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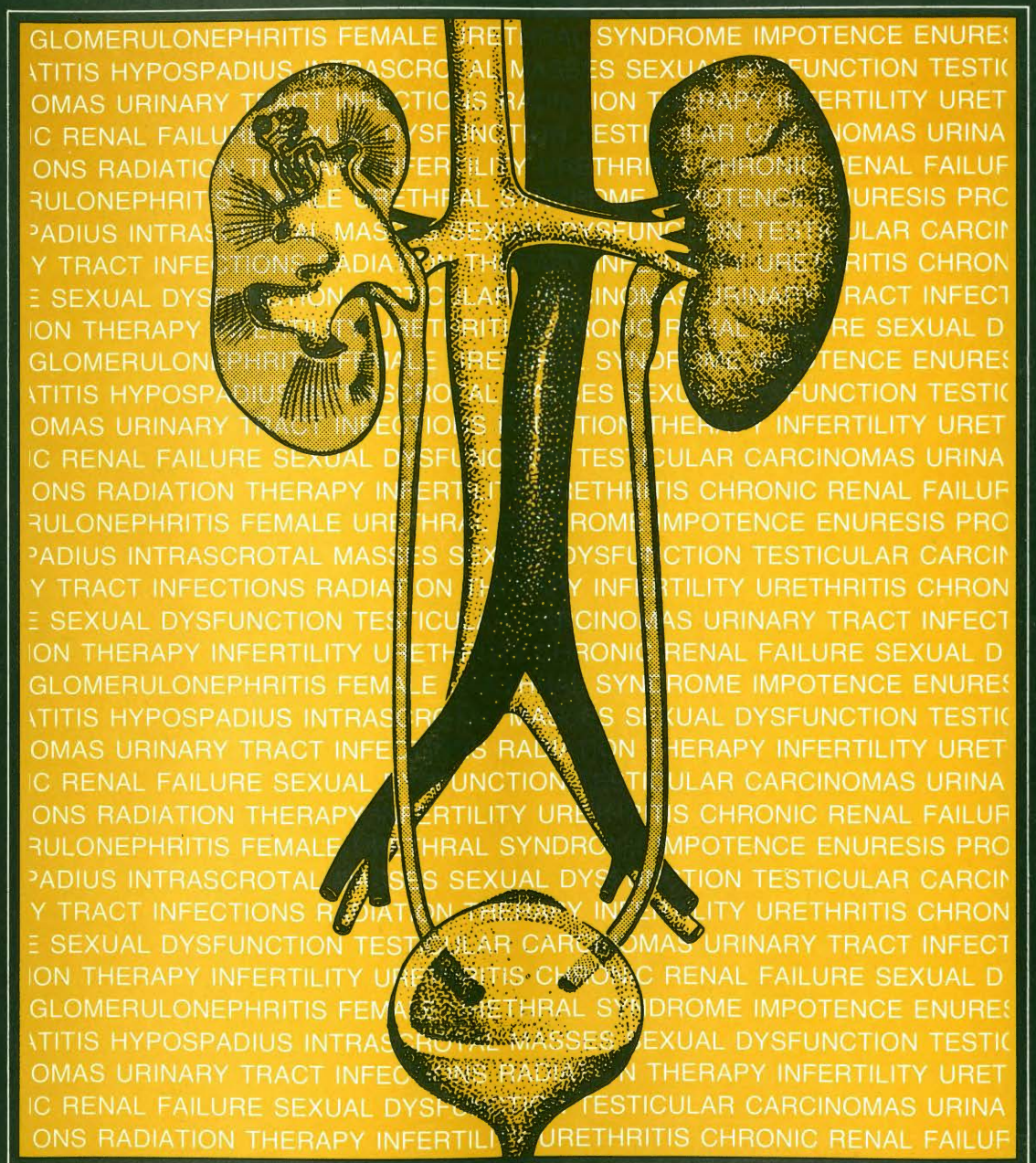

Management of Urological Problems in Primary Care

PROGRAM FOR THE 49TH ANNUAL MCGUIRE LECTURE SERIES

Management of Urological Problems in Primary Care

Presented

by the Division of Urology and the Department of Continuing Medical Education

Saturday, December 3, 1977

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THE 49TH ANNUAL MCGUIRE LECTURE SERIES
Management of Urological Problems in Primary Care
Presented by the Division of Urology and the Department of Continuing Medical Education
WARREN W. KOONTZ, JR., M.D., *Guest Editor*

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INTRODUCTION

The purpose of this group of papers is to present an up-to-date review of common urologic problems that confront the primary care physician. Two papers are presented on urinary tract infections, the most common complaint faced by physicians in their offices. Another paper covers congenital anomalies of the urinary tract which represent an important part of pediatric diseases. Dr. William McRoberts, one of the McGuire Lecturers, reviews aspects of male infertility, a significant concern in today's society. Other topics discussed in this issue are parenchymal kidney disease, the management of the patient with end-stage renal disease, and urinary tract cancer. These subjects are both timely and important in the every day practice of the primary care physician.

The Female Urethral Syndrome and Urethritis and Prostatitis in the Male

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Two common urological problems frequently encountered by the primary care physician are the female urethral syndrome and urethritis in the male. Although I will touch on chronic prostatitis in this discussion, I question whether it is anything but a relatively uncommon entity.

Female Urethral Syndrome

While the female urethral syndrome is neither life-threatening nor even serious, it causes great discomfort to the patient and is probably the most common genitourinary (GU) complaint bringing women to the primary care physician. Combined with cystitis it may account for as many as two thirds of the outpatient visits to the urologist, at least in my experience.

The symptoms of the syndrome are:

1. Frequency of voiding with or without burning,
2. Discomfort in the region of the urethra,
3. Pressure low in the pelvis,
4. Urgency and/or nocturia, and
5. Terminal dysuria.

By far the most common symptom is the frequency of urination with or without burning, and it may occur with any or all of the other symptoms.

Anatomically, the female urethra is homologous to the prostatic urethra, proximal to the ejaculatory duct. It is about 3 to 5 cm in length and is surrounded by suburethral and paraurethral glands, the ducts of which empty for the most part into the distal portion of the urethra near the urethral meatus. Normally, the urethra is colonized by a certain number of introital bacteria, usually limited to the distal portion of the urethra, and when the bacteria are limited to this area, there are usually no symptoms. However, when bacterial colonization extends to the proximal suburethral and paraurethral glands, the symptoms of the female urethral syndrome occur.

Diagnosis

When a patient comes to the physician with symptoms of the female urethral syndrome, diagnostic evaluation should be based on the following procedures:

1. *Urinalysis and urine cultures.* The findings in a patient with one or more symptoms will usually show a modest pyuria of 15 to 20 white cells per high power field. Culturing the urine—aerobic, anaerobic and, in selected cases, acid fast—is imperative because, unless negative cultures, which are a feature of the syndrome, are established, the patient's symptoms may be confused with bacterial cystitis.

2. *Urograms and cystograms.* When symptoms persist, an excretory urogram should be done. Usually the results will be normal, but occasionally there will be a patient with a stone in the distal ureter that can produce the symptoms of urgency and frequency. While the patient's bladder is full of the contrast medium that has come down from the kidneys, she should also be asked to void under x-ray control. This will often demonstrate whether or not a urethral

This is an edited transcript of the lecture delivered by Dr. Rous at the 49th Annual McGuire Lecture Series, December 3, 1977, at the Medical College of Virginia, Richmond, Virginia.

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diverticulum exists, and the presence of one can sometimes mimic the symptoms of the syndrome. If a urethral diverticulum is suspected, the patient should additionally undergo a retrograde urethrogram.

3. *Vaginal examination.* Not only is a vaginal examination important to check for gynecological pathology but it is useful specifically to detect the presence of a urethral diverticulum. This is a readily detectable mass which varies in size from a pea to a golf ball and is found in the midline on the anterior vaginal wall. It may or may not have stones in it.

4. *Cystoscopy and urethroscopy.* These procedures establish conclusively the diagnosis of the female urethral syndrome. In appearance the urethra will look very similar to a red cobblestone road and this is called a granular urethritis; the pathology sometimes extends up into the trigone and is then called a granular urethro-trigonitis.

Treatment

There are several ways in which to treat the female urethral syndrome. Systemic antimicrobial therapy is usually unsuccessful because the antimicrobials are not able to penetrate the suburethral and paraurethral glands in sufficient quantities. However, with some of these patients I have used Furacin* Urethral Inserts® which put the antimicrobial agent in direct proximity to the suburethral and paraurethral ducts. It is well worth the time spent to show these patients how to use the inserts. There are two methods I have found helpful. One method is to put a mirror on a stool, have the woman put one leg up on it, and looking into the mirror, guide the suppository into her urethra. She should then lie down and put her legs tightly together for 20 to 30 minutes. The other method is best for supple individuals who can sit upright, put a mirror between their legs, and then guide the suppository into the urethra.

Another means of treating the syndrome is by urethral dilatation in selected patients. The rationale behind this is that the procedure opens the paraurethral and suburethral ducts and promotes drainage from the underlying glands as well as stretches the urethral meatus to promote a more rapid flow of urine. This procedure is best used in combination with the urethral inserts.

Finally, there are a number of surgical methods for treating this condition such as unroofing the suburethral and paraurethral ducts and fulgurating them.

* Unfortunately, Furacin inserts have just been removed from the market. An acceptable substitute is Protargol Urethral suppositories (17%) which can be made-to-order in pharmacies.

Urethritis and Prostatitis in the Male

Urethritis is probably the single most common urological problem bringing men to the primary care physician or the urologist. It is defined as inflammation, with or without infection, of any portion of the urethra and is broken down into specific and nonspecific varieties.

Urethritis is very much more common than chronic prostatitis or prostatostasis with which it is often confused. This confusion between urethritis and prostatitis is not surprising in view of the anatomical relationship between the urethra and the prostate. The numerous ducts connecting the posterior urethra with the underlying prostate gland allow for a great similarity of symptoms of infection or inflammation between the two.

Causes

The etiology of urethritis is almost invariably that of sexual contact. It can be by conventional or anal intercourse, or, often, fellatio. Since it is well known that bacteria in the mouth can be more virulent than bacteria in the vagina or the anus, fellatio as a source of urethritis should always be kept in mind and the patient should be asked about the nature of his sexual contact.

There are a number of bacterial causes of urethritis. Specific urethritis is caused by the gonococcus organism. It affects the anterior portion of the urethra initially but will usually involve the posterior portion if left untreated. Mycoplasma, Trichomonas vaginalis, and Candida are causes of nonspecific urethritis, as are viruses, gram-positive organisms, and some others. Bacterial infections usually affect the posterior portion of the urethra.

The most common nonbacterial cause of inflammation is urethral "stripping." The affected patient does this every time he urinates and as many times in between voidings as privacy will allow. He takes out his penis, milks it out proximal to distal, and turns it up to look at the meatus to see if there is still some discharge. The urethral mucosa is almost as sensitive as the conjunctiva of the eye and if a urethra is traumatized by this vigorous stripping, a minimal discharge will often be produced, particularly in a urethra that has had recent infection in it. It is there-

fore very important to discourage patients from this practice.

Another much less common cause of urethritis is persistently alkaline urine. A certain number of patients seem to have urine that has a ph of 6.8 or higher. It may be that such patients consume large quantities of citrus juice which is metabolized to bicarbonate and produces an alkaline urine, or it may be for other reasons. In any case, during the act of voiding, the calcium phosphate crystals, which are precipitated out of solution because of the high ph, act as irritants to the urethra and continue to irritate it until the next voiding.

Symptoms

The symptoms of anterior gonococcal urethritis include a copious urethral discharge that ranges from green to yellow in color; it may at times be whitish. It is usually accompanied by burning on voiding and a feeling of discomfort in the penile or anterior urethra. Rarely, there may be minimal or no urethral discharge. The symptoms of posterior or nonspecific urethritis are virtually the same as chronic prostatitis or prostatostasis. They consist of an itching or burning "inside" or at the base of the penis; discomfort or itching in the urethra on voiding; and most common, a minimal, clear mucoid urethral discharge on arising in the morning, or a 2 to 3 cm brownish or yellowish stain inside the patient's shorts that is seen at night.

Diagnosis and Treatment

The technique of three-glass urine collection in conjunction with prostatic massage and/or the post-prostatic massage fourth-glass specimen is used for determining the anatomical source of urethral infection and more specifically for separating chronic prostatitis from nonspecific urethritis. A three-glass urine specimen is first obtained, then the patient is asked to hold his urethra tightly shut while the physician massages the prostate vigorously. After the prostatic massage, the patient is asked to release his urethra and a few drops of prostatic secretions will usually come out into the culture tube or onto a slide. If no secretions are obtained, the patient should void a few cc of urine into a fourth glass and this will contain the prostatic secretions. The specimens in the first, second, and third glasses are then cultured as are the prostatic secretions or the fourth-glass specimen. If the first and/or third-glass urine has more bacteria colonies than the prostatic secretions or the post-prostatic massage fourth-glass specimen, the infection is in the urethra. If the opposite is true, the infection is in the prostate. Bacterial colony counts from the urethra and prostate range from several hundred per cc up to a few thousand per cc. When these studies are carried out, it will be seen that true bacterial infection of the prostate gland is uncommon. There is, however, a condition called prostatostasis which occurs more frequently, but not, in my opinion, nearly as frequently as posterior urethritis. Prostatostasis can develop when a man goes from feast to famine sexually. The prostatic fluid is made continuously in abundant supply and when there is no ejaculation, the prostate gland enlarges and produces the symptoms already noted in conjunction with nonspecific posterior urethritis. The patient should be encouraged to masturbate frequently, and/or to have intercourse to relieve this condition. Both work equally well as does prostatic massage, although the latter is the least favored therapy.

For specific, or gonococcal, urethritis, a culture can be obtained from the discharge and, in the rare patient without discharge, from swabbing the distal urethra. The culture has to be made under increased CO_2 tension on a Thayer-Martin medium. It is best to do a smear and see gram-negative intracellular diplococci for the provisional diagnosis, but the culture should confirm it finally. The treatment of choice for gonococcal urethritis is aqueous procaine penicillin G with probenecid; alternative treatment is ampicillin with probenecid. For patients who are allergic to the penicillin group of drugs, spectinomycin and tetracycline are acceptable alternatives.

The mycoplasma organisms found with some cases of nonspecific urethritis can be confusing because these organisms have been reported in asymptomatic as well as symptomatic individuals. The organisms are cultured with a urethral swab or using the urine sediment, and the mycoplasma organisms are identified morphologically and by specific biochemical and bacteriologic tests. Patients with this infection are treated with one of the tetracycline group of drugs, although probably no more than 60% to 70% are cured by the medication.

Trichomonas vaginalis is not, in my experience, a common cause of urethritis in the male. However, it should be considered a possibility particularly if the consort has a trichomonas infection. The organism is seen either on a wet mount of the urine specimen or in urethral discharge. This infection is best treated with metronidazole (Flagyl®).

For those patients with inflammatory and non-organism causes of urethritis, treatment is relatively simple. The rare individuals with persistently alkaline urine can be successfully treated with ascorbic acid for two to three days until the symptoms disappear. However, care should be taken not to use this means on patients with known uric acid or cystine lithiasis. Inflammation due to urethral stripping can be cured by counseling the patient to refrain from this activity.

The most important point in treating patients with nonspecific urethritis is to reassure them that these infections are self-limited, not serious, and will not lead to impotency, sterility, prostatic hyperplasia, or prostatic cancer.

Appropriate Antibiotic Therapy for Urinary Tract Infections

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It was stated years ago that physicians pour medicines about which they know little, for diseases about which they know less, into human beings about whom they know nothing.[1] Although as a prophet this wag may have overstated the case as it concerns the therapy of urinary tract infections (UTI), the character of contemporary infectious diseases is, in part, due to the use and abuse of anti-infective agents.[2,3] One has only to look at the rising incidence of gram-negative bacteremia and the emergence of multiple antibiotic-resistant organisms over the past several decades to appreciate the impact physicians have made with these agents.[4,5] Despite the drawbacks, the benefits resulting from the use of antibiotics far outweigh the deleterious effects, a fact perhaps realized most vividly by physicians whose careers reach back to the pre-chemotherapeutic era. The enthusiasm for antibiotics makes them one of the most prescribed groups of drugs in the United States, accounting for 15% to 20% of all new and refill prescriptions.[6] Undoubtedly many of the prescriptions are used to treat persons with UTIs, in light of the fact that UTIs are said to rank second only to upper respiratory infections as the most common infections in the western hemisphere.[7]

Principles of Therapy

Without belaboring the point, how does the physician steer his way through the many antibiotics which are promoted so vigorously by pharmaceutical companies, perhaps in response to the competitive pressures and potential profits of what has become a multi-billion dollar industry? Certain characteristics are desirable in any antibiotic, and it behooves the physician to consider these characteristics when evaluating the potential usefulness of the agent.[8]

1. *Activity.* An agent with bactericidal activity against a wide spectrum of microorganisms, and one that doesn't disturb normal flora or lead to the emergence of resistant organisms should be sought.

2. *Toxicity.* Adverse reactions should be infrequent, and teratogenicity absent.

3. *Pharmacology.* Pharmacologic properties should be such that adequate concentrations of the drug are achieved and maintained near the organism for prolonged periods.

4. *Physicochemical properties.* The drug should be stable (dry or in solution) tolerant of pH changes, and readily absorbable from the gastrointestinal (GI) tract.

5. *Interactions.* The drug should not interact with other therapeutic agents.

6. *Cost.* The agent should be inexpensive and hence available to all who need it.

Of course, no such "magic bullet" exists, and because it doesn't, one should be guided, when treating UTIs, by certain fundamental principles.[9]

1. The presence of a bacterial infection should be established. Symptoms alone are not sufficient evidence for the diagnosis of UTI, as up to 50% of women with dysuria and frequency have sterile urine.[10] The finding of one or more bacteria per oil field in a Gram stain of uncentrifuged urine correlates

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well (over 90%) with the presence of 100,000 organisms or more per ml of urine. Numbers of this magnitude usually indicate true infection (significant bacteriuria) and not procurement contamination with gram-negative enteric bacilli. In an asymptomatic person, three consecutive daily urine cultures obtained by the clean-voided method and each containing 100,000 organisms per ml of the same bacterium indicate that the patient has at least a 95% chance of having a UTI.[11] In a symptomatic person, bacteria seen on microscopic examination and one urine culture containing 100,000 organisms or more per ml carries the same 95% probability of true infection.

2. The elimination of bacteriuria requires the use of antibiotics which are active against the common urinary pathogens and which achieve inhibitory concentrations in the *urine,* not the serum. Disappearance of bacteriuria correlates well with the sensitivity of the organism to achievable urinary levels.[12,13] This serves to underline the obvious discrepancies sometimes seen between antibiotic sensitivities in vitro and the eradication of bacteriuria.

3. Underlying urinary tract abnormalities, particularly obstructive or neurogenic lesions, should be corrected if possible; obstruction from whatever cause not only has a compromising effect on renal function but it also practically eliminates the likelihood of successful antibiotic therapy.

4. The hallmark for the eradication of infection is the absence of bacteriuria following the cessation of therapy. Symptomatic improvement is a poor indicator of successful therapy because symptoms may improve with only the slightest suppression of bacteriuria. In addition, while bacteriuria may disappear during therapy, recurrence of the original organism (see below) is common and can be detected only by obtaining cultures after the completion of therapy.

5. Prolonged follow-up is required to insure permanent cure of the UTI. Recurrence of an initially symptomatic and apparently successfully treated infection may be asymptomatic, and constant vigilance by the physician can pay dividends in reduced morbidity from UTIs. This is done usually by obtaining periodic urine cultures (Figure). A culture obtained between 48 to 72 hours after the initiation of therapy should be sterile. If it is not, then the therapy should be recognized as a failure and the patient should be treated with an appropriate antibiotic chosen on the basis of sensitivity tests. If the culture is negative, additional cultures should be obtained one to two weeks following completion of therapy, monthly for three months, then at three-month intervals for one to 1½ years. The patient should be considered cured if there is no recurrence during the period of observation.

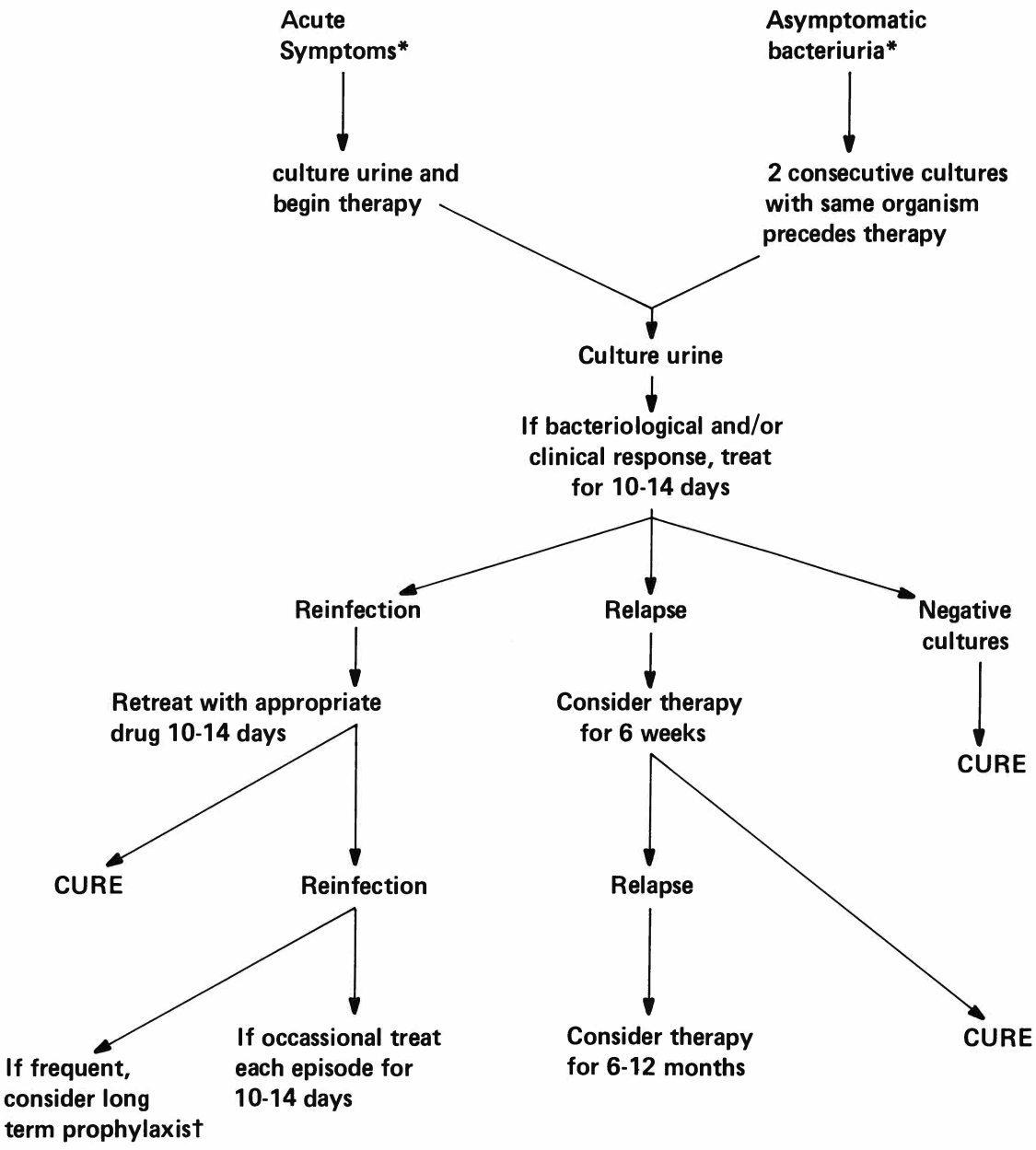
Therapeutic Agents

The goal of therapy for UTIs is the elimination of bacteriuria and the most effective way of achieving this is with antibiotic therapy. The antimicrobial agents frequently used to treat UTIs are listed in the Table. Most share the common characteristics of being active against the majority of common urinary tract pathogens and being excreted at high concentrations into the urine.

Sulfonamides. The sulfonamides were the first group of agents shown to be consistently useful for treating UTIs. Many effective sulfonamides are available, but the short-acting, oral nonabsorbable drugs, such as sulfisoxazole and sulfamethoxazole, are generally recommended. These agents achieve high urinary concentrations and are soluble at an acid pH. Toxicity is relatively infrequent. They are especially effective against *Escherichia coli* and *Proteus mirabilis* but generally are useful only for the first few episodes of infection because of the emergence of resistant bacteria. Although sulfonamides offer no real advantage over other agents, they are inexpensive (see Table) and hence available to most patients. Sulfonamides should not be used in persons with glucose-6-phosphate dehydrogenase deficiency, in pregnant women near term, and in newborn infants because of the danger of producing kernicterus in the neonate.

Penicillins. Among the penicillins, ampicillin remains the drug of choice for UTIs. It is effective against many gram-positive and gram-negative organisms and reaches adequate levels in the renal medulla. Ampicillin is the preferred agent for pregnant women and newborns, and is especially useful in treating UTIs due to susceptible organisms in patients with renal insufficiency. There is no evidence to indicate that ampicillin is superior to sulfonamides in the management of uncomplicated UTIs (see below), just as there is no evidence to indicate that newer penicillin derivatives, such as amoxicillin, are superior to ampicillin. Diarrhea is frequent and rashes occur in 5% to 10% of patients.[1]

Tetracyclines. The tetracyclines have been relegated to a less prominent role in the treatment of UTIs. The best urinary levels are achieved with tetracycline and oxytetracycline.[11] Newer derivatives,



* Radiographic evaluation should be obtained on all children, all men, young women, and probably in all patients with bacteremia

† Not in asymptomatic elderly without obstruction

Figure—Diagrammatic approach to the management of urinary tract infections.

TABLE
Antibiotics Useful in the Therapy of Urinary Tract Infections in Adults

Antibiotic	Tradename(s)	Dosage[a]	Cost in dollars (dose)[b]
Oral:			
Sulfisoxazole	Gantrisin	0.5-1.0 gm q 4-6 h	.04 (0.5 gm)
Sulfamethoxazole	Gantanol	1.0 gm q 8-12 h	.08 (0.5 gm)
Penicillin G	Many	0.4-0.8 × $10^6\mu$ q 6 h	.01 (0.2 × $10^6\mu$)
Ampicillin	Many	0.5-1.0 gm q 6 h	.09 (0.5 gm)
Amoxicillin	Larotid, Amoxil	0.25-0.5 gm q 8 h	.30 (0.5 gm)
Tetracycline	Many	0.25-0.5 gm q 6 h	.03 (0.5 gm)
Cephradine	Velosef, Anspor	0.5 gm q 6 h	.56 (0.5 gm)
Cephalexin	Keflex	0.5 gm q 6 h	.52 (0.5 gm)
Nitrofurantoin	Furadantin	0.05-0.1 gm q 6 h	.01 (0.05 gm)
	Macrodantin	0.05-0.1 gm q 6 h	.15 (0.05 gm)
Nalidixic acid	NegGram	0:5-1.0 gm q 6 h	.12 (0.5 gm)
Trimethoprim-Sulfamethoxazole	Bactrim, Septra	2 tablets q 12 h	.21 (per tablet)
Parenteral:			
Ampicillin	Many	0.5-2 gm q 4-6 h	1.11 (1 gm)
Carbenicillin	Geopen, Pyopen	1-5 gm q 4-6 h	2.20 (1 gm)
Cephalothin	Keflin	0.5-2 gm q 4-6 h	2.75 (1 gm)
Cefazolin	Ancef, Kefzol	0.5-1.5 gm q 6-8 h	5.05 (1 gm)
Gentamicin	Garamycin	1-1.7 mg/kg q 8 h	5.05 (per 80 mg vial)
Amikacin	Amikin	5 mg/kg q 8 h	4.93 (per 100 mg)

[a] Usual average or range of dosages in patients with normal renal function.
[b] Cost to pharmacist based on listings in the American Druggist Blue Book (Hearst Corp. Publishers), October 1977.

such as doxycycline and minocycline, although approved for use in UTIs, have significant extrarenal routes of excretion, so that the low urinary concentration achieved makes them less desirable for therapy.[14] Generic tetracycline is inexpensive (see Table). Resistance to tetracycline emerges rapidly during therapy; however, tetracyclines are probably as effective as the sulfonamides and ampicillin for treating uncomplicated UTIs (see below). Fulminant hepatitis has been induced in those receiving large parenteral doses of tetracycline (greater than 2 gm per day), and irreversible discoloration and maldevelopment of permanent teeth is a danger in children under age 8 who receive these drugs[14]; however, GI signs and symptoms are the most common side effects of therapy.[14]

Cephalosporins. The instances where cephalosporin antibiotics should be used are difficult to define, but they are indicated possibly for treating gram-positive coccal infections (except those caused by enterococci and methicillin-resistant staphylococci) in patients allergic to penicillin. These agents are useful in treating infections due to *Klebsiella pneumoniae* and antibiotic strains of *E coli, P mirabilis,* and other gram-negative bacilli. The use of cephalosporin antibiotics for central nervous system infections is contraindicated.[15] Although most of these drugs achieve good urinary levels, and are therefore effective agents for the therapy of UTIs, most are expensive (see Table) and should not be used when cheaper, equally effective drugs are available. The two most important oral agents, cephalexin and cephradine, are similar and can be used interchangeably.[16] Up to 5% of patients develop allergic reactions such as rash, fever, and, rarely, anaphylaxis[17]; 5% to 15% of penicillin-allergic patients will manifest allergy to the cephalosporins.[18]

Aminoglycosides. The aminoglycoside antibiotics are parenterally administered agents useful against a wide variety of gram-negative organisms. These drugs have the potential for causing significant oto- and nephrotoxicity[19] and should therefore be reserved for therapy of hospitalized patients with moderate to severe UTIs caused by organisms resistant to less toxic agents. Dosage should be adjusted for those with renal insufficiency; such alterations in dosage can be achieved by any of several published programs.[20-22] Gentamicin and amikacin are two commonly used aminoglycoside antibiotics which differ little in the incidence of toxicity.[23] However, amikacin is resistant to many more of the aminoglycoside-inactivating enzymes than gentamicin,[24] therefore its

greatest utility at present is in the therapy of UTIs caused by gentamicin-resistant organisms.

Nitrofurantoin. This drug is available in crystalline and macrocrystalline forms. The latter compound is absorbed from the GI tract and excreted more slowly than the crystalline form and allegedly causes less GI upset. Nitrofurantoin achieves high urine concentrations and is more active at an acid pH. It is effective against gram-positive and gram-negative organisms except *Pseudomonas* sp, some *Enterobacter* sp, *Serratia marcescens,* and indole-positive *Proteus.* The drug may be useful for lower *and* upper UTI.[11] Nitrofurantoin is contraindicated for use in patients with renal failure because little of the drug is found in the urine and because the incidence of irreversible peripheral neuropathy is increased under these circumstances.[11] Small amounts of this orally administered drug is found in the feces, which probably accounts for the relatively low incidence of resistant enteric organisms emerging during and after therapy. Thus, nitrofurantoin would appear to be a useful therapeutic and prophylactic agent for patients with recurrent UTIs[25] (see below).

Nalidixic acid. Nalidixic acid and its cogener, oxolinic acid, are oral antimicrobials which have virtually the same antibacterial spectrum, including most gram-negative urinary tract pathogens except for *Pseudomonas* sp, *Serratia marcescens* and indole-positive *Proteus.* Resistance develops rapidly and recurrence of infection with resistant organisms is not uncommon. Blood and, presumably, tissue levels are low. These agents are moderately expensive (see Table) and should be used as alternative therapy to other oral agents such as the sulfonamides and ampicillin.

Methenamine salts. Methenamine salts have a limited role in the therapy of UTIs. These agents are effective against most gram-negative organisms in vitro, but require an acid medium (pH of 6 or less) for release from methenamine of the bactericidal agent formaldehyde; tissue levels are low to absent. The main uses are for suppression of bacteriuria or prophylaxis between episodes of infection. The efficacy of methenamine salts in patients with chronic indwelling bladder catheters recently has been questioned.[26]

Trimethoprim-sulfamethoxazole (TMP-SMX). TMP-SMX is a fixed combination of drugs which acts additively or synergistically against a wide range of gram-positive (including enterococci) and gram-negative organisms, except *Pseudomonas* and *Alcaligenes* sp. The list of indications for TMP-SMX continues to grow and presently includes infections due to *Shigella* sp, *Salmonella typhi,* ampicillin-resistant *Haemophilus influenzae,* and *Pneumocystis carinii,* and diseases such as acute exacerbations of chronic bronchitis, acute otitis media, and gonococcal urethritis.[27] Its most practical applications are the treatment of and prophylaxis for recurrent UTIs caused by susceptible organisms.[25] Emergence of resistant organisms in the fecal flora has not been a major problem and because trimethoprim penetrates prostatic tissue, TMP-SMX is probably the drug of choice for recurrent or chronic prostatic infection.[28] The adverse effects of TMP-SMX represent the sum of reactions to trimethoprim (folate deficiency syndromes and possible teratogenic effects) and sulfamethoxazole (see above). The drug may be used in mild-to-moderate renal failure.[29]

Urinary Tract Infections

Urinary tract infections represent a broad group of clinical entities with bacteriuria as the common thread. Many classifications are possible, but those which include not only the type of infection but also the site of involvement allow for the most accurate assessment of antibiotic therapy. Although the site of infection in many instances is unknown, enough evidence is available to analyze antibiotic therapy in the following clinical categories of UTI: acute uncomplicated UTI; recurrent UTI; complicated UTI; asymptomatic bacteriuria; and catheter-related UTI.

Acute uncomplicated UTIs usually represent the first or second infection in young sexually active women without underlying urinary tract abnormalities, and are caused by antibiotic enteric bacilli (most commonly *E coli*) which emanate from antibiotic fecal flora. This type of infection responds well to practically all commonly used oral antibiotics, but because they are effective, inexpensive, and well-tolerated, the oral, nonabsorbable sulfonamides remain the therapy of choice. Treatment is usually given for 7 to 14 days. Longer courses of therapy are usually not necessary. Many alternative agents exist (see Table), but none have proven superior to the sulfonamides and most are more expensive. In the absence of an obstructive or neurogenic lesion, the urine should be sterile between 48 to 72 hours (Figure). If bacteriuria persists, therapy should be guided by the results of sensitivity testing.

Some patients with acute symptomatic infection

fail to respond to the initial antibiotic therapy or suffer *recurrence* of the infection. The recurrence may be a *relapse* of the initial infection with the same pathogen, suggesting a parenchymal focus of infection in the kidney or prostate or may be caused by different organisms, so-called *reinfections*. The source for reinfection is almost always the bowel flora. Approximately 80% of recurrences are reinfections and most are limited to the bladder. Antibiotic sensitivity testing assumes added importance in this situation because the pathogen will probably not be sensitive to sulfonamides if used initially. Ampicillin, tetracyclines, cephalosporins, and TMP-SMX are preferred and are given orally for 10 to 14 days. Each course of therapy will result in a 20% to 25% long-term cure rate.[11] Those having a second or third episode of infection should probably be evaluated urologically or radiographically (see Figure). Those with occasional recurrences (three or less per year) can be treated like acute uncomplicated infection. With more frequent recurrences, especially in the absence of urological abnormalities, the precise duration of therapy is not well established. Closely spaced recurrences are likely to be due to relapse and some have suggested treating true relapses for six weeks to one year.[10] Most authorities suggest six weeks of therapy with the realization that the optimal duration of therapy for this group of patients is controversial. An alternative approach consists of intensive initial treatment for 10 to 14 days, followed by daily low-dose nitrofurantoin (100 mg) or TMP-SMX (one half to one tablet). Prophylaxis should be continued for up to six months, then discontinued, and the patient observed.

Acute complicated UTIs are a third category of infections; they are almost always associated with underlying genitourinary tract or neurological disorders. Isolated organisms tend to be multiply drug-resistant. Permanent eradication of the bacteriuria is unlikely, but the goal is to control symptoms. Initial therapy ideally should be based on sensitivity studies, but pending culture results, an aminoglycoside antibiotic, that is, gentamicin, is an obvious choice. Therapy for 10 to 14 days is usually adequate. Emergence of resistant organisms in this setting is a probable event.

Asymptomatic bacteriuria represents a large group of UTIs with an incidence ranging from 1.2% in pre-school girls to over 15% in women over age 60.[11] Certain groups are known to be at risk for acquiring significant asymptomatic bacteriuria and subsequent symptomatic UTI. Included are pregnant women in the first trimester, women with diabetes, preschool- and school-age girls, and those with a previous history of urinary tract instrumentation. About 5% of pregnant women will have asymptomatic bacteriuria at the first prenatal visit and 20% to 40% of these will develop acute pyelonephritis.[9] Assuming that acute renal infection in the mother contributes to prematurity and fetal mortality, treatment should be initiated. The preferred agents are the penicillins, cephalosporins, nitrofurantoin, and short-acting sulfonamides (first trimester only). Treatment will eliminate bacteriuria in 80% of these patients. Some will have recurrence and for these patients, nightly prophylaxis through term with nitrofurantoin is recommended. The necessity to treat other groups of patients with asymptomatic bacteriuria is less certain, especially elderly women in whom bacteriuria tends to be recurrent even in the absence of underlying disease. Available evidence indicates that, in adults, progressive renal damage due to UTI is an uncommon occurrence in the absence of obstruction.[10] Several attempts at eradication seem worthwhile. If bacteriuria recurs, genitourinary evaluation is warranted. If no abnormalities are found, no further therapy is necessary in the elderly.

Catheter-related infections are the most common hospital-acquired infections and the most frequent causes of gram-negative bacteremia.[4,11] Patients acquiring bacteriuria with short-term closed drainage should be treated with an effective antibiotic for 7 to 10 days after the catheter is removed. Long-term drainage represents a different problem. Patients on long-term drainage are continuously infected but usually do well. Antibiotics will not clear bacteriuria permanently while the catheter remains in place. Therapy is reserved for acute episodes of infection.

A scheme for the management of patients with bacteriuria is given in the accompanying Figure. It is meant to serve only as a guide for the practicing physician and should be modified in light of future improvements in the diagnosis, localization, and therapy of UTIs. Optimal therapy awaits a more precise classification of UTIs, the end result of which will be a reduction in morbidity and mortality from UTIs, and a significant decrease in the cost of related health care.

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Intrascrotal Masses: Differentiation, Diagnosis, and Management

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The differentiation of scrotal masses consists of combining the basic principles of physical examination, particularly inspection and palpation, with an exact knowledge of the anatomy and pathology of the scrotum and its contents. The correct diagnosis of each of the nine common scrotal masses—epididymitis, epididymo-orchitis, torsion of the spermatic cord, hydrocele, scrotal hernia, spermatocele, varicocele, hematocele, and cancer of the testis—determines the treatment to be used, which can range from masterly inactivity to surgical intervention. Obviously, experience plays its part and the opportunity to examine scrotal masses should be an integral part of the education of the primary physician.

This is an abstract of the lecture given by Dr. Rous at the 49th Annual McGuire Lecture Series, December 3, 1977, at the Medical College of Virginia, Richmond, Virginia.

A limited supply of booklets by Dr. Stephen N. Rous entitled, "Intra-Scrotal Problems with Particular Reference to Palpatory Findings," may be obtained from him, as long as they remain available, through the Department of Urology, Medical University of South Carolina, Charleston, SC 29403.

Common Pediatric Problems: Hypospadias, Enuresis, and Circumcision

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Three topics of common pediatric interest from the urologist's viewpoint are congenital hypospadias, persistent enuresis, and complications of elective circumcision. None of these are usually life-threatening in severity, yet each problem can be of profound psychological importance and play an extremely important role in the child's subsequent development.

The least common of the three is a malformation or incomplete formation of the male urethra and the associated deformity of the foreskin and penile shaft known as hypospadias. This condition results from incomplete closure of the urethra in utero. Since the urethra normally begins closing from the proximal end of the penile shaft and progresses distally to the glans, it is possible for the hypospadiac meatus to be positioned at any location from the perineum to the coronal sulcus. The timing of the arrest of the urethral closure will determine the location of the meatus and the length of the deficient distal urethra. Since the portion of the urethra which is not closed is represented by fibrous tissue or what was destined to be normal corpus spongiosum, this material is nonelastic and is represented by a fibrous band or tract. When erection occurs, this tissue pulls down on the penile shaft and produces the curvature of the penis or ventral chordee seen in classical hypospadias. The urethral closure is also responsible for the formation of the normal prepuce. When hypospadias occurs, the foreskin is incomplete ventrally, producing the typical "dorsal hood" of preputial tissue seen in this condition.

Over the years, numerous types of surgery have been recommended to correct this malady. Often these procedures were only partially successful, and individual surgeons developed their own modifications of previously described techniques. A very effective method was used about 200 BC by the Greeks, Helidous and Antius. They simply guillotined the distal end of the penis at the level of the meatus. In this maneuver, all three deformities were corrected; the curvature was gone, the dorsal hood excised, and the meatus was now at the end of the penis. The stump end of the penis was then cauterized with a red-hot iron which provided hemostasis and produced a swollen, knotty stub at the end of the penis which occasionally resembled a glans penis. There were also very few readmissions or requests for repeat surgery.

Surgical techniques improved over the centuries. In 1842, one of the first successful, planned hypospadias repairs was performed by Dr. John Peter Mettauer in the western part of Virginia. With present-day techniques it is possible to completely repair even the most severe degree of hypospadias and, when healing is complete, to have a relatively normal-appearing penis capable of normal micturition and sexual function.

While the multitude of surgical repairs will not be individually discussed, most severe degrees of hypospadias require corrective surgery performed in stages. This often results in a child returning to the

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operating room at regular intervals over a period of several years. This is undesirable from a financial as well as a psychological standpoint. Fortunately, in the mid-1950s, single-stage repairs became possible; this not only decreased the psychological stresses on the patient and family, but also produced excellent cosmetic results. The tube graft repair for hypospadias was popularized by Drs. Devine and Horton in Norfolk, Virginia. While the original technique has been altered somewhat, the basic procedure is sound and continues to produce excellent results in the hands of many surgeons throughout the world. In the late 1960s, the single-stage "flap" procedure was devised by Dr. Norman Hodgson which added another useful tool to the urologist's armamentarium.

These new methods have changed our concept of what is considered a satisfactory repair. In 1950, Dr. Campbell's textbook, *Urology,* stated that if the hypospadias were mild and the meatus were located in the distal part of the penile shaft, no attempt should be made to correct the condition. If the patient had "free urination and adequate insemination," any further surgical repair was "meddlesome"; however, today there is concern about the cosmetic appearance as well as the functional capabilities of the penis. If the chordee is mild and the meatus located distally, it may still be desirable to correct these conditions and position a new meatus on the tip of the glans penis. This is now possible, using one of the new single-stage procedures; however, since both types of repair require the use of excess skin which ideally can be taken from the foreskin or dorsal hood, it is extremely important not to circumsize the child. If there is any question about the possibility of subsequent surgical correction at the time of birth, circumcision should be postponed.

Enuresis

The second pediatric problem the urologist is often asked to evaluate is far more common than hypospadias. This is the problem of the persistent bed-wetter. This problem is not unique to our country, but occurs throughout the world. It is interesting, however, to note that the frequency differs greatly from one country to another. For example, in the United States there is an incidence of enuresis at age 5 of about 15% to 20%, whereas in Brazil the incidence in this age group is close to 2%. This suggests that social and environmental factors contribute to enuresis. With increasing age, enuresis generally becomes less common so that in our country by age 10, only 5% of the children are enuretic and by age 15, only 1%. The reported incidence of 2% enuresis in military recruits must be viewed carefully as the individual may be influenced by the fact that bed-wetting is one of the criteria for military rejection. On the basis of these statistics, it is valid for the family physician to recommend to the family that treatment for enuresis is not always necessary and if given enough time the bladder will "mature and the child will outgrow his or her bed-wetting."

Until the age of 3 years, enuresis or daytime wetting is physiological and probably the result of incomplete myelinization of the innervation. The age of 3 years is purely an arbitrary cutoff point, but most authorities agree that beyond this point, enuresis should be considered to be either functional or organic. The majority of these enuretic children will demonstrate a functionally decreased bladder capacity; however, under general anesthesia the bladder volumes are within normal limits. In general, if the wetting occurs only at night and there are no other urologic symptoms, little is to be gained by doing an extensive urologic evaluation. This impression is borne out by the study of Dr. Tony Middleton of Salt Lake City who studied the results of 216 enuretic children who were completely evaluated and had only enuresis. He concluded that the likelihood of identifying any major urologic abnormality was nil, although, if there were other symptoms or findings such as urinary tract infection, diurnal enuresis, or difficulty with urination, base line urologic evaluation was helpful. According to this study, approximately 10% of the children required some type of surgical repair.

It is interesting to note that many of these functional enuretic children came from a family in which other members were enuretic. If both the mother and father had enuresis, there was an 80% chance that one of their children would be enuretic. Also, if the mother or father developed their control at age 10, then it was quite likely that their child would stop wetting the bed at about the same age. Also, an identical twin would be more likely to have enuresis than a dizygotic twin.

There is a vast spectrum of recommendations concerning the treatment for essential enuresis; however, most measures fall into one of three main categories.

1. *Bladder training maneuvers and fluid restriction:* Effort is directed to keep records of voiding times and the volumes passed with each voiding. The

patient is aroused during the middle of the night and required to empty his bladder in order to keep the bladder as empty as possible. Also, the youngster is not allowed to drink any additional liquids, following a set time of day such as after the evening meal or before bedtime.

2. *Drug therapy:* Antispasmodics such as belladonna or propantheline bromide (Pro-Banthine) are effectively used to increase functional bladder capacity. Other agents such as the tricyclic antidepressives are prescribed for their altered sleep patterns and their direct action upon bladder musculature. In the group of antidepressive agents, the most popular one at the present time is imipramine (Tofranil).

3. *Waking devices:* The sleeping youngster is aroused from deep sleep by activation of some electrical device when urine leakage occurs. The urine causes electrical contact to occur and completes a circuit which in turn sets an alarm, electrical stimuli, or flashing lights. The waking devices are said to be very popular in England and are reported to be quite effective in terminating enuresis. In the United States and Canada more emphasis has been placed upon the bladder training program and drug therapy. Both techniques are reported to be effective in 65% to 80% of enuretic patients.

Circumcision

Today, circumcision is the second most frequently performed operation on the male. While it is often performed for religious purposes and less often for strict urologic indications, the largest number of circumcisions are done for hygiene or simply as a routine procedure. Dr. Julien Ansell at the University of Washington in Seattle evaluated all the circumcisions performed in the University Hospital during a 10-year period of time. It is of note that of 5,882 male births, 5,521 or 94% were circumsized before they left the hospital. Of the remaining 361 male infants who were not circumsized, 22 were denied the operation because of some degree of hypospadias. This correlates well with the reported incidence of hypospadias of about 1 per 267 male births.

About half the circumcisions were done with the Gomco® clamp and the remaining half performed by the Plastibell® apparatus. The overall complication rate from routine elective circumcision was slightly in excess of 1%. This was most often due to hemorrhage occurring equally often with the Gomco® clamp and the Plastibell®. Most bleeding problems were easily managed by application of an adrenaline (1-1,000) soaked sponge applied to the area of bleeding (25 out of 59 patients were successfully handled by this measure). The others required placement of a suture or ligature to provide hemostasis. Infections were uncommon, occurring in less than 0.4% of patients and were generally managed with local measures such as cleaning and soaks. Only four patients, all of whom had Plastibell® circumcisions, required systemic antibiotics. Nine patients had wound-healing problems such as dehiscence and denudation of the penile shaft skin. Eight of these patients had Gomco® clamps used for the circumcision. In general, it was concluded that circumcisions can be performed routinely with a low complication rate and those complications that do occur are relatively easy to manage. The type of clamp used for the operation does not appear to make a significant difference.

Management of Carcinoma of the Kidney and Urinary Bladder

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Carcinoma of the Kidney

Tumors of the upper urinary tract constitute 1% to 2% of all cancers, and each year 11,000 new cases are diagnosed in the United States. Approximately half of these patients have metastatic disease at the time of diagnosis. Hypernephroma, or renal cell carcinoma, was first described in 1863 by Grawitz. These tumors arise from tubular epithelial cells and are correctly termed renal cell carcinoma or renal cell adenocarcinoma. There is evidence that further identifies the cell of origin as being from the proximal convoluted tubular epithelium. There does not appear to be a specific racial or ethnic incidence although it occurs three times more often in men than in women. Few epidemiological studies of this disease have been undertaken, although there is some association between the use of tobacco and an increased incidence of renal cell carcinoma. The classical triad of hematuria, pain, and a palpable mass are late findings with a poor prognosis which occurs in 10% of the patients and usually represents metastatic disease. Forty percent of the patients may have hematuria or other urinary complaints. Local effects of the tumors are hematuria, pain, and a flank mass, but the presenting symptoms may include a varicocele in the male which is produced by direct pressure of the tumor on the spermatic vein or because of stasis caused by an obstructing tumor thrombus in the vena cava. Systemic toxic effects such as hyperpyrexia may be of an intermittent or variable nature. Anemia or abnormal liver chemistries may also be present. Erythrocytosis, hypertension, and hypercalcemia may also be manifest.

Once a renal mass is found, a number of procedures can be followed in order to evaluate the patient before surgery. These include the use of intravenous excretory urography, retrograde pyelography, nephrotomography, renal angiography, and venacavography, along with sonographic examination of renal masses and the evaluation of renal masses by the use of computerized axial tomography.

The staging classification developed by Robeson is probably the most widely accepted: Stage 1—tumor confined within the kidney; stage 2—perirenal fat involvement confined within Gerota fascia; stage 3—a. gross renal vein or inferior vena cava involvement, b. lymphatic involvement, and c. vascular and lymphatic involvement; stage 4—a. adjacent organs other than the adrenal involved, and b. distant metastases. Renal vein involvement without perinephric involvement or lymphatic spread does not seem to alter the prognosis at 5-10 years where lymphatic involvement is an ominous sign.

Treatment

Surgical removal of the tumor for cure is the basic management of the patient with hypernephroma. The single, most significant advance in technique and its influence on survival were pointed out in 1968 by Robeson, who used the combination of early ligation of the renal artery and vein, complete

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removal of the perinephric envelope, and surgical extirpation of the lymphatic field. Caution in handling of the renal vein is important, especially if there is tumor involvement of the veins, as portions of renal vein tumor may break off and cause acute pulmonary embolization.

Preoperative Radiation

Several investigators have advocated the use of preoperative radiation in the management of renal cancer, but random clinical trials to date have not shown that this has improved long-term survival. In certain patients, however, a preoperative course of radiotherapy of 3,000-4,000 rads to the kidney in four weeks has markedly decreased the vascularity of the tumor. There is some evidence that postoperative radiotherapy may have a beneficial effect on survival statistics, especially if there has been extracapsular invasion and tumor has been left behind.

Chemotherapy

The use of chemotherapy in the management of metastatic renal carcinoma has proven particularly disappointing. Good results have been quoted by some investigators with the use of medroxyprogesterone (Provera) 100 mg t.i.d. and a number of other chemotherapeutic agents singly or in combination.

Special Management Problems

Involvement of the renal vein and vena cava are of interest because of the possible use of extracorporal circulation in order to approach the patient with tumor thrombus in the renal vein, the vena cava, and the atrium of the heart.

Carcinoma arising in a solitary kidney provides a real therapeutic dilemma. Procedures such as partial nephrectomy in situ, bench surgery with the removal of the kidney, perfusing the kidney for preservation, surgical excision of the tumor with repair of the kidney and autotransplantation back into the patient, and total extirpation with homotransplantation at a later date have all been used.

Approximately 12% of upper urinary tract malignancies are from renal pelvic tumors. These are often transitional cell carcinomas, but a few are of the squamous cell variety. The diagnosis is usually based on the appearance of a filling defect on intravenous urography or retrograde pyelography. A differential diagnosis from a nonopaque stone or blood clot may be difficult. As these tumors tend to be multiple, the therapy for them is total removal of the kidney and renal pelvis with removal of the entire ureter and a cuff of bladder. For those people who have undergone only partial removal of the ureter, recurrence in the stump of ureter has been high.

Bladder Cancer

Carcinoma of the urinary bladder accounts for 4% to 5% of all new cancers. Approximately 30,000 new cases of bladder cancer are found in the United States each year resulting in over 9,500 deaths. The incidence is three times more prominent in men than in women and four times more common in whites than in non-whites. Age distribution reveals a peak in patients 75-84 years of age, and 80% of these tumors occur after age 50.

The known and suspected causes of bladder cancer are grouped into four categories: 1) Industrial chemicals; 2) metabolites of foodstuffs; 3) tobacco tar; and 4) chronic mechanical irritation and infection.

All but 3% to 4% of bladder tumors originate in the transitional cell epithelium. Transitional cell carcinoma of the bladder occurs in approximately 90% of the patients, with squamous cell carcinoma accounting for 6% to 7% and adenocarcinoma 1% to 2%. Transitional cell carcinomas may be very small and papillary in character but may be multiple, large and sessile tumors; the surface may be intact or ulcerated, crusted, and bleeding. Squamous cell cancer, on the other hand, is usually flat, ulcerated, and sometimes necrotic; adenocarcinoma appears grossly as transitional or squamous and must be differentiated microscopically.

Diagnosis

Painless, gross hematuria is found in 75% to 85% of the patients presenting with carcinoma of the bladder. As the tumor enlarges, other symptoms such as frequency, urgency, dysuria, and decrease in caliber or force of the urinary stream may be present. These symptoms may be secondary to infection of the bladder or may be irritations caused by the tumor. As the tumor progresses, the suprapubic pain and a palpable mass may become prominent, these being associated with obstructive uropathy and uremia.

The diagnosis is made at the time of cystoscopy when a tumor is seen and biopsies can be obtained. It is important that a rectal and bi-manual examination be done to assess the size of the mass. A palpable,

hard, indurated mass is usually a sign of an advanced tumor and a poor prognosis.

Intravenous urography is an important step in the assessment of the patient with bladder cancer. The urogram will indicate the functional status of the kidneys and the possibilities of ureteral obstruction. By using triple-phase contrast studies of the bladder, one can ascertain fixation of the bladder wall and the possibility of invasion. If this is combined with pelvic arteriography in conjunction with perivesical and intravesical gas or with computerized axial tomography, a better evaluation of the size of the tumor may be found.

Grading and Staging

All tumors can be graded histologically based on the degree of cellular anaplasia. Grade I or well-differentiated tumor has a much better prognosis than a grade III or IV or poorly differentiated tumor. Staging in the United States has usually been by the A, B, C, D classification of Jewett and Strong, and Marshall. Recently the TNM (Tumor, Nodes, Metastasis) classification of the International Union Against Cancer has been publicized in order to get physicians in the United States to switch to that classification of all tumors. In general, however, a stage O tumor is one that is localized only to the mucosa; stage A is limited to the submucosa, and stage B_1 indicates that the tumor has invaded the bladder muscle but is less than half-way through the bladder wall. Stage B_2 tumors extend through the bladder muscle but do not invade the perivesical fat, and stage C indicates perivesical fat involvement or involvement of the capsule of another organ. Stage D_1 tumors are those that have spread to the regional pelvic lymph nodes or have invaded the pelvic wall or rectus muscle or both. Stage D_2 tumors exist when the tumor has spread beyond these limitations and is outside the pelvis and the immediate bladder area. Metastases occur most often to the regional lymph nodes, lungs, liver, and bone.

Treatment

The treatment of the patient with a superficial tumor is usually by means of endoscopic surgery with transurethral resection. Careful follow-up examination with repeat cystoscopies every three months for one year, and every six months for five years, and every year thereafter are necessary in order that any residual or recurrent tumors may be promptly found and the appropriate treatment instituted. For the patient with multiple recurring tumors, the use of intravesical therapy (ThioTepa), partial or total removal of the bladder, or radiation are possible therapeutic choices. For the patient with invasive transitional cell carcinoma, endoscopic procedures are not adequate. One cannot endoscopically tell the degree and extent of the tumor, therefore, an open surgical procedure with removal of the entire tumor or radiation therapy is indicated. It would appear as of this writing, that the best results are obtained from preoperative radiation followed by open surgical extirpation of the tumor, usually a radical cystectomy with urinary diversion. There is some discussion about whether 2,000 rads in one week, 4,000 rads in 4 weeks, or 4,500 rads in 6 weeks followed by either immediate or delayed cystectomy is best.

Chemotherapy

Long-term survival is rare once the tumor has spread beyond the confines of the bladder. One means of destroying metastases, however, may be through the use of combinations of chemotherapeutic agents. Drugs used in the management of patients with transitional cell carcinoma of the bladder have been 5-fluorourocil, bleyomycin, adriamycin, cyclophosphamide (Cytoxan) and the cis-platinum compounds.

Testicular Carcinomas and Carcinoma of the Prostate

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Testicular Carcinomas

Incidence

Testicular neoplasms are relatively rare with approximately two new cases per 100,000 male population occurring per year. The peak occurrence is between the ages of 20 and 40. Because of their highly malignant characteristics testicular neoplasms must be treated aggressively if cure is to be achieved.

Etiology

The most significant etiologic factor is the predisposition for the occurrence of carcinoma in the cryptorchid or undescended testicle. The cryptorchid testis is at 40 to 50 times the risk of the normal scrotal testicle for developing a cancer; various theories for this predisposition to malignancy have been proposed. The most likely is that the cryptorchid testicle is inherently abnormal (a very strong argument also to explain its failure to descend) and therefore provides a fertile ground for neoplastic change.

Histology

Testicular tumors may be divided into neoplasms of germ cell origin (arising from the spermatogonia within the seminiferous tubules) and of non-germ cell origin (arising from the supporting Leydig and Sertoli cells). The latter constitute only 5% of all testicular tumors.

For purposes of histology and treatment regimens the germ cell tumors are divided into the seminomatous tumors which are most common, constituting approximately 60% of all testicular tumors, and the non-seminomatous tumors constituting the remaining 35% of tumors. The non-seminomatous tumors consist of embryonal carcinoma, teratocarcinoma, teratoma, or choriocarcinoma. Rarely do each of these types exist in absolutely pure form; most nonseminomatous tumors combine the elements of embryonal and teratomatous carcinomas and these may have elements of choriocarcinoma as well. With the exception of pure choriocarcinoma, a distinctly rare entity comprising less than 1% of tumors, the treatment regimen for the nonseminomatous tumors is identical to and independent of the percentage of each histologic type that constitutes the mixed tumor.

Diagnosis:

All testicular masses must arouse suspicion of carcinoma and some swellings such as testicular hematomas, orchitis, and epididymitis may cause induration difficult to distinguish from a tumor diagnosed only by inguinal exploration and biopsy.

Treatment

When a testicular mass is suspect of carcinoma, it must be explored through an inguinal incision. A rubbershod or umbilical tape is used to obstruct the venous return and therefore reduce or eliminate embolic dissemination during manipulation of the testicle. If there is some doubt about the diagnosis, the testicle is isolated with towels, and a biopsy and a frozen section are performed prior to orchiectomy and removal of the cord. The testicle must never be biopsied through the scrotum, either by incision or by needle aspiration; by doing so an entirely new nodal

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chain for metastases is established. The testicle drains to the para-aortic nodes, the scrotum to the inguinal nodes. If the tumor cells seed in the scrotal incision, which can easily occur, then the entire inguinal chain is at risk for embolic metastases.

The diagnosis of testes tumors is too often delayed for a number of reasons. Routine and careful bimanual examination of the testes is often omitted in routine examinations. Furthermore, patients who note testicular masses are often reticent to present their complaints to a physician because of embarrassment, or fear of association with venereal disease.

Metastatic evaluation. Once a diagnosis is made a number of radiologic studies, serum studies, and urine studies are warranted to stage the neoplasm and identify areas of metastases. The chest represents a common area of distant metastases and should be evaluated not only by anteroposterior and lateral x-ray, but by pulmonary tomograms. Lesions are frequently bilateral and multiple. The primary route of drainage of the testicular lymphatics is to the para-aortic and paracaval nodes between the superior mesenteric and the inferior mesenteric arteries. Cross-over drainage does occur and is most frequent from the right side to the left. Bipedal lymphangiography is of importance in identifying spread to the retroperitoneal nodes. Para-aortic and paracaval nodes are well visualized as is, frequently, the supraclavicular node. Intravenous pyelogram also assesses the retroperitoneum by evaluation of renal and/or ureteral deviation, compression, and deformity. Computerized axial tomography (CT) scanning and ultrasound studies can be used to delineate retroperitoneal masses precisely and may be used as noninvasive techniques to follow these masses periodically during the course of chemotherapy or radiotherapy to evaluate treatment.

Staging of testes tumors is as follows:

Stage A: Tumor limited to testes, that is, no metastases.

Stage B: Tumor present in testes with metastases limited to regional nodes, that is, para-aortic nodes below diaphragm.

Stage C: Tumor present in testes with metastases beyond regional nodes, that is, metastases to scalene node, lung, bone, liver, and so forth.

Seminomatous tumors. These neoplasms are characteristically very radiosensitive. Radiotherapy constitutes the main method of treatment and rarely, if ever, is surgery indicated. If the tumor is Stage A (negative lymphangiogram and pulmonary tomograms), radiation is given in the dose of 2,500 R to the ipsilateral-iliac nodes and to the para-aortic nodes bilaterally to the level of the diaphragm.

If the tumor is Stage B (evidence of nodal involvement on lymphangiogram), the fields are extended so as to include the mediastinum and both supraclavicular areas, and the infradiaphragmatic area is treated to 3,000 R. The 5-year survival rate for patients with Stage A tumors, so treated, ranges around 95%. If the tumor is Stage B (evidence of positive para-aortic nodes), the 5-year survival rate will range around 80%.

If the tumor is Stage C (evidence of pulmonary visceral or osseous metastases), radiation therapy may be given to these areas of metastatic involvement if they are relatively isolated, that is, one or two pulmonary nodules in one lung lobe. If disease is more diffuse, however, a radiomimetic chemotherapeutic agent, either chlorambucil (Leukeran) or cyclophosphamide (Cytoxan) is used. Five-year survival rates for Stage C tumors range between 40% and 50%.

The only indication for surgery for seminomatous tumors arises with the failure of what has been diagnosed as seminoma to respond satisfactorily to radiotherapy. In such a case one must suspect the presence of non-seminomatous elements, and surgery with excisional biopsy will eliminate the lesion, confirm a change in histology, and dictate a change in treatment to that used for non-seminomatous neoplasms.

Non-seminomatous tumors. There is significant controversy as to the optimal management of non-seminomatous tumors with North American urologic centers applying surgery, and European centers employing radiation therapy as the primary modes of treatment of the retroperitoneal area. Non-seminomatous tumors are much more difficult to control with radiation than the seminoma and therefore radiation failures are more common.

In the United States a non-seminomatous neoplasm is approached as follows: if the tumor is Stage A, a retroperitoneal node dissection is undertaken; if lymph node dissection reveals no evidence of histologic metastases to the nodes, no further treatment is undertaken; and if the nodes are positive, chemotherapy is administered as the tumor is pathologically Stage B.

If the tumor is Stage B, a node dissection is again performed and chemotherapy instituted postopera-

tively. If nodal dissection is incomplete or there is tumor spillage, radiotherapy postoperatively to the retroperitoneal area is recommended. Chemotherapy is administered for two years after the last evidence of clinical disease is noted.

If the tumor is Stage C, chemotherapy is instituted and if clinically measurable metastatic disease regresses, a node dissection is then considered.

Five-year survival rates for Stage A, non-seminomatous tumors range from 85% to 90% (the pathologist is not always 100% accurate and may have missed microfoci in the excised lymph nodes and/or metastases may have skipped the retroperitoneal nodes and dissiminated distantly without nodal involvement). Five-year survival rates for Stage B disease are 60% to 70% and for Stage C, 25% to 30%.

Tumor markers. Until recently, 24-hour urinary choriogonadotropin was measured in patients with testicular tumor in an effort to identify those with choriocarcinoma which as a functioning cell would produce choriogonadotropins detectable in the urine. The assay used is a biological one and has all the inherent difficulties of bioassays.

A serum radioimmunoassay has been developed to overcome this difficulty. It measures the B chain of human choriogonadotropin (termed Beta sub unit) and is very sensitive and specific. Any elevation in the male is abnormal and indicates the presence of functioning tumor cells.

Alpha-fetoprotein is a protein produced by the fetus, but its production ceases and levels fall to nanogram marks soon after birth. Testis carcinoma cells may revert to the metabolic machinery of the fetal cell and produce alpha-fetoprotein, causing increased serum levels. Like the Beta sub unit, elevated alpha-fetoprotein identifies the presence of active tumor.

Tumor markers are sensitive indicators of residual microfoci of disease long before any evidence of clinical or radiologic disease may appear. Active chemotherapy must continue until tumor markers are reduced to and remain within normal levels.

Carcinoma of the Prostate

Incidence

The incidence of carcinoma of the prostate is steadily increasing; at the present time it is the most common genitourinary malignancy and the second leading cause of death from cancer among males in the United States. Its incidence of 60 new cases/100,000 population and 20 deaths/100,000 population per annum is exceeded only by carcinoma of the lung. The incidence of carcinoma of the prostate increases with age, and autopsy studies have revealed it in 50% to 80% of males who have survived to age 80. Thus, we can anticipate that with greater longevity the diagnosis of prostatic carcinoma will be made more frequently and the problems of treatment of a malignancy in an aged population will be of increasing concern.

Etiology

No specific carcinogen has been identified as the cause of prostate cancer. The most likely inciting event at present is a change in the hormonal milieu which occurs as a natural consequence of aging. The nature of the change and the hormone fluctuations involved are as yet unidentified.

Anatomy and Histology

The prostatic glandular elements can be divided into two major sectors—the inner periurethral glands and the peripheral tuboalveolar glands which are connected by long ducts to the prostatic urethra. The periurethral glands are those which most frequently give rise to benign hypertrophy and the peripheral tuboalveolar glands to adenocarcinoma of the prostate.

Natural History

Carcinoma of the prostate is a neoplasm with varied growth characteristics and degrees of malignancy. The tumor may be rapidly metastatic and cause death within one to two years or it may be slowly growing, metastasizing only five to ten, or even fifteen, years after discovery of the primary lesion; another five or more years may pass before the metastases become life-threatening. This variability makes it difficult to assess the efficacy of therapy, and makes it necessary to follow patients for ten to fifteen years after initiating treatment in order to judge its value. The reason for this is that, given a tumor with a relatively slow-growing and benign course, one cannot state whether prolonged survival is based on the treatment administered or the low biologic potential of that tumor. Unfortunately, at the present time there are few characteristics, other than the grade of anaplasia, that can be measured to identify at the time of diagnosis which tumors will follow a benign course from those which will not.

Diagnosis

While a high index of suspicion may be generated by induration felt on digital rectal examination, carcinoma of the prostate must be ultimately diagnosed by histologic proof of malignancy. A number of other causes for induration of the prostate include prostatic calculi, granulomatous prostatitis, nodular prostatic hypertrophy and, more rarely, tuberculous granulomas. Once a suspicious area of induration or nodularity is identified a transperineal or transrectal needle biopsy employing the Vim-Silverman needle is used to obtain tissue for histologic examination.

Other warning signals in the elderly male of prostatic cancer include the onset or recent exacerbation of low back pain, possibly a reflection of osseous metastases; the presence of sciatic pain, possibly a reflection of sciatic nerve impingement by massive retroperitoneal lymphadenopathy secondary to metastases; and the rapid progression of bladder outlet obstruction which can be identical to that seen with benign prostatic hypertrophy (BPH).

Radiographic identification of carcinoma of the prostate is facilitated by the characteristic radiodense or osteoblastic lesions most frequently found in the pelvic bones and the lumbosacral spine. These may be identified on routine skeletal survey, but more early identification is provided by the technetium 99 phosphorous bone scan which identifies metastases prior to radiographic skeletal changes. (It has been shown that more than 50% of the bone must be destroyed or replaced by malignancy before a routine skeletal survey becomes positive). Intravenous pyelography may demonstrate obstruction at the ureterovesical junction secondary to prostatic malignant growth and, specifically, involvement of the seminal vesicles. Also the ureters may be displaced by retroperitoneal metastatic adenopathy.

Biochemical or serum abnormalities occur with prostatic carcinoma. Serum acid phosphatase represents the most characteristic and distinct abnormality; in essence, it is a tumor marker. It can frequently be used to identify the presence of metastatic disease, and its levels may be followed as a means of monitoring treatment; however, it is not a specific test as acid phosphatase may be elevated in a number of other diseases such as pulmonary embolism, muscle necrosis, Gaucher disease, and osteosarcoma, to mention a few. It is also not a very sensitive marker as diffuse metastases may be present in the face of a normal acid phosphatase. The recent development of a radioimmunoassay for measurement of prostatic acid phosphatase offers significant advantages for tumor staging, and follow-up. The immune assay is *specific* for the *prostatic fraction* of acid phosphatase and is *sensitive* to extremely minor changes in serum levels of the enzyme. Elevation of alkaline phosphatase is a reflection of bony destruction and repair. Serum calcium may be elevated as a result of extensive osseous metastases.

Treatment

Many methods of treatment are used either individually or in combination. Transurethral resection of the prostate is used to relieve obstruction. This is obviously palliative and relieves symptoms but does nothing to stem or alter the growth of the neoplasm. Radical prostatectomy, namely the total removal of the prostate gland and the seminal vesicles, is performed with the intent to cure by removal of all neoplasm. Curative radiation therapy delivered from a linear accelerator or cobalt source is directed at the prostate and often the pelvic lymph nodes as well. Interstitial implantation of radioactive seeds is used in an effort to deliver high local doses.

Treatment is based on the staging of the disease at the time of presentation: Stage A—carcinoma entirely unsuspected on physical examination, or on serum chemical or radiographic examination but which is found incidentally on pathologic examination of the prostate excised for presumed BPH, that is, in the transurethrally resected prostatic chips or the prostate enucleated by an open technique. Stage B—tumor confined to the prostate gland on physical examination specifically without lateral or seminal vesicle extension; Stage C—tumor locally confined to the pelvis but demonstrating lateral extension and seminal vesicle invasion; Stage D—metastases to lymph nodes, bone, lung, and so forth.

Management of Stage A depends to a large extent on the patient's age, the grade of lesion, and the extent of the involvement. When only microfoci of well differentiated neoplasm are present, it is reasonable to pursue no further treatment. If the tumor is more extensive or poorly differentiated, treatment is as outlined for Stage B.

For Stage B, either radical excision of the prostate and seminal vesicles (radical prostatectomy) or treatment with external beam radiotherapy or interstitial implantation of radioactive sources (I-125 seeds) may be employed. The advantages of radiotherapy are the inclusion of the periprostatic tissue (and thereby hoped-for sterilization of microscopic

extensions outside the prostate) and avoidance of the side effects of surgery, namely universal impotence and a 10% to 20% incidence of incontinence.

The survival rates for Stage B carcinoma of the prostate are approximately 75% at five years, 45% to 50% at ten years, and 25% to 35% at fifteen years.

In Stage C carcinoma of the prostate, extension beyond the confines of the prostate and seminal vesicles usually makes cure by radical prostatectomy highly unlikely; therefore, radiation therapy, either external beam or interstitial seeds, constitutes the mainstay of treatment. Occasionally it is also necessary to relieve prostatic obstruction by transurethral prostatectomy either before treatment or immediately afterwards. Five- and ten-year survival rates for Stage C are approximately 45% and 30% respectively.

The philosophy for treatment of Stage D carcinoma of the prostate varies throughout the country. It is our policy to await the appearance of symptoms prior to the institution of therapy. Cure of Stage D prostatic neoplasm has not been documented, and therefore palliation of symptoms, and prolongation of survival remain the primary objectives of treatment. Conditions warranting treatment include systemic symptoms such as weight loss, fatigue, weakness, bone pain, ureteral obstruction, and bone marrow replacement as evidenced by anemia.

Hormonal manipulation (estrogen or orchiectomy) is the mainstay of treatment for metastatic carcinoma of the prostate. Dramatic relief from pain and regression of metastases, and at times complete disappearance of the primary prostatic lesion, follow the administration of hormones, or castration. The administration of estrogens works via the negative feedback system whereby high-estrogen doses suppress luteinizing hormone (LH) and follicle-stimulating hormone (FSH), both of which are pituitary trophic hormones stimulating the testes to produce testosterone. Orchiectomy removes the source of androgen production. It is felt at the present time that either one of these modes is equally effective and can be expected to produce regression in approximately 80% of patients with prostate carcinoma. There is no documented advantage from using both methods, that is, estrogen plus orchiectomy as opposed to either one or the other alone, nor unfortunately is a second regression seen with any frequency by applying one of these modes when a relapse occurs after the institution of the other.

Estrogens have certain distinct disadvantages; an orally ingested pill is required daily, nausea can occur, as can gynecomastia and other secondary sex changes. Of greater significance is data demonstrating an increased incidence of death from cardiovascular disease, namely fluid retention, pulmonary edema, and congestive heart failure in patients receiving estrogen therapy. Orchiectomy, a simple surgical procedure that can be performed under local anesthesia, avoids these secondary effects of estrogen treatment.

Other forms of hormonal ablation include adrenalectomy and hypophysectomy, but these are rarely used and have not been consistently successful in offering extended palliation.

Local radiation therapy to painful osseous lesions may significantly relieve discomfort. Radiation is reserved for treatment of well-localized areas of painful metastases.

Cytotoxic agents have just come under investigation in clinical trials and hold some promise for treatment of estrogen failures. Investigation of certain cytotoxic agents linked to hormones (Estracyst = estrogen + nitrogen mustard; Leo = prednisone + chlorambucil) suggests that cytotoxic agents may be delivered within the prostatic cancer cell by steroid carriers which attach to hormone receptors. Other agents which depend on the acid phosphatase enzyme for cleavage to the active form are also in developmental stages.

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Adenocarcinoma of the Prostate: The Rationale and Role for Radiotherapy in its Management

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Until recently the treatment of carcinoma of the prostate was limited either to radical prostatectomy by the perineal or retropubic route, or to hormonal manipulation. Approximately 5% of all patients with this disease are suitable candidates for radical surgery. Hormonal manipulation is palliative in nature and is generally used when there is evidence of metastatic disease (in about 50% of patients). There thus remains a group of patients (40% to 45%) in whom the disease is localized, yet too extensive for surgical treatment, for whom definitive radiotherapy can play a major role.

Pre-treatment Evaluation

Once the histological diagnosis of carcinoma of the prostate has been made it is desirable to delineate the exact extent of disease in order to provide certain guidelines for optimal management and for predicting prognosis. In an attempt to evaluate the various diagnostic procedures, we at the Medical College of Virginia are conducting an ongoing study where all patients with clinically localized prostatic carcinoma undergo the following work-up:

1. Laboratory Studies
   a) WBC, hematocrit, platelets
   b) Total and prostatic fraction of acid phosphatase (blood is obtained either prior to or at least 24 hours after rectal examination).
   c) Alkaline phosphatase and BUN.
   d) Bone marrow biopsy for histological examination, and radioimmunoassay for prostatic acid phosphatase.
2. Radiological Studies
   a) Chest x-ray
   b) Intravenous pyelography
   c) Bipedal lymphangiogram
   d) ^{99}m Tc Labeled di-phosphate bone scan

Radiation Therapy

Although the use of ionizing radiation in the treatment of carcinoma of the prostate was first reported in 1911 by Pasteau,[1] the majority of reports have appeared within the last ten years. In a recent comprehensive review of the subject Ray and his colleagues[2] have documented clinical studies which collectively report on 880 cases in which external beam irradiation was the primary mode of treatment. They have concluded "that potentially tumoricidal dosage of irradiation can be delivered to the prostate with relative safety and in general the initial response of the local tumor to irradiation in survival rates at five years were encouraging."

Results

Local. In general, the reports of various authors support our experience that 70% to 80% of patients show marked resolution of the disease within six months on clinical examination. We do not, at the present, recommend post-treatment prostatic biopsies as a routine procedure.

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Survival. On reviewing the results of various investigators dealing with the definitive treatment of adenocarcinoma of the prostate with megavoltage irradiation therapy, one finds that the five-year survival rate varies from 60% to 70% and the ten-year survival rate varies from 30% to 40%. Ray and his colleagues[3] from Stanford University have reported the results of treatment for two clinical groups of patients based upon the extent of the disease as determined by digital examination. In one group of patients the disease was limited to the prostate and this group of patients had a 71% and 41% survival rate at five and ten years respectively. In the other group of patients the disease had extracapsular extension and this group of patients had 41% and 31% survival rates at five and ten years respectively. Hillaris and his colleagues[4] from Memorial Hospital have reported that all patients with intracapsular disease (T_1, T_2, and T_3) and negative lymph nodes were alive and free of disease at five years while disease-free survival decreased to 70% in patients with extracapsular disease and negative nodes or in patients with intracapsular disease with positive nodes. Only 50% of patients with extensive local disease (T_3 and T_4) and positive nodes were alive without evidence of disease at five years. It has been my experience that dissemination of disease is more frequent in patients with a large primary tumor, with a high-grade tumor, and in the presence of histologically positive lymph nodes. In addition, there is rapid systemic dissemination of the disease once the para-aortic lymph nodes are involved.

Present Area of Clinical Investigation

The major cause of failure of definitive radiotherapy in carcinoma of the prostate is the spread of tumor, outside the high dose of radiation field, either to the lymph nodes or to the bones. It is generally accepted that young patients (below 65 years), patients with a high-grade tumor and with diffuse involvement of the prostate gland (multiple chips involved, post-transurethral resection of the prostate) have a poor survival rate even when they present with early (stage A) disease. It remains to be seen whether definitive radiation therapy in this select group of patients with stage A carcinoma of the prostate will alter the natural history and provide an improved survival rate.

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Management of Acute Glomerulonephritis

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Glomerulonephritis is responsible for over one half of all cases of end-stage chronic renal failure and, in its most fulminant form, is a cause of acute, irreversible renal failure. Electron microscopy and immunofluorescent studies together with newly recognized clinical associations have revealed a wide variety of histologic subgroups and myriad etiologies for what was once regarded as a single, simple entity. The addition of electron microscopy has lent an entirely new dimension to the delineation of glomerulonephritis subtypes and offers a more reasonable approach to the search for treatment of these subtypes. It is, after all, not unreasonable to suppose that different etiologic factors and host responses are involved in the various pathologic lesions so clearly defined on electron microscopy. Immunofluorescent studies identify the presence of immune globulins and complement components in glomerular lesions and aid in recognition of their localization sites; they may reveal the contribution of fibrin deposition or specific antigens in the pathogenesis of glomerular involvement.

Most, if not all, forms of glomerulonephritis are acknowledged to be the result of immunologic processes, and many can be mimicked by immunologic manipulations in laboratory animals. A growing body of research data has incriminated circulating immune complexes, activation of the complement cascade and the coagulation system, antibodies directed specifically against the glomerular basement membrane, proteolytic activity of leukocytes, and other phenomena in the mediation of particular types of glomerular injury. In experimental animals, at least, manipulation of the antigen:antibody ratio or depletion of complement and/or polynuclear leukocytes may blunt the severity of, or prevent entirely, lesions which are otherwise inevitable and severe. In the rabbit, the prophylactic administration of anticoagulants has marked beneficial effects on the development of glomerulopathy. Unfortunately, comparable benefit is not observed when these maneuvers are performed after glomerular abnormalities are already established.

Most experimentally induced glomerulopathies are self-limiting and of brief duration. Aside from the maneuvers mentioned in the previous paragraph, therapy which would be considered suitable for use in man appears for the most part to be of little benefit in the laboratory. In man, the value of currently available treatments intended to halt or reverse the progression of glomerular abnormalities is no more impressive. Corticosteroids, immunosuppressive agents, and anticoagulants are of proven value in only a minority of histologically specific lesions (for example, hypersensitivity angiitis, Wegener granulomatosis, minimal lesion nephrotic syndrome), and their efficacy in other forms of glomerulonephritis is strongly debated. The very existence of such debate, over 25 years after the introduction of steroid therapy and 15 years after azathioprine (Imuran) became available, should indicate that current treatment modes are less than optimally effective. New forms of treatment must be developed.

Working on the assumption that immunologic mechanisms are the key to the appearance of glomerular injury, one would ideally search for new

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means of turning off or minimizing the impact of those mechanisms, an approach which meets with considerable success in the prevention of renal transplant rejection. Having been largely unsuccessful in achieving suitable manipulation of immune mechanisms with our present knowledge, we can at least attempt to minimize the impact of the immune system on the kidney. In that regard, a new approach to the problem is under study here at the Medical College of Virginia and elsewhere—plasmapheresis. This technique involves the removal of the patient's plasma and replacing it with donor's plasma so as to remove circulating immune complexes and/or preformed antikidney antibodies. Preliminary data indicate that, in selected cases, significant improvement in renal function may follow such treatment. The overall value of plasmapheresis is still under review, however, and will not be known until suitable numbers of patients have received this treatment.

Use of the "Melbourne cocktail"—a combination of dipyridamole, corticosteroid and heparin therapy—has been reported to reverse the most fulminating and devastating form of acute glomerular disease termed "rapidly progressive glomerulonephritis." While the clinical presentation of oligoanuria with virtually complete cessation of glomerular filtration in children is often completely reversible, it is rarely so in adults. Fibrin deposition, formation of luxuriant epithelial crescents, and marked cellular proliferation of the glomerular tuft typify this subgroup of patients. Employing a treatment which affects platelet aggregation and intracapillary coagulation seems entirely rational but is not without hazard to the patient. Once this particular form of fulminating glomerulonephritis is recognized, however, the prognosis for return of renal function is so poor that the cocktail is being investigated in several centers. Evaluation of such treatment requires experience, ideal patient management and careful patient selection, and should be undertaken only under the most stringent precautions if we are to establish its efficacy in a controlled fashion.

The Management of End-Stage Renal Disease (ESRD)

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End-stage renal disease (ESRD) may be defined as a state of renal insufficiency of such severity that the affected individual is unable to carry out his usual activities because of symptoms usually attributed to the uremic syndrome. This state has been reached, or is imminent, when the serum creatinine concentration rises above 10 mg/100 ml and/or the creatinine clearance falls below 5 to 10 ml/min and reversible causes of renal failure such as obstructive uropathy, bilateral renal vascular disease, severe accelerated hypertension, hypercalcemic nephropathy, uric acid nephropathy, and certain immunologic diseases such as Wegener granulomatosis have been excluded. Prospective analysis of a population of patients meeting these biochemical criteria has clearly shown that at least 80% will require dialysis within 150 days and 40% will require this method of treatment within 60 days to sustain life.[1] Thus, when ESRD is reached, weighty decisions concerning the patient's care must be made. It is the purpose of this paper to review the management of ESRD and to point out some of the problems which may complicate the several therapeutic modalities.

The alternative methods of management of the patient with ESRD are dialysis and transplantation. These two therapeutic modalities are by no means mutually exclusive and, as we shall see, should be considered complementary. However, virtually all patients must undergo a period of dialysis, even those awaiting transplantation. Therefore, dialysis is the first mode of treatment encountered by a patient entering an ESRD program.

At the present time there are few absolute contraindications to entrance into an ESRD program for dialysis and transplantation. However, patients with uncontrolled psychotic behavior, extreme old age, advanced artherosclerotic vascular disease, or disseminated malignancy are probably not candidates for therapy.

Principles of good conservative management of renal failure such as restriction of dietary protein, careful attention to fluid and electrolyte balance with tailoring of dietary sodium intake to the obligatory sodium loss, and the administration of sodium bicarbonate supplements and oral phosphate binders where appropriate may postpone the absolute need for dialysis or transplantation if introduced when the patient has moderately severe renal insufficiency. Recent studies have demonstrated that the period of conservative management can be prolonged even further by the administration of a special mixture of the keto-analogues of the essential amino acids.[2] This maneuver allows for the dietary administration of very limited quantities of nitrogen and is predicated on the assumption that some of the urea nitrogen will be recycled into the synthesis of essential as well as nonessential amino acids. Unfortunately, these keto-acids are not commercially available at present, but perhaps will be in the future.

Survival rates for patients treated by hemodialysis at home and those who have received a well-matched transplant from a living related donor are both greater than 80% at two years.[3] It is worth noting, however, that this represents patient survival

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and not graft survival which is only about 70%, thus indicating that some 10% to 15% of the transplant recipients who survive two years have suffered an undetermined amount of morbidity in association with rejection of their graft. Survival with in-center dialysis and cadaver transplantation is less good, with a two-year survival rate of approximately 70% in each case.[3] The two-year graft survival in patients with cadaver transplants is less than 50%. These statistics suggest the desirability of home dialysis and living related donor transplantation, but do not demonstrate a clear superiority of in-center dialysis or cadaver transplantation. Thus, factors other than survival must be considered in selecting a mode of therapy.

Age is a major factor which may influence therapeutic selection. Children and adolescents tend to have diminished growth and maturation while on dialysis[4] and they frequently rebel against the rigid dialysis schedule. Therefore, most authorities favor transplantation as a mode of therapy in the young.[5] On the other hand, older individuals with a well-established, stable lifestyle may prefer not to run the risk of the lost time from work and the potential complications of transplantation. The patient's psychological state also may be of importance in selecting a mode of therapy. Some older patients, like the children, may find the confining life of the dialysis patient to be more than they can tolerate and be willing to risk the uncertainties of cadaver transplantation.

The presence of complicating medical disorders may influence the type of management selected. Diabetics may fare better with transplantation because progression of atherosclerotic vascular disease and retinopathy may be less rapid than on dialysis.[5] Patients with certain enzyme defects such as Fabrey disease may also benefit from transplantation because the transplanted organ may serve as a source of the defective enzyme.[6] On the other hand, transplantation is contraindicated in patients with antibasement membrane antibody nephritis with circulating antibodies[7] and in patients with large quantities of circulating cytotoxic antibodies[7] because of the likelihood of rapid graft destruction after transplantation. Additionally, the immunosuppressive medication given to patients may allow for enhanced tumor growth, and most surgeons will not consider performing transplantation in a patient with a history of malignancy unless there is clear evidence that the patient has been tumor-free for at least one year.[7] The presence of lower urinary tract dysfunction and an inadequate bladder are still considered relatively strong contraindications to transplantation.

Having decided that a patient's life will be sustained, a decision must be made about the form of dialysis to be instituted. Although chronic peritoneal dialysis has been an effective modality in some hands,[8] most authorities consider it to be less desirable than chronic hemodialysis, and the remainder of this discussion will be concerned with hemodialysis.

Two types of vascular access are available for connecting the patient to a dialysis machine. These are the silastic, external arteriovenous (AV) shunt[9] which protrudes through the skin and the internal AV fistula communication, using the patient's own vessels[10] or a foreign graft material.[11] The latter lies immediately under the skin and must be punctured with a needle at each dialysis. The fistula is preferred by most physicians and patients because of the freedom of movement and the safety which it provides. Where possible, it is our policy to anticipate the ultimate need for dialysis and to have the surgeon electively establish an AV fistula at about the time the serum creatinine reaches a concentration of 8 mg/100 ml. This allows time for maturation of the fistula prior to its initial use, and obviates the need for emergency surgery to establish vascular access in an ill patient.

Hemodialysis is usually initiated in the medical center, but when the patient has an acceptable helper, every effort should be made to encourage the couple to learn home dialysis. The training program can be mastered by anyone of average intelligence and takes about two months to complete. As mentioned previously, patients on home dialysis have better survival statistics and are better rehabilitated.[12]

Whether dialysis is performed at home or in a center facility, there are a number of common complications of which the physician should be aware. Bacterial infection of the shunt or fistula is a frequent problem that may lead to metastasization and requires aggressive drainage and antibiotic treatment.[13] Hepatitis B infection has been a frequent occurrence among dialysis patients.[14] It presents a particular problem in dialysis units because patients may become carriers and transmit the virus to staff and other patients. Virtually all patients on dialysis have some degree of anemia.[15] In the past, transfusion of potential transplant candidates was kept to a minimum because of possible sensitization to transplant antigens. However, recent evidence suggests that frequent transfusions may actually enhance rather than inhibit

the frequency of organ acceptance.[16] Therefore, transfusions, particularly of saline-washed red cells, are now being given with less concern than in the past. Pericarditis continues to be a frequent and poorly understood complication in the dialysis patient and it does not always appear to be a manifestation of inadequate dialysis.[17] Hypertension is seen frequently in the dialysis population and may be related either to expansion of the extracellular fluid volume or to the release of pressor substances from the residual damaged kidneys.[18] In the latter circumstance, bilateral nephrectomy may produce a dramatic return of the blood pressure to normal.[19] Neuropathy is frequently noted at the onset of dialysis but seldom progresses if dialysis is adequate.[20] Impotence is seen more frequently than not in male dialysis patients, and dialysis against a bath containing a high concentration of zinc has recently been proposed as effective therapy.[21] As more patients are sustained alive for prolonged periods of time it is becoming clear that osteodystrophy[22] and accelerated atherosclerosis[21] are problems of great magnitude. Therapy of the former includes the use of oral phosphate binders to maintain the serum phosphorus concentration levels at normal, and a supplemental vitamin D preparation to enhance intestinal calcium absorption; there does not appear to be any effective therapy for the latter.

Many of the problems mentioned above will be corrected by a functioning transplant. However, there are a number of problems which are unique to the transplant population. Most of the difficulties associated with early transplant rejection are managed by the transplant team prior to discharge from the hospital after surgery, and these will not be considered here. Chronic rejection may occur late after transplantation, is characterized by a slow deterioration in function, and is generally unresponsive to therapy. Infection remains the major cause of morbidity and mortality among transplant patients.[23] Because of the constant need for immunosuppressive medication these patients have an increased susceptibility to both common bacterial pathogens and to opportunistic viruses such as herpes hominis and cytomegalovirus; fungi such as cryptococcus and aspergillus; and protozoa such as pneumocystis and toxoplasmosis. Hypertension also is a frequent complication of transplantation and may be difficult to control. A diabetic diathesis may be brought out by the administration of steroids as immunosuppressive agents.[24] Osteoporosis may develop as a complication of long-term steroid administration.[24] The constant immunosuppression may also allow for the development of tumor growth and there is a much higher incidence of malignancy in transplant patients than in a comparable, non-immunosuppressed population.[24] Gastrointestinal bleeding is a feared complication of transplantation that is frequently fatal.[24] Consequently, many transplant surgeons perform prophylactic gastric surgery in any potential candidate who has the slightest history of ulcer disease.

It is our feeling that selection of a proper therapeutic modality in a patient with ESRD requires careful consideration of the medical, psychological, social, and economic aspects of the patient's illness. His needs may change through the course of illness and, as a consequence, the ESRD prescription may require alteration. Thus, a patient might initially be managed with home dialysis, receive a living related donor transplant after a sibling decided to become a donor, and return to home dialysis after rejection occurred.

The economic costs of ESRD treatment are staggering.[25] At present there are more than 37,000 individuals receiving some type of ESRD therapy in the United States at an annual cost of $902 million. By 1982 it is projected that the cost for 55,900 patients will be 2.3 billion. Most patients are eligible for financial coverage of the major portion of their dialysis or transplantation cost either via private insurance carrier, Medicare, or the Veterans Administration. At present the annual cost of in-center dialysis is approximately $23,400 while that of home dialysis is $12,480. The initial cost of hospitalization for transplant surgery is about $17,000. These estimates do not include the cost of hospitalization for various complications of either the dialysis or transplant state; and, as suggested earlier, these may be formidable.

In the future, dialysis equipment may be made more compact and a satisfactory portable dialyzer may be developed. The use of sorbent materials may allow dialysis with small quantities of fluid, and high potency antithymocyte globulin may improve the early survival of cadaver grafts. Techniques also may be developed for the stimulation of blocking antibodies in the recipient which will allow for improved graft survival with lower doses of immunosuppressive drugs. However, none of these innovations seem likely to dramatically change the management of ESRD in the near future.

The management of ESRD has been briefly re-

viewed; both dialysis and transplantation are useful modalities of therapy and are not mutually exclusive. Management in a given patient should be designed to best meet his medical, psychological, social, and economic needs.

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Male Infertility: The Clinical Aspects of Evaluation and Management

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Introduction

At a time when limiting family size has become of national interest, increasing numbers of married couples are moving in a different direction—to overcome infertility and conceive children. Reasonably reliable statistics indicate that approximately 3.5 million couples, or nearly 15% of those of childrearing age, are subfertile. If one adds the cases of secondary infertility, in which a pregnancy or a miscarriage has already occurred in the marriage but is followed by years of difficulty conceiving another child, the magnitude of the infertility problem is indeed impressive. At the personal level, involuntary childless couples may suffer doubts about their own sexuality and are often caught in intense emotional, family, and societal pressures emanating from their inability to conceive.

Furthermore, the incidence of infertility seems to be slowly increasing due to a number of factors including the increased risk of prolonged anovulation following the use of birth control pills and to adnexal infections associated with the use of intrauterine devices. Additionally, there is a definite trend by women to delay having children until later in life and thus to bypass the time of their optimal fertility potential between 22 and 26 years of age.

Whether or not the true incidence of infertility is increasing, there is a definite and substantial increase in the demand for treatment. This reflects a growing awareness by childless couples that treatment for infertility in many instances can be effective and that the number of babies available for adoption have been sharply reduced by birth control, liberalized abortion laws, and an increasing tendency of unwed mothers to keep their babies.

Until recently, most physicians were not particularly enthusiastic about treating patient infertility. The reasons for this attitude centered around a general pessimism about being able to help the patient, combined with the fact that the physicians' training ill-prepared them for evaluating and managing these patients with the result that male infertility has probably been the most misunderstood item since the IRS short form. Presently, a more optimistic view is warranted as therapy is now effective in achieving pregnancy for about 45% of these couples.

The objective of this article is to present the most recent information regarding the clinical aspects of male infertility and subfertility. The information will be practical and directed to understanding both the causes of male infertility and the various methods of evaluating and managing male patients with this problem.

Definition of Male Infertility and Subfertility

Based on semen analysis, a precise definition of male infertility and subfertility is difficult because the quality of semen that will achieve a pregnancy for one couple and not another will vary due to the relative fecundity of the female partner and the variable interaction of infertility co-factors. In other words, data suggest that there are degrees of fertility for both sexes, depending on the partner.[1] Nevertheless, given a female partner who is fertile by most standards, lower limits for semen quality have been established

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under which a pregnancy is likely to occur.[2-4] These *minimal* values are as follows:

Total ejaculate volume: 1.5-5.0 ccs
Sperm count: 20 m/cc
Sperm motility: 60% motile
Sperm speed: 2+ (Scale 1-4)
Sperm morphology: 60% normal forms

These minimal values must be considered as part of the overall semenogram and may be adjusted if one index is of particularly high quality, for example, a patient with a 10 m/cc sperm density may well be fertile if his sperm motility is excellent.

History and Physical Examination

Beyond obtaining a basic medical and marital history, the infertility history should be directed at uncovering the specific factors that are known to contribute to subfertility. These factors can be conveniently divided into four groups: childhood illnesses; adult illnesses; drugs; and environmental-occupational hazards.

Specific childhood illnesses that can adversely effect fertility include cryptorchidism, mumps, spermatic cord torsion, direct trauma, and the timing of puberty as well as specific surgical procedures including herniorrhaphy, orchiopexy, hypospadias repair, urethroplasty, and Y-V plasty of the bladder neck to relieve "obstruction."

Adult illnesses that are similarly important include tuberculosis of the genital tract, mumps, orchitis, prostatitis, epididymitis, gonorrhea, diabetes, vaginitis in the female partner, and such surgical procedures as noted under childhood illnesses plus retroperitoneal surgery (lymphadenectomy, sympathectomy, and so forth), vasectomy, and prostatic surgery.

Drugs that are known to interrupt or alter spermatogenesis include the nitrofurantoins, amebicides, hormones (for example, testosterone, estrogens, corticosteriods), as well as most of the anti-cancer chemotherapeutic drugs.

The patient's occupation may have a bearing on his fertility status if he is under a great deal of stress or if the testicles are exposed to undue heat or radiation.

The physical examination should include a thorough examination of the external genitalia and prostate. Testicular size and consistency are particularly important; measurement is facilitated by the use of calipers. The normal adult testis measures approximately 4.6 cm in greatest diameter (range 3.6-5.5 cm) and 2.6 cm in width (range 2.1-3.2 cm). Because the germinal epithelium comprises about 80% of the normal testicular mass, atrophy of the seminiferous tubules will be reflected in a smaller than normal testicle. On the other hand, normal testicular size does not assure normal semen quality. If the patient's body habitus appears abnormal, laboratory investigation should be directed at determining any abnormality of the hypothalmic-pituitary-gonadal axis.

The Semen Analysis

The semen analysis is without doubt the single most important step in the evaluation of male infertility. It is to male infertility what cystoscopy is to bladder tumors, that is, it is the most critical item in the initial evaluation process and is important in therapy follow-up.

The semen analysis, or semenogram, is a study of the characteristics of the spermatozoa that are clinically important in assessing fertility. While noncellular components of the semen also contribute to fecundity, for clinical purposes the semenogram will reflect their influence on the spermatozoal characteristics that are decisive in determining fertility potential, and a separate biochemical analysis of these components is neither necessary nor practical.

Because of its importance, a minimum of two and preferably three semen analyses should be obtained. Additionally, multiple collections are necessary because of physiological variations in the same patient and because of technical variations in analyzing the specimen, for example, acceptable counting errors vary from 10% to 20% with the same specimen.

Preferably, the semen specimen should be collected by masturbation into a clean, wide-mouthed glass or plastic container. The container, such as a standard urine specimen bottle or ointment jar, should be supplied by the physician to avoid factitious results secondary to the container's previous contents or cleaning agents. The specimen should be kept warm and delivered to the laboratory for analysis within 60-90 minutes. The timing of specimen collection should reflect the couple's usual coital frequency pattern, or if that is variable, an abstinence period of 2-4 days is recommended. Personal or religious beliefs may require the use of a silastic seminal fluid collecting device. It is critical that the specimen represents the entire ejaculate since there are significant variations in the seminal values from one portion to the other with regard to motility, sperm den-

sity, and viscosity as compared with the total ejaculate.

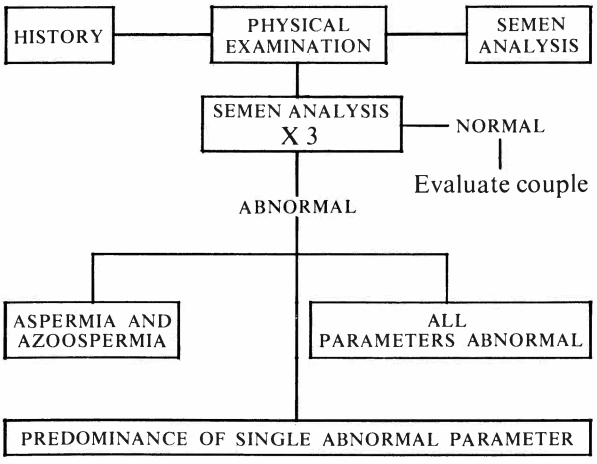
The specific techniques of analyzing the semen will not be discussed because they are beyond the space limitations of this presentation and, additionally, are available in recent texts.[5] Five principal indices should be reported on the semen analysis. Representative values for fertile men are as follows:

1. Total ejaculate volume: 2-5 ccs
2. Sperm count (density in millions/cc): greater than 50 m/cc
3. Sperm motility (% motile cells): 65% to 85%
4. Sperm speed (forward progression speed): 3-4 (scale 0-4)
5. Sperm morphology: 60% to 85% normal oval forms

Additionally: The specimen is normally viscous and opalescent with a grayish-white color. There should be no hyperviscosity, pyospermia, or significant sperm agglutination.

Systematic Approach to Male Infertility

A systematic approach to male infertility can be facilitated with the use of the following diagnostic flow sheet (modified after Lipshultz[6]):



The flow sheet is based on the semen analysis and the identification of the three broad seminal categories of: 1) aspermia and azoospermia, 2) predominance of a single abnormal parameter, and 3) all parameters abnormal.

Aspermia and Azoospermia

Somewhat less than 5% of male infertility patients will present with either aspermia or azoospermia. In the aspermic patient there is failure of any ejaculate to appear at the time of orgasm. On the other hand, the azoospermic patient experiences both ejaculation and orgasm, but the ejaculate contains no spermatogenic elements.

The absence of ejaculation in aspermic patients is generally due to neurogenic causes[7] and, less commonly, to retrograde ejaculation. The neurogenic causes include pituitary tumors, olfactogenital dysplasia (Kallman syndrome), and absent contraction of the seminal vesicles and vasa differentia following retroperitoneal lymph node dissection for the treatment of testicular tumors (and not due to retrograde ejaculations as previously thought).

The neurogenic causes can be successfully treated in most cases by specific replacement therapy.

The common causes of retrograde ejaculation include those in which the anatomy of the internal sphincter is disrupted as in transuretheral resection (TUR) of the prostate or vesicle neck surgery, or where the nerve supply of the internal sphincter is distrupted as in spinal cord injury, surgical sympathectomy, chemical sympathectomy [guanethidine (sulfate) (Ismelin)], and diabetes visceral neuropathy.

Apart from a history of a previous elective vasectomy, the azoospermic patient's differential diagnosis rests between obstruction or atresia of the epididymal or vasal ducts and testicular failure as seen in germinal cell aplasia, marked spermatogenic arrest, chromosomal defects, severe peritubular fibrosis, and Klinefelter syndrome.

The seminal specimens of all azoospermic patients should be tested for the presence or absence of fructose: this is quantitatively determined by adding the reducing reagent resorcinol to a small portion of the seminal specimen and bringing it to a boil.[5] If fructose is present, an orange color will appear within half a minute of boiling. The presence of fructose, a product of the seminal vesicles, effectively rules out congenital bilateral absence of the vasa as the presence of the seminal vesicles depends on the existence of the vasa which embryologically give rise to the former. On the other hand, the presence of fructose only rules out bilateral obstruction of the ejaculatory ducts but does not assure ductal patency throughout the vasa and epididymi. Therefore, in a setting of azoospermia and a normal testicular biopsy, vasograms should be obtained to identify the site of ob-

struction which can be corrected surgically by microsurgical techniques, depending on its location.

Predominence of a Single Abnormal Parameter

Approximately a third of subfertile male patients will have a semen analysis characterized by the predominence of a single abnormal parameter, most commonly sperm viability/motility. Asthenospermia, a decrease in sperm motility below 60%, can be caused by a number of factors including sperm immobilizing antibodies, infection, endocrinopathy, varicocele, and epididymal dysfunction.

It is now widely appreciated that testicular spermatozoa acquire their fertilizing capacity and motility as they pass through the epididymis. Important for these considerations is the fact that testosterone is transported, bound to androgen-binding-protein, from the seminiferous tubular fluid to the epididymis in concentrations about 20 times that of serum. In the epididymis, the antigen-binding-protein disappears and the free testosterone diffuses into the epididymal cell. Therefore, the functional integrity of the epididymis may be compromised either by failure of the Leydig cells to produce high enough local concentrations of testosterone, by failure of the Sertoli cells to produce adequate amounts of androgen-binding-protein, or by failure of the epididymal epithelium to utilize effectively the free testosterone. In any event, the end result is a local epididymal environment not optimal for the normal development of sperm motility. Therapy is directed at improving the local epididymal environment by the administration of gonadotropins which stimulate Leydig cell production of testosterone and androgen-binding-protein by the Sertoli cells. Therapy has been effective in somewhat less than half the patients so treated. Low-dose androgen therapy in the form of fluoxymesterone (Halotestin) 2-5 mg, b.i.d., has not been effective.

Additionally, epididymal dysfunction may be secondary to complete or partial obstruction, or to changes in the functional integrity of the epididymis itself due to such conditions as epididymitis. Treatment is directed at the specific disorder and involves short-circuiting the obstruction by microsurgical techniques and by appropriate antibiotic treatment of the epididymitis.

The most profound manifestation of a viability-motility/disorder is necrospermia which fortunately is rare as there is no successful treatment.

In patients with high ejaculate volumes (>3.5 ml) and a secondary decrease in sperm count (oligospermia of less than 20 million/ml), sperm density may be improved in about 80% of patients by use of the split-ejaculate technique. To collect a split or fractionated ejaculatory specimen, the patient is given two collection jars which are numbered #1 and #2 and secured together with adhesive tape. The first one third of the ejaculate is collected in jar #1 and the remainder in jar #2. In 80% of patients, the sperm density will be significantly higher in the first portion of the ejaculate. The more favorable first portion may be delivered to the cervical os by a withdrawal coital technique (penis withdrawn from the vagina after the first spurt of ejaculate) or by insemination. In properly selected cases, pregnancy results are about 60%.

Diffuse Abnormality of All Seminal Parameters

The most common (60%) abnormal presentation of the semen analysis is a diffuse abnormality of all seminal parameters, that is, low sperm density, poor sperm viability, and more than 40% abnormal sperm forms. While nonspecific stress, subclinical endocrinopathy, and epididymal dysfunction or block are rare causes of diffuse seminal abnormality, they must nevertheless be considered and treated.

However, the most common cause of diffuse seminal abnormality is a varicocele which accounts for one third of all cases of male infertility. The varicose enlargement of the veins of the spermatic cord (pampiniform plexus) is caused by valvular incompetence of the internal spermatic vein with secondary retrograde flow of venous blood from the left renal vein into the internal spermatic vein. Because of the characteristic anatomy of the internal spermatic vein on the left side, varicoceles clinically occur more commonly on that side, that is, 80% left, 19% bilateral, and 1% right. Even if a varicocele is clinically limited to one side, venous dilatation occurs bilaterally due to the liberal cross-venous circulation of the pampiniform plexus, and the germinal epithelium of both testes is pathologically affected.

Varicoceles are best diagnosed with the patient standing erect as recumbency will decompress the varices. Small varicoceles can be more readily appreciated by having the patient perform a Valsalva maneuver. The diagnosis of small, subtle, and even subclinical varicoceles can be facilitated by use of the Doppler stethoscope[8]; their diagnosis is equally important as there is no correlation between the size of the varicocele and the reduction in spermatogenesis based on testicular biopsies and semen analyses.[9]

The mechanism whereby the varicocele causes

the deleterious effect on the germinal epithelium remains unresolved. But of the two principal postulated causes (venous reflux of adrenal "toxins" vs increased intrascrotal temperatures secondary to venous stasis), the weight of recent evidence favors elevated intrascrotal temperatures as the probable cause of depressed spermatogenesis.

The treatment of varicoceles is surgical and is directed at preventing retrograde venous flow by interrupting the course of the internal spermatic vein at the level of the inguinal canal (Ivanissevich method)[10] or the retroperitoneum (Palomo procedure).[11] Attempts to directly remove the dilated scrotal veins through a transscrotal incision are to be avoided as they are not effective.

The overall results of surgery are excellent with an improvement in semen quality of 70% and a pregnancy rate of 45%.

Conclusion

The prognosis for a previously infertile couple of achieving a pregnancy has improved substantially over the past 5-8 years. This has been made possible by a variety of diagnostic and therapeutic advances based on a greater understanding of testicular and epididymal function and disorder, hypothalamic-pituitary-gonadal interrelationships, and reproductive immunological and physiological factors. This knowledge, combined with a more comprehensive and systematic approach to the evaluation and management of the infertile male patient, has made possible the identification of the cause in 80% of patients as well as effective therapy in approximately 50% of couples under the age of 30 and approximately one third of those who are older.

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Maxillary and Mandibular Jaw Size in Pre-Columbian Peru

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Introduction

Varying techniques of measurement coupled with lack of sufficient data have presented great difficulties in the comparison of dental arch dimensions obtained by different workers. Several authors[1-7] have attempted to delineate the arches. Lavelle et al[7] measured the dental arches of adults from several different ethnic groups and found little difference between the modern British Caucasian, Australian aborigines, and North American Indians. They did, however, see considerable differences between these modern populations and a group of Anglo-Saxons and a group of West Africans.

Several studies[8-10] have shown that there has been a reduction in the dimensions of the maxilla and mandible in modern times, although no reduction in tooth size was reported. A variety of explanations have been put forth to explain this reduction in jaw size, among them evolutionary change[11] and consistency of diet.[12] Others[13-16] have shown that bone size is affected by mechanical stress or the lack of it. Since the modern diet is softer than that of past periods, it is reasoned that the soft diet requires less mechanical force to masticate and thus less mechanical stress on the bone. This reduction in mechanical stress is assumed then to lead to reduction of jaw size.

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The present study was undertaken to investigate any changes in jaw size that occurred within the time period (2300 years) encompassed by the six pre-Columbian Peruvian cultures studied, and from that period to modern times.

Materials and Methods

Measurements were made on 84 adult maxillae and 114 adult mandibles from the pre-Columbian Peruvian material housed in the Museo Regional de Ica, Ica, Peru; these were made up of the following number of specimens from each of the six cultures: Paracas, 33 maxillae and 33 mandibles; Nazca, 6 maxillae and 20 mandibles; Huari, 10 maxillae and 14 mandibles; Ica, 19 maxillae and 24 mandibles; Inca, 1 maxilla and 2 mandibles; and Colonial, 15 maxillae and 21 mandibles. These six cultures flourished during the following periods: Paracas, 600 BC–AD 100; Nazca, 100 BC–AD 800; Huari, AD 800–AD 1200; Ica, AD 1200–AD 1450; Inca, AD 1450–AD 1532; and Colonial, AD 1534–AD 1700. The dating of this material was carried out by both archaeological and C-14 dating. Sex determinations were carried out as outlined by Allison and Gerszten,[17] although these could not be made accurately on some of the material; the values for this unsexed material appear in the tables under the heading "unknown."

A total of 12 jaw dimensions were measured; 4 of the maxilla and 8 of the mandible. The dimensions of arch width were measured between the centers of the corresponding teeth on each side of the dental arch at the first premolars, first molars and second molars in both the maxillae and mandibles. Maxillary arch length was measured as outlined by Moyers.[18] All measurements of the maxilla were made using dial calipers with an accuracy of 0.1 mm. Measurements of the mandible were taken[19] using dial calipers with an accuracy of 0.1 mm and a mandibular board. While the measurements of the maxillary and mandibular arch widths at the first premolar and the first and second molars have been explained, the maxillary arch length and the other mandibular measurements must be defined. Maxillary arch length was measured by laying a bar across the central fossae of the first molars and measuring from the midline point along this bar to the incisal edge of the central incisors. The mandibular angle is the angle between the standard horizontal plane and the ramal planes. The height of the ramus is from the most superior point on the left condyle to the standard horizontal plane (base of mandibular board) measured in the vertical plane. The body length is from the most anterior point in the symphysis area to the intersection of the standard horizontal and ramal planes. Bigonial width is the maximum width between the right and left gonion of the mandible. Bicondylar width is the maximum width between the lateral points of the right and left condyles. Although Hrdlička[4] states that bicondylar measurement is completely useless as the width is affected by the width of the skull at its base, many other authors have used bicondylar measurement to define the mandibular arch and it is, therefore, included in this study.

While 84 adult maxillae and 114 adult mandibles were measured, all totals for each of these measurements will not come to these numbers because of missing teeth, fractured condyles, and other factors.

Results

Females in all cultures shown in Table 1 have the larger maxillary arch size in three of the four measurements made. Maxillary arch width at the first premolar is larger in males in all cultures except the Ica. No reduction of maxillary arch size is seen during the approximately 2300-year period studied in this pre-Columbian Peruvian culture except in the width of the arch at the first molar; a reduction is seen here from the most ancient cultures studied to the most modern. The Inca culture exhibited the smallest maxillary arch length while the Huari culture, followed closely by the Nazca, showed the greatest. The smallest arch width at the maxillary first premolar was seen in the Inca culture and the Colonial exhibited the largest width. The largest arch width at the maxillary first molar was seen in the Nazca culture; the Colonial had the most narrow arch at the first molars. The Huari displayed the smallest and the Ica the largest arch widths at the maxillary second molars.

Table 2 gives five mandibular jaw measurements. The males of this pre-Columbian Peruvian population exhibited the larger arch width at the first mandibular molar, the larger bigonial width, and the larger bicondylar width; other measurements presented (mandibular arch width at the first premolar and second molar) were similar in both sexes. A trend toward smaller mandibular jaw size was evident by a reduction in jaw size at the first molar, second molar, and bigonial widths. The Nazca culture and the Paracas culture had the largest mandibular arch widths at the first premolars. The arch width at the first and second mandibular molars and the bigonial width

TABLE 1
Maxillary Arch Measurements

	Maxillary arch length				Maxillary arch width at first premolar				Maxillary arch width at first molar				Maxillary arch width at second molar			
Culture	M	F	U	T	M	F	U	T	M	F	U	T	M	F	U	T
Paracas																
N	0	0	6	6	0	0	22	22	0	0	33	33	0	0	28	28
Mean	—	—	25.4	25.4	—	—	39.6	39.6	—	—	48.8	48.8	—	—	53.6	53.6
S.E.	—	—	0.9	0.9	—	—	0.6	0.6	—	—	0.6	0.6	—	—	2.8	2.8
Nazca																
N	1	0	3	4	1	1	4	6	1	0	5	6	1	1	3	5
Mean	22.7	—	27.2	26.1	36.1	36.1	39.9	39.8	53.4	—	49.6	50.3	57.0	51.4	54.3	54.3
S.E.	0.0	—	1.1	1.4	0.0	0.0	0.7	1.0	0.0	—	0.3	0.7	0.0	0.0	1.8	1.3
Huari																
N	1	0	4	5	1	1	4	6	1	2	7	10	1	2	6	9
Mean	27.0	—	26.8	26.8	40.3	36.3	39.9	39.4	47.2	48.0	47.8	47.8	52.3	52.8	53.1	52.9
S.E.	0.0	—	1.0	1.0	0.0	0.0	0.8	0.8	0.0	2.5	1.1	0.8	0.0	2.9	1.0	0.8
Ica																
N	1	9	4	14	1	13	1	15	1	11	7	19	1	7	2	10
Mean	25.3	27.0	26.2	26.7	39.4	39.7	39.0	39.6	50.7	48.7	45.8	47.8	52.7	54.6	56.7	54.8
S.E.	0.0	0.7	0.9	0.5	0.0	0.5	0.0	0.4	0.0	0.8	1.9	0.9	0.0	0.7	0.7	0.6
Inca																
N	0	0	1	1	0	0	1	1	0	0	1	1	0	0	1	1
Mean	—	—	24.8	24.8	—	—	36.9	36.9	—	—	47.9	47.9	—	—	54.2	54.2
S.E.	—	—	0.0	0.0	—	—	0.0	0.0	—	—	0.0	0.0	—	—	0.0	0.0
Colonial																
N	0	12	3	15	2	12	0	14	1	10	2	13	1	11	0	12
Mean	—	24.9	25.9	25.1	42.4	40.0	—	40.3	45.6	48.3	46.4	47.8	52.3	53.6	—	53.5
S.E.	—	0.4	1.2	0.4	0.3	0.6	—	0.5	0.0	0.6	1.0	0.5	0.0	0.7	—	0.7

M = male
F = female
U = sex unknown
T = total
N = number
S.E. = standard error

were larger in the Nazca culture. The Huari, followed closely by the Nazca culture, had the greatest bicondylar width. The mandibular jaw size measurements presented in Table 2 were consistently smaller in the Inca culture, although this figure can be misleading due to the small sample size.

For three other mandibular jaw measurements (mandibular angle, ramus height, and body length) presented in Table 3, the male specimens in this study have the larger measurements, although no reduction in jaw size is seen from the most ancient to the most modern cultures. The Paracas culture exhibits the largest mandibular angle and the Nazca the smallest in this pre-Columbian Peruvian population. The Paracas culture shows the smallest ramus height and the Colonial has the greatest. In examining the body length measurements, the Nazca culture specimens have the longest mandibular body and the Inca have the shortest.

Discussion

The size and shape of the dental arches are subject to considerable variation.[3] Factors such as growth[20] and the location of the teeth in relation to

TABLE 2
Mandibular Jaw Width

	Mandibular arch width at first Premolar				Mandibular arch width at first Molar				Mandibular arch width at second Molar				Bigonial width				Bicondylar width			
Culture	M	F	U	T	M	F	U	T	M	F	U	T	M	F	U	T	M	F	U	T
Paracas																				
N	0	0	19	19	0	0	18	18	0	0	14	14	1	1	28	30	1	1	30	32
Mean	—	—	34.9	34.9	—	—	44.8	44.8	—	—	49.8	49.8	96.0	96.0	93.3	93.5	121.5	112.0	116.9	116.9
S.E.	—	—	0.5	0.5	—	—	0.6	0.6	—	—	0.7	0.7	0.0	0.0	1.4	1.3	0.0	0.0	1.7	1.6
Nazca																				
N	1	1	10	12	1	1	14	16	1	0	13	14	1	1	18	20	1	1	18	20
Mean	35.5	35.4	34.8	34.9	48.2	43.7	46.5	46.4	55.7	—	51.4	51.7	90.0	81.5	95.0	95.8	111.0	118.0	118.5	118.1
S.E.	0.0	0.0	0.5	0.4	0.0	0.0	0.4	0.4	0.0	—	0.4	0.6	0.0	0.0	2.1	2.4	0.0	0.0	1.3	1.3
Huari																				
N	1	2	8	11	1	1	7	9	1	0	6	7	2	2	9	13	2	2	9	13
Mean	32.5	33.8	34.1	33.9	42.6	42.3	45.9	45.2	47.0	—	51.6	50.9	101.5	85.8	93.4	93.5	124.0	120.5	118.1	118.6
S.E.	0.0	0.4	0.6	0.5	0.0	0.0	0.4	0.6	0.0	—	1.2	1.2	0.0	0.2	1.7	1.7	1.0	2.5	2.3	1.8
Ica																				
N	2	14	4	20	1	11	8	20	1	10	1	12	4	16	7	27	4	17	7	28
Mean	37.2	35.0	33.3	34.9	49.2	45.5	44.4	44.9	52.4	49.8	56.3	50.4	94.1	93.6	90.4	92.8	119.3	118.9	117.2	118.5
S.E.	2.5	0.5	1.2	0.5	0.0	0.8	1.1	0.7	0.0	0.6	0.0	0.8	3.0	1.3	2.2	1.4	1.8	1.2	3.0	1.1
Inca																				
N	0	0	1	1	0	0	1	1	0	0	1	1	0	1	1	2	0	1	1	2
Mean	—	—	31.3	31.3	—	—	42.6	42.6	—	—	48.1	48.1	—	94.0	88.0	91.0	—	118.5	111.0	114.8
S.E.	—	—	0.0	0.0	—	—	0.0	0.0	—	—	0.0	0.0	—	0.0	0.0	3.0	—	0.0	0.0	3.8
Colonial																				
N	3	16	1	20	1	9	0	10	0	10	0	10	3	18	2	23	3	17	1	21
Mean	34.3	35.0	32.8	34.7	43.8	43.3	—	43.3	—	48.6	—	48.6	95.2	90.0	80.8	88.0	121.7	116.7	115.0	117.3
S.E.	0.8	0.4	0.0	0.4	0.0	0.2	—	0.2	—	0.6	—	0.6	2.6	1.7	1.8	1.6	3.4	1.0	0.0	1.0

M = male
F = female
U = sex unknown
T = total
N = number
S.E. = standard error

TABLE 3
Other Mandibular Measurements

	Mandibular Angle				Ramus Heighth				Body Length			
Culture	M	F	U	T	M	F	U	T	M	F	U	T
Paracas												
N	1	1	31	33	1	1	30	32	1	1	29	31
Mean	115.0	121.5	121.3	121.1	63.0	53.5	56.8	56.9	82.0	71.5	74.1	74.3
S.E.	0.0	0.0	1.0	1.0	0.0	0.0	1.2	1.1	0.0	0.0	1.0	1.0
Nazca												
N	1	1	18	20	1	1	18	20	1	1	18	20
Mean	118.0	114.5	118.0	117.9	60.0	55.0	60.1	59.8	68.5	68.0	78.3	77.3
S.E.	0.0	0.0	1.7	1.5	0.0	0.0	1.0	1.0	0.0	0.0	1.3	1.3
Huari												
N	2	2	10	14	2	2	10	14	2	2	10	14
Mean	123.5	116.5	119.8	119.8	60.8	55.8	59.6	59.2	76.2	76.3	73.1	74.7
S.E.	3.0	5.0	1.7	1.4	2.3	1.8	2.3	1.7	1.2	2.8	2.5	2.1
Ica												
N	4	16	5	25	4	17	6	27	4	16	8	28
Mean	119.5	116.9	122.0	118.3	59.0	60.2	59.4	60.6	78.9	75.3	73.3	74.1
S.E.	3.8	1.3	3.5	2.4	1.7	0.8	1.8	0.6	2.1	1.0	2.4	1.2
Inca												
N	0	1	1	2	0	1	1	2	0	1	1	2
Mean	—	121.5	116.0	118.8	—	54.5	59.5	57.0	—	71.0	74.0	72.5
S.E.	—	0.0	0.0	2.8	—	0.0	0.0	2.5	—	0.0	0.0	1.5
Colonial												
N	3	17	2	22	3	16	2	21	3	16	2	19
Mean	117.0	117.5	124.5	118.5	62.3	60.0	56.3	60.0	74.8	75.6	76.0	75.0
S.E.	5.6	1.6	0.0	1.5	2.0	1.1	1.3	1.0	1.4	1.0	0.0	0.0

M = male
F = female
U = sex unknown
T = total
N = number
S.E. = standard error

the basal bone[21] have been shown to influence arch size and shape. Gould and Picton[22] pointed out that the equilibrium between the adjacent orofacial musculature and the arch affects its size and shape. The degree of tooth attrition or abrasion has also been noted to affect arch size and shape. Several of these factors, particularly attrition and growth, could have influenced jaw size and shape in this study, giving the wide degree of variation seen between and within the cultural groups.

Studies of Swedish maxillae and mandibles,[8] British palates[10] and dental arches,[23] and European mandibles,[24] have all shown a reduction in jaw dimensions in recent times in Europe. Several of these studies have also shown that this reduction was not accompanied by a corresponding diminution in tooth size. The present study shows a reduction in the width of the maxillary arch at the first molar during the time period studied. The most recent pre-Columbian Peruvian cultures also showed a reduction in jaw size in the mandible as noted in the diminution of arch width at the first and second molars and in the bigonial width. This reduction in jaw dimensions in more recent times was, however, accompanied by a corresponding reduction in tooth size.[25]

Many authors[26,27,12] have blamed this reduction

of jaw size on soft diet. The soft diet requires little mechanical force to masticate and thus less stimulation of the bone. If changes in the consistency of the diet were the principal factor responsible for this reduction, then the mandibular ramus would be reduced in size.[28] One should bear in mind that the mandibular ramus is the point of insertion of the muscles of mastication. In the present study, while a reduction in jaw size was exhibited by the more modern cultures as compared to the earlier ones, a reduction in the mandibular ramus was not seen. Although the presumptive evidence is strong that the reduction of the jaws is the direct result of less mechanical stress produced by the mastication of a soft diet in some studies, the possibility that genetic change may also be involved cannot be completely ruled out. Archaeological study of these cultures has shown that while differences in diet were seen between "inland" and "coastal" cultures, little change occurred in the diet within these groups over the period studied. The influx of outside groups of individuals into the cultures studied, either by conquest or peaceful assimilation, could have resulted in the acquisition of new genetic traits, which leaves open the possibility that genetic change has influenced the reduction in jaw size.

Conclusion

In this study of 84 adult maxillae and 114 adult mandibles a reduction in jaw dimensions was seen in the more modern cultures. This reduction could not be explained by diet alone and the possibility that genetic change from gene mutation or population migration is suggested. Due to the small number of male specimens identified in this population, few, if any, valid comparisons can be made between the sexes concerning jaw dimensions. Future studies should be conducted to remedy this discrepancy.

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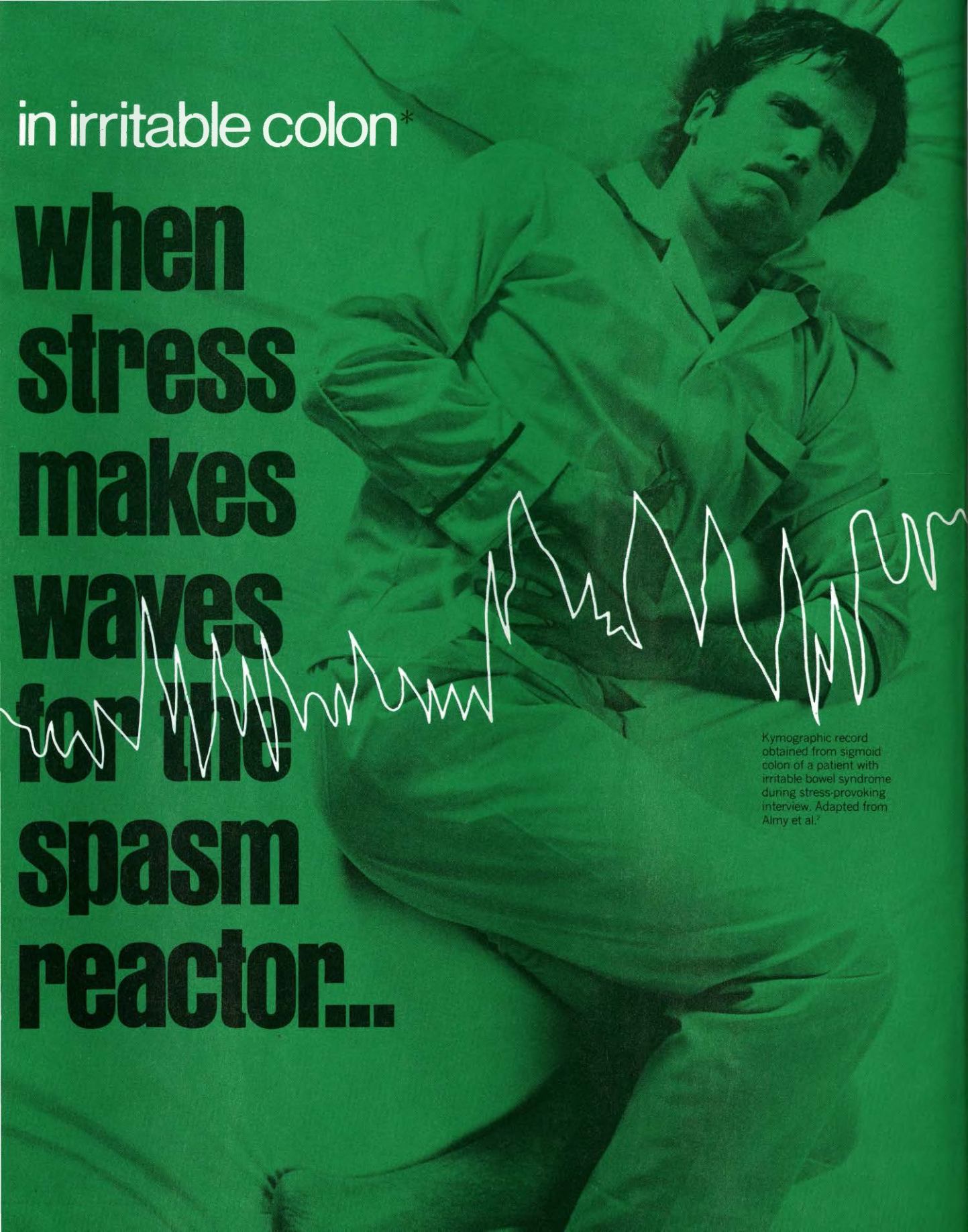

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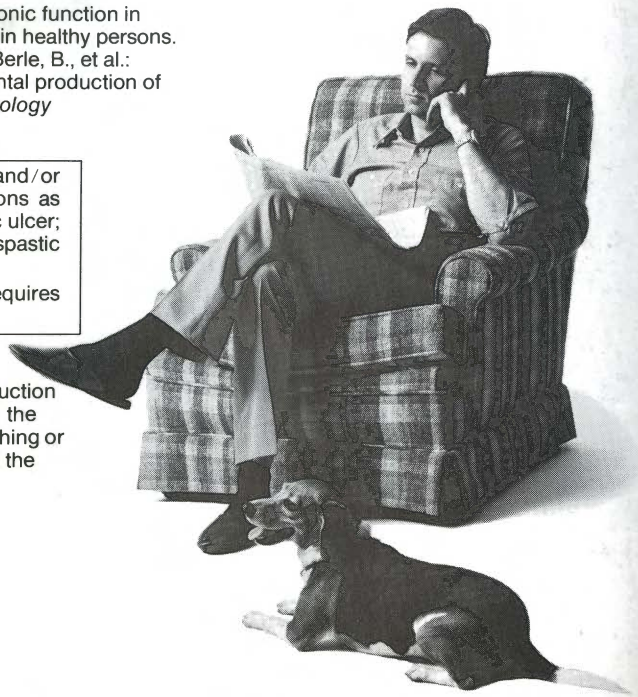

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