associated with vesicoureteral reflux, hydronephrosis, or amyloidosis) resulting in renal insufficiency has been a rare occurrence in over 2,000 paraplegics we have treated at McGuire VA Hospital.

**Amyloidosis.** Amyloidosis is a common cause of death in the paraplegic who survives for a sig-

TABLE 2  
SIMPLE CLASSIFICATION OF CORD INJURY  
NEUROGENIC BLADDER

I. Upper Motor Neuron
A. Reflex Bladder
1. Good bladder (balanced)
2. Poor bladder (unbalanced)
B. Nonreflex Bladder
Poor bladder
II. Lower Motor Neuron
A. Nonreflex Bladder (autonomous)
Poor bladder
III. Mixed Lesion

TABLE 3  
IVP GRADING

Grade
0—Normal
1—Minimal Caliectasis
2—Mild-to-Moderate Caliectasis, Minimal Dilatation of the Ureter and Pelvis
3—Moderate-to-Marked Caliectasis, Moderate Dilatation of the Ureter and Pelvis
4—Severe Hydronephrosis and Hydroureter

nificant period of time. In an autopsy study at our hospital (1) it was significant that of 26 patients with proven amyloidosis, 18 of these deaths were due directly to renal failure. In addition, 16 of these 18 patients had 2+ or greater proteinuria. Prolonged suppurative disease—as seen with chronic decubitus ulcer disease and/or osteomyelitis—is the most likely major underlying factor. Continual urethral sepsis probably should be included in the overall problem.

**Hydronephrosis and Hydroureter without Vesicoureteral Reflux.** Hydronephrosis and hydroureter without vesicoureteral reflux are encountered in a small percentage of paraplegics. The etiology of this upper tract deterioration is the result of high residual urine or excessive spasticity of the bladder. This increase in spasticity is often due to severe cystitis and/or the development of eggshell calculi. Treatment consists of removing the calculi as well as clearing up the bladder infection.

Some paraplegics develop a small, contracted, spastic bladder due to erratic persistent impulses from the distal stump of the spinal cord. This hypertrophy of the detrusor muscle in the area of the intramural ureter produces obstruction to the ureters. This obstruction is evidenced on intravenous pyelograms, but there is no obvious blockage at the ureterovesical junction, for large size ureteral catheters or bulbs will easily pass this area. If there is no improvement in the condition of the upper tracts with good bladder hygiene, then therapy must be directed toward interrupting the nerve impulses from the spinal cord. The results of selective sacral rhizotomy are impressive, if the bladder has not become irreversibly contracted due to loss of elastic tissue and replacement by collagen. This must be determined prior to the rhizotomy by performing cystometrograms before and after spinal anesthesia. There should be at least a 100% increase in bladder capacity following spinal anesthesia. For best results,

the anterior and posterior roots of S-2, S-3, S-4 must be sectioned. Many of these spastic bladders are converted into more easily managed flaccid autonomous bladders. Misak, Bunts and others (6) reported on 28 patients undergoing selective rhizotomy, and 25 of these acquired a good autonomous bladder with good voiding potential. It was interesting that 23 of these patients actually became catheter-free. The best results were obtained in the cord injury patient who could use his upper extremities and abdominal muscles. The procedure also decreases the spasticity of the external urinary sphincter.

High residual urine can produce rather marked hydronephrosis and hydroureters. These patients usually have done well for years, voiding into an external urinary appliance, and therefore are classified as having a good reflex bladder. After this decompensation, long-term drainage may be needed for bladder tone to return. If the sphinctermetrogram reveals high intraurethral pressure, external sphincterotomy is indicated. If high residual urine is persistent, the patient must remain on permanent urethral catheter drainage.

The upper urinary tract in the paraplegic shows marked lability, and in many cases, is reversible. It must be determined that the deterioration of the upper urinary tracts cannot be reversed before some type of urinary diversion such as an ileal conduit is considered.

**Vesicoureteral Reflux.** In the paraplegics dying from renal failure at our hospital, irreversible reflux was present in over 60%. Reflux is considered to be irreversible if present on three consecutive cystograms or if persistent on three consecutive six-month checkups. The incidence of reflux remains about 15% after the patient has had 5–10 years of paraplegic life. Permanent vesicoureteral reflux is definitely detrimental to the kidneys in the paraplegic. It is usually the high pressure type and associated with chronic cystitis (4).

We place the patient in one of four groups based on the condition of the kidneys and bladder for the purpose of management. Table 3 illustrates how we grade the pyelogram.

*Group A—Good Reflex Bladder, Grade 0-1 Urograms.* Permanent reflux rarely develops in a good reflex bladder. After it has been determined that the patient does not carry significant residual urine and that the reflux is indeed permanent, vesicoureteroplasty is indicated. Vesicoureteroplasty is only indicated in a good reflex bladder. Dr. Rich-

ard Reece is currently evaluating the results of this procedure. In our hands, a successful vesicoureteroplasty is obtained in 70–80% of the cases if the reflux is unilateral. The results are worse if a bilateral reimplant is performed, because in about 50% of the cases, one side will fail. We do not perform repeat vesicoureteroplasties for the results are poor.

*Group B—Poor Reflex Bladder, Grade 0-1 Urograms.* The whole purpose here is to try to convert the poor bladder into a good reflex bladder, in other words, to make the patient catheter free. The reason for the poor bladder status may be high residual urine secondary to excessive external sphincter spasticity. As discussed earlier, external sphincterotomy may help rehabilitate this bladder. If successful, the external sphincterotomy has placed the patient now in Group A, and a vesicoureteroplasty could be entertained.

The largest number of paraplegics with permanent reflux have a small, contracted, spastic bladder. Naturally, this would be high pressure reflux. Nerve interruption procedures should be considered in this situation after bladder infections and/or calculi have been eliminated as the cause of the hypertonicity. As stated previously, we prefer sacral rhizotomy. If after a sacral rhizotomy the patient develops a good autonomous bladder, thereby being maintained on external appliance drainage, then a vesicoureteroplasty may be performed. A modification of the *Hutch I* vesicoureteroplasty has yielded the best results in our hospital.

The patient may have a good reflex neurogenic bladder, but due to persistent vesicoureteral reflux, catheter drainage must be continued. This problem would be alleviated if the vesicoureteroplasty was successful. However, in some cases of bilateral vesicoureteroplasty, one side would fail. Since repeat vesicoureteroplasty is uniformly unsuccessful in the paraplegic, we have turned to performing transureteroureterostomy. There have been 11 transureteroureterostomies at our hospital performed over the last several years and the results have been excellent. Of the 11 cases, only one kidney deteriorated, and this was due to a technical error in that the anastomosis into the recipient ureter was inadequate. All of these ureters were essentially of normal caliber, and there was no deterioration postoperatively. It is safe, however, to transfer a dilated ureter to a normal size ureter.

*Group C—Grade 2-3 Urograms.* Up to this point the discussion has centered on how to prevent

any deterioration of kidney function. Most patients with a good reflex neurogenic bladder and with careful follow-up should not develop this deterioration. Faced with persistent and/or progressing deterioration of the upper tracts, and failure of bladder hygiene and sacral rhizotomy to alleviate this problem, an ileal conduit must be considered. As one can tell from the previous discussion, we are conservative in recommending this procedure, but there is a definite indication for its use. We have performed about 25 conduits and are generally impressed with the results. The renal units will uniformly improve after ileal diversion if ureteral peristalsis is adequate and renal function is not too impaired. In reviewing some of our cases, it is evident that renal insufficiency could not have been expected to improve by conduit diversion because of poor ureteral peristalsis.

*Group D—Grade 4 Urograms.* Marked hydro-nephrosis must be treated with immediate loop nephrostomies (9). These cases are uniformly uremic and usually acidotic. The ureters are dilated and tortuous. We feel that the loop nephrostomy is a definite surgical advancement over the routine Cabot type nephrostomy in the paraplegic. It is technically simple and there are no leakage problems. The catheters are easily maintained, which is important because some of these nephrostomies are permanent.

Each patient is periodically evaluated to determine if there has been enough return of kidney function and ureteral function so that the patient may be reconverted to an ileal conduit. In some cases, the creatinine clearance improves but the ureteral function remains inadequate. Cineureterograms show poor peristalsis, and in many cases retroperistalsis. We do have two patients with enough improvement in creatinine clearance and ureteral peristalsis that ileal diversion will be undertaken.

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# Pediatric Uro-Radiology\*

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"Routine" radiologic studies do not, often enough, concentrate on the part of the anatomy and physiology of importance for the diagnosis. The close cooperation between the pediatrician, urologist and the radiologist will insure more useful uro-radiographic studies on which rational clinical decisions can be based. The child's signs and symptoms, as well as the anatomic and physiologic information needed, dictate the type and order of the radiographic studies. It is beyond the scope of this paper to go into the indications for specific uro-radiographic studies. The radiographic techniques will be presented.

**Cystourethrography.** There are several methods for studying the bladder, urethra and vesicoureteral reflux. The method used most often is filling the bladder via a urethral catheter in a retrograde manner, either by gravity or by injecting the contrast material. Radionuclide introduced into the bladder can be used as an adjunct to radiographic investigation of reflux.

Cystourethrography can be done at the end of the intravenous pyelogram. This method avoids a urethral catheter and would appear to be more physiologic. The child voids immediately before the intravenous injection of contrast material. The administration of as much as 5 ml per kg of 50% or 60% contrast material is recommended. There are, however, several limitations of this method—the patient must be cooperative and usually several years of age. Another disadvantage is that often parents or an aid must be kept in the Radiology Department with the patient for several hours, adding to generally crowded waiting areas. The bladder must become sufficiently distended to stimulate the urge to void.

Contrast in the lower portion of the ureter during the voiding phase presents the problem of differentiating between urine flow from the kidney and reflux into a ureter that maintains its normal caliber.

Cinecystourethrography came into wide use in the mid 1950's. The chief contribution of cine recording was its revelation of the importance of performing the procedure under fluoroscopic control. Fluoroscopy during the voiding phase of cystourethrogram allows optimal timing of films for the permanent record. Dissatisfaction with the cine procedure is that it has poor resolution, and that it delivers a large radiation dose to the patient's gonads. Fluoroscopy with video tape recording for the documentation of motion, and spot filming with 70, 90 or 105 mm film is diagnostic with less radiation than cinefluoroscopy. Video tape recording delivers no additional radiation to the patient beyond that required for image-intensification fluoroscopy.

Retrograde filling of the bladder by gravity permits the observation of reflux at low or high water pressure. In the absence of infection, low pressure reflux is considered a more significant observation when making a decision about reimplanting a ureter. Sufficient distention of the bladder can be obtained by gravity filling to stimulate voiding.

The normal male urethra demonstrates many variations. Sequential spot x-rays avoid confusion of normal anatomical structures (fig. 1). It is necessary to identify accurately the urethrovesical junction and prevent the error of considering the trigonal canal as part of the urethra.

Controversy exists among urologists about the existence or frequency of bladder neck obstruction and meatal stenosis in boys or girls. Posterior urethral valves, lesions probably existing only in males, appear to be the most common bladder outlet or urethral obstruction. From the Hospital for Sick Children in London, 165 children were recently

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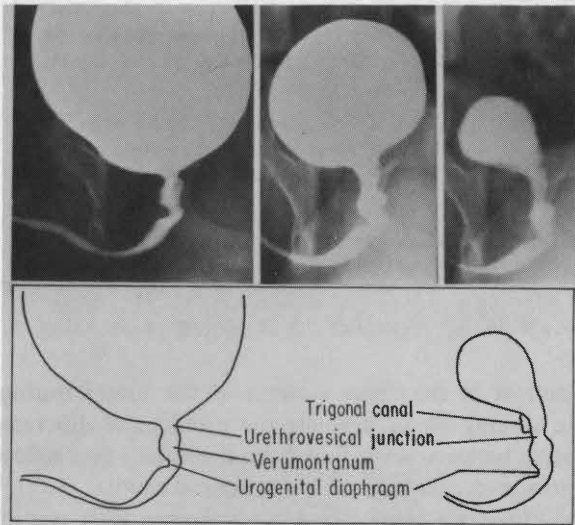


Fig. 1—Sequential spot filming during voiding demonstrates a normal male urethra. The urethrovesical junction can be identified and not confused as existing along the trigonal canal.

reported with lesions at or below the bladder neck which interfered with normal urine flow. From 1959 to 1970, of 130 boys and 35 girls, all were under the care of Mr. Ennis Williams. The most common lesions were posterior urethral valves and ectopic ureteroceles. Stenosis or atresia of the urethra and



Fig. 2—A. One-day-old male that did not urinate. Abdominal mass was palpated; on radiograph the mass extended from the pelvis to the eleventh ribs posteriorly.



Fig. 2—B. Voiding cystourethrogram demonstrates bilateral reflux and a dilated posterior urethra due to posterior urethral valves.

bladder neck obstruction were uncommon. A palpable bladder was the most common physical finding in this group of patients.

A one-day-old boy had not voided since birth and a large abdominal mass was felt (fig. 2, A). Catheterization of the bladder revealed a large volume of urine. The catheter was left in place and a cystourethrogram was done. During fluoroscopic observation reflux occurred when the bladder was partially filled (low pressure), and during the act of voiding it was noted that massive reflux occurred in dilated ureters and calyces (fig. 2, B). The posterior urethra was dilated and distal to this point, the urinary stream was narrow. The association of posterior urethral valves and reflux is common. Posterior urethral valves may be present, however, with competent ureterovesical valves and normal ureters and kidneys.

In boys, defects in the anterior urethra are less

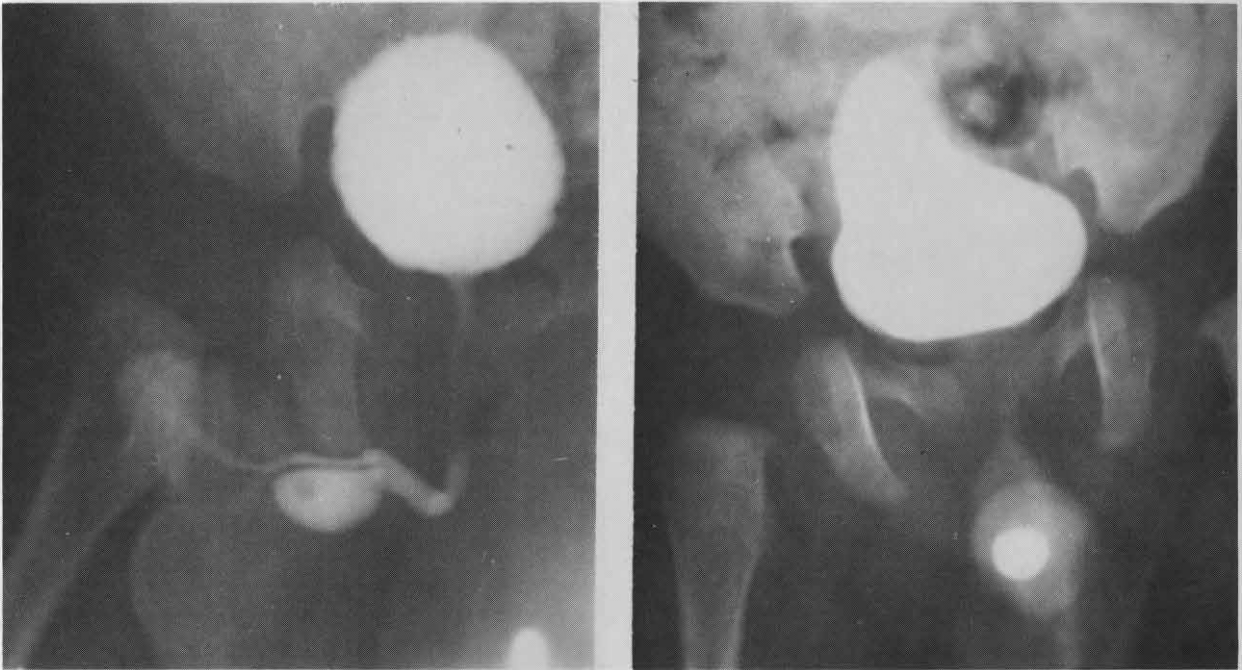


Fig. 3—A. (left) Four-month-old male with urinary tract infection. Voiding cystourethrogram demonstrates an anterior urethral diverticulum. No reflux occurred.

Fig. 3—B. (right) Residual contrast in diverticulum persisted after the bladder emptied. After surgical removal of the diverticulum the infant remained free of infection.

common than in the posterior urethra. Most often a single "pouch" in the anterior urethra is non-obstructive and represents Cowper's ducts or glands.

Other lesions in the anterior urethra appear to represent congenital diverticulae or anterior urethral valves which may cause obstruction or be a cause of infection because of stasis in the diverticulum (figs. 3, A, B).

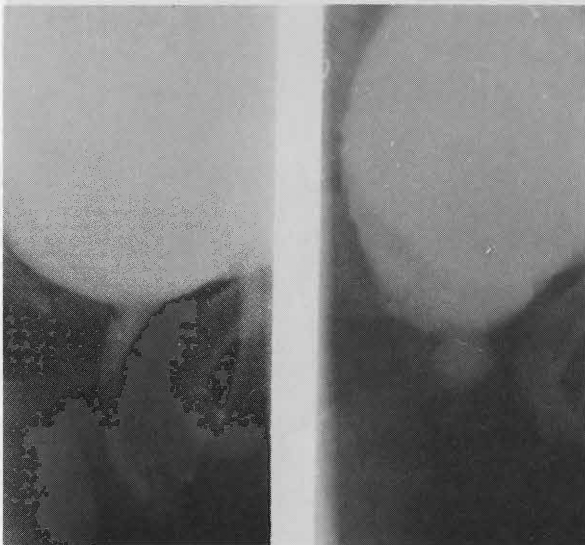


Fig. 4—A. (left) Normal female urethra during voiding.  
Fig. 4—B. (right) With the stopping of micturition the "spinning top" deformity develops and is a normal variation.

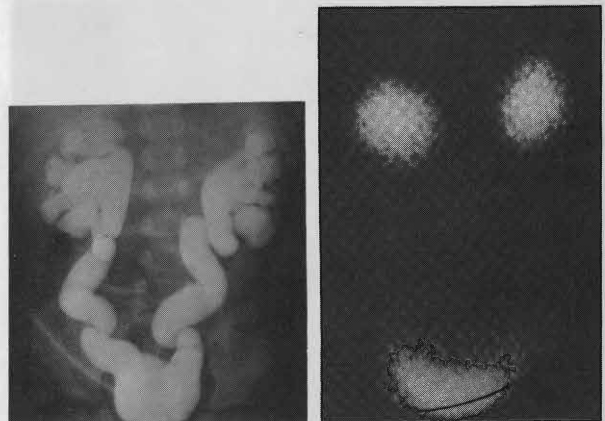


Fig. 5—A. (left) Cystogram with water soluble contrast material demonstrates massive reflux into both ureters and kidneys.

Fig. 5—B. (right) Cystogram with technetium 99 M pertechnetate, followed by scanning over the kidneys detects reflux into the kidneys.



Fig. 6—Interval vesical ureterocele causing a lucent defect in the bladder. Ureterocele developed from the ureter draining the upper pole of a double right renal collecting system. Obstruction caused hydronephrosis and nonfunction of the upper pole with downward displacement of the lower pole collecting system. Double collection system is present in the left kidney.



Fig. 7—Nephrotomography demonstrated the rim of functioning renal tissue in the right upper pole suggesting a duplicate renal system. Ectopic ureter was obstructed in the posterior urethra.

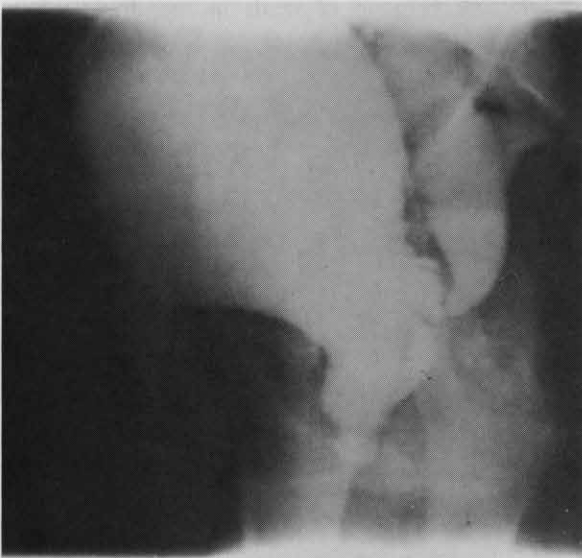


Fig. 8—A. Prolapsed ureterocele dilates the posterior urethra. Density of the contrast material around the ureterocele obscures the lucency normally seen. Reflux into dilated ureter also is noted.



Fig. 8—B. Retrograde urethrogram demonstrates the lucency in the bladder caused by the ureterocele.



Fig. 9—Ectopic ureter from a solitary ureter insertion at the bladder neck demonstrating reflux during voiding.

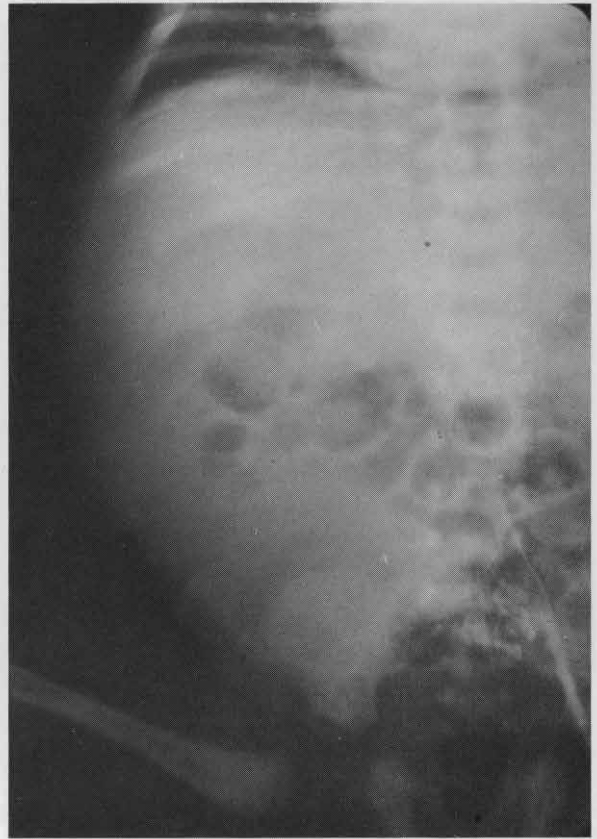


Fig. 11—Early during intravenous pyelogram, the well vascularized organs opacify and a lesion with poor blood supply produces a lucent defect as was noted in this newborn with a multicystic kidney.



Fig. 10—Newborn with left flank mass. Large lucent areas in large left renal mass. Lucent defect in bladder due to ureterocele from a solitary ureter.

In the early 1960's, the "spinning top deformity" of the female was considered a sign of urethritis or of meatal stenosis. It is now regarded as a normal variation in most instances. A single roentgenogram during voiding may be exposed when the patient is beginning or stopping micturition, and it is during this phase of voiding that the "spinning top" configuration is most common (figs. 4, A, B). Video tape recording and multiple spot x-rays usually show the normal anatomy and demonstrate physiologic function. At any rate, bladder neck obstruction and meatal stenosis are not radiographic diagnoses.

There is a high correlation of urinary tract infection in children with vesicoureteral reflux. In some patients, an obvious anatomic abnormality in the urinary tract is present; in many children, however, no discernible defect is found. Vesicoureteral reflux while a child has a urinary tract infection

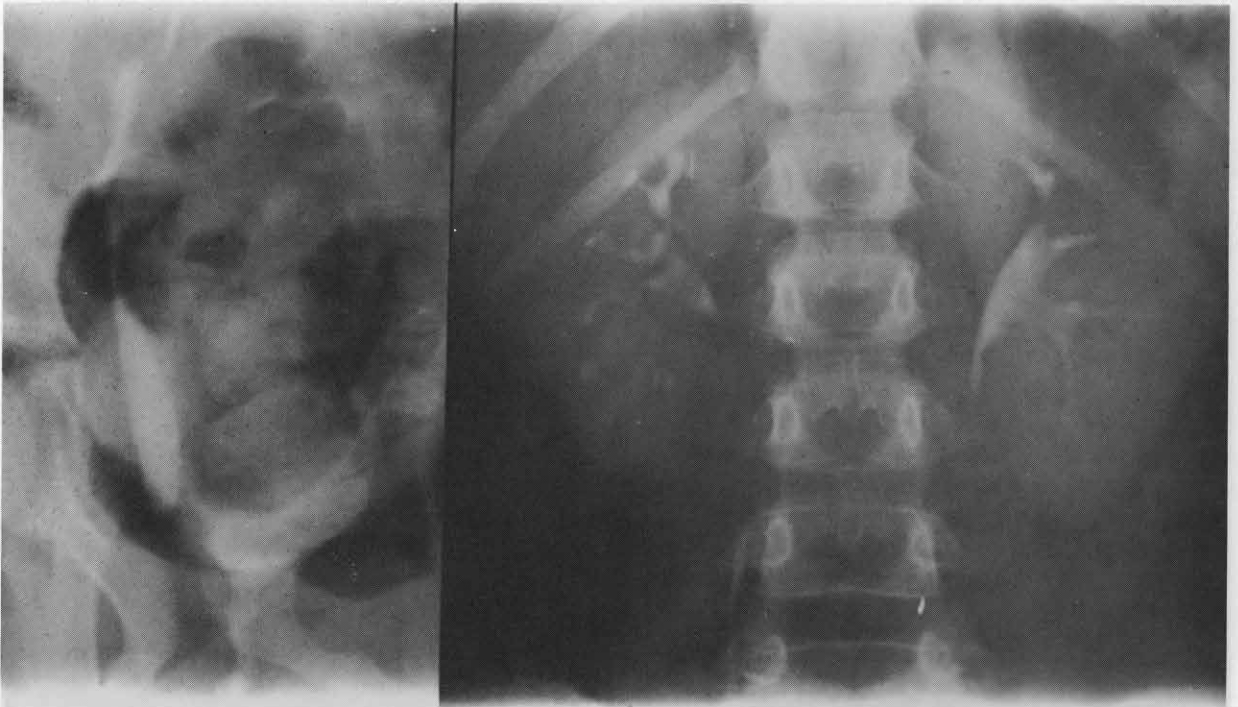


Fig. 12—A. (left) Right ureteral reflux during voiding cystourethrogram. B. (right) Right kidney demonstrates caliectasis and decreased amount of cortex.

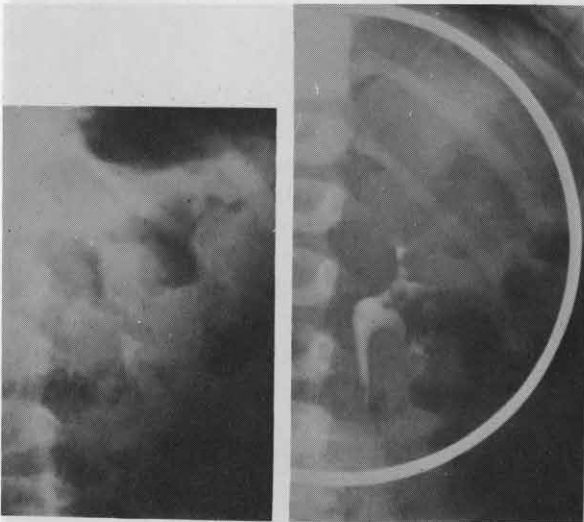


Fig. 13—A. (left) Poor delineation of the left kidney due to overlying gas and feces.

Fig. 13—B. (right) Paddle with an inflated balloon displaces the bowel contents and delineated the calyceal system.

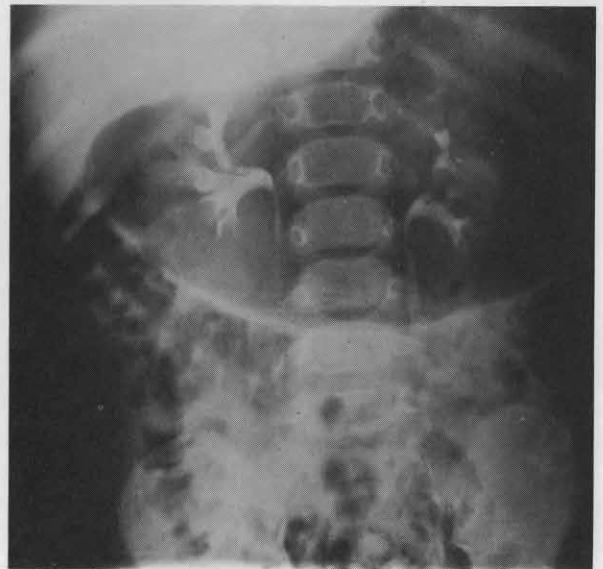


Fig. 14—Carbonated beverage or carbon dioxide capsules contrast the calyces and renal outlines.

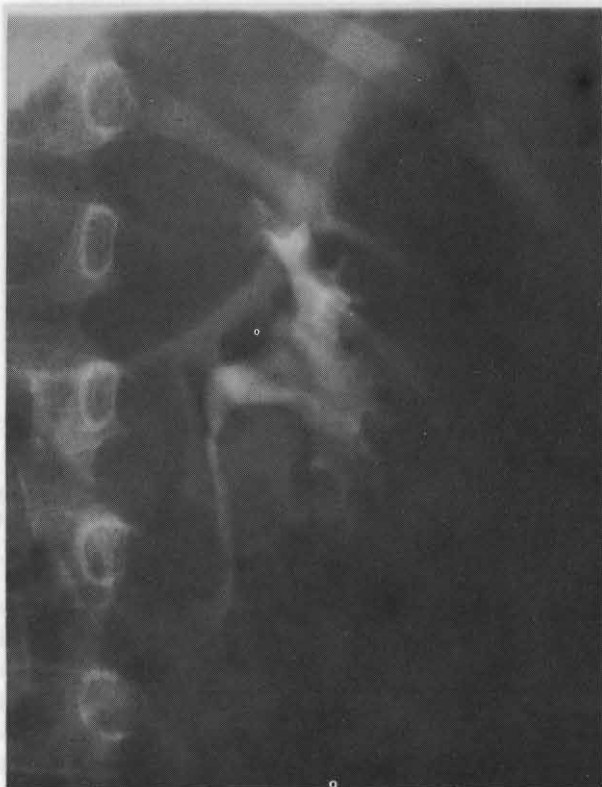


Fig. 15—Nephrotomography demonstrates the renal outline in a patient with normal calyces on urogram. Evaluation of the cortex was important in this patient.

may be due to inflammation of the vesicoureteral orifice; therefore, it is preferable to do a cystourethrogram when the patient has been free of infection for more than two weeks.

The main use of cystourethrography is the detection of ureterovesical reflux. Instillation into the bladder of a short-lived pure gamma-emitting radiopharmaceutical, such as technetium 99m pertechnetate, followed by scanning over the kidneys (fig. 5), can be an adjunct to the radiographic investigation of reflux. This procedure does not give the detail of standard radiographic methods, nor does it detect transient ureteral reflux. The markedly lower gonadal dose of radiation may make this method useful as a means of following patients for gross reflux into the kidneys.

Ectopic ureters, with or without a ureterocele, are most frequently present with renal duplication. The upper renal pole drains into a ureter whose orifice is medial and inferior to the normal orifice. Approximately three-quarters of the patients with

ectopic ureters in association with renal duplication are female. Bilateral renal duplication is present in approximately one-quarter of the patients with an ectopic ureter.

The intervesical ectopic ureter balloons out as a cyst-like mass within the bladder lumen causing a lucent defect (fig. 6). The poorly functioning hydronephrotic upper pole is outlined by thinned renal parenchymal. Generally there is function in the lower pole of the involved kidney. The lower pole calyces may be displaced downward and laterally by the dilated medially positioned ureter.

The distal end of the ectopic ureter may be stenotic and terminate in the bladder neck, ("posterior") urethra, or in the vagina, with dilation of the proximal portion of the ureter. Nephrotomography may be necessary to visualize the rim of functioning renal tissue (fig. 7).

Ureteroceles may prolapse into the urethra causing dilatation of the posterior urethra on a cystourethrogram, which mimics posterior urethra





Fig. 16—Nephrotomography in infant with poor renal function demonstrates a hypoplastic right kidney and small normal left kidney. Visualization was not successful on intravenous pyelography.

valves (fig. 8, *A*). Slow filling of the bladder via retrograde urethrography demonstrates a large lucent defect due to a ureterocele (fig. 8, *B*).

An ectopic ureter from a solitary ureter occurs in 20–30% of all ectopic ureters. Its site of insertion is similar to ectopic ureters associated with renal duplication. Ureterovesical reflux may occur when the ectopic ureter inserts in the bladder or urethra (fig. 9).

A newborn infant was noted to have a left flank mass. Nonfunction of the left kidney could have been due to hydronephrosis or a multicystic kidney (fig. 10). The lucency in the bladder suggested the correct diagnosis. This latter observation was important so that the ureterocele could be surgically removed in order to prevent the opposite ureterovesical junction from becoming obstructed.

Various simple techniques may help make a

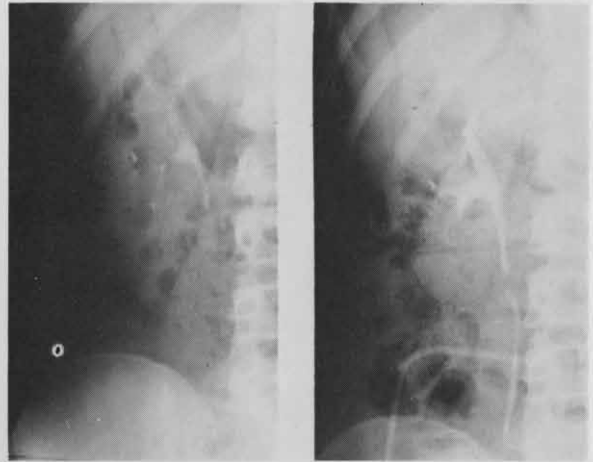


Fig. 17—*A*. (left) Incomplete filling of calyceal system on intravenous pyelogram.

Fig. 17—*B*. (right) Compression band on lower abdomen and inflatable balloon causes partial stenosis of ureter and filling out of normal ureter and pelvocalyceal system.



Fig. 18—*A*. On intravenous pyelogram no visualization is seen in the left kidney. The right kidney demonstrates moderate ureteropelvic obstruction. Large left flank mass was palpated.

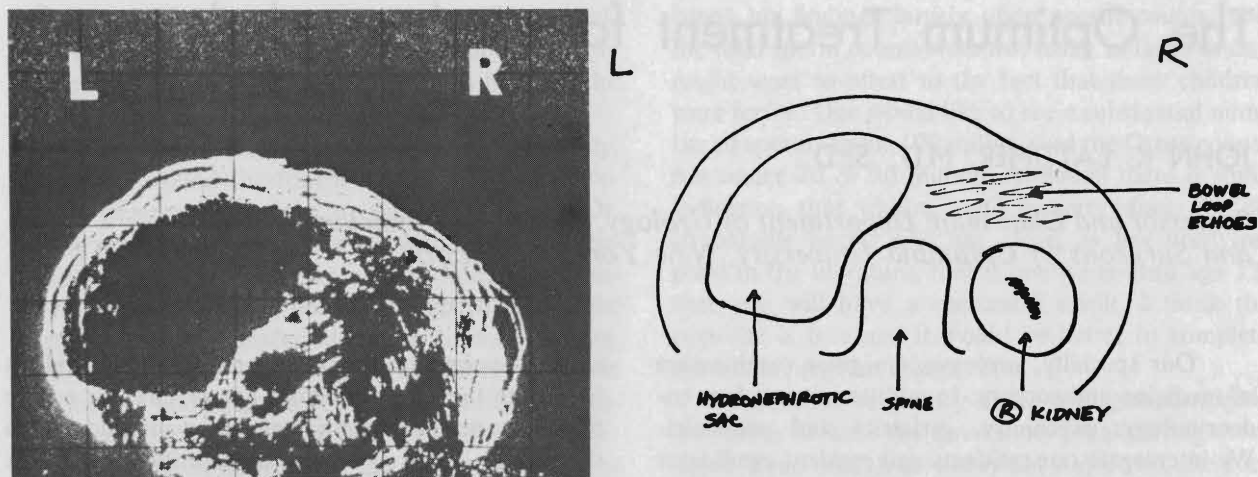


Fig. 18—B. Ultrasound shows a large echo free area in left flank indicating a cystic mass. At surgery, a hydronephrotic kidney was found.

correct radiographic interpretation. The "bodygram" is the result of high dose (4 ml per kg) intravenous urography. Thirty seconds to one minute after the injection of urographic contrast material, there is opacification of well vascularized abdominal organs. Lesions with little or no blood supply produce lucent defects within the opacified structures, as was noted in a newborn that had a multicystic kidney (fig. 11).

Because of decreased concentrating ability of the kidneys of newborns for many days after birth, poor visualization on intravenous pyelography will not be improved by an immediate repeat dose. If possible, wait five or more days before repeating the intravenous pyelogram. Satisfactory visualization is usually obtained on the delayed study.

Prolonged nephrograms, lasting many hours-to-days, may be seen in newborns or infants who were dehydrated or oliguric prior to excretory urography. It is postulated that a mucoprotein (Tamm-Horsfall), normally produced by renal tubular cells, forms a precipitate that blocks the lumen of the renal tubules. Since diagnostic visualization can be obtained without iatrogenic dehydration, no fluid restriction is necessary prior to excretory urography.

Ureterovesical reflux causes damage to the kidneys because of the frequently associated infection and to a lesser degree the effect of the "back pressure" on the kidneys. Therefore, it is essential to be

able to evaluate the renal outline, cortex and calyceal system. Often this can be done on the pyelogram (fig. 12, A, B).

The radiologist has various devices to obtain maximal information from excretory urography, often obviating the necessity for retrograde pyelography. A paddle with an inflatable balloon can be used to displace confusing bowel gas from the renal areas (fig. 13, A, B). Carbon dioxide in the stomach may contrast the renal outline and delineate the calyceal structures (fig. 14). Usually, nephrotomography will outline the kidney contour (fig. 15), and has been useful when kidneys fail to visualize well because of poor renal function (fig. 16). If visualization of the pelvocalyceal system is not adequate, compression bands may be placed on the lower abdomen, causing partial ureteral stasis with better filling of the structures in question (fig. 17, A, B).

The question of whether a flank mass that does not visualize on intravenous pyelography is cystic or solid can now be answered by ultrasonography. This procedure is noninvasive and emits no radiation. Low energy waves from a probe passed over the structure in question reflects echoes (sound reflection occurs at tissue interfaces) which are recorded as densities if the mass is solid in nature; if the mass is cystic, the recording will be echo "free" (fig. 18, A, B).

# The Optimum Treatment for Undescended Testis\*

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Our specialty, urology, is a great combination of medicine and surgery. In addition, it involves endocrinology, psychiatry, geriatrics and pediatrics. We interrogate our residents and resident candidates very closely as to why they go into urology. The most important point that they express over and over again is that urology is not just surgery but a combination of medicine and surgery. They also emphasize the quality of the diagnostic techniques which we use. Usually, when we operate, we know what we are going to find, where we are going to find it, and where the artery is going to come into it so that we can go right to it to clamp it off and thus minimize the bleeding. Thanks to our x-ray colleagues, these capabilities are multiplied continually. We are better off than the man who does only surgery. It is wise, in my opinion, that we urologists do not get categorized as just surgeons who want to cut. We are willing to undertake medical treatment for the children with cryptorchidism. If it does not work, we are then capable of operating on them and curing them with surgery. Of course, this philosophy enters into the field of adrenal diseases and into many other disorders that we handle.

In determining when we should operate on a child with an undescended testis, one of the concerns is the growth of the testis itself. Dr. Earl Engle did the first clinical research work in this field 30 or 40 years ago. He measured the tubular diameters and determined that in the normal child's testis, the tubular diameter increased progressively with age. We determined that the increase continued in the child who had an undescended or hidden testis until about age seven, and then it stopped. From this crude physiological index, we have an indication that we

should operate on the child and bring the hidden testis into the scrotum before age seven. Our advice to parents and to pediatricians who want guidance in this matter is that age seven is the critical age when the testis should be brought down into the scrotum.

The next question is, when is the optimum time to start treatment before this seventh year? No one likes to do an elective operation before the child is one year old, if it can be avoided. The child is much bigger and stronger and more stable after age one. The child develops the capacity to worry and be upset, and as a consequence, we do not like to do elective surgery until the child is able to talk. If we operate before the child can talk, he is somewhat terrorized by having been taken into the hospital and having been taken away from his parents and then subjected to this smothering, anesthetizing operation on an area of the body, which even at that age may have some more than usual implications. As a consequence, we would like to defer the operation until the child is at least four years old.

The next anniversary of consequence is the fifth birthday because after the fifth birthday some children begin to inspect each other's genitalia. This is not always true, but this has been carefully documented in nursery school children. If you neglect this matter and leave this child deficient in the sense of having one missing testis or a testis that disappears unpredictably, that is, the migratory testis, then you are depriving this child for psychological reasons. You are allowing him to continue in an embarrassing condition in which his self-image could be threatened, and the invitation for possible trouble does exist. You may say that this is exaggerating the problem and that Freud was not always accurate, but there is evidence that this is of importance. If you operate on such a child and his behavior improves markedly, you can look back and realize that he was a very bad actor because of some psychological concern which must, because of the circumstances, have been

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due to the undescended testis. The supportive evidence has influenced us in our decision that the optimum time for fixing the condition is between the fourth and fifth birthday.

We initiate treatment, as a matter of policy, sometime around the fourth birthday—usually hormone treatment, brought to our attention by Dr. Engle who did the pioneer work with the gonadotrophic hormone. He demonstrated in immature monkeys that injections of gonadotrophin will bring the testis down. He transferred this to human patients, and it was found that it did bring down a certain number of undescended testes. Our hormone treatment consists of giving 10,000 units of gonadotrophic hormone in three doses, every other day. These three injections do bring down 15% of the children's testes that are going to come down. If these injections fail to bring it down, we then give the old standard course of 10,000 units over six weeks so that you give 500 units every other day or three times a week for six weeks. The advantage of giving the first 10,000 units all in one week, every other day in three injections, is that there is no enlargement of the penis and no growth of pubic hair. Whereas, with the six-week course, you get a very definite slight enlargement of the penis and a very definite growth of pubic hair in many children. The change is not enough to be grotesque or objectionable, and very often it is very supportive for the child and for the parents. The parents may have felt inadequate, deprived, guilty, or embarrassed about the deficiency of the genitalia of their child; thus, a little growth of the penis does not harm anyone.

The scrotum will often be stimulated to grow slightly, and it will give you a little more capacity to accommodate the new testis if you have to operate on it. There is no harm in giving the gonadotrophin. We have not been able to detect any stunting of growth or damage to the testis with a dosage of 20,000 units distributed over six weeks. We start at the fourth birthday and try to be finished by the fifth birthday, and we would certainly like to have the condition corrected by the seventh birthday.

Dr. Gross, in Boston, reported a number of bilateral cryptorchids on which he did not operate until age 12, and he reported some fertility among these youngsters. It is the only information on the topic, and Dr. Gross is a very sincere and earnest person with a large series of cases. The retrospective analysis of these cases was done mostly by mail, so it is not definite that they were fertile. Furthermore, he

based his findings largely upon sperm counts, and the total sperm counts were not really as large as one might want to attest to the fact that these children were fertile. One would like to see a substantial number of sperm, about 100 million and the Gross counts run under 20 or 30 million. Although there is some indication that waiting until puberty does not do irreparable harm, it is not clear, as has been implied in the literature, that if one waits until age 12, that you will have a successful result. I think the opposite is true and it would be better to complete the whole program by age seven.

We treat the migratory testes with gonadotrophic hormones because the three shots usually bring them down. Even though they may not stay down, the doctor can tell the child that it can be brought down at any time, and the child is not quite as worried about the situation. A pediatric psychiatrist on our staff is convinced that the migratory testis is just as much a disturbance to the child as the undescended testis because it disappears in a way that the child cannot control. A three-day-dose course of 10,000 units over five days does not increase the size of the penis. The six week course will definitely increase its size.

The success rate of gonadotrophic therapy in bilateral undescended testis, where there is more likely to be a hormonal deficit, is about 33%. The unilateral cases, where you are more likely to have a mechanically poor point of attachment for gubernaculum, are more difficult. Usually the gubernaculum is attached directly under the skin so that the testis turns back up over the external oblique fascia or in the top of the scrotum. Thus, there is a mechanical reason why it does not come all the way down. In those cases the hormone therapy is not as likely to work. It has always surprised me that it worked in even 15% of the cases. We do have an occasional pleasant surprise, even with unilateral undescended testis and we continue to at least acquaint the parents with the possibility of medical treatment. Sometimes, parents will say, "I do not want to do that because my child dreads needles," or "The one thing he dreads is going to the doctor and the one thing he pleads for is that we will not take him back for needles." If this is the reaction, the parents may not want to have the hormone treatment, that is, at least the long-term treatment. The total success rate with these methods is in the 20% range. Parents should be informed of the possible treatments available and then allowed to make their own decision.

The histology of the normally descended testis

is usually normal, and these children are usually fertile because of the good testis. Yet, the one that is undescended is very often retarded. We regard it as almost always expressing a degree of maldevelopment or poor development as a cause of it being undescended. This is brought out by biopsies of the series that we have tested.

We apply an additional dimension in analyzing all of our tissue. We grow a biopsy for four or five days in a tissue culture medium containing radioactive isotopes, which will be picked up with every mitotic event, put a photographic emulsion on it and develop it. Little black spots will appear where there was activity. This is called "radioautography." Thus, we have a way of expressing the physiological potential of this tissue in addition to the histology. This activity has very little relation to what the tissue looks like on the *H* and *E* stains, and it is quite revealing. We know now that you cannot tell from the histology what the potential is; in other words, the radioautography gives you a different answer. The appearance of the *H* and *E* stains may look good when it may not really be very good; the opposite may also be true. Thus, the histology alone is not sufficient. There are other methods, and this is a good field for research. We, as urologists, should accept the responsibility of looking into these areas; they are offered to us; we have the opportunity to apply them, and we should provide the populace with the information available to us by applying advanced techniques to our material.

You may try to cure the child, even though the histology may not look very encouraging at the beginning. A defect that is sometimes present with undescended testis is that the epididymis does not link up with the testis. With each operation for undescended testis, you should look at the epididymis to see if this is the case. You will very often find the epididymis separated from the testis by an abnormal distance; look to see if there is an actual failure of union. Tell the parents about this so they not only will know it as a matter of fact, but also, they will not hold you responsible if the child is not fertile at a later date. This does not occur too often, but it does occur often enough to be aware of it and to document it for the record.

Almost all undescended testes have an associated hernia, or at least a potential hernia, in the form of an open processus vaginalis going from the peritoneal cavity down around the cord and enveloping the testis. This potential hernia has to be

repaired every time you do an operation. Occasionally, you will find one where the hernial sac is only at the upper end, but more often, it is through the full length of the cord. Since this is almost always present, the next question is, if you give hormone treatment and bring the testis down without an operation, does this hernial sac persist, and will these children develop a hernia sometime later in life? This is, of course, a possibility. Ed Sacher at the Navy hospital in Philadelphia did a study and a follow-up on his patients. He demonstrated that hernias did become clinically evident in a certain substantial percentage, but probably the majority of his patients never developed hernias. This sac may have united and closed off, or the patient may never have pushed anything out into it. It is not enough of a threat to cancel out the effectiveness of hormone therapy. Nevertheless, it does exist, and the parents should be told that the child is more likely to develop a hernia than other children.

Cancer is another possibility. If you leave a testis up in the abdomen, the first sign of cancer may be a chest metastasis. The retained testis inside the abdomen develops a testis tumor and, being inside the abdomen, it cannot be detected. It does not happen frequently enough to be a reason to take out every undescended testis, although this has been proposed. Even though you bring the testis down into the scrotum, it retains the possibility of developing a cancer at a later date. The chance of this happening is not so great as to force you to recommend that an orchidectomy be done, but it is another reason for urging that orchiopexy be done so that the testis is out in the open where it can be watched. Yet, it would be advisable to suggest the options to the parents as a possibility and let them make a decision on their own volition. I have been surprised at how many of the parents know about this and question me about it. Cancers of the undescended testis only rarely develop before puberty, and most of them develop about the age 20. The parents do not know this, and you may get a pair of parents who become panicky about the possibility of cancer and start to watch the child very closely at age six or seven. They are greatly relieved that they do not have to start worrying about it until many years later.

Some conditions include an undescended testis as part of the condition, such as the prune belly syndrome. The children have an absence of abdominal musculature, or at least a deficiency of it. The wrinkled

appearance of the skin is the basis of the so-called prune belly description of the syndrome. These children have massively enlarged ureters, and the ureters may get in the way of the descending testis and prevent it from descending. The cord is practically nonexistent, and the testis is at the bottom of the kidney on each side. In my opinion, it may be worth giving a trial to gonadotrophic hormone therapy, and it may be worth waiting a while, but it is not advisable to try to do orchiopexy on children with prune belly syndrome. It is often the case that the cord is very short. Warn the parents in advance that the odds are that you are not going to be able to get the testis down or even to get it out into the inguinal canal. In many cases, even if you cannot get it down to the bottom of the scrotum on the first try, you can usually get it down on the second try after a couple of years. In this case, with this particular syndrome, be aware at the beginning that you are probably not going to have enough cord to work with, even with two operations.

The technique and surgical principles of orchiopexy utilized in our hospital are as follows. The initial incision should be made in the skin crease. If you cannot make out the skin line, push the skin together and the lines will become apparent. We usually mark the line for precision, taking a lesson from the plastic surgeons. I encourage all of my residents to take some plastic surgical training in their preliminary studies to learn the skin stress lines that we use for our incisions. The initial incision is done carefully. In many cases, the hernial sac will have turned back under the skin, and it will be in the line of your incision. If you cut vigorously into this area, you may cut into the hernial sac or into the testis itself. Be aware that it may be in the subcutaneous fat at the lower end of your incision.

Following incision of the external oblique aponeurosis, the spermatic cord is then dissected free by sharp and blunt dissection. The dissection is carried to the internal inguinal ring and the floor of the inguinal canal, and the transversalis fascia is stretched allowing the surgeon to proceed retroperitoneally. The spermatic vessels are freed toward their origin. If the internal ring is not large enough and the operator cannot reach far enough retroperitoneally to get much length of the vessels, the fascial opening may be made larger. Usually you can open this hole large enough to dissect behind the peritoneum to get all the length needed and the inferior epigastric

vessels do not need to be divided. The conjoined tendon may be divided laterally for one-half inch or more giving increased exposure. The peritoneum may be found on the medial side of the spermatic cord and the hernial sac may be opened. The hernial sac is then divided from the vessels and spermatic cord. If this is difficult to do and the spermatic cord cannot be easily dissected away, a hypodermic needle can be used to raise a bleb of saline beneath the surface of the hernial sac and it will lift off and make the dissection easy. The hernial sac is then closed with a purse-string suture of nonabsorbable material. The spermatic vessels are held laterally by strands of fascia, referred to as the "lateral spermatic fascia." This fascia maintains a lateral position of the spermatic cord in the retroperitoneal space, thus forming an angle down toward the scrotum. If one cuts these fascial bands and eliminates the angle, the cord can then drop more medially, and the vessels will take a more direct route into the scrotum. By skeletonizing the cord down to the epididymis even more length can be obtained. I have discovered to my surprise that many of the old-time surgeons who did this sort of operation never went above the peritoneal wall. They confined themselves only to the inguinal area and gained enough length by skeletonizing the spermatic cord so that they could make the testicle come down. By stretching the cord over a finger the operator can become more aware of the thin firm strands of fascia within the cord. By dividing these bands the cord will lengthen just a little more.

Next a finger is placed in the empty side of the scrotum and an Allis clamp is used to tug on the bottom of the scrotum until a point can be found that will stretch the farthest down, and that is where the testicle should be brought to with the traction suture. Having determined this point, an incision is then made through the scrotal wall, as if in a window. A pocket, what I refer to as the subcutaneous or scrotal pocket, can then be developed with sharp and blunt dissection. Here the testicle will lie outside of the dartos and the cremasteric fibers that might pull it back up by muscular action.

An easy plane can be developed from the incision under the skin, and a pocket can be developed both downward and upward. Most of the skin on that side of the scrotum must be liberated in order to make the pouch big enough. By passing the fingers down within the scrotum an incision can be made down onto the finger. Using a long clamp and

following the finger up into the groin the clamp can be used to take hold of the testicle and draw it down through the canal and out the scrotal opening. The testicle, having been pulled out through the side of the scrotum, can now be fixed in the pocket.

We take an atraumatic round needle with 3.0 silk and pass it through the tunica vaginalis. Then the needle is passed through the very bottom of the scrotum in a new location. Interrupted sutures of chromic atraumatic 5.0 are used to close the scrotum. The testicle is then kept in the subcutaneous pouch and the groin wound is closed in a routine manner.

The traction sutures should be an extension of the line of pull which you want on the testis to keep the cord down. In the technique that we recommend, the sutures are applied to the testis and brought to the opposite leg. If too much tension is placed on the cord, you will squeeze it flat and bring about ischemia. The next day there will be edema of the testis and edema of the scrotum, which means necrosis, an infarction and the death of the testis. The traction should be very gentle. We put on just enough traction to keep the thread from sagging; as the child moves around in bed, he will give a tug on it several times a day, and that is all you need. If there is too much tension, not only is it going to be painful, but it will also probably destroy the testis. That is one reason why the old Torek operation, where the testis was sewn directly to the fascia of the leg, through a counter incision, frequently brought about necrosis of the testis. It was too tight and rigid, and it destroyed the testis rather than helped it.

Over the years we have used a variety of substitute testes (prosthetic testes), including ping pong balls and marbles, in children and adults who had a missing testis. Then they were made out of hard plastic or metal. The Dow Company developed prosthetic testes made of silicone rubber. We have

been using them for several years, and they are more or less elastic. In the last few years, the 14- and 15-year-olds have complained that these testes are too hard and they want them to feel more natural. The Dow Company then developed jell-filled silicone silastic testes which have a beautifully normal consistency. They come in several different sizes and have little tabs on the end. You want to be able to put a suture through the tab to suture it to the bottom of the scrotum so that it will retain the desired position. A purse string is then put around the neck of the scrotum and it is sutured. We replace these as the children grow bigger to keep pace with their normal size. A larger than normal size is needed for a child who has only one testis. His good testis is going to undergo compensatory hypertrophy or, at least, it is going to grow to a larger than normal size. Consequently, we have one super size, the fourth size, which is bigger than normal, for that reason.

In summary, there are many reasons why orchiopexy should be done, and certainly, the cancer worry is a very distinct one. Yet, I think the psychological reason, the "locker room appearance" situation, is the most frequent, and therefore, an important factor. I do think that we should exercise our favored position of being able to offer hormone treatment first. If that does not work, then go on with the surgery as required. The timing, in my opinion, should be to start at the fourth birthday and to have the program completed by the fifth birthday. Although physiological considerations do enter into our choice, the precise definition of this time interval is primarily decided on the psychological aspects of the matter. I urge you to consider these, and I think that you will find the fourth-to-fifth-year interval works out very satisfactorily.

# Wilms' Tumor and Neuroblastoma: Results of Therapy\*

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As a result of intensive research during the past 20 years, there is now a more optimistic attitude toward the treatment of children with cancer. Success with new therapies of Wilms' tumor and acute lymphoblastic leukemia have been important factors in generating this new optimism. Despite these and other advances, little success has been achieved in the treatment of children with neuroblastoma. The poor prognosis of these patients is due to the high percentage of widespread disease at the time of diagnosis and lack of effective treatment for advanced disease.

Wilms' tumor and neuroblastoma are numerically among the most common noncerebral malignant solid tumors in children. The purpose of this report is to describe the recent results of therapy.

**Incidence of Wilms' Tumor and Neuroblastoma.** To provide a perspective of these two diseases, a list of malignant diseases in children under 16 years of age reported to the Medical College of Virginia Tumor Registry between 1964 and 1970 is shown in Table 1. Acute leukemia was the most common malignancy, followed by central nervous system tumors. Wilms' Tumor accounted for 9.7% and neuroblastoma, 6.4% of all the malignancies reported. The importance of these two tumors is considerably increased, however, when we consider only noncerebral solid tumors of childhood; Wilms' tumor accounted for 16% and neuroblastoma, 11% of these tumors.

**Wilms' Tumor.** Advances in chemotherapy of

Wilms' tumor, along with improved treatment modalities in radiotherapy and surgery have increased the survival rate from a 20% two-year survival rate three decades ago to an 80% plus rate within the last 10-year period.

The use of dactinomycin and vincristine accounts for the improvement in chemotherapy. In the early 1950's, nitrogen mustard was tried in the treatment of metastatic Wilms' tumor with little apparent benefit. In 1955, Farber pioneered in the use of dactinomycin in children with or without metastases. This drug has been shown, after extensive trial, to be of considerable benefit in preventing recurrences and in eradicating recurrent and metastatic disease.

Improved radiation treatment has resulted from the development of more sophisticated equipment and from an improved understanding of the natural history of Wilms' tumor. Supervoltage equipment with increased definition has allowed delivery of lower dosages to the tumor, with less radiation scattered into surrounding normal tissue. Additionally, less of the dose is directed to growing bone than with previous orthovoltage equipment when normal bone might absorb as high as 15-20% over that delivered to the tumor.

Improved understanding of the disease includes the observation that the tumor remains localized in its pseudocapsule until the very late stages, allowing the use of localized irradiation of the renal fossa after surgery rather than more widespread treatment. Another observation that lymph node involvement is rare, saves the need for routine irradiation for possible para-aortic node involvement. At the same time, greater understanding of the tumor has

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TABLE 1.

Pediatric Cases of Malignant Diseases Reported to the Medical College of Virginia Tumor Registry, 1964-1970

DISEASES	NUMBER OF	
	CASES	PER CENT
Central Nervous System Tumors		
Optic Glioma	5	2.3%
Astrocytoma	15	6.9
Medulloblastoma	9	4.1
Ependymoma	5	2.3
Craniopharyngioma	3	1.4
Meningioma	1	0.4
Acute Leukemia	48	22.2
Lymphosarcoma	25	11.5
Hodgkin's Disease	9	4.1
Wilms' Tumor	21	9.7
Lymphoepithelioma	7	3.2
Rhabdomyosarcoma	12	5.5
Neuroblastoma	14	6.4
Malignant Schwannoma	3	1.4
Osteogenic Sarcoma	7	3.2
Mixed Mesodermal Tumor	2	0.9
Dysgerminoma	3	1.4
Carcinoma of the Pancreas	1	0.4
Carcinoma of the Maxillary Sinus	4	1.8
Composite Parotid Tumor	1	0.4
Retinoblastoma	4	1.8
Ameloblastoma	3	1.3
Arrhenoblastoma	2	0.9
Ewing's Tumor	2	0.9
Fibrosarcoma	2	0.9
Hemangioendothelioma	2	0.9
Hepatoma and Hepatoblastoma	2	0.9
Osteochondroma	2	0.9
Teratoma	2	0.9
	Total 216	100%

been developed through the efforts of pathologists, with the recognition of a subgroup—the mesoblastic nephroma. This lesion would seem to be of low grade malignancy and may contribute to the well-known better survival in infants.

In the presence of lung metastases, which account for approximately 90% of the cases in which Wilms' tumor metastasizes, it has been observed that low-dose radiation plus chemotherapy can preserve pulmonary function as it cancels disease in at least 60% of such patients. It has also become evident that since two of three patients will have generalized pulmonary involvement, bilateral total pulmonary

irradiation is necessary even in the patient with evidence of only one lesion.

According to Tefft, experience has shown that irradiation cannot be relied upon to control liver metastases. Surgical excision is the only sure control of a lesion in the liver if it is solitary or localized to one lobe. When liver irradiation is indicated, a total dose of 3000 rads to the total liver in three weeks time should not be exceeded.

**National Wilms' Tumor Study (NWTS).** Since the national yearly incidence of Wilms' tumor, estimated to be 500, is too small to permit single institutions and investigators to gain significant information about the treatment of this disease without the investigation being unduly protracted, groups of investigators and institutions combined their efforts in a single investigation so that early answers can be obtained to longstanding questions regarding therapy.

The primary objective of the NWTS, activated in 1969, was to refine methods of treatment. Thus, two specific questions were asked: 1) Is post-operative radiotherapy necessary for treatment of patients with well-encapsulated, localized lesions after what appears to be their total removal? 2) Which of the two chemotherapeutic agents (dactinomycin, vincristine) known to be effective against Wilms' tumor gives the better result and can this result be improved by their combined use?

The secondary objective was to obtain a better understanding of the neoplasm by defining the extent of the lesion at diagnosis (clinical grouping or staging) and relating it to the response to treatment. Five clinical groups (stages) of disease were defined:

Group I—Tumor limited to the kidney and completely resected

Group II—Tumor extends beyond the kidney but is completely resected

Group III—Residual nonhematogenous tumor confined to the abdomen

Group IV—Hematogenous metastases

Group V—Bilateral renal involvement either initially or subsequently

Children were randomized at diagnosis according to their clinical group determined by the surgeon and pathologist. Those in group I were randomized following surgery to receive either dactinomycin alone or dactinomycin plus postoperative irradiation to the tumor bed. Dactinomycin was started and

given in five-day courses (15 µg/kg/d, i.v.) within 48 hours of diagnosis and repeated at 6 weeks, 3, 6, 9, 12 and 15 months, thereafter.

Children in groups II and III, following resection, all received irradiation to the tumor bed. At the same time they were randomized to receive either dactinomycin alone, vincristine alone or the combination. Dactinomycin was administered as outlined for group I patients. Vincristine was given weekly for 7 weeks (1.5 mg/m<sup>2</sup> i.v.) starting at the time of diagnosis, then at 3, 6, 9, 12 and 15 months thereafter, giving two doses four days apart.

Children in group IV received either a preoperative course of vincristine (day 0 and 7) and then had surgery on day 14 or surgery was carried out immediately. Treatment then was identical to that for groups II and III.

**Results.** It is still too early to draw any definite conclusions from any of the preliminary data. Certain patterns seem to be emerging, however, and are worthy of mention.

Of 208 patients registered, 21 were incorrectly diagnosed. More than half of these cases turned out to be either neuroblastoma or polycystic kidney. Other diagnoses included renal carbuncle, benign teratoma, congenital renal vein thrombosis, hemorrhage into the subrenal gland, hypernephroma and rhabdomyosarcoma. Two cases of mesoblastic nephroma were also registered.

One hundred eighty-seven patients were randomized according to protocol. Patients with clinical group I disease (the lesion limited to the kidney and completely resected) formed the most frequent group and accounted for 83 of these patients. Disease groups II, III and IV were less frequent and contained 47, 39 and 18 patients respectively. The accrual rate by month has shown no seasonal variation in the incidence of the disease.

The mean age at diagnosis for the entire series of 187 patients was 41 months. Group I patients were the youngest (approximately 30 months) and group IV, the oldest (approximately 60 months). The mean ages of groups II and III were approximately equal at 39 months. From the data, it seems clear that with increasing age at diagnosis, the disease is likely to be more advanced.

Approximately 16% of all the patients were black and 48% were females. The right kidney was involved in 46% of the cases. No differences were apparent among the four groups in these parameters.

With regard to the results of therapy, approxi-

mately 90% of the patients in clinical group I were free of disease from one to more than 21 months after treatment was instituted. There is no difference in recurrence rate thus far between those who received dactinomycin alone and those who received it in combination with postoperative radiotherapy. If further follow-up substantiates that radiotherapy produces no added benefit in this clinical group, the study will have borne important fruits. The possible untoward late effects of radiation are well known. Disturbances of normal bone growth, radiation nephritis, radiation hepatitis and pulmonary fibrosis are some. Induction of primary tumor by the irradiation of normal structures, while not frequent, is nonetheless a matter of real concern.

Of those with clinical groups II and III involvement, approximately 75% continued in complete remission from one to 21 months after the start of treatment and approximately 60% of these in clinical group IV were similarly free of disease for the same period of time. No differences are apparent thus far between the various treatment regimens in these three groups.

All but one of the metastases or recurrences in relapsed patients developed during the first year of treatment. By far, the most common site of metastases was the lung. Other sites were liver, nodes, bone, spleen and brain. Abdominal recurrences were infrequent. In most instances death was attributed to tumor, but in a few cases no tumor was found and infection was thought to be the cause.

Toxicities to therapy included leukopenia and thrombocytopenia with occasional anemia, nausea and vomiting, radiation dermatitis and hepatitis and alopecia. These were usually reversible.

At the Medical College of Virginia, 11 patients, ranging in age from five months to eight years, have been entered on study (Table 2). Three had clinical group I disease, seven, clinical group II disease, and one, clinical group IV disease. All but one attained complete remission with therapy. Two of the 11 developed metastases at 13 and 16 months following diagnosis and one of them has expired. Eight of the 11 are free of disease from five months to nearly three years after treatment was started. The three oldest patients (3½, 5 and 8 years) in this small series developed recurrences or metastases.

**Neuroblastoma.** Although there has been marked improvement in survival of children with Wilms' tumor during the last decade, this has not been the case for metastatic and nonmetastatic

TABLE 2.

National Wilms' Tumor Study Medical College of Virginia Patients

CASE	AGE AT DIAGNOSIS	DATE ON STUDY	CLINICAL GROUP	TREATMENT	STATUS
1	19 mos.	4/10/70	I	S, R, Dact	NED
2	10 mos.	6/29/70	I	S, R, Dact	NED
3	23 mos.	2/28/72	I	S, R, Dact	NED
4	5 yrs.	10/29/69	II	S, R, Dact, Vcr	Expired 1/4/71
5	2 yrs.	5/14/70	II	S, R, Dact, Vcr	NED
6	2 yrs.	8/26/70	II	S, R, Dact, Vcr	NED
7	8½ mos.	3/19/71	II	S, R, Vcr	NED
8	1 yr.	7/1/71	II	S, R, Vcr	NED
9	3½ yrs.	10/11/71	II	S, R, Vcr later Dact Adriamycin Cytosan	Expired 2/5/72 (no response)
10	5 mos.	9/16/72	II	S, R, Vcr	NED
11	8 yrs.	4/6/71	IV	S, R, Dact, Vcr	Recurrence right lung 8/72, later brain

S—Surgery  
R—Radiotherapy  
Dact—Dactinomycin  
Vcr—Vincristine  
NED—No evidence of disease

neuroblastoma for the same time period, primarily due to the difficulty in early diagnosis and lack of effective treatment for advanced disease. Chemotherapy, in contrast to Wilms' tumor, has not been very successful. An overall cure rate of 35–40% has been reported. In patients under one year of age who have localized disease, survival rates as high as 68–70% have been achieved; however, in generalized disease the survival rate has been estimated at about 12%.

Between 1957 and 1968, 21 children with neuroblastoma and two children with ganglioneuroblastoma were treated at the Medical College of Virginia. Of the entire group, only two patients are alive; one child with intrathoracic neuroblastoma, age five months at diagnosis, has no evidence of disease after resection and postoperative radiotherapy. Another, age 6 months at diagnosis with widespread disease, has been free of disease for four years, after one year of treatment with cyclophosphamide and vincristine. Six of the patients were under one year of age, and 14 were two years or older at diagnosis.

The commonest site of the primary tumor was the adrenal gland (52%). Other less common sites included the retroperitoneum (17%), posterior mediastinum (17%) and the brain (4%).

In the majority of cases (74%), the disease

was already widespread at the time of initial examination. Distant metastases occurred most often in bones (48%), bone marrow (48%), and liver (48%), although at autopsy an unusually high percentage (35%) had metastases to the lungs and pleura. Those with regional disease developed metastases within 12 months of diagnosis. Only three children, all with regional disease, had complete resection of tumor. All others had either partial resection or biopsy.

Four children died before any treatment could be instituted. Fifteen of 23 received postoperative radiotherapy. A variety of chemotherapeutic agents including vincristine and cyclophosphamide were included as part of the initial treatment program in 15 patients with distant metastases and in four with regional disease.

The median survival time for the entire group was six months, with the longest survivor still alive at seven years. Those with the primary site located in the adrenal gland had the shortest median survival time (4 months).

Sawitsky and Desposito (3) have reported their results using either cyclic or sequential vincristine and cyclophosphamide in high or low dosage for treatment of generalized neuroblastoma. Their results also do not bear out the early enthusiasm shown for these agents for treatment of neuroblastoma. Of 47

TABLE 3  
Staging of Neuroblastoma

STAGE I:	Tumor confined to the organ or structure of origin.
STAGE II:	Tumors extending in continuity beyond the organ or structure of origin but not crossing the midline. Regional lymph nodes on the homolateral side may be involved.
STAGE III:	Tumors extending in continuity beyond the midline. Regional lymph nodes may be involved bilaterally.
STAGE IV:	Remote disease involving skeleton, organs, soft tissue, distant lymph node groups, etc. (See IV-S.)
STAGE IV-S:	Patients who would otherwise be Stage I or II, but who have remote disease confined only to one or more of the following sites: liver, skin or bone marrow (without radiographic evidence of bone metastases on complete skeletal survey).

patients treated, only two are alive for more than 24 months with no evidence of disease. The median survival in the whole group was 37 weeks. If a response occurred, median survival was prolonged to 65 weeks.

Other drugs used have also produced disappointing results and include 6-mercaptopurine, prednisone, methotrexate, dactinomycin, daunorubicin, and nitrogen mustard. Newer agents such as adriamycin and ifosphamide are currently under investigation.

Although results of treatment continue to be poor, advances have been made in the understanding of the disease process. A new staging system has been developed based on certain patterns of origin and clinical behavior found to affect prognosis, which takes into account the peculiarities unique for neuroblastoma (Table 3) (1). Data based on this system indicates that: 1) Patients with stage IV-S have a better prognosis than those with stage IV

disease; 2) The proportion of patients in stages III and IV increases with age; 3) The presence of bone metastases, to be distinguished from bone marrow involvement with positive x-ray findings, almost always heralds a fatal outcome; and 4) Data confirm the well-known better survival of patients under one year of age.

A second potential contribution has been the development of a simple, reliable "dip-stick" test for detecting the early presence of neuroblastoma (2). The test is based on the fact that up to 80% of the children with this disease excrete excess catecholamine or one of its metabolites, 3-methoxy-4-hydroxy-mandelic acid (VMA) in the urine. Strips of chromatography paper impregnated with paranitroaniline, sodium nitrate, and anhydrous potassium carbonate are dipped into a urine sample or just pressed against a wet diaper. Within ten minutes, the color of the paper changes to orange or purple if either VMA or normetanephrine is present in urine. The test may be used by private practicing physicians for routine screening on all children under five years of age. If used at regular yearly intervals, it is conceivable that a significant impact upon survival of neuroblastoma may be achieved by early diagnosis before metastasis has occurred.

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# Surgery of the Genitalia in Children\*

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I shall confine my paper to the external male genitalia. Most of the problems that we have dealt with have been congenital from simple meatal strictures to more severe, although not necessarily more serious, situations. In the last 18 years, I have worked closely with Dr. Charles Horton, and much of this report represents our joint efforts.

We sometimes see exotic traumatic lesions. One little boy, who was rather dull mentally, was the victim of a couple of "flim-flam men." Two of his companions convinced him that they should all put rubber bands on their penises, but he was the only one who did it. Three days passed before his parents brought him to the Emergency Room for treatment. On examination the rubber band was discovered and immediately removed after which he was admitted to the hospital. Our group was consulted because the penis failed to improve. Surgical exploration revealed a restrictive fibrotic band of dead skin and subcutaneous tissue beneath the area where the rubber band had been. We excised this band and debrided the penis. Healing was slow but satisfactory.

Hypospadias is the most common congenital lesion we have encountered. In this condition the urethral meatus is located more proximally than normal on the ventral surface of the penis and is accompanied by a ventral curvature called chordee. Because of an increased incidence of upper urinary tract anomalies associated with hypospadias, we do an intravenous pyelogram on all of these patients. In the more severe conditions with the meatus in the region of the scrotum or perineum, there are often hypoplasia and undescended testes. We evaluate

such patients with sex chromatin and chromosome studies as their sex may not be obvious from external examination.

We have treated several patients with perineal hypospadias who actually were male pseudohermaphrodites with internal female organs and undescended testes. These patients require abdominal exploration; and testes, which if present and cannot be brought down, should be removed. We recently saw a male pseudohermaphrodite who had had a testis biopsy 25–30 years prior to our seeing him, and the testis had been left *in situ*. A large mass occupying the pelvis which proved to be seminoma had produced a foot drop by nerve compression. This mass completely disappeared on radiation therapy, and at second exploration we could find nothing except necrotic tissue. Hopefully he has been cured. Recent evidence indicates that the undescended testis in male pseudohermaphrodites is more prone to malignancy than the ordinary undescended testis.

Hypospadias represents the cessation of normal development of the male external genitalia. At one point in embryologic development, the external genitalia of the male and female are identical. The interstitial cells of the developing testes are quite prominent and furnish a hormone that causes male development. Hypospadias is caused by premature cessation of the formation of this hormone which results in an incompletely formed penis. We have repaired all types of hypospadias with only one stage of surgery including chordee without hypospadias and glanular, distal penile, mid-penile, scrotal and perineal locations. When chordee is present, surgery is necessary regardless of the location of the urethral meatus.

The normal urethra is surrounded by corpus spongiosum, Buck's fascia, dartos fascia and skin. In hypospadias, these structures are missing; the mesenchyme, distal to the urethral meatus which

\* This is an edited transcription of a lecture presented by Dr. Devine at the 26th Annual Stoneburner Lecture Series, February 23, 1973, at the Medical College of Virginia, Richmond.

normally forms them, undergoes fibrous dysplasia and forms a band of tissue which must be removed in order to release the chordee and straighten the penis; otherwise chordee is likely to recur.

We usually repair chordee at age two; but if the penis is small, we sometimes wait until age three or four. Hormone therapy enlarges the penis but also makes the fibrous tissue layers more prominent and tougher, rendering surgery more difficult. Surgical repair is more difficult on older patients whose structures have become more prominent due to natural hormone production.

It is important for mothers to stay with their children during hospitalization. Dr. Panayotis Kelalis recently reported on a preliminary study that he and psychiatrists at the Mayo Clinic have done on the psychological aspects of surgery on the genitalia. They feel that operation on the genitalia when the child is under the age of two or three is not nearly so important to the child's psyche as is separation from his mother.

In over 250 total cases of hypospadias, we have found 22 patients with chordee without hypospadias including three different types. In class I, just the epithelium has grown together leaving an epithelial-lined urethra covered by skin with fibrous tissue lying beneath it causing chordee. In class II, there has been further development of the mesenchyme around the urethra with formation of the urethra in the corpus spongiosum with fibrous tissue causing chordee lying beneath and lateral to it. In class III, Buck's fascia has also formed around the corpus spongiosum. The fibrous tissue causing the chordee is only the deficient dartos layer, and correction does not require dissection beneath Buck's fascia. In chordee without hypospadias there is a typically sharp bend; the prepuce is complete and the meatus is located in the glans. The median raphe deviates to the side ending in a structure resembling a knuckle lying on the top of the penis. Chordee without hypospadias can also be corrected without severing the urethra. A longitudinal incision should be made with careful dissection, and fibrous tissue removed to straighten the penis. The urethra will stretch to fit. One of the most distressing patients with whom we have dealt in the recent past is a young man of 19. Seventeen years ago he underwent his first operation for chordee without hypospadias. When we saw him four years ago after 10 operations he still had chordee, but it was penoscrotal junction hypospadias with

a lot of scar tissue. We have completed his surgery in four additional stages.

We have done dorsal meatotomy on patients who have a very distal strictured urethral meatus and no chordee. We raise a V-flap of glans tissue, make a dorsal incision in the urethral meatus and insert the flap of tissue in order to enlarge the opening in a distal direction. We then proceed with circumcision.

The glanular V-flap is now used in all of our hypospadias repairs. Dissection is carried out beneath the glans and along the surface of the corpora cavernosa. There is a good cleavage plane between the glans and the corpora. The tissue which causes the chordee actually inserts on the undersurface of the glans and not on the corpora cavernosa. The chordee will not be completely corrected if any tissue is left to keep the cap of the glans tilted ventrally. An anteriorly based flap is taken from the midline, freed up, and sewn back on to the corpora. Construction of the urethra is based on this allowing the urethral meatus to be placed at the tip of the glans where it should be. Before we developed the glanular V-flap, we used a tube graft for all urethral repairs. Now when the flap reaches the urethra after dissection is complete, we use what we call a "flip-flap" to complete the urethra. The penis is circumcised and the V-flap outlined on the glans. Tissue causing the chordee is removed, straightening the penis. A proximal flap based on the urethral meatus is outlined, incised, elevated and left attached to the urethra. After the glans has developed, an incision is made in the dorsal surface of the urethra. The urethra and flip-flap are anastomosed to the V-flap of glans. Lateral wings of glans are then brought around and closed, placing the meatus at the tip of the penis. The prepuce is used to cover the ventral part of the penis with skin. If the glanular V-flap will not meet the urethra, a distal portion of the prepuce is used to make a skin graft tube, which is anastomosed proximally to the urethra and distally to the skin flap, to extend the urethra to the tip. The rest of the prepuce will be adequate then for penile coverage.

In repair of perineal hypospadias, we usually will find a good groove of hairless skin between the two portions of the cleft scrotum which we utilize as a Tirsch-Duplay type of tube to bring the urethra from the meatus to the penoscrotal junction. We make a tube from the distal portion of the prepuce

and join it to the Tirsch-Duplay tube. The distal end of this tube is then anastomosed to the glanular V-flap to complete the procedure.

Urine must be diverted. A urethrostomy tube drains better than a suprapubic tube; however, if the urethral meatus is far posterior, we use a suprapubic tube. Red rubber tubes are softer and have a better consistency than plastic tubes. Diversion is continued for 10 days, and stinting tubes are left in for seven days.

We have performed over 250 hypospadias op-

erations. Seventy-five percent of these are complete after one stage of surgery. Most of our complications are small urethrocutaneous fistulae which require further surgical repair. We are still developing our technique and changing our operation to improve the results. Each case requires individual consideration, and the technique must be adapted to the patient. All surgeons doing this type of work must be familiar with all the types of repair as some facet of another surgical procedure may be just what is needed to solve a difficult problem.

*In Memoriam*

JOHN HUTCH, M.D.

1918—1972

Associate Professor of Urology  
University of California at San Francisco







# the long-range analgesic

**in chronic pain: continued relief without risk of tolerance**

Though Talwin® Tablets can be compared to codeine in analgesic efficacy, Talwin is not subject to narcotic controls. For patients who require potent analgesia for prolonged periods, Talwin can provide consistent, long-range relief, with fewer of the consequences you've come to expect with narcotic analgesics.

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- **Not subject to narcotic controls:** convenient to prescribe—day or night—even by phone.

- **Generally well tolerated by most patients:** infrequently cause decrease in blood pressure or tachycardia; rarely cause respiratory depression or urinary retention; seldom cause diarrhea or constipation. If dizziness, lightheadedness, nausea or vomiting are encountered, these effects may decrease or disappear after the first few doses. (See last page of this advertisement for a complete discussion of Adverse Reactions and a Brief Summary of other Prescribing Information.)

50 mg. Tablets

**Talwin**<sup>®</sup>  
brand of  
**pentazocine** (as hydrochloride)

**in moderate to severe pain**

# the long-range analgesic

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50 mg. Tablets

**Talwin**®  
brand of  
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# the long-range analgesic

in chronic pain: continued  
relief without risk of tolerance

**Talwin® Tablets brand of pentazocine (as hydrochloride)  
Analgesic for Oral Use—Brief Summary**

**Indications:** For the relief of moderate to severe pain.

**Contraindication:** Talwin should not be administered to patients who are hypersensitive to it.

**Warnings: Drug Dependence.** There have been instances of psychological and physical dependence on parenteral Talwin in patients with a history of drug abuse and, rarely, in patients without such a history. Abrupt discontinuance following the extended use of parenteral Talwin has resulted in withdrawal symptoms. There have been a few reports of dependence and of withdrawal symptoms with orally administered Talwin. Patients with a history of drug dependence should be under close supervision while receiving Talwin orally.

In prescribing Talwin for chronic use, the physician should take precautions to avoid increases in dose by the patient and to prevent the use of the drug in anticipation of pain rather than for the relief of pain.

**Head Injury and Increased Intracranial Pressure.** The respiratory depressant effects of Talwin and its potential for elevating cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a preexisting increase in intracranial pressure. Furthermore, Talwin can produce effects which may obscure the clinical course of patients with head injuries. In such patients, Talwin must be used with extreme caution and only if its use is deemed essential.

**Usage in Pregnancy.** Safe use of Talwin during pregnancy (other than labor) has not been established. Animal reproduction studies have not demonstrated teratogenic or embryotoxic effects. However, Talwin should be administered to pregnant patients (other than labor) only when, in the judgment of the physician, the potential benefits outweigh the possible hazards. Patients receiving Talwin during labor have experienced no adverse effects other than those that occur with commonly used analgesics. Talwin should be used with caution in women delivering premature infants.

**Acute CNS Manifestations.** Patients receiving therapeutic doses of Talwin have experienced, in rare instances, hallucinations (usually visual), disorientation, and confusion which have cleared spontaneously within a period of hours. The mechanism of this reaction is not known. Such patients should be very closely observed and vital signs checked. If the drug is reinstated it should be done with caution since the acute CNS manifestations may recur.

**Usage in Children.** Because clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

**Ambulatory Patients.** Since sedation, dizziness, and occasional euphoria have been noted, ambulatory patients should be warned not to operate machinery, drive cars, or unnecessarily expose themselves to hazards.

**Precautions: Certain Respiratory Conditions.** Although respiratory depression has rarely been reported after oral administration of Talwin, the drug should be administered with caution to patients with respiratory depression from any cause, severe bronchial asthma and other obstructive respiratory conditions, or cyanosis.

**Impaired Renal or Hepatic Function.** Decreased metabolism of the drug by the liver in extensive liver disease may predispose to accentuation of side effects. Although laboratory tests have not indicated that Talwin causes or increases renal or hepatic impairment, the drug should be administered with caution to patients with such impairment.

**Myocardial Interction.** As with all drugs, Talwin should be used with caution in patients with myocardial infarction who have nausea or vomiting.

**Biliary Surgery.** Until further experience is gained with the effects of Talwin on the sphincter of Oddi, the drug should be used with caution in patients about to undergo surgery of the biliary tract.

**Patients Receiving Narcotics.** Talwin is a mild narcotic antagonist. Some patients previously given narcotics, including methadone for the daily treatment of narcotic dependence, have experienced mild withdrawal symptoms after receiving Talwin.

**CNS Effect.** Caution should be used when Talwin is administered to patients prone to seizures; seizures have occurred in a few such patients in association with the use of Talwin although no cause and effect relationship has been established.

**Adverse Reactions:** Reactions reported after oral administration of Talwin include *gastrointestinal:* nausea, vomiting; infrequently constipation; and rarely abdominal distress, anorexia, diarrhea. *CNS effects:* dizziness, lightheadedness, sedation, euphoria, headache; infrequently weakness, disturbed dreams, insomnia, syncope, visual blurring and focusing difficulty, hallucinations (see *Acute CNS Manifestations under WARNINGS*); and rarely tremor, irritability, excitement, tinnitus. *Autonomic:* sweating; infrequently flushing; and rarely chills. *Allergic:* infrequently rash; and rarely urticaria, edema of the face. *Cardiovascular:* infrequently decrease in blood pressure, tachycardia. *Other:* rarely respiratory depression, urinary retention.

**Dosage and Administration: Adults.** The usual initial adult dose is 1 tablet (50 mg.) every three or four hours. This may be increased to 2 tablets (100 mg.) when needed. Total daily dosage should not exceed 600 mg.

When antiinflammatory or antipyretic effects are desired in addition to analgesia, aspirin can be administered concomitantly with Talwin.

**Children Under 12 Years of Age.** Since clinical experience in children under 12 years of age is limited, administration of Talwin in this age group is not recommended.

**Duration of Therapy.** Patients with chronic pain who have received Talwin orally for prolonged periods have not experienced withdrawal symptoms even when administration was abruptly discontinued (see *WARNINGS*). No tolerance to the analgesic effect has been observed. Laboratory tests of blood and urine and of liver and kidney function have revealed no significant abnormalities after prolonged administration of Talwin.

**Overdosage: Manifestations.** Clinical experience with Talwin overdosage has been insufficient to define the signs of this condition.

**Treatment.** Oxygen, intravenous fluids, vasopressors, and other supportive measures should be employed as indicated. Assisted or controlled ventilation should also be considered. Although nalorphine and levallorphan are *not* effective antidotes for respiratory depression due to overdosage or unusual sensitivity to Talwin, parenteral naloxone (Narcan®, available through Endo Laboratories) is a specific and effective antagonist.

Talwin is not subject to narcotic controls.

**How Supplied:** Tablets, peach color, scored. Each tablet contains Talwin (brand of pentazocine) as hydrochloride equivalent to 50 mg. base. Bottles of 100.

50 mg. Tablets

**Talwin®**  
brand of  
**pentazocine** (as hydrochloride)

in moderate to severe pain

**Winthrop** Winthrop Laboratories, New York, N.Y. 10016

(1607H)



Before prescribing, please consult complete product information, a summary of which follows:

**Indications:** Tension and anxiety states, somatic complaints which are concomitants of emotional factors; psychoneurotic states manifested by tension, anxiety, apprehension, fatigue, depressive symptoms or agitation; symptomatic relief of acute agitation, tremor, delirium tremens and hallucinosis due to acute alcohol withdrawal; adjunctively in skeletal muscle spasm due to reflex spasm to local pathology, spasticity caused by upper motor neuron disorders, athetosis, stiff-man syndrome, convulsive disorders (not for sole therapy).

**Contraindicated:** Known hypersensitivity to the drug. Children under 6 months of age. Acute narrow angle glaucoma; may be used in patients with open angle glaucoma who are receiving appropriate therapy.

**Warnings:** Not of value in psychotic patients. Caution against hazardous occupations requiring complete mental alertness. When used adjunctively in convulsive disorders, possibility of increase in frequency and/or severity of grand mal seizures may require increased dosage of standard anticonvulsant medication; abrupt withdrawal may be associated with temporary increase in frequency and/or severity of seizures. Advise against simultaneous ingestion of alcohol and other CNS depressants. Withdrawal symptoms (similar to those with barbiturates and alcohol) have occurred following abrupt discontinuance (convulsions, tremor, abdominal and muscle cramps, vomiting and sweating). Keep addiction-prone individuals under careful surveillance because of their predisposition to habituation and dependence. In pregnancy, lactation or women of childbearing age, weigh potential benefit against possible hazard.

**Precautions:** If combined with other psychotropics or anticonvulsants, consider carefully pharmacology of agents employed; drugs such as phenothiazines, narcotics, barbiturates, MAO inhibitors and other antidepressants may potentiate its action. Usual precautions indicated in patients severely depressed, or with latent depression, or with suicidal tendencies. Observe usual precautions in impaired renal or hepatic function. Limit dosage to smallest effective amount in elderly and debilitated to preclude ataxia or over-sedation.

**Side Effects:** Drowsiness, confusion, diplopia, hypotension, changes in libido, nausea, fatigue, depression, dysarthria, jaundice, skin rash, ataxia, constipation, headache, incontinence, changes in salivation, slurred speech, tremor, vertigo, urinary retention, blurred vision. Paradoxical reactions such as acute hyperexcited states, anxiety, hallucinations, increased muscle spasticity, insomnia, rage, sleep disturbances, stimulation have been reported; should these occur, discontinue drug. Isolated reports of neutropenia, jaundice; periodic blood counts and liver function tests advisable during long-term therapy.

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