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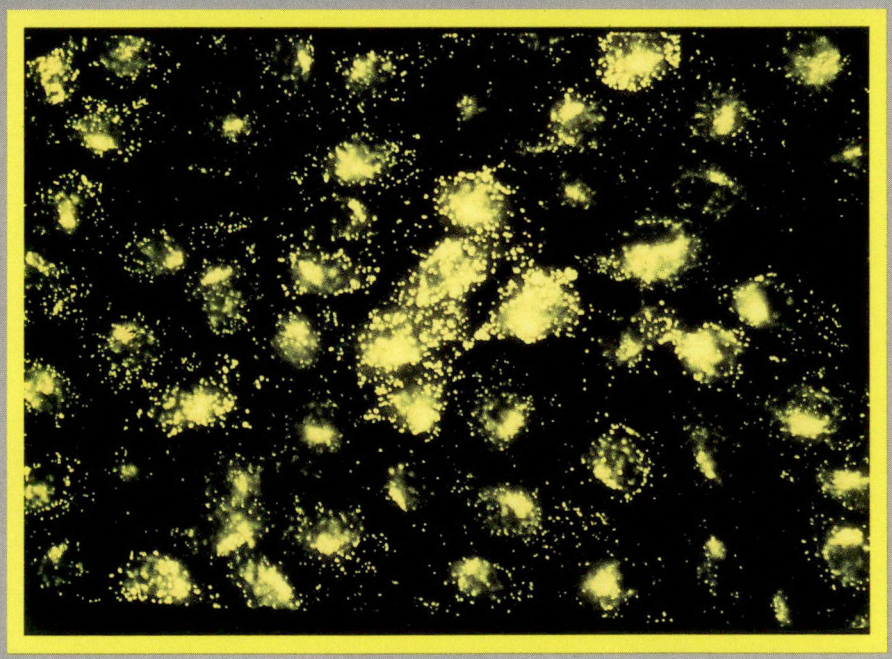

- Neoadjuvant Treatment, Local Control Sarcomas
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← For prescribing information see page 382

ORIGINAL ARTICLES

Cover picture

Immunofluorescent staining of pulmonary artery epithelial cells using anti-Factor VIII fluorescein-labelled monoclonal antibodies. (Courtesy of J. Hobson and R. Thies, St. Paul's Hospital Pulmonary Research Laboratory, Vancouver, BC.) (See editorial pages 317 and 319.)

Treatment of Advanced Cancer of the Prostate

W.L. Orovan, MD, FRCSC, FACS

Associate Professor of Surgery (Urology), McMaster University. Chief, Department of Surgery, St. Joseph's Hospital, Hamilton, Ont.

After the pioneering work of Charles Huggins and Clarence Hodges in 1941,[1] who demonstrated the efficacy of androgen deprivation in palliative treatment of advanced prostatic cancer, there were few new developments in this field. Large studies carried out in the United States by the Veterans Administration Cooperative Urological Research Group (VACURG)[2] in the 1970s did confirm improvement in symptom-free intervals, but no study has demonstrated conclusively a survival benefit for patients treated with androgen manipulation.[3] The two major modalities of hormone manipulation used during this time were bilateral orchiectomy and the administration of exogenous estrogens in doses ranging from 1 to 5 mg/d. The latter, especially at higher dosage, was associated with an increased risk of cardiovascular complications and death. Benefits of treatment were not universal; only about 75% of patients responded and the median duration of response was about 3 years.[4]

In the late 1970s and early 1980s, partly in response to the cardiovascular risk factors identified with exogenous estrogen and the reluctance of some patients to undergo surgical orchiectomy, alternative means of hormone manipulation became available. These agents fit broadly into three categories: luteinizing hormone-releasing hormone (LHRH) analogues, antiandrogens and the synthetic imidazoles.

The LHRH agonists act primarily on the central feedback control of luteinizing hormone release. An initial surge of luteinizing hormone can precipitate a transient increase of the patient's symptoms (flare reaction), but subsequently a reduction in circulating androgens to castrate level occurs. The LHRH

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Detailed instructions to contributors, in English and French, appear on page 14 of the January 1989 issue.

All prescription drug advertisements in the Journal have been precleared by the Pharmaceutical Advertising Advisory Board.

agents are administered by subcutaneous injection, either daily or, more recently, monthly in timed-release form. Side-effects have been less severe than those noted with exogenous estrogens and an equivalent treatment benefit has been documented.[5]

The antiandrogens, cyproterone acetate (Adrocur) and flutamide (Euflex), can be administered orally. They have proven equivalent in efficacy to exogenous estrogens or surgical castration and in addition provide benefit by reducing the incidence of treatment complications.[6]

The duration of response to hormone manipulation is limited and virtually all patients will eventually relapse and the disease will progress. Treatment options available for this apparently androgen-independent or "hormonally escaped" treatment group are limited.

Cytotoxic chemotherapy using cyclophosphamide, 5-fluorouracil, Adriamycin and others, either individually or in combination regimens, have given mixed results. Administration of these toxic agents in generally aged and debilitated patients, many of whom manifest other cardiovascular or pulmonary diseases, has severely limited their effectiveness.

In this issue of the Journal (pages 349 to 352), Eichenberger and Trachtenberg present their early findings with the use of synthetic imidazoles to treat patients with androgen-independent prostatic cancer. They note that the imidazole ketoconazole, primarily an antifungal agent, when used frequently at a high dose has been demonstrated to inhibit the production of both adrenal and testicular androgens. Studies in patients with previously untreated advanced prostatic cancer have demonstrated that this compound can produce castrate levels of circulating androgens;[7] thus, it represents an alternative in the first-line treatment of advanced prostatic cancer. Moreover, the authors suggest that these compounds may also have a role in the treatment of androgen-independent or "hormonally escaped" patients. The data from this uncontrolled study suggest subjective improvement in symptoms as reflected by the patients' reduced need for analgesics and a trend toward halting the progression of disease in some patients. The latter finding must be treated with some skepticism in view of the variable rate at which the disease progresses.

Of interest is the authors' assertion that no significant difference in duration of response could be demonstrated between the patients who had been treated with conventional forms of androgen ablation and the 14 patients who failed total androgen ablation. The concept of total androgen ablation was introduced by Labrie and associates,[8] who contended that simple ablation of testicular androgens is insufficient for adequate hormonal treatment and that total androgen deprivation, including adrenal sources, must be effected before an adequate response of hormone-dependent prostatic cancer can be achieved. This controversial theory is at present being evaluated by a randomized prospective trial in the United States. The finding of Eichenberger and Trachtenberg that ketoconazole seems to affect both groups equally suggests that ketoconazole may, in fact, have a non-androgen-based effect on prostatic cancer. The authors quote one in-vitro study[9] to support this contention and speculate about the site of action of direct cytotoxic effects of ketoconazole on androgen-independent human prostatic cancer cells.

With the rapid evolution of alternative hormonal treatment options for advanced prostatic cancer, the most difficult clinical problem remains that of androgen-independent late-stage disease. The usefulness of ketoconazole in this context remains to be defined but the early results quoted by Eichenberger and Trachtenberg give some reason for optimism.

If the authors' contentions are borne out through further in-vitro and prospective randomized controlled clinical trials, this will represent an important advance in the treatment of this difficult and common malignant condition.

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Monoclonal Antibodies — Gazing Into the Submicroscopic

Nis Schmidt, MD, MSc, FRCSC

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Humans have always been dissatisfied with their limitations. Climbing onto horseback extended their ability to travel; harnessing steam increased muscle power out of all proportion; computerization expanded the capacity to store and sort data beyond expectation. Raising antibodies to protein antigenic material is going beyond the microscope when appropriate labelling and manipulation of these complex biologic substances are carried out. Monoclonal antibodies, developed in 1975 by Köhler and Milstein,[1] opened a new era in immunobiology which continues to expand in exponential shock waves, touching all aspects of medicine and surgery in areas of diagnosis, prophylaxis, treatment and research.

The July issue of the *Canadian Journal of Surgery* (pages 279 to 282) contained an article entitled "Immunohistologic diagnosis of multiple carcinomas. The role of monoclonal antibodies against carcinoembryonic antigen" by Guiot and associates, in which they present a whole new world of diagnostic possibilities by using anti-carcinoembryonic antigen (CEA) monoclonal antibodies to differentiate and clarify the relationship between multiple adenocarcinomas in individual patients. Five cases were presented in which the monoclonal antibodies helped to differentiate the multiple carcinomas and to arrive at an appropriate plan of management. In each case, the diagnostic problem was ascertaining the nature of a second tumour in patients with a history of colonic cancer. The question concerned the treatment of a second tumour as a separate entity or as a metastasis from the colonic cancer.

The application of this new biologic science to diagnosis is far from simple. Initially, the antibodies developed were mouse and rodent xenoantibodies, and they were associated with the expectant problems of foreign proteins. For diagnostic and therapeutic application, human antibodies are obviously more desirable. The antibody used by Guiot and colleagues was a mouse anti-CEA antibody (D14), which has been shown to be quite specific and sensitive to CEA, hence the success in their investigation. Human monoclonal antibodies for routine use in diagnosis and investigation are yet to come.

Monoclonal antibodies were the result, initially, of sensitizing laboratory animals with viable lymphoid and myeloma cell lines, resulting in antibodies with detectable sensitivity but poor specificity. The evolution of clones of cells has allowed greater sensitivity and specificity of the antibodies, and research is now at the point where the established names and catalogued antibodies are available for diagnostic, therapeutic and research activities the world over. Refinements of the process now identify not only cell lines but cell surface receptor antigens, even protein molecules and genetically manipulated material, all of which have become feasible as specific antigenic material to raise antibodies of high sensitivity and specificity. In addition to raising and purifying the antibodies, labelling procedures add immunofluorescent, immunoenzymatic and immunonucleotide tags, greatly adding to the scope and use in practical and research procedures. For example, immunofluorescence has facilitated the development of practical cell sorters and cell counters for laboratory use in hematology.

Besides the use of monoclonal antibodies for imaging and investigational purposes, monoclonal antibody toxin conjugates open up possibilities of aiming "magic bullets". Antibody toxin conjugates will find extensive application in immunosuppression. Antibody pharmaceutical conjugates conceivably will find use in specific antigen selectivity for tumour therapy, antimicrobial therapy and the suppression and treatment of diseases for which cellular secretion can be suppressed or ablated.

Much of this is still conjectural, since the cloning of cell lines, isolation of antigens, purification and accumulation of the antibody, re-

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PRESCRIBING INFORMATION

ACTIONS
Ciprofloxacin, a synthetic fluoroquinolone, has a bactericidal mode of action. This action is achieved through inhibition of DNA gyrase, an essential component of the bacterial DNA replication system. Inhibition of the alpha subunit of the DNA gyrase blocks the resealing of the nicks on the DNA strands induced by this alpha subunit, leading to the degradation of the DNA by exonucleases. This bactericidal activity persists not only during the multiplication phase, but also during the resting phase of the bacterium.

Ciprofloxacin retained some of its bactericidal activity after inhibition of RNA and protein synthesis by rifamycin and chloramphenicol, respectively. These observations suggest ciprofloxacin may possess two bactericidal mechanisms, one mechanism resulting from the inhibition of DNA gyrase and a second mechanism which may be independent on RNA and protein synthesis.

INDICATIONS AND CLINICAL USES
CIPRO® (Ciprofloxacin Hydrochloride Monohydrate) may be indicated for the treatment of patients with the following infections caused by susceptible strains of the indicated microorganisms:

RESPIRATORY TRACT INFECTIONS:
Acute bronchitis and acute pneumonia caused by:

Enterobacter cloacae	*Proteus mirabilis*
Escherichia coli	*Pseudomonas aeruginosa*
Haemophilus influenzae	*Staphylococcus aureus*
Klebsiella pneumoniae	*Streptococcus pneumoniae*

Due to the nature of the underlying conditions which usually predispose patients to *Pseudomonas* infections of the respiratory tract, bacterial eradications may not be achieved in patients who display clinical improvement despite evidence of *in vitro* sensitivity. In patients requiring subsequent courses of therapy, CIPRO® should be used alternately with other anti-pseudomonal agents. Some strains of *Pseudomonas aeruginosa* may develop resistance during treatment. Therefore, susceptibility testing should be performed periodically during therapy to detect the emergence of bacterial resistance.

URINARY TRACT INFECTIONS:
Upper and lower urinary tract infections, such as complicated and uncomplicated cystitis, pyelonephritis, and pyelitis, caused by:

Citrobacter diversus	*Proteus mirabilis*
Citrobacter freundii	*Pseudomonas aeruginosa*
Enterobacter cloacae	*Serratia marcescens*
Escherichia coli	*Staphylococcus aureus*
Klebsiella pneumoniae	*Staphylococcus epidermidis*
Klebsiella oxytoca	*Streptococcus faecalis*
Morganella morganii	

SKIN AND SOFT TISSUE INFECTIONS:
caused by:

Enterobacter cloacae	*Pseudomonas aeruginosa*
Escherichia coli	*Streptococcus pyogenes*
Klebsiella pneumoniae	*Staphylococcus aureus*
Proteus vulgaris	*Staphylococcus epidermidis*
Proteus mirabilis	

BONE AND JOINT INFECTIONS:
caused by:

Enterobacter cloacae	*Serratia marcescens*
Pseudomonas aeruginosa	*Staphylococcus aureus*

INFECTIOUS DIARRHEA: (When antibacterial therapy is indicated)
caused by:

Escherichia coli (enterotoxigenic strains)	*Shigella flexneri*
Campylobacter jejuni	*Shigella sonnei*

Appropriate culture and susceptibility tests should be performed prior to initiating treatment in order to isolate and identify organisms causing the infection and to determine their susceptibilities to ciprofloxacin. Therapy with CIPRO® may be initiated before results of these tests are known. However, modification of this treatment may be required once results become available or if there is no clinical improvement. Culture and susceptibility testing performed periodically during therapy will provide information on the possible emergence of bacterial resistance.

CONTRAINDICATIONS
CIPRO® (Ciprofloxacin Hydrochloride Monohydrate) is contraindicated in patients who have shown hypersensitivity to ciprofloxacin or other quinolone antibacterial agents.

WARNINGS
Children
The safety of CIPRO® (Ciprofloxacin Hydrochloride Monohydrate) in children has not yet been established. Damage to juvenile weight-bearing joints and lameness were observed both in rat and dog studies but not in weaned piglets (see Product Monograph: TOXICOLOGY). Histopathological examination of the weight-bearing joints of immature dogs revealed permanent lesions of the cartilage. Consequently, CIPRO® should not be used in prepubertal patients.

Pregnancy
The safety of CIPRO® in the treatment of infections in pregnant women has not yet been established (see PRECAUTIONS).

PRECAUTIONS
General
Anaphylactic reactions including cardiovascular collapse have occurred rarely in patients receiving therapy with CIPRO® (Ciprofloxacin Hydrochloride Monohydrate). These reactions have occurred within the first 30 minutes following the first dose and may require epinephrine and other emergency measures.

CIPRO® may cause central nervous system (CNS) stimulation which may lead to tremor, restlessness, light-headedness, confusion, and very rarely to hallucinations or convulsive seizures. Therefore, CIPRO® should be used with caution in patients with CNS disorders, such as severe cerebral arteriosclerosis or epilepsy. Patients with known convulsive seizure disorders should only be treated with CIPRO® if anticonvulsive therapy has been initiated.

Crystalluria related to ciprofloxacin has been reported only rarely in man because human urine is usually acidic. Patients receiving ciprofloxacin should be well hydrated and alkalinity of the urine should be avoided. The recommended daily dose should not be exceeded. Crystals of ciprofloxacin have been observed rarely in the urine of human subjects but more frequently in the urine of laboratory animals.

Prolonged use of CIPRO® may result in the overgrowth of nonsusceptible organisms. Careful observation of the patient is therefore essential, and if superinfection should occur during therapy, appropriate measures should be taken.

Pregnancy
The safety of CIPRO® in pregnancy has not yet been established. CIPRO® should not be used by pregnant women unless the likely benefits outweigh the possible risk to the fetus. CIPRO® has been shown to be non-embryotoxic and non-teratogenic in animal studies.

Nursing Mothers
It is not known whether ciprofloxacin is excreted in human milk. However, it is known that ciprofloxacin is excreted in the milk of lactating rats and that other drugs of this class are excreted in human milk. A decision should be made to discontinue nursing or to discontinue the administration of CIPRO®, taking into account the importance of the drug to the mother and the possible risk to the infant.

Drug Interactions
Concurrent administration of ciprofloxacin with theophylline may lead to an elevated plasma concentration and prolongation of elimination half-life of theophylline. This may result in increased risk of theophylline-related adverse reactions. If concomitant use cannot be avoided, plasma concentrations of theophylline should be monitored and dosage adjustments made as appropriate.

Ciprofloxacin has been shown to interfere with the metabolism and pharmacokinetics of caffeine. Excessive caffeine intake should be avoided.

Probenecid blocks renal tubular secretion of ciprofloxacin and has been shown to produce an increase in the level of ciprofloxacin in the serum.

Concomitant administration of a nonsteroidal anti-inflammatory drug with ciprofloxacin has been reported to increase the risk of CNS stimulation and convulsive seizures.

Antacids containing aluminum or magnesium hydroxide have been shown to reduce the absorption of ciprofloxacin. Concurrent administration with these agents should be avoided.

Renal Impairment
Since ciprofloxacin is eliminated primarily by the kidney, CIPRO® should be used with caution and at a reduced dosage in patients with impaired renal function (see DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS
CIPRO® (Ciprofloxacin Hydrochloride Monohydrate) is generally well tolerated. During worldwide clinical investigation, 8,861 courses of ciprofloxacin treatment were evaluated for drug safety. (Included in this evaluation were data from 283 patients who received ciprofloxacin only intravenously and 169 patients who received sequential intravenous/oral ciprofloxacin therapy.)

Adverse events, whether drug-related or not, occurred in 10.2% of patients. These adverse events occurred in the following frequencies: Gastrointestinal System (5.0%), Central Nervous System (1.6%), Skin/Hypersensitivity (1.4%), and Adverse Laboratory Changes (5.6%).

The most frequently reported events, drug-related or not, were nausea (1.6%) and diarrhea (1.2%).

Additional events that occurred in less than 1% of ciprofloxacin courses are listed below:
Gastrointestinal: vomiting, dyspepsia, abdominal pain, anorexia
Central Nervous System: dizziness, light-headedness, headache, nervousness, anxiety, agitation, restlessness, tremor, lethargy, drowsiness, somnolence
Skin/Hypersensitivity: rash, pruritus, local edema, urticaria, increased perspiration, photosensitivity

Most of the adverse events were described as only mild or moderate in severity.

There have been 9 reports of arthropathy associated with CIPRO®. Three of these reports involved children. Arthralgia was usually the first symptom which led to rapid assessment and withdrawal of the drug. No irreversible arthropathies have been observed.

Adverse Laboratory Changes
Changes in laboratory parameters listed as adverse events without regard to drug relationship (5.6%):

Hepatic:	Elevations of: SGPT (1.3%), SGOT (1.4%), Alkaline Phosphatase (0.4%), γ-glutamyl transpeptidase (0.3%), LDH (0.3%), Serum bilirubin (0.1%)
Hematologic:	Eosinophilia (0.6%), leukopenia (0.2%)
Renal:	Elevations of: Serum creatinine (0.3%), BUN (0.3%)

Other changes occurring in less than 0.1% of courses were: elevated uric acid, elevated cholesterol, increase in blood platelets, monocytes, and leukocytes.

SYMPTOMS AND TREATMENT OF OVERDOSE
Overdose has not yet been reported with CIPRO® (Ciprofloxacin Hydrochloride Monohydrate). In the event of acute overdosage, the stomach should be emptied by inducing vomiting or by gastric lavage. The patient should be carefully observed and given supportive treatment.

DOSAGE AND ADMINISTRATION
The determination of dosage for any particular patient must take into consideration the severity and nature of the infection, the susceptibility of the causative organism, and the status of renal function.

CIPRO® (Ciprofloxacin Hydrochloride Monohydrate) may be taken before or after meals. Absorption is faster on an empty stomach. Patients should be advised to drink fluids liberally and not take antacids containing magnesium or aluminum.

finement of sensitivity and specificity, understanding of the interaction of in-vitro and in-vivo responses still depend on untold hours of laboratory time and thought, not to mention all the dollars required to finance the research.

Practical application is, however, well advanced. Testing for carcinoembryonic antigen in gastrointestinal carcinoma and breast cancer estrogen receptor binding is commonplace. Endocrine function studies, including parathormone and adrenocorticotropic hormone levels, are in daily use. "OKT3" antibody, which appears to exact direct immunosuppressive activity and inactivate lymphoid T cells from circulation, is currently being used in the treatment of acute rejection in histocompatible renal grafts and for in-vitro prevention of graft versus host disease in recipients of bone marrow transplants. Monoclonal antibody BB5-M[2] causes stimulation of parathyroid hormone release in human parathyroid cell cultures, indicating that a possible specific cell-surface macromolecule may be operative in the regulation of calcium and parathormone, and this promises control in calcium disorders. Enzyme immunoassay has allowed accurate pregnancy testing in a simple, across-the-counter kit.

The scope of the subject of monoclonal antibodies is overwhelming and beyond a simple editorial review. Suffice it to say that this subject, which only 15 years ago occupied the thought of scientists observing mice in cloistered laboratories, has now evolved sufficiently to influence the everyday clinical practice of surgeons, as described in the article by Guiot and colleagues in their stimulating and imaginative report. It is obvious that if we keep our eyes open, we will be in store for more surprises from the submicroscopic in the area of monoclonal antibodies.

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Ethics of Funding Clinical Investigation

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Recent federal legislation on drug patents has given pharmaceutical manufacturers in Canada prolonged terms of patent protection. In return for this protection, these companies have committed a substantial portion of their income into drug research. As a result, a great deal of "research" money has become available to investigators willing to be involved with clinical trials, and drug testing and reporting.

This research effort has become a major source of funding in many areas, providing space, personnel and equipment. In effect, the drug being evaluated supports the ongoing function of the laboratory and the investigation. In some instances, the result of the study becomes the property of the pharmaceutical company and may not be presented without the company's approval. This type of financial support is also being used to fund conferences and seminars, the subjects of which are related to the pharmaceutical products. Often the entire seminar, including invited speakers and expenses of the organization or university division holding the seminar, is financed by the drug company involved.

The ethical problems involved in this type of "investigation" and reporting are obvious, and just a generation ago would not be condoned in our universities. There is, however, a substantial shortfall of available research funding from granting agencies, particularly for part-time and new researchers and agencies. More and more investigators are turning to industry for support and, indeed, universities at higher levels are fostering joint industry-university projects. Our medical professional organizations at local, national and international levels depend on industry's financial support through commercial exhibits and direct grants to preserve the calibre of meetings and maintain a reasonable registration fee. These companies are providing essential and otherwise unavailable support. In this respect they need to be encouraged.

What is lacking are guidelines regarding this type of investigation and financial support, particularly concerning ethical reporting of this work to physicians and the public. The current, apparently compromised position of the investigator and indeed the profession needs immediate and close scrutiny. The financial need, no matter how worthy, must not compromise the principles of academic investigation and reporting in our institutions. If we, the profession, do not address this subject, other regulating agencies representing the public will. ■

SESAP VI Question

Item 245

The statistical five-year survival rates for cancer may be artificially improved by all of the following EXCEPT

(A) detection of disease with a screening test before symptoms develop

(B) a change in the staging of patients due to earlier detection of metastases

(C) treatment prolonging the disease-free interval

(D) loss of patients to follow-up

(E) an improved method of treatment of disease

For the incomplete statement above, select the one completion that is best of the five given.

For the critique of Item 245 see page 339.

CORRESPONDENCE

Contributions to the Correspondence section are welcome. They should be typewritten and double spaced.

Rupture of the Diaphragm

To the editors. I have just finished reading the article "Spontaneous rupture of the diaphragm in labour: a case report" (*Can J Surg* 1989; 32: 212–213). I read it with interest because I am a general surgeon doing obstetrics and gynecology almost exclusively.

Looking at the sequence of events, I wonder if the authors considered that the diaphragm might have been ruptured by the efforts at cardiopulmonary resuscitation made when the patient suffered a cardiac arrest on the way to the radiology department.

The possibility of a pulmonary embolus or some other catastrophe resulting in cardiac arrest would be more likely than a ruptured diaphragm occurring as a result of labour. Since the patient did not die for 3 weeks, an autopsy to determine possible pulmonary embolism or other causes of her initial pain may not have been helpful.

I would be interested in the authors' comments.

G.E. Rosenquist, MD, FRCSC

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To the editors. Dr. Rosenquist's comments are well taken and obviously it is impossible to exclude completely an alternative explanation for the patient's clinical course. However, several facts argue against a pulmonary embolus or other, presumably cardiac, cause. The patient's initial complaints were epigastric and left shoulder pain, and vomiting. Vomiting and epigastric pain are unusual with pulmonary embolism, yet expected with a ruptured diaphragm with stomach herniated into the chest. The patient then gradually deteriorated over the next 21 hours before cardiac arrest, a finding compatible with cardiorespiratory embarrassment from abdominal contents gradually herniating into the chest but unusual for pulmonary embolism where one would expect either resolution or complete cardiovascular collapse.

The patient was extremely unstable until the herniated viscera were reduced and the diaphragm was repaired, after which she had no further problems. This implies that it was the presence of the herniated viscera that was the underlying problem.

Finally, the patient was bedridden postoperatively for the 3 weeks until life support was terminated due to her encephalopathy. During this time no further difficulties with cardiac rhythm, cardiac output or oxygenation were encountered. If an underlying venous thrombosis was present, we would have expected further problems.

David B. Ross, MD

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Doctor or Mister?

To the editors. I am indebted to Doctors (or is it "Misters"?) Cairns, de Gara, Rees-Davies, Fraser and Thomas for their interest in my article on the correct appellation of British surgeons, and why it differs from the virtually universal designation of Doctor.

As I believe I tried to indicate, the title Mister has a great deal to do with early English history when surgery and barbery appear to have developed synchronously, often at loggerheads with each other as to their proper domain.

It was King Henry VIII who finally separated the two divisions of the cutting process, honouring each with the epithet "Master". In time, as the Oxford English and Skeat's dictionaries show, "Master" was corrupted into "Mister".

I doubt that there will ever be a change. English surgeons will continue to shudder to the end of foreseeable time at the mere thought of giving up the venerable title. American surgeons will adhere to their incorrect designation, by English standards, according to some of your correspondents.

Both, however, have much to be proud of. English "Misters" produced a Lister and American "Doctors" a Halsted.

P. Eibel, MD, FRCSC

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Does the Surgical Trauma of "Exploratory Thoracotomy" Affect Survival of Patients With Bronchogenic Carcinoma?

A. Paul, MD; D. Marelli, MD; J.A.S. Wilson, MD, FRCS(Edin), FRCSC; R.C-J. Chiu, MD, PhD; D.S. Mulder, MD, MSc, FACS, FRCSC

A retrospective review was carried out to assess the possible adverse immunosuppressive effect of exploratory thoracotomy on the survival of patients with non-small cell carcinoma of the lung with N2 nodal metastases.

Between 1960 and 1982, 48 patients with non-small cell bronchogenic carcinoma underwent exploratory thoracotomy; lung resection was not done because mediastinal lymph nodes were involved. The survival of these patients was compared with that of 64 patients in whom N2 disease was established by mediastinoscopy alone and who did not undergo thoracotomy.

There were no significant differences with respect to age, sex, tumour type and adjunctive radiotherapy. There were slightly more T4 tumours in the thoracotomy group (50% versus 30%). The hospital stay was longer in the thoracotomy group (2.3 ± 1.1 versus 1.5 ± 0.9 months [mean ± SD]). However, follow-up studies showed that, although these patients had a more traumatic procedure, the actuarial survival curves for the two groups were virtually identical, and the 12-month survival rates were less than 20% for both groups. The median survival was 6.0 months for the thoracotomy group and 7.0 months for the mediastinoscopy group. These findings failed to demonstrate an adverse immunosuppressive effect of thoracotomy on lung cancer patients.

Cette étude rétrospective a été faite à évaluer la réaction immunosuppressive possible de la thoracotomie exploratrice sur la survie des patients souffrant de cancers pulmonaires autres que le cancer à petites cellules, avec métastases ganglionnaires au stade N2.

Entre 1960 et 1982, 48 patients souffrant de cancers bronchopulmonaires autres que le cancer à petites cellules, ont subi une thoracotomie exploratrice; dû à l'atteinte des ganglions lymphatiques médiastinaux, il n'y eut pas de résection pulmonaire. La survie de ces malades a été comparée à celle de 64 patients dont le stade évolutif N2 fut établi par médiastinoscopie seule, sans thoracotomie.

Il n'y avait aucune différence pour ce qui était de l'âge, du sexe, du type de tumeur ou de la radiothérapie adjuvante. Il y avait un peu plus de tumeurs au stade T4 dans le groupe soumis à la thoracotomie (50% par rapport à 30%). L'hospitalisation a été plus longue dans le groupe de thoracotomie (2.3 ± 1.1 mois par rapport à 1.5 ± 0.9 mois [moyenne ± écart type]). Toutefois, la surveillance des suites thérapeutiques a révélé que, même si ce groupe avait subi une intervention plus traumatique, les courbes de survie actuarielles étaient virtuellement identiques; la survie à 12 mois était inférieure à 20% pour les deux groupes. La survie médiane fut de 6.0 mois pour le groupe de thoracotomie et de 7.0 mois pour le groupe de médiastinoscopie. Ces résultats n'ont pas fait la preuve que la thoracotomie produit un effet immunosuppressive chez les patients souffrant de cancers pulmonaires.

It is widely believed that major surgical procedures decrease host resistance to cancer.[1-5] Several experimental reports have shown that lymphocyte function is depressed after surgery and accelerated tumour growth has been demonstrated in such models.[1-5] Survival has been shorter for two-stage resection of obstructing colonic cancer than for primary resection. Enhanced tumour growth secondary to immunosuppression caused by surgery itself has been proposed as an explanation for this difference.[6] To our knowledge there are no data concerning the influence of surgical trauma on the clinical outcome in lung cancer patients.

To test the hypothesis that major surgical trauma may adversely affect the survival of patients with unresectable lung cancer, we took

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advantage of the fact that, in the past, N2 nodal involvement was established only after exploratory thoracotomy (a major surgical intervention) and that, recently, cervical mediastinoscopy has replaced thoracotomy for this purpose. Currently, because of the high sensitivity and specificity of mediastinoscopy in detecting N2 disease,[7] exploratory thoracotomy for lung cancer is carried out only when preoperative staging fails to detect unresectable stage III disease. It was reasoned that if major surgical trauma is detrimental to the survival of patients with terminal cancer, those who undergo exploratory thoracotomy may have a shorter survival than those who do not, provided the tumour staging and other risk factors are comparable. We, therefore, undertook a retrospective review of patients with bronchogenic carcinoma determined to be inoperable after thoracotomy revealed mediastinal lymph-node involvement. This historical cohort, consisting mainly of patients treated before mediastinoscopy was used, was compared to a control group who had the same nodal involvement diagnosed by mediastinoscopy alone. The purpose of this study was to assess the effect of exploratory thoracotomy on survival of these patients.

Patients and Methods

All patients admitted to the Montreal Chest Hospital for investigation of bronchogenic carcinoma are clinically staged by history-taking, physical examination, chest x-ray, tomography, liver function studies and bronchoscopy. Liver and bone scanning are performed if indicated. Since 1965, mediastinoscopy has been used with increasing frequency so that, now, virtually all patients who are candidates for tumour resection undergo this procedure.

Between 1960 and 1982, sampling of mediastinal lymph nodes, with frozen-section histologic examination during exploratory thoracotomy revealed preoperatively undiagnosed N2 disease in 48 patients with non-small cell carcinoma (group 1). Tumour resection in these patients was contraindicated because of the nodal involvement. As a control group, we selected 64 consecutive patients evaluated for bronchogenic carcinoma between 1978 and 1982 (group 2). These patients had non-small cell carcinoma and N2 nodal metastases histologically proven by mediastinoscopy alone; they did not undergo exploratory thoracotomy. Patients were re-staged according to the present TNM classification.[8,9] In all cases, disease was limited to stage III at the time of diagnosis. Only patients with squamous cell carcinoma or adenocarcinoma were included. Follow-up consisted of periodic clinical and radiologic evaluation.

If patients had no evidence of ongoing infection and were in good overall physical condition, they were offered radiotherapy (5000 to 6000 rad). An additional 12 patients who underwent exploratory thoracotomy were not included in the study because they received nonstandardized chemotherapy.

The χ^2 test was used to compare the patients in each group for age, sex, preoperative weight loss and primary tumour classification at the time of diagnosis. Actuarial survival was calculated for both groups of patients as well as for those who received adjunctive radiotherapy.[10] When autopsy was not available, cause of death was established on clinical, radiologic and laboratory bases.

Results

In group 1 patients, N2 disease was discovered and histologically proven. Preoperative mediastinoscopy was equivocal or negative in 20 of these patients. The other 28 did not undergo mediastinoscopy. Postoperative complications were

Table I. Distribution of Age, Sex, Radiotherapy and Weight Loss

		Age, yr		Sex		Radiotherapy		Weight loss	
Group	No.	Mean	Range	M	F	Yes	No	<10%	>10%
1: thoracotomy (1960 – 1982)	48	62	42 – 77	38	10	26	22	42	6
2: mediastinoscopy alone (1978 – 1982)	64	61	36 – 75	48	16	36	28	56	7

Table II. Primary Tumour Classification and Distribution of Cell Type

	Primary tumour class			Cell type	
Group	T2	T3	T4	Squamous	Adenocarcinoma
1: thoracotomy	12	12	24	30	18
2: mediastinoscopy alone	21	24	19	43	21

limited to pneumonia and atelectasis in seven patients and did not prevent hospital discharge in any case. One patient had a fatal pulmonary embolism on postoperative day 7. In group 2 patients the N2 disease was histologically proven by mediastinoscopy alone. There were no serious complications in this group. The use of blood transfusions for replacing intraoperative blood loss was comparable in the two groups.

Patients in both groups were comparable for age and sex (Table I). Differences in weight loss and frequency of adjunctive radiotherapy were not significant. The TNM classification of primary tumours in both groups ranged from T2 to T4. Although T4 tumours were more common in the thoracotomy group, differences in overall primary tumour distribution were not statistically significant (Table II). Similarly, tumour cell types were comparable for both groups.

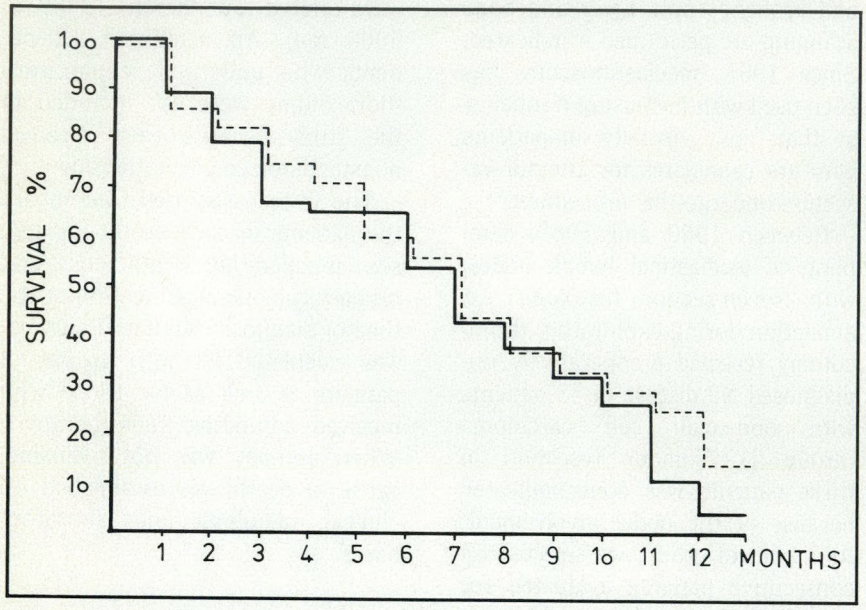

FIG. 1. Actuarial survival rates for patients who underwent exploratory thoracotomy and those who did not (straight line = thoracotomy, n = 48; dotted line = no thoracotomy, n = 64).

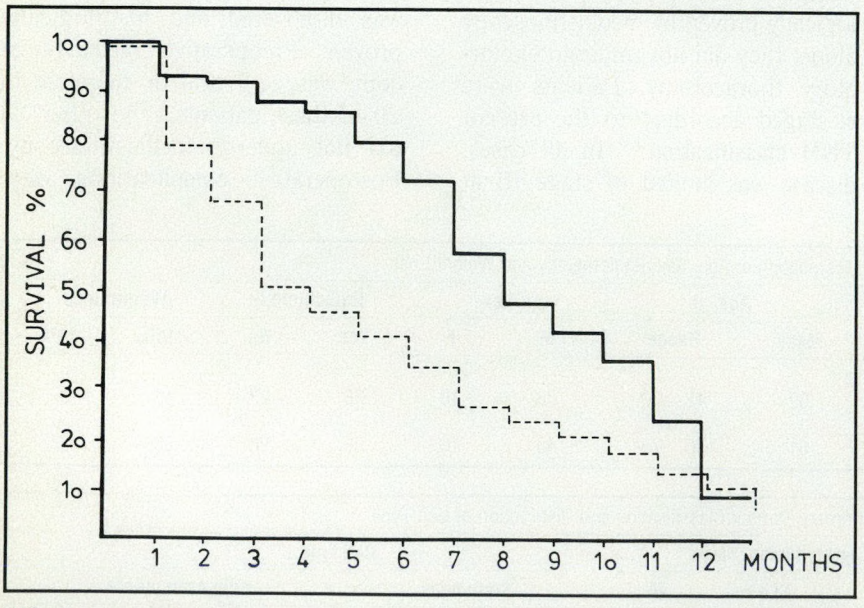

FIG. 2. Actuarial survival rates for patients who underwent adjunctive radiotherapy and those who did not (straight line = radiotherapy, n = 62; dotted line = no radiotherapy, n = 50).

Eleven patients from group 1 were lost to follow-up between 1 and 11 months postoperatively, and 12 patients in group 2 were lost to follow-up between 1 and 8 months after the diagnosis was established. Thus, follow-up rates were 77% and 81% respectively.

The median hospital stay was 2.0 months (range from 0 to 4 months) for patients in group 1, compared with 1.0 months (range from 0 to 6 months) for group 2. This was found to be statistically significant (Student's *t*-test, $p < 0.05$). Figure 1 shows that actuarial survival curves were virtually identical for both groups. Median survival for group 1 patients was 6.0 months (range from 0 to 15 months) and for group 2, 7.0 months (range from 0 to 50 months). Overall survival after 1 year was less than 20% for both groups. The power of these data in detecting a 15% difference in the 12-month actuarial survival rate is 0.80. In all cases, death was secondary to disease progression. The cell type and the primary tumour classification did not affect survival.

All patients who received adjunctive radiotherapy had increased median survival regardless of whether they underwent thoracotomy (9.0 months versus 5.0 months, $p < 0.005$). However, actuarial survival curves comparing these patients with those not receiving adjunctive treatment revealed that radiotherapy did not change the 1-year survival rate significantly (Fig. 2).

Discussion

Surgery has been suspected to have an immunosuppressive effect, which may promote tumour growth. Experimentally, there is a correlation between accelerated tumour growth and multiple operative procedures.[8] Other models have revealed increased pulmonary metastases and impaired immunity after surgical trauma.[2] Eggermont and colleagues[3] have made similar observations in animals subjected to major surgical trauma, but not in those subjected to minor procedures. In this model, immune function was only transiently impaired. This would suggest a time-limited immunosuppressive effect.

Clinical results have not been as conclusive. Perioperative blood transfusions have been found to exert a negative effect on survival in patients with rectal cancer.[11] An immunosuppressive effect is suspected. Surgery and anesthesia have produced a measurable depression in immune response in normal patients.[4] The clinical implications of this observation are not known. Fielding and Wells[6] retrospectively noted shortened survival in patients who underwent two-staged resection of obstructing colonic cancer compared with those who underwent primary resection. These results have been used to support the hypothesis that surgery itself facilitates tumour growth. Alternatively, these findings may be explained by the decision of the surgeon to select more complicated cases for staged resection.

This study is concerned exclusively with stage III non-small cell lung cancer. The poor prognosis associated with this tumour stage is widely recognized.[12–14] Thus, survival as an end point to study possible accelerated tumour growth seems to be appropriate in these patients. Patients who underwent exploratory thoracotomy were retrospectively compared with a group who had the same disease classification but had not been subjected to a major surgical procedure. Both groups of patients were comparable with respect to age, sex, preoperative weight loss, intraoperative use of blood products, cell type and use of adjunctive radiotherapy.

It should be stressed that although this is a retrospective study, there is no selection bias, because patients were assigned to the groups, not by surgeon's judgement but by the historical fact that mediastinoscopy was not routinely practised when the earlier patients underwent thoracotomy. These patients were then compared with those who had similar lesions but did not require thoracotomy simply because they were seen after mediastinoscopy became available.

Since the group 1 patients predate group 2, it is possible that improvements in postoperative care could affect the comparison. However, if this were the case, it should increase rather than reduce the difference in the survival data. The fact that we could not find such a difference indicates that even with improved postoperative management, avoiding exploratory thoracotomy did improve prognosis. Thus, the use of historical controls in this case strengthens rather than weakens our conclusions.

Patients who underwent thoracotomy were found to have significantly increased hospital stay. This may be in part related to normal postoperative care and to deterioration of physical condition and quality of life secondary to exploratory thoracotomy.[15] The fact that all patients but one were eventually discharged implies that this effect was a transient one attributable to operative trauma. Nevertheless, to spend 1 month of their limited expected survival in hospital rather than at home with their families, is a human cost that cannot be measured in dollars or in days. Therefore, the use of mediastinoscopy in N2 disease patients, although it does not improve survival, has benefits beyond avoiding the less desirable exploratory thoracotomy, which is often more painful in the postoperative period.

When patients who received adjunctive radiotherapy were compared with all others, regardless of thoracotomy, they were found to have significantly increased survival. However, this result was subject to a selection bias because only patients with good performance were offered radiotherapy. From these data, we cannot conclude, therefore, that radiotherapy has a beneficial effect on survival in patients with stage III non-small cell disease. This emphasizes the need for a randomized trial of radiotherapy in these patients so that results may be compared to an untreated control group.[16–19]

In conclusion, our data failed to demonstrate any adverse effect of surgical trauma on the survival of patients with bronchogenic carcinoma. Any immunosuppressive effect an "exploratory thoracotomy" may cause was not reflected in patient survival.

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Omental Pedicle Grafting in the Treatment of Poststernotomy Mediastinitis

J. Pierre Bédard, MD, FRCSC; Farid Shamji, MD, FRCSC; Wilbert J. Keon, MD, FRCSC

Mediastinitis after median sternotomy may be life-threatening. It should be managed by providing adequate mediastinal drainage, removing all foreign material (including infected and dead tissues) and obliterating any dead space.

Obliterating dead space may be difficult using the usual method of creating a vacuum with large-bore tubes. Alternative methods consist of muscle or omental transpositions. The authors describe the cases of two men who had mediastinitis, 1 week and 3 months respectively, after coronary artery bypass grafting. In both cases, the mediastinitis was treated successfully by omental pedicle grafting.

From their experience, the authors recommend omental grafting as a method of obliterating a large mediastinal dead space when the sternal edges can be approximated but the space cannot be closed by conventional methods.

La médiastinite consécutive à une sternotomie médiane peut mettre en danger la vie du malade. Elle doit être traitée par un drainage médiastinal adéquat, le retrait de toute substance étrangère (y compris les tissus infectés ou morts) et l'élimination de l'espace mort.

Il peut être difficile d'éliminer l'espace mort lorsqu'on utilise la méthode habituelle qui consiste à faire le vide à l'aide d'un tube de gros calibre. Les transpositions du muscle ou de l'épiploon constituent des alternatives. Les auteurs décrivent les cas de deux hommes qui ont souffert d'une médiastinite, respectivement 1 semaine et 3 mois après pontage aortocoronarien. Dans les deux cas, la médiastinite a été traitée avec succès par greffe d'un pédicule d'épiploon.

D'après leur expérience, les auteurs recommandent la greffe d'épiploon comme méthode d'éliminer les espaces morts médiastinaux importants, quand les bords du sternum peuvent être rapprochés mais que l'espace ne peut être refermé par les méthodes conventionnelles.

Median sternotomy is the most common incision used in cardiac surgery. Although wound infection is rarely associated with this incision, its occurrence may lead to mediastinitis, which carries significant mortality and morbidity.

As for any wound infection, the treatment should consist of extensive débridement, adequate irrigation and drainage and the administration of appropriate antibiotics. Sometimes the wound is difficult to close and alternative methods, such as omental pedicle graft or muscle transposition, must be considered.

We present two cases of poststernotomy mediastinitis treated successfully with débridement and omental pedicle grafting.

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Case Reports

Case 1

A 55-year-old man underwent four-vessel aortocoronary bypass grafting in October 1986. Three months later, chest pain, fever and hemoptysis developed. A chest film revealed an anterior mediastinal mass, and an echocardiogram confirmed the presence of a large false aneurysm of the ascending aorta. Cardiopulmonary bypass was established with femorofemoral bypass. Using profound hypothermia (at 18°C) and circulatory arrest, the median sternotomy incision was opened, and the false aneurysm was entered, blood clots were evacuated and the hole on the ascending aorta was identified. The false aneurysm was related to an infection and dehiscence of a proximal coronary artery graft anastomosis. The defect on the aorta was controlled with interrupted Prolene suture, cardiopulmonary bypass was resumed and the patient warmed.

After the false aneurysm was repaired, we were left with a large defect in the mediastinum and extensive raw surface on the medial aspect of the upper lobe of the left lung. While the patient was being warmed, the sternotomy incision was extended down to the umbilicus so that a well-vascularized omental pedicle could be obtained. Once mobilized, the omentum was brought up to the anterior mediastinum so that it would cover both the mediastinal defect and the raw area of the lung. The chest wall was closed in layers and two rubber catheters were left in the mediasti-

num for irrigation using 0.5% Proviodine solution. The patient was discharged home 4 weeks after the operation. He was free of infection 2 years later.

Case 2

A 62-year-old man had undergone three coronary artery bypass grafting operations. Six days after the last one, he suffered sternal dehiscence, which required débridement and reapproximation. Then, 6 days after that, the sternal dehiscence recurred with severe mediastinitis. Further management included radical débridement of the sternum, anterior mediastinal tissue and subcutaneous fat, followed by irrigation with antiseptic solution and packing of the mediastinum for 1 week. Because there was a large dead space in the anterior mediastinum due to marked fibrosis from previous operations, a laparotomy was carried out and an omental pedicle graft obtained and moved up into the anterior mediastinum to close the dead space. The sternum was reapproximated as usual. The patient was discharged home 3 weeks later and was free of infection after 1 year.

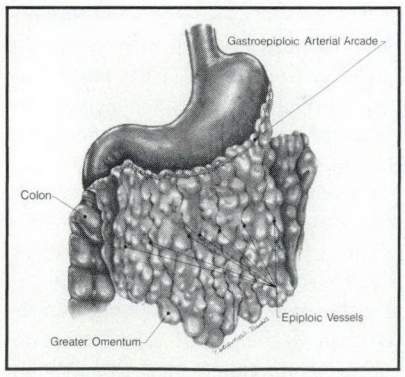

FIG. 1. Anatomy and blood supply of greater omentum.

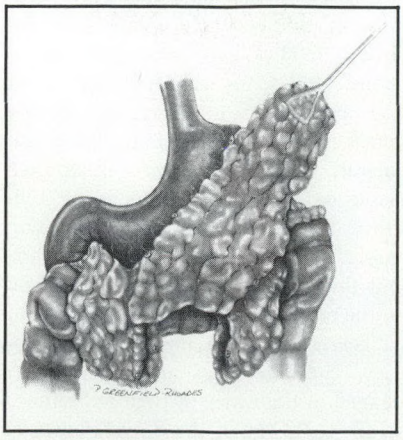

FIG. 2. Mobilization of vascularized omental pedicle graft.

Technique for Mobilizing an Omental Pedicle Graft

The median sternotomy incision is extended inferiorly and the peritoneal cavity entered through the linea alba. A well-vascularized omental pedicle graft is then prepared as follows.

The greater omentum hangs down from the lower convexity of transverse colon in front of the coils of small intestine. It is a continuation downwards of the gastrocolic omentum from the greater curvature of stomach and it receives its blood supply from the epiploic branches of the gastroepiploic arcade (Fig. 1). This arcade runs along the greater curvature of the stomach. The attachment of greater omentum to the lower convexity of the transverse colon along the avascular plane is exposed by gently lifting the greater omentum upwards over the costal margin. This avascular plane is divided to separate a segment of greater omentum 8 to 10 cm wide from the transverse colon. The preparation of this segment of greater omentum by ligating and dividing lymphatics and blood vessels in the gastrocolic omentum is continued as far as 5 to 6 cm from the greater curvature of the stomach. This allows the gastroepiploic arterial arcade to be preserved and maintains the blood supply to the omental pedicle graft through its epiploic branches. Hence, the omental pedicle graft usually does not need to be detached from the greater curvature of the stomach (Fig. 2). The omental pedicle is then delivered into the anterior mediastinum through a retrosternal tunnel, making sure that gastric outlet obstruction from volvulus is avoided. The omental pedicle graft is anchored in place in the anterior mediastinum with absorbable sutures.

Discussion

The principles of treatment of wound infections apply to poststernotomy mediastinitis. First, all foreign material (including necrotic tissue and dead bone) must be adequately debrided. This is followed by irrigation with an antiseptic solution and immediate direct closure of the sternum if possible. Cultures of the wound are obtained and coverage with broad-spectrum and then specific antibiotics is provided.

An important factor contributing to failure of treatment for poststernotomy mediastinitis is the presence of a dead space posterior to the sternum.[1] It may be present in the mediastinum because of the rigidity of the retrosternal compartment. The use of an omental flap is helpful in those cases as it will not only fill up the dead space, but also provide healthy tissue with a propensity for new blood supply and granulation.[2]

The omentum has a number of properties that offer protection from infection: it has a rich vascular and lymphatic supply which favours neovascularization;[3] it possesses a rich source of macrophages which will resist infection and seal areas of inflammation;[4] because of its double layer of peritoneum it offers a large absorptive surface which will favour absorption of fluids;[5] finally, its

bulkiness will seal areas of inflammation, fill up dead space and cover tissue defects.[2,3,6] Because of its advantages, the omentum is becoming more widely used by the cardiothoracic surgeon.

In our first patient, the omentum was used not only to fill up the large dead space left behind by the false aneurysm but also to seal communications with the bronchial tree and cover the stitches used to close the aorta. In our second patient, the omentum was used to fill up the large dead space provided by the rigid wall of the mediastinum due to the three previous coronary artery bypass graft operations.

It is worth re-emphasizing that the basic treatment of poststernotomy mediastinitis remains adequate débridement and drainage. The use of an omental flap is not necessary in all cases, but is useful under certain circumstances.

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BOOK REVIEWS

CARDIOTHORACIC TRAUMA. Panagiotis N. Symbas. 404 pp. Illust. W.B. Saunders Company Canada Limited, Toronto, 1989. $128.25. ISBN 0-7216-2817-3.

This textbook on chest trauma is written by a surgeon with more than two decades of experience in a major US trauma centre. In addition to his extensive clinical experience, he is also the director of an active surgical research laboratory where problems associated with cardiothoracic trauma have been studied. Many of the strengths of this book are the result of the author's experience.

The book is well organized, concise and clearly written, and the quality of the illustrations, particularly the roentgenograms, is superb. The extensive references following each chapter will be especially useful for readers who wish to obtain source material or detailed information on specific subjects.

In the preface it is stated, "The material described in this text is designed to be of benefit to any provider of health care to patients with thoracic injury either in the early or late postinjury period". The systematic and authoritative essays certainly fulfil this objective. For nonthoracic surgeons, such as emergency room physicians and paramedic staff, and for surgical residents and medical students, the detailed description of basic concepts of care for chest trauma, including early resuscitation and chest-tube drainage, is particularly useful. However, it is important for these readers to keep in mind that this text should not be read and used in isolation. Many patients who suffer cardiothoracic trauma also have injury to other organs. For example, patients with blunt trauma requiring intubation and respiratory support may also have suffered cervical spine injury, and inappropriate manipulation may cause permanent paraplegia. Setting priority in the management of multiorgan damage is not within the scope of this book; these aspects are emphasized in the ATLS (Advanced Trauma Life Support course of the American College of Surgeons, Committee on Trauma).

For the cardiothoracic surgeon who provides definitive operative care, this book can also serve as a useful reference. Again, its strength is the authoritative statements based on the author's experience. Consequently, in the discussion of each subject, particularly the controversial areas, one notices personal biases. For example, the potentially lethal complications of systemic air embolism associated with penetrating injury of the lung are dealt with in a single sentence. Neither its pathophysiology nor the diagnosis and management are discussed. On the issue of shunting for the repair of vascular injuries involving the innominate or carotid artery, the author relies largely on information obtained from carotid endarterectomies. There is considerable difference in the available collateral circulation for endarterectomy if the carotid artery is occluded at its bifurcation or if the common carotid or innominate artery is occluded unilaterally. In the former, only intracranial collaterals can perfuse the territory of the occluded internal carotid artery. In the latter, however, extracranial collaterals via the branches of the external carotid arteries provide much more important and reliable collaterals. Likewise, repair of ruptured descending thoracic aortas using centrifugal pumps without heparinization has given good results in recent years, but this approach is not elaborated on in the present text.

There are other minor inconsistencies. The references are generally arranged in the order of their appearance in the text, but of the 28 references in

continued on page 372

Catheter Drainage of the Pericardium: Its Safety and Efficacy

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A retrospective chart review identified 46 consecutive patients who underwent catheter drainage of the pericardium over 3 years. Cardiac tamponade was present in the majority of patients, and the underlying cause was tumour metastasis in 72%. Pericardial catheterization was accomplished by the Seldinger technique using the subxiphoid approach. Catheter insertion was successful in 42 of the 46 patients, and in only 1 was there a serious complication. The mean duration of catheter drainage was 3 days. The pericardial space was successfully drained in all but one patient, who subsequently required surgery. Intrapericardial chemotherapy was administered in 27 patients. There was no instance of catheter-associated sepsis. Supraventricular arrhythmias occurred in 19% of patients, but all were managed medically. There were no late complications attributable to the period of drainage. The authors conclude that catheter drainage of the pericardium is a safe and effective means of providing definitive drainage of the pericardial space.

Une étude rétrospective des dossiers médicaux a permis d'identifier 46 patients qui, au cours d'une période de 3 ans, ont subi un drainage par cathéter du péricarde. Dans la majorité des cas, une tamponade était présente et la cause sous-jacente, dans 72% des cas, était des métastases tumorales. Le cathétérisme péricardique fut réalisé grâce à la technique de Seldinger en utilisant un abord sous-xiphoïde. L'insertion du cathéter fut réussi chez 42 des 46 patients et on n'a rencontré qu'une seule complication sérieuse. La durée moyenne du drainage fut de 3 jours. L'espace péricardique fut drainé avec succès dans tous les cas, sauf un qui nécessita une intervention chirurgicale subséquente. Une chimiothérapie intrapéricardique fut administrée à 27 patients. On n'a enregistré aucun cas de sepsie due au cathéter. Des arythmies supraventriculaires sont apparues chez 19% des patients, mais elles purent être traitées médicalement dans tous les cas. Il n'y eut aucune complication retardée attribuable à la période de drainage. Les auteurs concluent que le drainage péricardique par cathéter est un moyen sûr et efficace d'offrir un drainage définitif de l'espace péricardique.

The approach to drainage of hemodynamically important pericardial effusions remains controversial. Although there is no question about the role of a definitive surgical procedure in cases of traumatic cardiac tamponade, patients with nontraumatic cardiac tamponade have traditionally been managed by needle pericardiocentesis. Unfortunately, this procedure is associated with serious complications, and frequently a single pericardial tap is unsuccessful in providing long-term relief.[1-3] Although there are some[4-6] who advocate open surgical drainage in this setting, these patients may tolerate surgery poorly due to advanced systemic disease. Our institution is allied to a major regional cancer institute and we have, of necessity, been required to manage a large number of patients with cardiac tamponade due to malignant disease. Concerns over the safety and efficacy of traditional medical and surgical management led us to explore the role of pericardial catheterization in this clinical setting.

Methods

A retrospective chart review identified 46 consecutive patients who underwent catheter drainage of the pericardium between May 1982 and May 1985. There were 36 women and 10 men (mean age 55 years). The procedure was performed for clinically suspected cardiac tamponade in all but three patients in whom the procedure was performed for diagnostic purposes. All patients had a moderate to large pericardial effusion (Table I) documented by preceding two-dimensional echocar-

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diography. All procedures were performed in the intensive care unit by a staff cardiologist or by a cardiology subspecialty trainee under the direct supervision of an attending cardiologist. Pericardial catheterization was performed by the Seldinger technique using the subxiphoid approach.[7,8] The patients were awake and supine. When necessary for patient comfort the head of the bed was elevated to 30°. After infiltration of the skin and subcutaneous tissues with 1% lidocaine without epinephrine, a small incision was made to the left of the xiphisternum to ease subsequent passage of the catheter. A 17-gauge 20-cm spinal needle with trocar was then inserted beneath the costal margin at approximately 30° to the horizontal plane and directed towards the midpoint of the left clavicle. The needle was advanced under continuous electrocardiographic guidance with the trocar frequently withdrawn until the pericardial sac was entered, as documented by free aspiration of pericardial fluid without ST-segment elevation or dysrhythmias. A J-tipped guide wire measuring 0.025 inches (0.064 cm) in diameter was inserted through the needle into the pericardial space under fluoroscopic guidance. No special effort was made to direct the guide wire posteriorly within the pericardial sac. That the wire had indeed entered the pericardial space and not a cardiac chamber was confirmed by (a) the observation that the guide wire could be advanced well into the known pericardial reflections off the great vessels, and (b) the absence of dysrhythmias with guide wire manipulation. The subcutaneous tissues were then carefully dilated using a no. 7F standard vein dilator. Under fluoroscopic guidance, a 25-cm long 6.5F polyethylene catheter (Vas Cath of Canada, Ltd., Mississauga, Ont.) with six 0.035-inch (0.089-cm) diameter side-holes, spirally arranged between 1 and 3 cm from the tip, was advanced into pericardial space so that its tip was no more superior than the centre of the cardiac silhouette (Fig. 1). The catheter was sutured to the skin and covered by a sterile occlusive dressing.

The pericardial effusion was drained continuously by gravity using a closed system. A stopcock was included to permit sampling of the pericardial fluid and instillation of chemotherapeutic agents. Opening of the system was kept to a minimum and strict aseptic technique was emphasized. Heparin was not used to maintain catheter patency. Fluid was sent for cytologic examination, cell counts and Gram's staining and, in addition, was cultured daily. A chest x-ray film was obtained after the procedure to document catheter location. All patients underwent continuous electrocardiographic monitoring while the catheter was in situ.

Table I. Causes of Pericardial Effusions in 46 Patients

Cause	No.	%
Malignant disease	33	72
Uremia	6	13
Connective tissue disease	3	6.5
Virus	3	6.5
Hypothyroidism	1	2

Results

Percutaneous catheter insertion was successful in 42 of the 46 patients. In two of these, the catheter entered the right atrium, resulting in a nonfatal cardiac arrest in one and no sequelae in the other. In both instances, immediate repeat catheterization was successful. Both these cases occurred early in our experience when a straight guide wire was being used. Since switching to a J-tipped guide wire,

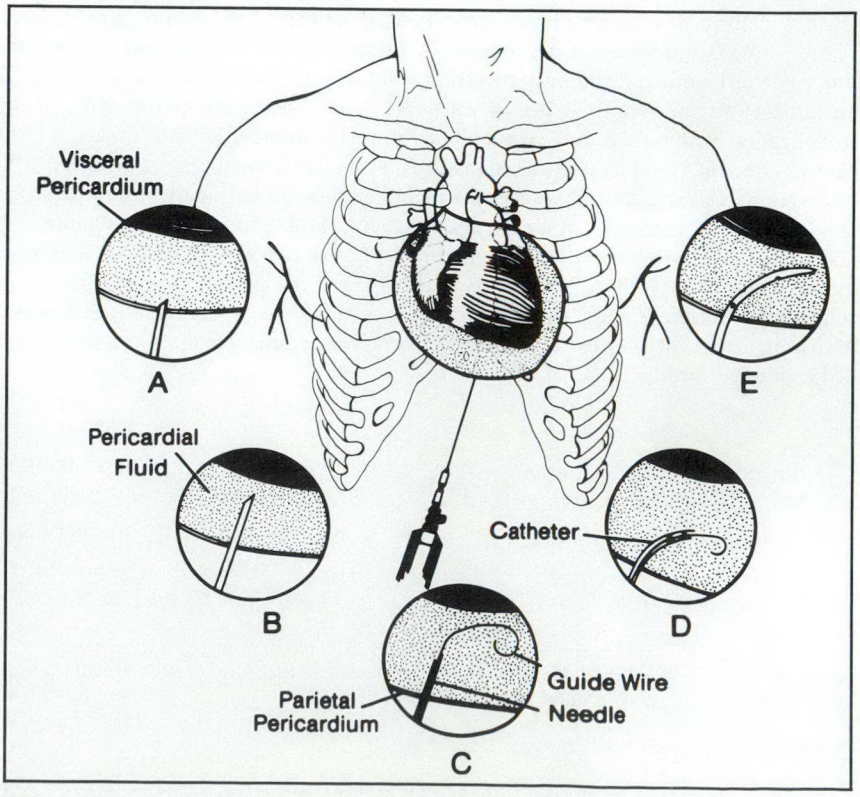

FIG. 1. Diagram showing technique of catheter insertion.

we have not seen this complication. In two patients, no fluid was obtained through the needle despite adequate fluid demonstrated by echocardiography. In two other patients, the catheter could not be passed over the guide wire despite apparently adequate subcutaneous dilatation. In 41 of the 42 patients successfully cannulated, the effusion was adequately drained. One patient suffered recurrent tamponade, despite initial successful drainage and a patent catheter. In this patient, the catheter tip travelled anterior to the right ventricle and was likely too far superior for adequate drainage. The catheter was repositioned and tamponade was relieved. The patient ultimately required a pericardial window. Of the entire group, this was the only patient who required surgical intervention.

The mean duration of catheter drainage was 3 days (ranging from 1 to 5 days) and during this time 27 patients received intrapericardial tetracycline and 3 intrapericardial steroids. When indicated, tetracycline poudrage was performed as described previously.[9] Briefly, this involved the daily intrapericardial instillation of 500 mg of tetracycline to a maximum total of 2.0 g. Daily cultures from all pericardial effusions were sterile. Eleven (26%) of 42 patients had a fever with a temperature greater than 38.5°C. Two (5%) of 42 catheter tips cultured positive for *Staphylococcus epidermidis* upon removal. This was most likely due to skin contamination; no subsequent local infections developed. In the majority of febrile patients, a potential alternative cause of fever could be identified. There were no sustained dysrhythmias during the insertion procedure. Subsequently, a new supraventricular tachycardia developed in 8 (19%) of 42 patients during the period of drainage. All of these patients had also received intrapericardial tetracycline. No patient suffered hemodynamic compromise and the dysrhythmias were successfully treated medically. One (2%) of 42 patients required catheter removal due to refractory pericardial pain. Even though we did not use heparin or vacuum-assisted drainage, there were no instances in which, because of clotting, the catheter had to be removed before the drainage or planned course of treatment was completed. There were no late complications attributable to catheter drainage.

Discussion

Malignant disease and uremia are common causes of hemodynamically important nontraumatic pericardial effusion. Primary malignant tumours of the pericardium are exceedingly rare. Secondary involvement is most frequently encountered with carcinomas of the lung and breast. Large pericardial effusions are reported to occur in up to 7% of patients on long-term dialysis,[10] and when cardiac tamponade occurs, it cannot be managed by dialysis alone. Needle pericardiocentesis will relieve nontraumatic tamponade in 60% to 90% of cases.[1,2] Although useful in the acutely deteriorating patient with tamponade, it is less effective for long-term management. Krikorian and Hancock[1] reported that 76% of patients required multiple taps, placement of indwelling catheters or definitive surgical drainage. Guberman and associates[2] noted that 20% of patients with nontraumatic tamponade ultimately required pericardial resection for recurrent accumulation of fluid.

Our results indicate that when an indwelling catheter is used routinely as part of the initial drainage procedure, the need for subsequent surgical intervention or repeat drainage procedures falls to less than 10%. This may, in part, be because the indwelling catheter permits repeated administration of intrapericardial chemotherapy. The complication rate in this series is lower than that reported with needle pericardiocentesis.[1-3,10] Only one of our patients had a life-threatening complication. In comparison with previous studies, all had at least a moderate pericardial effusion as demonstrated by two-dimensional echocardiography. Failure to obtain pericardial fluid in two patients may have been due to the presence of intrapericardial clot, loculations, fibrous tissue or tumour masses.[11] The fact that previous studies included patients who had not undergone echocardiography may have contributed to the higher complication rates in some earlier reports.[3]

The incidence of supraventricular dysrhythmias (19%) in this series is higher than that reported previously. This may be the result of either the continued dysrhythmogenic potential of a foreign body in the pericardial space over a prolonged period or the intense inflammatory reaction seen after intrapericardial instillation of tetracycline. The latter mechanism is supported by the observation that all patients who had supraventricular dysrhythmias also received intrapericardial tetracycline.

There has been concern that the presence of an indwelling catheter could lead to septic pericarditis. In our series, 26% of patients had a temperature greater than 38.5°C recorded while the catheter was in situ. Many patients had clinically apparent foci of infection elsewhere, and pericardial fluid cultures were uniformly negative. The occurrence of fever did not bear any relation to the concurrent intrapericardial use of tetracycline. These results confirm that the risk of infection is

negligible when appropriate aseptic technique is used both at the time of catheter insertion and during subsequent manipulations of the system such as fluid aspiration for culture and instillation of chemotherapeutic agents.

In this series, catheter blockage, when it occurred, could always be managed by manual flushing of the catheter with a small volume of physiologic saline solution. Elaborate precautions against catheter clotting do not appear necessary.[12] The size and arrangement of the side-holes near the catheter tip may be important in preventing catheter blockage,[13] but with the data from this series we cannot directly address this issue.

Conclusions

We recommend that catheter drainage of the pericardium be undertaken in the cardiac care unit, intensive care unit or cardiac catheterization laboratory, where appropriate resuscitation equipment is immediately available. In our experience, the keys to safe and successful pericardial catheterization include the following: (a) the use of a J-tipped guide wire, (b) continuous electrocardiographic and fluoroscopic monitoring and (c) adequate dilatation of all tissues from skin to pericardium before the catheter is introduced. Percutaneous catheter drainage of hemodynamically significant nontraumatic pericardial effusions is a safe and effective alternative to conventional surgical intervention. The technique may be of particular value in critically ill patients who may be poor candidates for surgery. The ability to administer intrapericardial chemotherapy through the catheter is an important adjunctive measure in the control of malignant pericardial tamponade.[9]

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Clinical Science for Surgeons. 2nd edition. Edited by Vernon Marshall and John Ludbrook. 754 pp. Illust. Butterworths, Stoneham, Mass., 1988. $65.00 (US). ISBN 0-409-49454-2.

The CO_2 Laser in Otolaryngology and Head & Neck Surgery. Edited by V.H. Oswal, H.K. Kashima and L.M. Flood. 200 pp. Illust. Butterworths, Stoneham, Mass., 1988. $130.00 (US). ISBN 0-7236-0587-4.

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Current Operative Morbidity Associated With Elective Surgical Resection for Lung Cancer

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To determine the current operative morbidity for elective surgery of lung cancer, the authors reviewed the charts of 1076 consecutive patients who underwent pulmonary resection between 1978 and 1984 at two major Canadian teaching hospitals.

Of these patients, 731 (68%) had a normal course. Minor complications occurred in 206 patients (19%); the majority were supraventricular arrhythmias (100 events) and atelectasis (41 events). Nonfatal major complications occurred in 105 patients (9.8%). The overall operative death rate was 3.2%. If supraventricular arrhythmias are excluded, nearly 80% of patients had a smooth postoperative course.

In order to correlate the occurrence of complications with pre- and perioperative data, several possible risk factors were analysed. For major complications and death, the age, the forced expiratory volume, weight loss, coexisting disease, stage of cancer and extent of resection were significant risk factors ($p < 0.05$).

The data show that elective pulmonary surgery can be done safely and complications prevented. The necessary requirements are: proper selection of patients, a well-performed operation and prompt treatment of potential problems.

Pour déterminer la morbidité associée à la chirurgie élective d'un cancer du poumon, les auteurs ont revu les dossiers de 1076 malades ayant subi une résection pulmonaire entre 1978 et 1984 dans deux hôpitaux universitaires canadiens.

Sept cent trente et un malades (68%) ont eu des suites postopératoires entièrement normales. Deux cent six malades (19%) ont présenté des complications d'ordre mineur, ces dernières étant surtout des arrythmies supra-ventriculaires (100 malades) ou des atélectasies (41 malades). Des complications majeures mais non fatales sont survenues chez 105 malades (9.8%) et la mortalité opératoire a été de 3.2%. En excluant les arrythmies supra-ventriculaires, quelques 80% des malades ont eu des suites opératoires normales.

Dans le but d'établir une corrélation entre morbidité et données pré- ou périopératoires, plusieurs variables ont été étudiées. Pour les complications majeures et décès opératoires, l'âge, la fonction respiratoire, la perte de poids, les maladies co-existantes, le stade de la tumeur et l'étendue de la résection ont été identifiés comme facteurs de risque statistiquement significatifs ($p < 0.05$).

Ces résultats démontrent que la chirurgie pulmonaire peut être pratiquée de façon sécuritaire, la plupart des complications pouvant être prévenues. Un effort doit cependant être fait pour bien sélectionner les malades, bien faire la chirurgie et traiter sans délai les problèmes potentiels.

Although pulmonary resection is recognized as the best treatment for lung cancer, there is little published information on the 30-day morbidity associated with such operations. Nagasaki and colleagues[1] from the Memoral Sloan-Kettering Cancer Center reported a 19% operative morbidity, but their series included 202 patients with either biopsy only or with interstitial implantation of radioisotopes. Keagy and associates[2] analysed

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morbidity and mortality in 369 consecutive pulmonary lobectomies performed between 1970 and 1983 and found that 41% of patients had postoperative management problems. Much of the remaining literature is limited to the reporting of specific postoperative problems or to collective reviews of potential complications after elective resections.[3]

This analysis of 1076 consecutive resections done during the years 1978 and 1984 at two major Canadian hospitals was undertaken to determine the current complication rate for operative treatment of lung cancer. In addition, possible risk factors were analysed in the hope of correlating the occurrence of complications to pre- and perioperative data.

Study Population

We reviewed the records of 1076 consecutive patients (907 men, 169 women) who underwent elective resection for lung cancer between 1978 and 1984. The patients ranged in age from 29 to 86 years.

For all cases, preoperative workup included posteroanterior and lateral chest roentgenography, bronchoscopy, electrocardiography, basic biochemical tests, and liver function studies; 62% (672 patients) had pulmonary function studies. These tests were usually limited to measurement of forced expiratory volume (FEV_1), forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO). Arterial blood-gas determinations, exercise tolerance tests and isotopic regional function studies were also performed in selected patients with compromised function. Mediastinoscopy was done in 92% of cases, with random node sampling at three different levels. Very few patients were subjected to thoracotomy when nodal metastases were identified by mediastinoscopy.

All tumours were staged according to the TNM classification.[4] Staging was based on complete clinical and pathological assessment of the primary tumour (T status) and surgical sampling of at least the bronchopulmonary, hilar and mediastinal nodes (N status).

The types of procedures performed at thoracotomy are listed in Table I. Limited resections (segmental/wedge) were carried out only when the patient's pulmonary reserve was thought to be compromised; these were done infrequently. Lobectomies included all simple lobectomies, bilobectomies, sleeve lobectomies or extended lobectomies. Similarly, standard, intrapericardial or extended pneumonectomies were all included in the pneumonectomy group. A complete resection was defined as removal of all gross carcinoma, disease-free resection margins and the highest mediastinal node free of tumour. According to these criteria, 89% of procedures were considered complete.

Operative death was defined as death occurring within 30 days of the surgery or directly related to the operation if it occurred after 30 days. For example, a patient who died on the 40th postoperative day of a bronchopleural fistula would fall into the operative death group.

Nonfatal postoperative complications were classified as minor or major. Minor complications were defined as events that had no important impact on the patient's postoperative course; in contrast, major complications were events considered to be life-threatening. When a given patient had both minor and major postoperative complications, he was coded as having major complications only, although the nature of the minor complication was also recorded.

The influence of each selected pre- or perioperative risk factor on the development of postoperative complications was examined by χ^2 analysis. For this purpose, patients

Table I. Type of Procedure in Patients Who Underwent Thoracotomy

Procedure	No. of patients (%)
Limited resection (wedge or segmental)	58 (5)
Lobectomy	616 (57)
Pneumonectomy	402 (38)

Table II. Minor Complications After Elective Pulmonary Surgery

Complication	No. of events
Respiratory	
Atelectasis requiring no or only one bronchoscopy	41
Air leak for > 14 d	25
Cardiovascular	
Atrial or ventricular arrhythmias responding to drug treatment	100
Pleural	
Pneumothorax requiring tube drainage	25
Pleural effusion requiring thoracentesis or tube drainage	9
Miscellaneous	39
Total	239

Table III. Major Complications After Elective Pulmonary Surgery

Complication	No. of events
Respiratory	
Atelectasis requiring two or more bronchoscopies	21
Pneumonia/lung abscess	20
Respiratory failure	15
Cardiovascular	
Myocardial infarction	2
Pulmonary embolism	2
Congestive heart failure	4
Cerebral thrombosis	6
Pleural	
Empyema and/or bronchopleural fistula	29
Miscellaneous	
Hemorrhage requiring reoperation	9
Wound dehiscence	2
Chylothorax	2
Cardiac herniation	1
Other	20
Total	133

were included in one of two categories for each factor as follows: (a) older or younger than 60 years, (b) FEV_1 greater or smaller than 2.0 L, (c) weight loss greater or smaller than 10% of ideal body weight, (d) presence or absence of coexisting diseases, (e) carcinoma stage I or stages II and III, and (f) limited resection and lobectomy or extended resection and pneumonectomy.

Table IV. Deaths After Elective Pulmonary Resection

Primary cause of death	No.
Respiratory	
Respiratory failure	13
Cardiovascular	
Cerebral thrombosis	4
Pulmonary embolism	2
Pleural	
Empyema and/or bronchopleural fistula	8
Miscellaneous	
Hemorrhage	1
Esophagopleural fistula	2
Tumour embolism	2
Other	2
Total	34

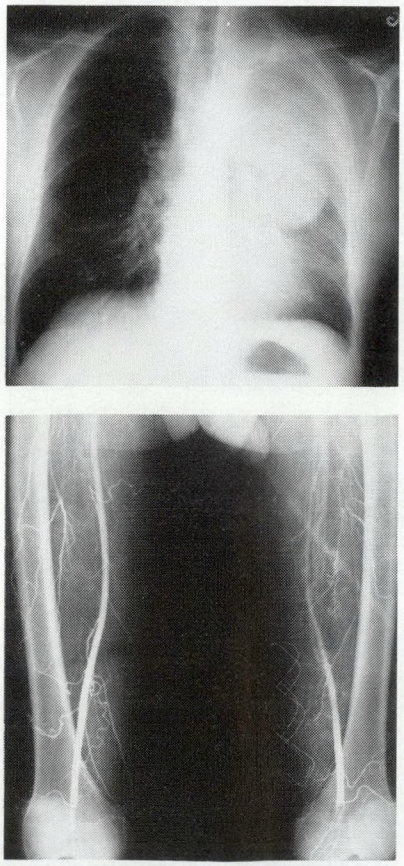

FIG. 1. (Top) Preoperative chest x-ray film of 68-year-old man who underwent left pneumonectomy for large necrotic tumour of upper lobe. (Bottom) Angiogram done 24 hours postoperatively, showing occlusion of both femoral arteries by tumour embolism.

Results

Of the 1076 patients, 731 (68%) had a normal course, whereas 206 patients (19%) had 239 minor complications (Table II). These included atelectasis (41 patients), prolonged bronchoalveolar air leaks (25), supraventricular arrhythmias (100) and simple pneumothorax requiring tube drainage (25 patients). If supraventricular arrhythmias are excluded, nearly 80% of patients had an uncomplicated postoperative course.

One hundred and thirty-three nonfatal major complications occurred in 105 patients (9.8%), most of these being pleural or respiratory in nature (Table III). Major atelectasis requiring two or more bronchoscopies was noted in 21 patients, pneumonia in 20 and respiratory failure requiring mechanical assistance in 15 patients. Only two patients had a myocardial infarction, which in both cases was not fatal. Wound complications were also uncommon since only two individuals had a wound dehiscence and none a wound infection. Unusual complications included chylothorax (two patients) and postpneumonectomy cardiac herniation (one).

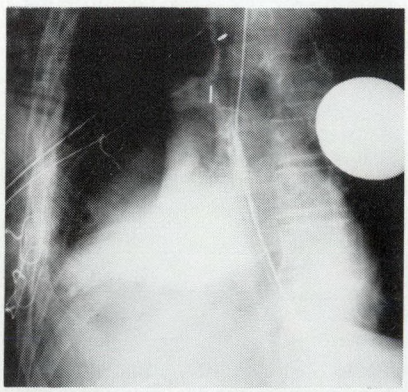

FIG. 2. Barium swallow showing extravasation at site of esophagopleural fistula following right pneumonectomy.

Thirty-four (3.2%) of the 1076 patients died postoperatively (Table IV). The commonest primary causes of death were respiratory failure (13 patients), bronchopleural fistula (8) and cerebral thrombosis (4). Fatal esophagopleural fistulas occurred in two patients (Fig. 1) and tumour embolism in two others (Fig. 2).

Comparison by χ^2 analysis of the group with major complications or death and those without, or with only minor complications, showed that all six variables were significant risk factors. Complications were more common in patients older than 60 years of age, in patients with an FEV_1 smaller than 2 L, in patients with weight loss greater than 10% of normal body weight, in patients with coexisting diseases, in patients with lung cancer stages II and III, and in patients who had an extended resection or pneumonectomy.

Discussion

In general, the reported morbidity after operative treatment of lung cancer is high because the majority of patients are elderly and most have chronic obstructive lung disease. Breyer and associates[5] have shown, however, that advanced age is not necessarily associated with high morbidity. They reported an overall death rate of 3% among 218 thoracotomies performed in patients older than 70 years and concluded that no patient should be denied thoracotomy because of age. Similarly, the Lung Cancer Study Group[6] retrospectively looked at the

operative death rate among patients in the various participating institutions during the years 1979 to 1981. There were 81 deaths among 2220 resections, an incidence of 3.7%. Although the death rate was significantly higher for pneumonectomy patients (6.2%) and for patients 70 years or older (7.1%), it was concluded that major resections could be done with acceptable mortality even in elderly patients.

Preoperative pulmonary function is regarded by many as the most important predictor of operative morbidity. Keagy and colleagues[7] have shown, however, that the results of three spirometric tests (FEV_1, FVC and FEV_1/FVC) did not correlate with postoperative morbidity or mortality in patients who underwent pneumonectomy for carcinoma of the lung. In a similar study on lobectomy patients, Keagy and colleagues[2] showed an increased number of complications among male patients and those older than 60 years. Stepwise discriminant analysis included FEV_1 as a significant predictor of postoperative complications.

In this series, the variables considered to be significant for the development of major complications or death were old age, compromised pulmonary function, coexisting diseases, weight loss, extent of resection and stage of disease.

The analysis of age as a risk factor (Table V) shows a substantial increase in the number of complications after the fifth decade. This difference is greater in the seventh decade being 13% in the 60 to 69 years age group and 24.5% in the 70 to 79 years age group. The lower morbidity seen in older patients (80 years or older) reflects more rigorous preoperative selection.

Morbidity was also found to be significantly higher in patients with compromised pulmonary function (Table VI), this being most significant ($p < 0.005$) in patients with an FEV_1 smaller than 1.2 L. Prolonged air leaks, atelectasis and respiratory failure were the commonest management problems seen in this group.

Among all variables analysed, one of the most important was the extent of weight loss suffered preoperatively (Table VII). Major complications occurred about twice as often in patients with a weight loss greater than 10%.

The stage of disease and, most importantly, the extent of operation (Table VIII) were important predictors of morbidity. With simple resections, the incidence of complications was around 10%, no matter how much lung was removed. In contrast, there was a significant increase in the number of complications among patients who needed more extended procedures such as the removal of the chest wall, pericardium or trachea.

There are several reasons why the morbidity observed in this series is relatively low and in keeping with recently published information (Table IX). Medical operability requires consideration of age, weight loss,

Table V. Age-adjusted Morbidity According to Decade (1076 Patients)

Age, yr	Major complications and death, %	
< 50	3.0	
50 - 59	10.7	
60 - 69	13.0	p < 0.001
70 - 79	24.5	
≥ 80	20.0	

Table VI. Pulmonary Function: Adjusted Morbidity According to Forced Expiratory Volume/s (FEV_1) (672 Patients)

FEV_1, L	No. of resections	Major complications and death, %	
< 1.2	100	22	
1.2 - 2.0	297	14	p < 0.005
> 2.0	275	14	

Table VII. Weight Loss: Adjusted Morbidity According to Percentage Weight Loss (1015 Patients)

Weight loss, %	No. of resections	Major complications and death, %	
None	681	9	
≤ 10	208	12	p < 0.001
> 10	126	20	

Table VIII. Extent of Resection: Adjusted Morbidity According to Type of Operation (1076 Patients)

Type of operation	No. of resections	Major complications and death, %	
Lesser resection	58	10.4	
Simple lobectomy	495	11.2	
Simple pneumonectomy	121	10.0	p < 0.005
Extended lobectomy	231	20.0	
Extended pneumonectomy	171	17.0	

Table IX. Literature on Operative Morbidity and Mortality for Pulmonary Resection

Series	Years analysed	No. of cases	Complications, %	Operative mortality, %
Nagasaki and colleagues, 1982[1]	1973-1980	961*	21	2
Ginsberg and colleagues, 1983[6]	1979-1981	2200	–	3.7
Keagy and colleagues, 1985[2]	1970-1983	369†	41	2.2

*Includes 202 nonresected patients.
†Lobectomies only.

coexisting diseases and cardiopulmonary function. Similarly, the assessment of technical resectability requires consideration of the clinical stage of disease and possible extent of resection. Patients in their seventh or eight decade, those with compromised pulmonary function or with locally advanced disease may be operated on with reasonably low levels of morbidity and mortality, but they must be carefully selected.[8,9] Golebiowski[10] has emphasized the hazards of coexisting diseases in elderly patients.

Patients should be optimally prepared preoperatively by learning the methods for coughing, deep breathing, incentive spirometry and chest physiotherapy. In addition, all patients should receive proper explanations about the nature of the surgery and its possible hazards. The procedure itself should be well and rapidly performed; the anesthetist must know about all modern techniques of intubation, one-lung anesthesia and perioperative monitoring. Postoperatively, new methods of analgesia such as epidural or cryoanalgesia should be routinely used and finally, but most important, potential problems must be recognized and treated at the earliest stage possible.

Conclusions

The morbidity rates for elective surgery of lung cancer, collected from consecutive cases at two major teaching units for thoracic surgery, show that pulmonary surgery can be done safely and complications prevented if an effort is made to select patients properly, perform the operation well and treat any potential problem promptly. During the presurgical work-up, special consideration must be given to age, pulmonary function and extent of resection that may be required.

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SESAP VI Critique

Item 245

Physicians must regularly read and interpret data regarding improved methods of treatment of disease. Recently, several questions have been raised as to the actual or artifactual improvement of survival rates. If new detection methods pick up disease earlier, the survival may seem longer simply because the patient has had the disease longer, rather than because the cure rate is better. For example, liver-spleen or bone scans can now reveal previously undetectable metastases, thus shifting a tumor, formerly diagnosed as "favorable," to a higher stage. This shift artifactually improves the survival of both groups. Such considerations mandate caution in recommending different treatment without careful consideration whether the method of treatment is truly better than the previous method.

E

Reference

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℞PRIMAXIN®

(imipenem and cilastatin sodium for injection)

Antibiotic

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN® especially when recommended dosages based on renal function and body weight were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or who have compromised renal function. However, there were rare reports in which there was no recognized or documented underlying CNS disorder. Close adherence to recommended dosage schedules is urged, especially in patients with known factors that predispose to seizures.

ACTION

Imipenem exerts a bactericidal action by inhibiting cell wall synthesis in aerobic and anaerobic gram-positive and gram-negative bacteria.

PRIMAXIN® consists of two components: (1) imipenem, a derivative of thienamycin, a carbapenem antibiotic; and (2) cilastatin sodium, a specific inhibitor of dehydropeptidase-I a renal enzyme which metabolizes and inactivates imipenem. Cilastatin blocks the metabolism of imipenem in the kidney, so that concomitant administration of imipenem and cilastatin allows antibacterial levels of imipenem to be attained in the urine.

Inhibition of cell-wall synthesis is achieved in gram-negative bacteria by the binding of imipenem to penicillin binding proteins (PBPs). In the case of *Escherichia coli* and selected strains of *Pseudomonas aeruginosa*, imipenem has been shown to have highest affinity for PBP-2, PBP-1a and PBP-1b, with lower activity against PBP-3. The preferential binding of imipenem on PBP-2 and PBP-1b leads to direct conversion of the individual cell to a spheroplast resulting in rapid lysis and cell death without filament formation. When imipenem is removed prior to complete killing of gram-negative species, the remaining viable cells show a measurable lag, termed a "post-antibiotic effect" (PAE), prior to resumption of new growth.

INDICATIONS AND CLINICAL USE

PRIMAXIN® (imipenem and cilastatin sodium for injection) may be indicated in the treatment of serious infections when caused by sensitive strains of bacteria. Where considered necessary, therapy may be initiated on the basis of clinical judgment before results of sensitivity testings are available. Continuation of therapy should be reevaluated on the basis of bacteriological findings and of the patient's clinical condition.

Imipenem is active *in vitro* against a wide range of gram-positive and gram-negative aerobic and anaerobic bacteria, including most strains which are beta-lactamase producing. Patients have responded while under treatment with PRIMAXIN® for single or mixed infections of the following body systems, when they were associated with a number of pathogenic species and strains of the genera listed:

1. Lower Respiratory Tract Infections
2. Urinary Tract Infections
3. Intra-Abdominal Infections
4. Gynecological Infections
5. Septicemia
6. Endocarditis caused by *Staphylococcus aureus*
7. Bone and Joint Infections
8. Skin Structure Infections

Gram-positive Aerobes

- *Listeria monocytogenes*
- *Nocardia asteroides*
- *Staphylococcus* (excluding many strains which are methicillin resistant)
- *Streptococcus* (excluding *S. faecium*)

Gram-negative Aerobes

- *Acinetobacter*
- *Citrobacter*
- *Enterobacter*
- *Escherichia coli*
- *Haemophilus influenzae*
- *Haemophilus parainfluenzae*
- *Klebsiella*
- *Morganella morganii*
- *Neisseria*
- *Proteus* (indole positive and indole negative strains)
- *Providencia*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

Gram-positive Anaerobes

- *Clostridium* (excluding *C. difficile*)
- *Peptococcus*
- *Peptostreptococcus*

Gram-negative Anaerobes

- *Bacteroides fragilis*
- *Bacteroides* (non-fragilis)

CONTRAINDICATIONS

PRIMAXIN® (imipenem and cilastatin sodium for injection) is contraindicated in patients who have shown hypersensitivity to either component of this product.

WARNINGS

PRIMAXIN® (imipenem and cilastatin sodium for injection) SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO STRUCTURALLY-RELATED DRUGS. IF AN ALLERGIC REACTION TO PRIMAXIN® OCCURS, DISCONTINUE THE DRUG. SERIOUS HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with the use of PRIMAXIN®. Therefore it is important to consider this diagnosis in patients who develop diarrhea during or after therapy. This colitis may range from mild to life threatening in severity.

Mild cases of pseudomembranous colitis may respond to drug discontinuance alone. In more severe cases, management may include sigmoidoscopy, appropriate bacteriological studies, fluid, electrolyte and protein supplementation, and the use of a drug such as oral vancomycin, as indicated. Other causes of colitis should also be considered.

PRECAUTIONS

General

Prolonged use of PRIMAXIN® (imipenem and cilastatin sodium for injection) may result in overgrowth of resistant organisms. Repeated evaluation of the patient's condition is essential. If superinfection occurs during therapy, appropriate measures should be taken.

CNS adverse experiences such as myoclonic activity, confusional states, or seizures have been reported with PRIMAXIN® especially when recommended dosages based on renal function and body weight were exceeded. These experiences have occurred most commonly in patients with CNS disorders (e.g., brain lesions or history of seizures) and/or who have compromised renal function. However, there were rare reports in which there was no recognized or documented underlying CNS disorder. Close adherence to recommended dosage schedules is urged especially in patients with known factors that predispose to seizures (see DOSAGE AND ADMINISTRATION). Anticonvulsant therapy should be continued in patients with a known seizure disorder. If focal tremors, myoclonus, or seizures occur, patients should be evaluated neurologically and placed on anticonvulsant therapy if not already instituted. If CNS symptoms continue, the dosage of PRIMAXIN® should be decreased or discontinued.

Use in Patients with Impaired Renal Function

Dosage in patients with impaired renal function is based on the severity of infection but the maximum daily dose varies with the degree of renal functional impairment (see DOSAGE AND ADMINISTRATION - Dosage in Patients with Renal Insufficiency).

Use in Pregnancy

The use of PRIMAXIN® in pregnant women has not been studied, therefore, PRIMAXIN® should be used during pregnancy only if clearly needed. Use of this drug in women of childbearing potential requires that the anticipated benefits be weighed against possible hazards.

Reproduction studies with bolus I.V. doses suggest an apparent intolerance to PRIMAXIN® (including emesis, inappetence, body weight loss, diarrhea and death) at doses equivalent to the average human dose in pregnant rabbits and cynomolgus monkeys that is not seen in non-pregnant animals in these or other species. In other studies, PRIMAXIN® was well tolerated in equivalent or higher doses (up to 11 times the average human dose) in pregnant rats and mice (see REPRODUCTION STUDIES under TOXICOLOGY in the complete monograph).

Nursing Mothers

It is not known whether PRIMAXIN® is excreted in milk. If the use of PRIMAXIN® is deemed essential, the patient should stop nursing.

Pediatric Use

Efficacy and tolerability in infants under the age of 3 months have not yet been established; therefore, PRIMAXIN® is not recommended in the pediatric age group below the age of 3 months.

Drug Interactions

Concomitant administration of PRIMAXIN® and probenecid results in only minimal increases in plasma levels of imipenem and plasma half-life. It is not recommended that probenecid be given with PRIMAXIN®.

PRIMAXIN® should not be mixed with or physically added to other antibiotics. PRIMAXIN® has been administered concomitantly with some antibiotics, such as aminoglycosides.

There is no evidence to suggest that association of PRIMAXIN® with any other beta-lactam antibiotics has any therapeutic advantage.

ADVERSE REACTIONS

PRIMAXIN® (imipenem and cilastatin sodium for injection) is generally well tolerated. The following adverse reactions were reported on 1,723 patients treated in clinical trials. Many of these patients were severely ill and had multiple background diseases and physiological impairments, making it difficult to determine causal relationship of adverse experiences to therapy with PRIMAXIN®.

Local Adverse Reactions

Adverse local clinical reactions that were reported as possibly, probably or definitely related to therapy with PRIMAXIN® were:

	Incidence (%)
Phlebitis/thrombophlebitis	1.7
Infused vein pain	0.6
Vein induration	0.2
Infused vein infection	0.1

Systemic Adverse Reactions

Adverse clinical reactions that were reported as possibly, probably, or definitely related to PRIMAXIN® were:

	Incidence (%)
Gastrointestinal	
nausea	2.0
diarrhea	1.7
vomiting	1.6
tongue papillar hypertrophy	0.2
pseudomembranous colitis (see WARNINGS)	0.1
hemorrhagic colitis	<0.1
gastroenteritis	<0.1
abdominal pain	<0.1
glossitis	<0.1
heartburn	<0.1
pharyngeal pain	<0.1
increased salivation	<0.1
CNS	
fever	0.4
dizziness	0.3
seizures (see PRECAUTIONS)	0.2
somnolence	0.2
confusion	0.2
myoclonus	0.1
vertigo	0.1
headache	0.1
encephalopathy	<0.1
paresthesia	<0.1
Special Senses	
transient hearing loss in patients with impaired hearing	<0.1
tinnitus	<0.1
Respiratory	
dyspnea	0.1
hyperventilation	<0.1
thoracic spine pain	<0.1

Cardiovascular

hypotension	0.4
palpitations	0.1
tachycardia	<0.1

Renal

oliguria/anuria	<0.1
polyuria	<0.1

Skin

rash	0.9
pruritus	0.3
urticaria	0.2
skin texture changes	0.1
candidiasis	0.1
erythema multiforme	<0.1
facial edema	<0.1
flushing	<0.1
cyanosis	<0.1
hyperhidrosis	<0.1
pruritus vulvae	<0.1

Body as a whole

polyarthralgia	<0.1
asthenia/weakness	<0.1

Adverse Laboratory Changes

Adverse laboratory changes, without regard to drug relationship, that were reported during clinical trials were:

Hepatic: Increased SGPT, SGOT, alkaline phosphatase, bilirubin and LDH.

Hemic: Increased eosinophils, positive Coombs test, decreased WBC and neutrophils, increased WBC, increased platelets, decreased platelets, decreased hemoglobin and hematocrit, increased monocytes, abnormal prothrombin time, increased lymphocytes, increased basophils.

Electrolytes: Decreased serum sodium, increased potassium, increased chloride.

Renal: Increased BUN, creatinine.

Urinalysis: Presence of urine protein, urine red blood cells, urine white blood cells, urine casts, urine bilirubin, and urine urobilinogen.

TREATMENT OF OVERDOSAGE

There are no data available on overdosage.

PRIMAXIN® (imipenem and cilastatin sodium for injection) is cleared by hemodialysis.

DOSAGE AND ADMINISTRATION

The dosage recommendations for PRIMAXIN® (imipenem and cilastatin sodium for injection) represent the quantity of imipenem to be administered by I.V. infusion only. An equivalent amount of cilastatin is also present in the solution.

The dosage of PRIMAXIN® should be determined by the severity of the infection, renal function, body weight, the antibiotic susceptibility of the causative organism(s) and the condition of the patient. Doses cited are based on body weight of 70 kilos.

The median duration of treatment with PRIMAXIN® in clinical trials for infections of the various body systems ranged from 6 to 10 days except for endocarditis and bone and joint infections for which the median duration of treatment was 4 weeks.

Dosage in Adults

The recommended daily dose is 1 to 2 g administered in equally divided doses every 6 to 8 hours (see Table 1).

TABLE 1

ADULT DOSAGE OF PRIMAXIN®

	I.V. Administration		
Severity of infection	Dose (mg of imipenem)	Dosage Interval	Daily Dose
Mild	250 mg	6 h	1.0 g
Moderate	500 mg	8 h	1.5 g
Severe (fully susceptible)	500 mg	6 h	2.0 g
Severe× infections due to less susceptible organisms or life threatening conditions	1000 mg 1000 mg	8 h 6 h	3.0 g 4.0 g

× Primarily some strains of *Ps. aeruginosa*.

The maximum daily dose should not exceed 4 g or 50 mg/kg, which ever is less.

Dosage in Elderly Patients

The recommended dosage of PRIMAXIN® in elderly patients with normal renal function is the same as given for adults above. Renal status of elderly patients may not be accurately portrayed by measurement of BUN or creatinine alone. Determination of creatinine clearance is suggested to provide guidance for dosing in such patients.

Dosage in Patients with Renal Insufficiency

Patients with creatinine clearances of ≤5 mL/min/1.73 m² (≤0.08 mL/s/1.73 m²) should not receive PRIMAXIN® unless hemodialysis is instituted within 48 hours. Both imipenem and cilastatin are cleared from the circulation during hemodialysis. The patient should receive PRIMAXIN® after hemodialysis and at 12 hour intervals timed from the end of that hemodialysis session. Dialysis patients, especially those with background CNS disease, should be carefully monitored; for patients on hemodialysis, PRIMAXIN® is recommended only when the benefit outweighs the potential risk of seizures (see PRECAUTIONS). Currently, there are inadequate data to recommend the use of PRIMAXIN® in patients undergoing peritoneal dialysis.

TABLE 2

MAXIMUM DOSAGE OF PRIMAXIN® IN RELATION TO RENAL FUNCTION

RENAL FUNCTION	CREATININE CLEARANCE mL/min/1.73 m² (mL/s/1.73 m²)	DOSE (g)	DOSAGE INTERVAL (h)	MAXIMUM TOTAL DAILY DOSAGE (g)
Mild impairment	31 - 70 (0.52 - 1.17)	0.5	6 - 8	1.5 - 2
Moderate impairment	21 - 30 (0.35 - 0.50)	0.5	8 - 12	1 - 1.5
Severe× impairment	0 - 20 (0 - 0.33)	0.25 - 0.5	12	0.5 - 1.0××

× Patients with creatinine clearance of 6 to 20 mL/min/1.73 m² (0.1 - 0.3 mL/s/1.73 m²) should be treated with 250 mg (or 3.5 mg/kg whichever is lower) every 12 hours for most pathogens. When the 500 mg dose is used in these patients, there may be an increased risk of seizures.

×× The highest dose is only recommended for infections due to less susceptible organisms primarily some strains of *Ps. aeruginosa*.

When only the serum creatinine level is available, the following formula (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance (mL/min). The serum creatinine should represent a steady state of renal function.

Males: $$\frac{\text{Weight (kg) x (140 - age)}}{\text{72 x serum creatinine (mg/100 mL)}}$$

Females: 0.85 x above value.

When using the International System of units (SI), the estimated creatinine clearance (mL/s) in males can be calculated as follows:

$$\frac{\text{(lean body weight, kg) x (140 - age, years) x 1.4736}}{\text{(72) x (serum creatinine concentration, } \mu\text{mol/L)}}$$

and in females the estimated creatinine clearance (mL/s) is:

$$\frac{\text{(lean body weight, kg) x (140 - age, years) x 1.2526}}{\text{(72) x (serum creatinine concentration, } \mu\text{mol/L)}}$$

PRIMAXIN® is cleared by hemodialysis. After each dialysis session the dosage schedule should be restarted.

Dosage in Infants and Children

The recommended total daily dosage of PRIMAXIN® in children and infants 3 months of age and older is 60 to 100 mg/kg of body weight divided into 4 equal doses given at six hour intervals. The higher dosages should be used for infants and young children. The total daily dosage should not exceed 2 grams. Clinical data are insufficient to recommend an optimum dose for infants and children with impaired renal function.

Administration

CAUTION: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

Each reconstituted 250 mg or 500 mg dose should be given by intravenous infusion over twenty to thirty minutes. Each 1000 mg dose should be infused over 40 to 60 minutes. In patients who develop nausea during the infusion, the rate of infusion may be slowed.

RECONSTITUTION

Contents of the vials must be suspended and transferred to 100 mL of an appropriate infusion solution.

A suggested procedure is to transfer approximately 10 mL from the 100 mL of the appropriate infusion solution to the vial (see list of diluents under COMPATIBILITY AND STABILITY). Shake well. Return the resulting 10 mL of suspension to the remaining 90 mL of the infusion solution.

Repeat, using 10 mL of the diluted suspension, to ensure complete transfer of the contents of the vial to the infusion solution.

CAUTION: CONTENTS OF VIALS NOT FOR DIRECT INFUSION.

COMPATIBILITY AND STABILITY

List of diluents

- 0.9% Sodium Chloride Injection
- 5% or 10% Dextrose Injection
- 5% Dextrose Injection with 0.02% sodium bicarbonate solution
- 5% Dextrose and 0.9% Sodium Chloride Injection
- 5% Dextrose Injection with 0.225% or 0.45% saline solution
- NORMOSOL-M in D5-W
- 5% Dextrose Injection with 0.15% potassium chloride solution
- Mannitol 2.5%, 5% and 10%

Reconstituted solutions

Solutions of PRIMAXIN® range from colourless to yellow. Variations of colour within this range do not affect the potency of the product.

PRIMAXIN®, as supplied in vials and reconstituted as above maintains satisfactory potency for four hours at room temperature and for 24 hours under refrigeration (4°C). PRIMAXIN® has been found to be stable in 0.9% Sodium Chloride Injection for 10 hours at room temperature and 48 hours under refrigeration.

DOSAGE FORMS

AVAILABILITY

PRIMAXIN® is supplied as a sterile powder mixture in vials containing imipenem anhydrous and cilastatin sodium as follows:

3514 Ca - 250 mg imipenem equivalent and 250 mg cilastatin equivalent in vials.

3516 Ca - 500 mg imipenem equivalent and 500 mg cilastatin equivalent in vials.

STORAGE

The dry powder should be stored at a temperature below 30°C.

FULL PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(318-b,1,89)

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MSD
MERCK SHARP & DOHME CANADA

MEMBER
PAAB PMAC

P.O. BOX 1005, POINTE-CLAIRE
DORVAL, QUEBEC H9R 4P8

Prolonged Ventricular Support Using a Centrifugal Pump

Fredrick B.Y. Hoy, MD; Carol Stables, RN; Robert C. Gomez, MD; James R. Munns, MD; Dale M. Geiss, MD; Dennis Flack, CCP; David Filko, CCP; James Zischler, CCP, Dean Schmidt, RN

The Biomedicus centrifugal pump was required to provide prolonged ventricular support to 13 patients with hemodynamic instability: 11 after cardiovascular surgical procedures, 1 after myocardial infarction and 1 after failure of a heart transplant.

The duration of support ranged from 3.5 hours to 9 days (mean 72 hours). Complications included bleeding in six patients, renal insufficiency in three and central nervous system deficit in three. Six patients (46%) were successfully weaned from the pump. The patient with graft failure had hyperacute rejection of a second heart. Five patients were discharged from the hospital. There was one death 8 months postoperatively.

Prolonged ventricular support with the centrifugal pump may allow recovery of potentially reversible ventricular dysfunction in selected patients after cardiac surgical procedures.

L'usage de la pompe centrifuge Biomedicus fut nécessaire pour assurer un soutien ventriculaire de longue durée chez 13 patients souffrant d'instabilité hémodynamique: 11 après chirurgie cardiovasculaire, 1 après infarctus du myocarde et 1 après échec d'une greffe cardiaque.

La durée de l'intervention de soutien a varié de 3.5 heures à 9 jours (moyenne de 72 heures). Les complications rencontrées comprennent: saignement chez six patients, insuffisance rénale chez trois et déficit neurologique chez trois. Six patients ont pu être sevré de la pompe avec succès (46%). Le patient greffé a subi le rejet aigu d'un second coeur. Cinq patients ont pu recevoir leur congé de l'hôpital. Il y eut une mortalité, 8 mois après l'intervention.

Chez des patients choisis qui ont subi diverses chirurgies cardiaques, un soutien ventriculaire prolongé peut permettre la guérison de dysfonctionnements potentiellement réversibles.

Despite advances in surgical technique, myocardial preservation, anesthesia and pharmacology, some patients cannot be weaned from cardiopulmonary bypass after cardiovascular surgical procedures. Several devices are currently available for temporary support of the heart until it recovers sufficiently to sustain adequate cardiac output. This article outlines our experience with the use of the centrifugal pump for prolonged ventricular support.

Patients and Methods

Between July 1986 and July 1988, 13 patients, who ranged in age from 6 weeks to 69 years, required prolonged ventricular support with a centrifugal pump (Biomedicus Pump, Biomedicus, Minneapolis, Minn.). Use of the device was indicated in 11 patients who could not be weaned from cardiopulmonary bypass after open-heart surgical procedures, in 1 patient because of graft failure after orthotopic cardiac transplantation and in 1 patient because of cardiogenic shock after acute myocardial infarction.

All patients had refractory cardiogenic shock before mechanical assistance was instituted. This was defined as a cardiac index of less than 2.0 $L/min \cdot m^{-2}$ with a left or right atrial pressure, or both, greater than 20 mm Hg, a mean arterial pressure less than 60 mm Hg and urine output less than 20 ml/h despite maximal inotropic support, intra-aortic balloon counterpulsation, optimal pre-load and after-load and correction of metabolic abnormalities. In the pediatric population, refractory cardiogenic shock was characterized by persistent hypoten-

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sion, anuria or oliguria, poor peripheral perfusion and metabolic acidosis despite elevated filling pressures and maximal inotropic and vasodilator support.

In 10 patients, left ventricular support was used, with venous outflow from the left atrium and arterial inflow into the aorta. In one patient, right ventricular support was used, with right atrial venous outflow and pulmonary arterial inflow. Two patients were essentially on cardiopulmonary bypass with venous outflow from the right atrium and arterial inflow into the aorta and with the use of a Biomedicus pump and membrane oxygenator.

The duration of support ranged from 3.5 hours to 9 days (mean 72 hours). Flow rates were maintained at the highest rate afforded by the venous return. This ranged from 1.0 to 5.0 L/min in adults (mean 3 L/min) and 0.35 to 0.8 L/min for the two children. When hemostasis was secure after the surgical procedure, activated coagulation times were maintained in the range of 150 to 200 seconds using heparin. In eight patients, intra-aortic balloon counterpulsation had been instituted before the Biomedicus pump was inserted.

Attempts to wean the patient from ventricular support were begun when the patient's cardiac index was greater than 2 $L/min \cdot m^{-2}$ during temporary withdrawal of the support.

Results

Six (46%) of the 13 patients could be weaned from ventricular assistance. All of them had left ventricular support — after coronary artery bypass grafting in five and after extensive myocardial infarction in one. Five of the six patients also had an intra-aortic balloon pump in place.

Of the seven patients who could not be weaned from the ventricular support, one patient required right ventricular assistance after a repeat aortic valve replacement and coronary artery bypass grafting; this patient died of right ventricular failure. One patient on cardiopulmonary bypass after repair of the truncus arteriosus died of a cerebrovascular accident. One patient was on cardiopulmonary bypass after orthotopic transplantation and had acute rejection of a second heart. One patient, who was on left ventricular support after coronary artery bypass grafting, died of right ventricular failure. Another, on left ventricular support after repair of a double outlet right ventricle, also died of right ventricular failure. Of two others on left ventricular support after mitral valve replacement, one died of a cerebrovascular accident and the other of biventricular failure.

Complications were frequent. Bleeding occurred in six patients (46%). Renal failure occurred in three (23%); none survived. A documented cerebrovascular accident occurred in three patients (23%); only one survived.

Five patients were discharged from the hospital. One patient, although weaned from the device, died of low cardiac output 3 weeks later. This was the patient who suffered a large myocardial infarction and was considered too old for a heart transplant. One other patient died 8 months postoperatively of unknown cause.

Discussion

Much progress has been made in the field of mechanical ventricular assistance, ranging from intra-aortic balloon pumping, prolonged cardiopulmonary bypass and centrifugal pumping to pneumatically driven ventricles and use of artificial hearts.

The Biomedicus centrifugal pump uses the rotating motion of cones to accelerate the blood during its course between inlet and outlet ports of the pump, where rotational energy is recovered in the form of pressure-flow work. The pressure head created by the pump generates movement of blood. While operating at a given constant speed, the pump generates a nearly constant pressure over a wide range of flow rates. Power for the pumping action is transmitted via magnetic coupling to the mated drive magnet which is fixed to the motor drive.[1] The Biomedicus pump can be used with little or no heparinization; it will not pump or suck air and will not pump against increased resistance. The Biomedicus pump is also readily available, the cost is low and it is user friendly.

To be effective, a ventricular assist device must aid the ventricle in maintaining a reasonable perfusion pressure and cardiac output for vital organ perfusion. It must increase the myocardial oxygen supply or decrease myocardial oxygen consumption to make oxygen available to injured cells and reduce magnitude of myocardial injury. It must reduce pre-load to allow time to restore high-energy substrates, decrease edema and restore adequate function.

Cardiogenic shock refractory to medical management carries an 85% to 100% mortality.[2] Intra-aortic balloon pumping produces improvement in up to 75% of patients but can only be used if there is a reasonable amount of ventricular function remaining. Improvements in anesthesia, intraoperative myocardial protection, pharmacology and surgical techniques have left only a small number of patients who cannot be weaned from cardiopulmonary bypass. In these pa-

tients, optimal results may be obtained if ventricular assistance is instituted when the period of ischemia is short. The recognition of cardiogenic shock, as previously defined, should lead to the consideration of ventricular assistance in patients considered to have reversible ventricular dysfunction.

Problems associated with the use of ventricular assist devices include bleeding, inflow obstruction, renal insufficiency, infection and biventricular failure.

Heparin may be reversed postoperatively until hemostasis is secured. Activated coagulation times may then be maintained in the range of 150 to 200 seconds without thrombus forming in the centrifugal pump. The role of antiplatelet agents is still undetermined. Inflow obstruction may be minimized by using a large cannula in the left atrium or left ventricle via the mitral valve. A patent foramen ovale must be ruled out. The early use of arteriovenous ultrafiltration is important because of the frequency of renal insufficiency. Infection is also a potential problem because the cannulas must traverse the skin to the outside power supply. Right ventricular failure may not be recognized until left ventricular assistance has been instituted. Biventricular assistance should be considered if volume loading and administration of Isuprel do not maintain adequate cardiac output.

Our results are similar to those reported in other series. Zumbro and colleagues[3] reported a series of 33 patients, in which 25 were supported by the Biomedicus pump and 8 by the Pierce Donahey pump. Ten patients (30%) were discharged from the hospital. Complications were frequent; they included bleeding in 36%, central nervous system deficits in 18%, sepsis in 30%, renal failure in 61% and respiratory failure in 61%. There was a 30% incidence of biventricular failure.

Park and associates[4] reported on 41 patients supported by the Biomedicus pump for periods ranging from 2 to 186 hours. Twenty-one patients (51%) were weaned from the pump and 13 (32%) were discharged from the hospital. Death in most cases was the result of progressively decreasing cardiac function and multiorgan failure. Right ventricular support was used if the left ventricular assist device was incapable of producing a cardiac output greater than 1.8 L/min. Park and associates believed that nonpulsatile flow provided adequate support to preserve vital organ function.[4] Schoen and associates[5] reported on 41 patients supported with a pulsatile pump. Eleven patients (27%) were weaned and 6 patients (15%) were discharged from the hospital. The mean duration of ventricular assistance was 62 hours. Most patients who died survived less than 30 hours on ventricular assistance. The presence of established myocardial necrosis itself did not preclude a favourable hemodynamic response or survival. Pae and colleagues[6] reported that 12 (48%) of 25 patients were weaned from the Penn State device and 9 (36%) were discharged from the hospital. Long-term survivors had an excellent quality of life with minimal cardiac disability. Kanter and colleagues[7] reported 14 survivors (23%) of 62 patients supported by the Pierce Donahey or Biomedicus pump. There was a 67% rate of major complications in the survivors. Crippling cardiac disability in survivors was unusual.

In summary, a number of patients who have undergone technically satisfactory open-heart procedures experience cardiogenic shock. Those with potentially reversible ventricular dysfunction may benefit from the use of temporary ventricular support with a mechanical device. The most effective and cost-efficient device and the indications and contraindications to the use of these devices have yet to be defined and require further study.

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Change in Publication Dates

Readers and subscribers please note that starting in 1990 the publication dates for the *Canadian Journal of Surgery* will be February, April, June, August, October and December.

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in contaminated or potentially contaminated gastro-intestinal surgery

Claforan *"...was superior in preventing infectious morbidity and side effects and reduced hospital drug costs compared directly with multidose regimens of cefazolin or cefoxitin (p value not statistically significant)".*
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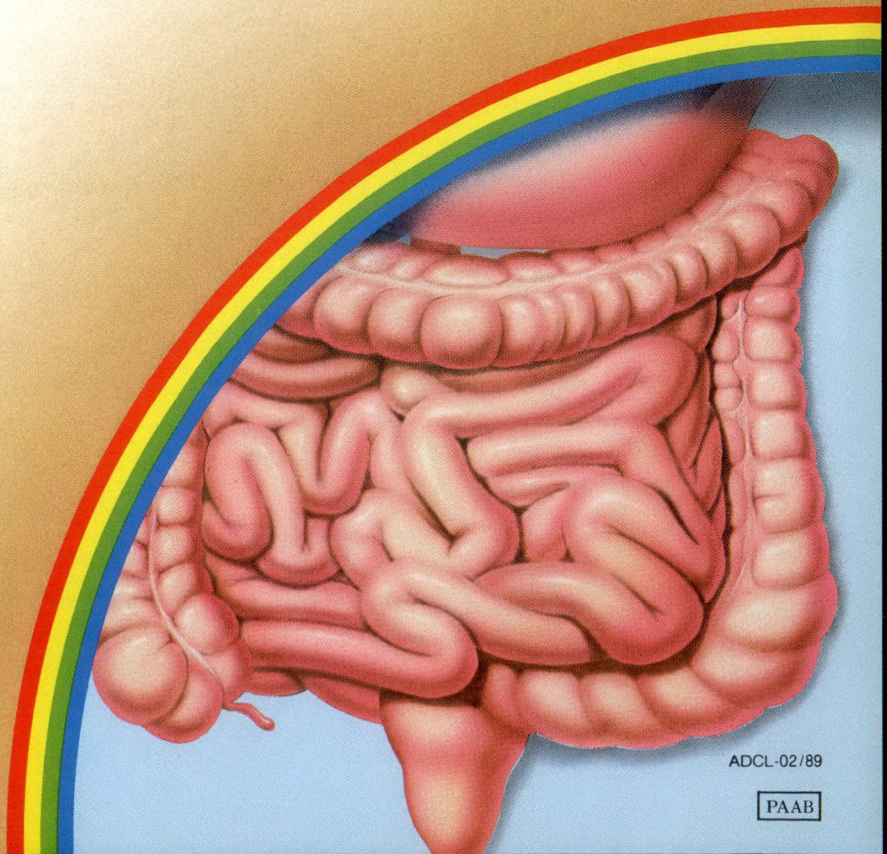

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Prescribing Information

Claforan® IV IM

cefotaxime sodium

Action

In vitro studies indicate that the bacterial action of CLAFORAN (cefotaxime sodium) a semi-synthetic cephalosporin antibiotic, results from inhibition of cell wall synthesis.

Indications and Clinical Uses

Treatment : CLAFORAN (cefotaxime sodium) may be indicated for the treatment of infections caused by susceptible strains of the designated micro-organisms in the diseases listed below.

Lower respiratory tract infections : pneumonia and lung abscess caused by *Streptococcus pneumoniae* (formerly *Diplococcus pneumoniae*), other streptococci (excluding enterocci, e.g. *S. faecalis*), *Staphylococcus aureus* (penicillinase and non-penicillinase producing), *Escherichia coli, Hemophilus influenzae*, (including ampicillin resistant strains) and unspecified *Klebsiella* species.

Urinary tract infections : caused by *Escherichia coli*, unspecified *Klebsiella* species (including *K. pneumoniae*), *Proteus mirabilis*, indole positive *Proteus, Serratia marcescens* and *Staphylococcus epidermidis*. Also, uncomplicated gonorrhea caused by *N. gonorrhoeae* including penicillin resistant strains.

Bacteremia / Septicemia : caused by *Escherichia coli*, unspecified *Klebsiella* strains and *Serratia marcescens*.

Skin infections : caused by *Staphylococcus aureus* (penicillinase and non-penicillinase producing, *S. epidermidis*, Group A streptococci, *Escherichia coli, Proteus mirabilis* and indole positive *Proteus*.

Intra-abdominal infections : caused by *Escherichia coli*, and unspecified *Klebsiella* species.

Gynecological infections : including pelvic inflammatory disease, endometritis and pelvic cellulitis caused by *E. coli*, Group A streptococci and *Staphylococcus epidermidis*; anaerobic bacteria including unspecified *Peptococcus* and *Peptostreptococcus* strains and some strains of *Bacteroides fragilis*. In several cases, although clinical cures were achieved, bacteriological follow-up was not available.

Clinical experience with CLAFORAN in anaerobic infections is limited. CLAFORAN has been used with some success in wound and intra-abdominal infections against some strains of unidentified *Bacteroides* and anaerobic cocci.

CLAFORAN has been shown to be active against some strains of *Pseudomonas*. In the treatment of infections encountered in immunosuppressed and granulocytopenic patients, results of therapy with CLAFORAN have not been impressive. CLAFORAN should not be considered in the treatment of enterococcal infections, i.e. *Streptococcus faecalis*.

Specimens for bacteriologic culture should be obtained prior to therapy in order to isolate and identify the causative organisms and to determine their susceptibilities to CLAFORAN. Therapy may be instituted before results of susceptibility studies are known; antibiotic treatment should be re-evaluated once these results become available.

Prophylactic Use : The administration of CLAFORAN perioperatively (preoperatively, intraoperatively and postoperatively) may reduce the incidence of certain infections in patients undergoing elective surgical procedures (e.g. abdominal or vaginal hysterectomy, gastrointestinal and genitourinary tract surgery) that may be classified as contaminated or potentially contaminated.

In patients undergoing caesarian section who are considered to be at increased risk of infection, intraoperative (after clamping the umbilical cord) and postoperative use of CLAFORAN may also reduce the incidence of certain postoperative infections. Effective use for elective surgery depends on the time of administration (see Dosage and Administration).

For patients undergoing gastrointestinal surgery, preoperative bowel preparation by mechanical cleansing as well as with a non-absorbable antibiotic (e.g. neomycin) is recommended.

If there are signs of infection, specimens for culture should be obtained for identification of the causative organism so that appropriate therapy may be instituted.

Contraindications

CLAFORAN is contraindicated in patients who have shown hypersensitivity to cefotaxime sodium, the cephalosporin or the penicillin groups of antibiotics.

Warnings

Before therapy with CLAFORAN is instituted, it must be carefully determined whether the patient has had previous hypersensitivity reactions to cefotaxime, cephalosporins, penicillins or other drugs. CLAFORAN should be given with caution to patients with Type 1 hypersensitivity reactions to penicillin. Antibiotics, including CLAFORAN should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to CLAFORAN occurs, the drug should be discontinued and the patient treated with the usual agents (e.g. epinephrine, antihistamine, pressor-amines or corticosteroids).

Pseudomembranous colitis has been reported with the use of cephalosporins (and other broad spectrum antibiotics); therefore, it is important to consider its diagnosis in patients who develop diarrhea during the administration of CLAFORAN. This colitis can range from mild to life-threatening in severity.

Treatment with broad spectrum antibiotics, such as CLAFORAN, alters the normal flora of the colon and may permit overgrowth of *Clostridium difficile* or other clostridia. It has been established that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of colitis may respond to discontinuation of CLAFORAN and replacement with a suitable specific antibiotic. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by discontinuance of CLAFORAN administration or when it is severe, an antibiotic specifically effective in antibiotic-associated pseudomembranous colitis (e.g. vancomycin) or other suitable therapy may be indicated. Other possible causes of colitis should also be considered (see Adverse Reactions).

Precautions

CLAFORAN (cefotaxime sodium) should be prescribed with caution in individuals with a history of lower gastrointestinal disease, particularly colitis.

The safety of CLAFORAN in pregnancy has not been established. Consequently, use of the drug in pregnant women requires that the likely benefit from the drug be weighed against the possible risk to the mother and fetus.

Use of CLAFORAN in women of child-bearing potential requires that the anticipated benefits be weighed against the possible risks.

Cefotaxime is excreted in human milk in low concentrations. Caution should be exercised when the drug is administered to nursing mothers.

Prolonged use of CLAFORAN may result in the overgrowth of nonsusceptible organisms. Constant evaluation of the patient's condition is essential. If superinfection occurs, therapy should be discontinued and appropriate measures taken. Although CLAFORAN rarely produces alterations in kidney function, evaluation of renal status is recommended, especially in severely ill patients receiving high doses.

Patients with markedly impaired renal function should be placed on the special dosage schedule recommended under Dosage and Administration, because normal dosage in these individuals is likely to produce excessive and prolonged serum antibiotic concentrations.

Positive direct Coomb's test is known to develop in individuals during treatment with the cephalosporin group of antibiotics, including cefotaxime sodium.

In laboratory tests a false positive reaction to glucose may occur with reducing substances but not with the use of specific glucose oxidase methods.

Adverse Reactions

The most frequent adverse reactions with their frequency of occurrence are :

Hypersensitivity (1.8%) : Rash, pruritus, fever. Local (5%) : Injection site inflammation with intravenous administration. Pain, induration and tenderness after intramuscular injection. Gastrointestinal (1.7%) : Colitis, diarrhea, nausea and vomiting. Symptoms of pseudomembranous colitis can appear during or after CLAFORAN treatment. Hemic and Lymphatic System (< 1%) : Mild, reversible leukopenia, granulocytopenia and thrombocytopenia have been reported. Some patients developed positive direct Coomb's test during treatment with CLAFORAN. Genitourinary System (< 1%) : Moniliasis, vaginitis. Liver (< 1%) : Transient elevations in SGOT, SGPT, serum LDH and serum alkaline phosphatase levels have been reported. Kidney (< 1%) : Increased serum creatinine and BUN have occasionally been observed. Central Nervous System (0.2%) : Headache.

Symptoms and Treatment of Overdosage

Since no case of overdosage has been reported to date with CLAFORAN, no specific information on symptoms or treatment is available. Treatment of overdosage should be symptomatic.

Dosage and Administration

CLAFORAN (cefotaxime sodium) may be administered intramuscularly or intravenously after reconstitution (see Table with recommended mode of reconstitution according to route of administration).

Dosage

Adults

The dosage of CLAFORAN should be determined by susceptibility of the causative organisms, severity of the infection and condition of the patient.

Guidelines for Dosage of CLAFORAN (cefotaxime sodium)

Type of Infection	Daily Dose (g)	Frequency and Route
Uncomplicated Gonorrhea	1	1 g IM (single dose)
Uncomplicated infections	2	1 g every 12 hours IM or IV
Moderately severe to severe infections	3-6	1-2 g every 8 hours IM or IV
Very severe infections (e.g. septicemia)	6-8	2 g every 6-8 hours IV
Life-threatening infections	up to 12	2 g every 4 hours IV

To prevent postoperative infection in contaminated or potentially contaminated surgery, recommended doses are as follows.

(a) 1 g IM or IV administered ½ to 1½ hours prior to the initial surgical incision to ensure that adequate antibiotic levels are present in the serum and tissues at the start of surgery

(b) 1 g IM or IV administered 1½ to 2 hours following the first dose; for lengthy operative procedures, additional intraoperative doses may be administered, if necessary, at appropriate intervals (1½ to 2 hours) during surgery

(c) 1 g IM or IV administered within 2 hours following completion of surgery

The total cumulative prophylactic dose should not exceed 6 g in a 12 hour period.

Caesarian Section Patients

The first dose of 1 g is administered IV as soon as the umbilical cord is clamped. The second and third doses should be given as 1 g IM or IV at 6 and 12 hours after the first dose.

Neonates, Infants, and Children

The following dosage schedule is recommended :

Neonates :	0-1 week of age	50 mg / kg IV q 12 h
	1-4 weeks of age	50 mg / kg IV q 8 h

Infants and children (1 month to 12 years) : For body weights less than 50 kg, the recommended daily dose is 50 to 100 mg / kg IM or IV of body weight divided into 4 to 6 equal doses, or up to 180 mg / kg / day for severe infections.

For body weights 50 kg or more, the usual adult dosage should be used.

The maximum daily dosage should not exceed 12 grams.

Administration of CLAFORAN should be continued for a minimum of 48 to 72 hours after the patient defervesces or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended for infections caused by Group A beta-hemolytic streptococci in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infections and may be required for several months after therapy has been completed; persistent infections may require prolonged treatment. Doses less than those recommended should not be employed.

Dosage for Patients with Impaired Renal Function

In patients with estimated creatinine clearance of less than 20 mL / min / 1.73m² the dose of CLAFORAN should be halved (see Precautions).

If serum creatinine values alone are available, the following formula (based on sex, weight, and age of the patient) may be used to convert these values into creatinine clearance.

Males : $\frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine}}$ Females : 0.85 x above value

Administration

Intramuscular : CLAFORAN should be injected well within the body of a relatively large muscle such as the upper outer quadrant of the buttock (i.e. gluteus maximus); aspiration is necessary to avoid inadvertent injection into a blood vessel.

Intravenous : The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

For bolus administration a solution containing 1 or 2 g of CLAFORAN can be injected over a period of 3 to 5 minutes. Using an infusion system, it may also be given over a longer period of time through the tubing system by which the patient may be receiving other intravenous solutions. Butterfly* or scalp vein type needles are preferred for this type of infusion. However, during infusion of the solution containing CLAFORAN, it is advisable to discontinue temporarily the administration of other solutions at the same site.

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Reconstitution

For Intramuscular Use : CLAFORAN should be reconstituted with Sterile Water for Injection or Bacteriostatic Water for Injection in accordance with the volumes recommended in the following table.

Reconstitution Table

Intramuscular	Volume to be Added to Vial (mL)*	Approximate Available Vol. (mL)	Approx. Average Concentration (mg/mL)
500 mg vial	2	2.2	230
1 g vial	3	3.4	300
2 g vial	5	6.0	330

*shake to dissolve.

For direct intravenous injection (bolus) and / or continuous intravenous infusion : 500 mg, 1 and 2 g vials should be reconstituted with at least 10 mL of Sterile Water for Injection. Reconstituted solution may be further diluted with 50 to 1000 mL of the fluids recommended for IV infusion.

Reconstitution Table

Intravenous	Volume to be Added to Vial (mL)*	Approximate Available Vol. (mL)	Approx. Average Concentration (mg/mL)
500 mg vial10	10.2	50	
1 g vial	10	10.4	95
2 g vial	10	11.0	180

*shake to dissolve.

Solutions for IV Infusion : CLAFORAN is compatible with the following infusion fluids :

- Sterile Water for Injection
- 0.9% NaCl injection
- 5% dextrose injection
- 0.9% NaCl and 5% dextrose injection
- 0.45% NaCl and 5% dextrose injection
- 0.2% NaCl and 5% dextrose injection
- Sodium Lactate injection
- 5% dextrose and 0.15% KCl injection
- Plasma-Lyte 56 Electrolyte Solution in 5% dextrose injection
- Ringer's injection
- Lactated Ringer's solution
- Lactated Ringer's with 5% dextrose injection

CLAFORAN is also compatible with lignocaine 1%.

A solution of 1 g of CLAFORAN in 14 mL of Sterile Water for Injection is isotonic.

Stability of Solution

Storage : Solutions of CLAFORAN range from light yellow to amber, depending on concentration and the diluent used. The solutions tend to darken depending on storage conditions and should be protected from elevated temperatures and excessive light.

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CLAFORAN reconstituted in the original vial as described under Reconstitution maintains satisfactory potency for 24 hours at room temperature (25°C) and for 48 hours under refrigeration (0-5°C). Only freshly prepared reconstituted solutions may be further diluted with 50 to 1000 mL of the recommended infusion fluids in Viaflex** intravenous bags. Such solutions maintain satisfactory potency for 24 hours at room temperature (25°C) and for 72 hours under refrigeration (0-5°C). Any unused solutions should be discarded.

CLAFORAN reconstituted with 1% lignocaine maintains satisfactory potency for up to 24 hours at room temperature and 48 hours under refrigeration (reference to lignocaine restrictions is advisable).

CLAFORAN solutions exhibit maximum stability in the pH 5-7 range.

Special Instructions : Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Solutions of CLAFORAN range from light yellow to amber, depending on concentration and diluent used. The dry powder as well as solutions tend to darken, depending on storage conditions.

Incompatibilities : Solutions of CLAFORAN must not be admixed with aminoglycoside solutions. If CLAFORAN and aminoglycosides are to be administered to the same patient, they must be administered separately and not as a mixed injection.

Solutions of CLAFORAN should not be prepared with diluents having a pH above 7.5 such as Sodium Bicarbonate Injection.

Availability

Claforan (cefotaxime sodium) is supplied as a sterile, white to pale yellow powder, in vials containing 500 mg, 1.0 and 2.0 g of cefotaxime sodium (expressed as acid on a dry basis).

Storage : CLAFORAN in the dry state should be stored at room temperature, protected from light and heat.

Product monograph available on request

Reference

Jones R.N. et al. : Antibiotic Prophylaxis of 1036 Patients Undergoing Elective Surgical Procedures. The American Journal of Surgery, 1987; 153 : 341-346.

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Lithotripsie des calculs biliaires: évaluation de l'ultrasonographie comme moyen de diriger le traitement par ondes de choc extracorporelles

Yves-Marie Dion, MD, FRCSC;* Jacques Morin, MD, FRCSC;* Bruno Laroche, MD, FRCSC;† Gilles Robert, MD, FRCSC;† Michel Thabet, MD, FRCSC†

La lithotripsie des calculs biliaires par ondes de choc extracorporelles est une procédure récemment développée qui serait une alternative au traitement chirurgical de la cholélithiase symptomatique. Selon la littérature, 15% à 25% des personnes symptomatiques seraient candidates à cette procédure si elle est prouvée efficace. Présentement, l'échographie semble un des meilleurs moyens d'évaluation et de suivi durant la procédure de lithotripsie. Les auteurs ont mis au point un modèle in vitro qui permet de comparer les événements qui surviennent dans le modèle expérimental et ce qui est en même temps noté à l'échographie. Les caractéristiques échographiques des différentes phases de la lithotripsie des calculs biliaires sont présentées.

Extracorporeal shock-wave lithotripsy is a procedure recently introduced to treat gallstone disease. According to the literature, 15% to 25% of symptomatic persons will be candidates for this procedure if it proves effective. Currently, sonography is one of the best methods for monitoring the performance of lithotripsy. The authors have confirmed this. They have designed an in-vitro model which allows comparison between what is actually happening during gallstone lithotripsy and what is being seen by real-time sonography. The sonographic characteristics of the different phases of gallstone lithotripsy are presented.

L'idée de la lithotripsie par ondes de choc extracorporelles a évolué à partir des observations faites par un groupe de physiciens qui travaillaient sur les effets produits par des nuages de pluie à travers lesquels passaient des avions supersoniques et sur les effets de petits météorites qui frappaient des satellites.[1] Ils ont noté que les gouttes d'eau et autres petites particules généraient des ondes de choc qui causaient des dommages, non seulement à la surface, mais aussi à l'intérieur de ces véhicules.[1] C'est ainsi qu'en 1974, le premier projet de recherche à visée médicale voyait le jour en Allemagne, avec comme hypothèse que les calculs rénaux pouvaient être détruits par des ondes de choc extracorporelles.[1] Depuis, plus de 60 000 patients ont été traité avec succès, cette technique étant applicable à 80% de tous les patients porteurs de calculs rénaux.[1] En 1983, Brendel et Enders[1] étudièrent les effets de la lithotripsie par ondes de choc extracorporelles sur les calculs biliaires humains implantés dans les vésicules biliaires de chiens. En février 1988, les résultats d'une étude clinique étaient publiés.[2] Les auteurs rapportent un taux de succès de 91%, 18 mois après la lithotripsie qui est combinée à un traitement aux acides chénodésoxycholiques et ursodésoxycholiques. Récemment, un article faisait le point sur les résultats obtenus à ce jour et sur les questions sur le sujet, qui demeurent sans réponse actuellement.[3] Cependant, après avoir consulté la littérature, nous n'avons noté aucun article décrivant la procédure de lithotripsie. Nous rapportons notre expérience suite à la fragmentation in vitro de 15 calculs biliaires.

Matériel et méthode

Le lithotripteur utilisé est l'appareil de seconde génération EDAP

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Accepté pour publication le 5 décembre, 1988

Les demandes de tirés à part doivent être adressées au: Dr Yves-Marie Dion, Service de chirurgie générale, Hôpital St-François d'Assise, 10, rue de l'Espinay, Québec, PQ G1L 3L5

LT-01. Les ondes de choc sont émises par des céramiques qui tapissent le fond d'une coupelle. Cette coupelle est recouverte d'une membrane qui est mise en contact avec le modèle expérimental grâce à un gel conducteur (fig. 1). Le modèle expérimental consiste en une cuvette dont la base est recouverte d'une membrane de même type que la coupelle. Deux litres et demi d'eau sont placés dans cette cuvette. Par la suite, un sac de fine polythène, dans lequel ont été précédemment placés 75 ml d'eau et le calcul, est inséré dans la cuvette (fig. 2). La cadence des ondes de choc a été établie à 20 coups/s. Ensuite, le calcul est repéré échographiquement et les ondes de choc sont mises au foyer au niveau du calcul grâce à un curseur qui apparaît sur l'appareil échographique (fig. 3). Quinze calculs biliaires de taille, de forme et de composition différentes ont été soumis à la lithotripsie. Les caractéristiques échographiques qui seront mentionnées sont le fruit de ces expériences. En vue de démontrer la séquence des évènements lors de la lithotripsie, les figures suivantes proviennent d'une séance effectuée sur un calcul mixte, à facettes, mesurant 1.6 cm dans son plus grand diamètre et pesant 1.41 g. Une fois l'image échographique jugée satisfaisante en début de procédure, les caractéristiques échographiques n'ont pas été modifiées.

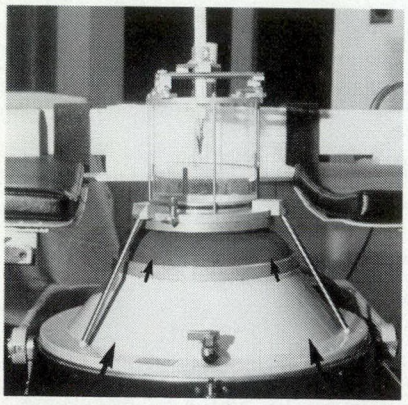

FIG. 1. Coupelle (longues flèches) de l'appareil EDAP LT-01, recouverte d'une membrane (courtes flèches) sur laquelle se trouve le modèle expérimental.

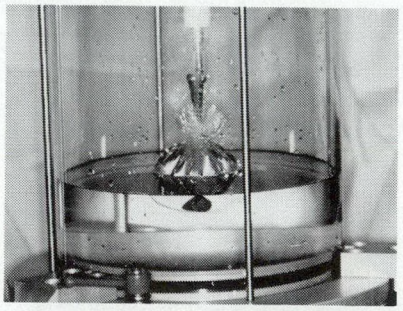

FIG. 2. Modèle expérimental fait d'une cuvette dont la base est recouverte d'une membrane perméable aux ondes de choc. Le calcul a été placé au fond d'un sac dont la dimension se compare à celle de la vésicule biliaire normale.

Résultats

Avant le début de la lithotripsie, le calcul est bien démontré par échographie (fig. 4). Les parois du petit sac de polythène que nous appellerons "vésicule biliaire" sont bien visibles; le calcul situé au fond de la "vésicule biliaire" est bien démontré ainsi que le cône d'ombre sus-jacent. Quelques minutes après le début de la lithotripsie, l'élargissement du cône d'ombre est démontré, ce qui témoigne du début de la fragmentation du calcul. En effet, les fragments se déposent au pourtour du calcul créant cet élargissement du cône. Le calcul est toujours visible à la base du cône d'ombre (fig. 4). Par la suite, à l'échographie, la "vésicule biliaire" devient de moins en moins échogénique. En effet, elle semble se remplir de matériel qui la rend plus

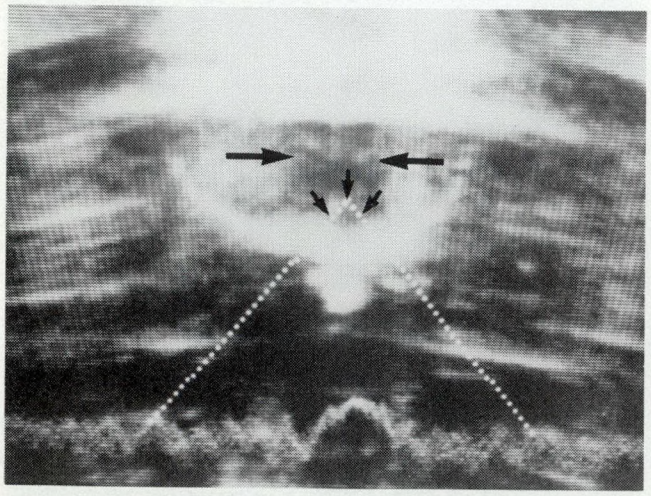

FIG. 3. Elargissement du cône d'ombre (longues flèches), témoin du début de la fragmentation du calcul. Le curseur (petites flèches) indique l'endroit où les ondes de choc convergent.

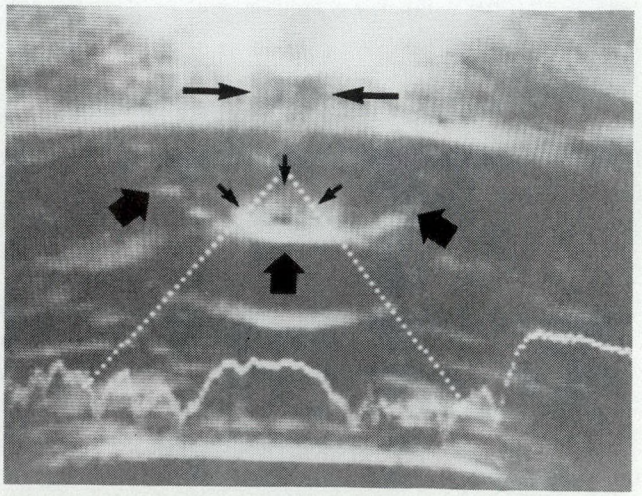

FIG. 4. Echographie du calcul biliaire démontrant le calcul (petites flèches) et le cône d'ombre sus-jacent (longues flèches). Le calcul se trouve au fond de la "vésicule biliaire" (flèches larges).

opaque sur l'image. Ce phénomène correspond au développement dans la "vésicule biliaire" d'un nuage de poussière bilieuse verdâtre (fig. 5). Plus tard, on note que le cône d'ombre s'amenuise (fig. 6) dans une "vésicule biliaire" qui devient de plus en plus opaque, c'est-à-dire, dans laquelle le nuage de poussière est devenu plus dense. Le rétrécissement du cône d'ombre confirme la désintégration progressive du calcul. Dans les dernières minutes précédant la fin de l'intervention, on procède à un balayage échographique de la "vésicule biliaire" à la recherche de cônes d'ombre résiduels (fig. 7). Ces endroits où l'on note de petits cônes d'ombre sont par la suite soumis à l'effet des ondes de choc en vue de désintégrer les fragments le plus possible. On note simultanément, au niveau du modèle expérimental, que ces fragments de 4 à 6 mm de diamètre devenus légers par la fragmentation vont et viennent dans la zone de turbulence créée par les ondes de choc. On note parallèlement, à l'échographie, l'apparition et la disparition alternative des petits cônes d'ombre correspondant à ces fragments (fig. 7).

L'indication échographique de la fin de la procédure nous apparaît démontrée de deux façons. La première consiste en la visualisation d'une vésicule biliaire complètement opacifiée par les fragments en suspension avec absence de cône d'ombre (fig. 8). Cette image indique que la quantité de matières en suspension rend l'échographie inapte à visualiser les calculs résiduels, s'il en demeure. Cependant, comme nous l'avons noté, cette image, lorsqu'elle est combinée à l'effet de balayage des ondes de choc, devient très suggestive que les fragments restants sont de petite taille.

L'autre image échographique ap-

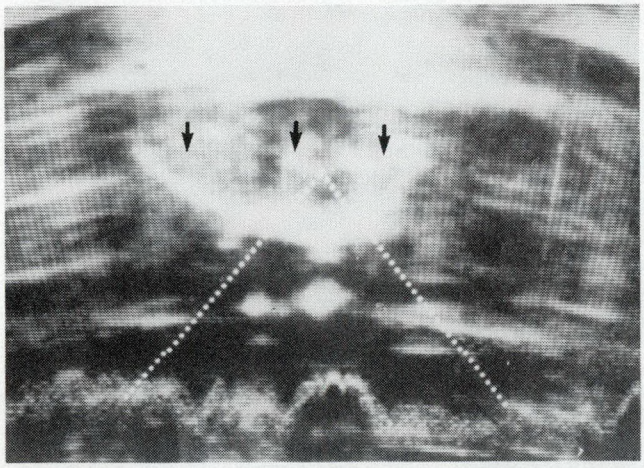

FIG. 5. "Vésicule biliaire" est plus échogénique (flèches) due à une suspension calculeuse qui la remplie peu à peu.

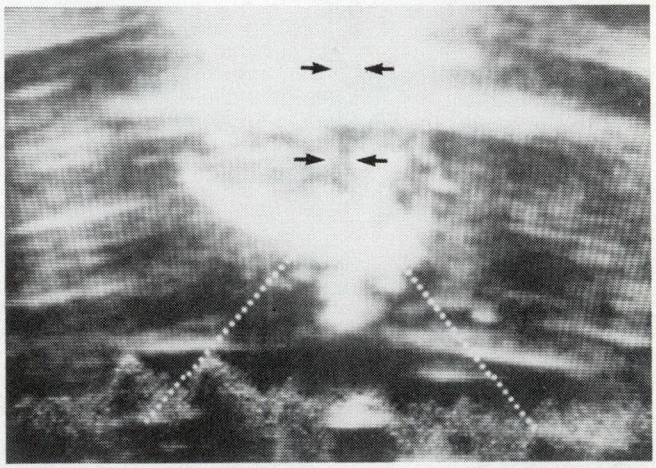

FIG. 6. Le cône d'ombre s'amenuise (flèches) dans "vésicule biliaire" de plus en plus échogénique.

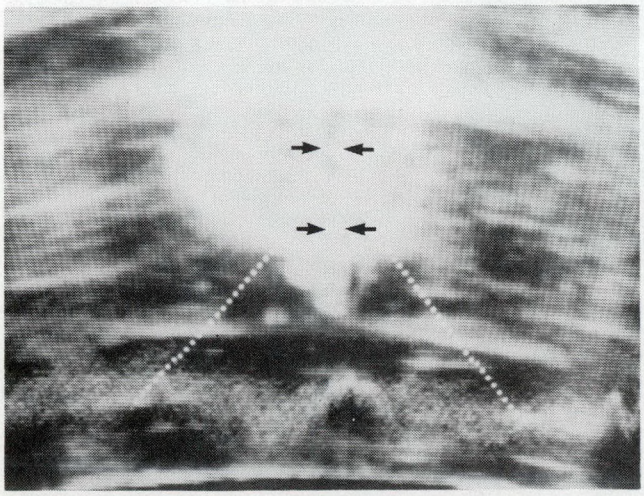

FIG. 7. Balayage de la vésicule biliaire à la recherche d'un petit cône d'ombre (flèches). Ces cônes d'ombre apparaissent et disparaissent, étant projetés sous l'effet des ondes de choc.

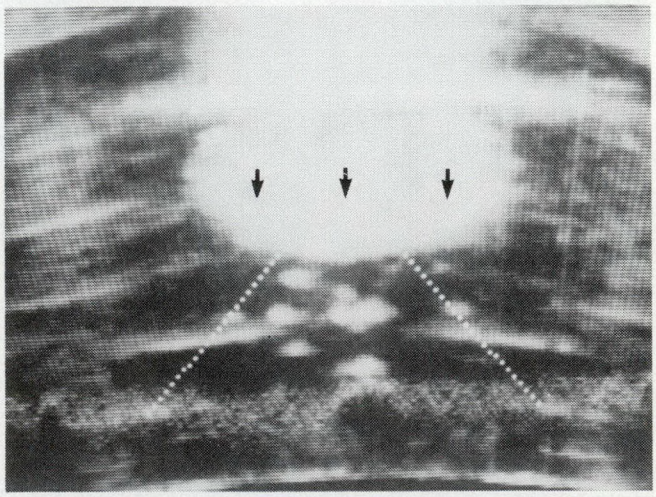

FIG. 8. Aspect final de la "vésicule biliaire" et de son contenu (flèches) à la fin de la lithotripsie. Elle est complètement imperméable aux ultrasons sans évidence de cône d'ombre.

paraissant démontrer la fin de la procédure se voit le plus souvent dans le cas de calculs de plus grand diamètre, c'est-à-dire au-delà de 1 cm. En effet, la quantité de débris non en suspension demeurant au fond de la "vésicule biliaire" est plus grande et ceux-ci s'étalent à l'endroit le plus déclive, ce qui cause l'élargissement du cône d'ombre (fig. 9). Cependant sous le cône d'ombre, il n'y a pas de calcul identifiable. Lorsque les ondes de choc sont dirigées à ce niveau, on peut noter à l'échographie la poussière et les petits fragments qui s'élèvent dans le cône d'ombre témoignant de leur petite taille.

Discussion

La lithotripsie des calculs biliaires est présentement le sujet de beaucoup d'intérêt. Plusieurs études ont démontré la possibilité de désintégrer les calculs par cette technique.[4-8] D'autres articles ont fait état de la fragmentation de calculs biliaires situés non seulement au niveau de la vésicule biliaire mais aussi dans le cholédoque et en position intra-hépatique.[9,10] Quinze pourcent à 20% des patients présentant des crises de coliques hépatiques seraient candidats à cette procédure si elle est prouvée efficace.[4]

A notre connaissance, la littérature actuelle n'indique pas de façon claire comment suivre la progression de la lithotripsie des calculs biliaires. Notre étude in vitro nous a permis de mettre en corrélation les évènements survenant au niveau du modèle expérimental et leur transposition échographique. Nous avons constaté que l'échographie permet de déterminer avec justesse les phases de la désintégration des calculs. Etant donné que l'échographie donne les informations en deux plans, ils revient à l'opérateur de manipuler l'appareil dans le troisième plan (profondeur) de façon à visualiser tout le contenu de la vésicule biliaire. Une fois l'image échographique du calcul ou du fragment obtenue, les ondes de choc sont dirigées vers la cible grâce à un curseur qui apparaît sur l'image échographique.

En résumé, l'échographie s'est révélée un moyen efficace de suivre la procédure de lithotripsie au niveau de notre modèle expérimental.

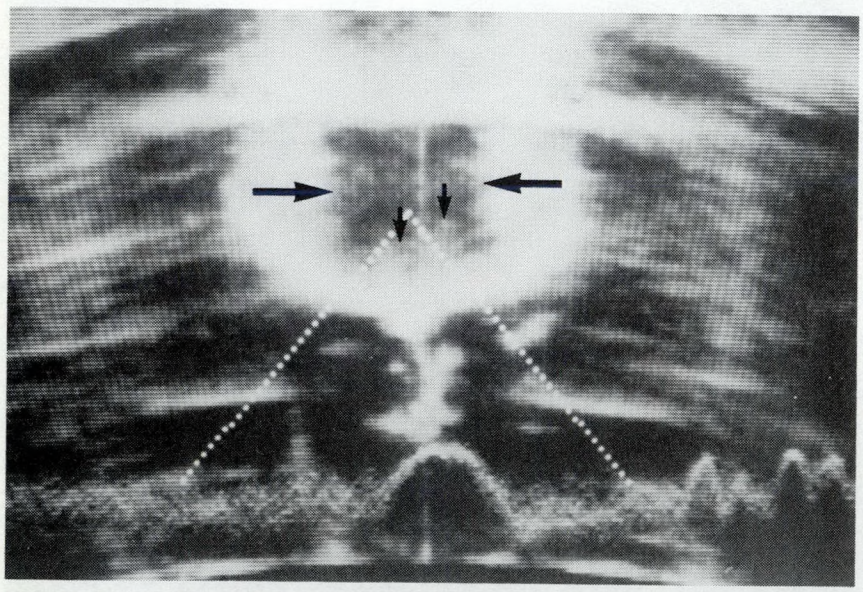

FIG. 9. Aspect alternatif de la "vésicule biliaire" et de son contenu à la fin de la lithotripsie, notable particulièrement lorsqu'un calcul de plus grande taille (au-delà de 1.0 cm) est désintégré: un large cône d'ombre (longues flèches) est visible de même que des petits fragments (petites flèches) qui sont projetés vers le haut dans le cône d'ombre.

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Effects of High-Dose Ketoconazole on Patients Who Have Androgen-Independent Prostatic Cancer

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Forty-four patients who had metastatic cancer of the prostate that had not responded to conventional hormonal manipulation were treated with high-dose ketoconazole (600 to 1200 mg/d). All had castrate serum concentrations of testosterone prior to therapy. All patients had been categorized as having progressive cancer on assessment by the criteria of the National Prostatic Cancer Project. After treatment with ketoconazole, 57% were recategorized as having stable disease. The majority showed marked subjective lessening of pain on this therapy. Objective responses were noted but were not consistent. Side-effects were common but tolerable. The mean survival time was 73.3 weeks. Ketoconazole may be a useful palliative adjunct in the treatment of hormone-refractory prostatic cancer.

Quarante-quatre patients porteurs de cancers métastatiques de la prostate qui n'avaient pas répondu aux manipulations hormonales habituelles, ont été traités avec de fortes doses de kétoconazole (600 à 1200 mg/j). Tous avaient des taux de testostérone sérique nuls avant le traitement. Tous les patients avaient été classifiés selon les critères du Projet national sur le cancer de la prostate comme ayant un cancer en évolutif. Après traitement au kétoconazole, 57% des patients ont été reclassifiés comme ayant une maladie stable. La majorité a manifesté une atténuation subjective marquée de la douleur grâce à cette thérapie. Des réponses objectives ont été observées, mais elles n'étaient pas constantes. Les réactions adverses ont été fréquentes mais tolérables. Le temps de survie moyen a été de 73.3 semaines. Le kétoconazole peut être un traitement palliatif d'appoint utile dans les cas de cancers de la prostate hormono-résistants.

Prostatic cancer is the second most common cause of death due to malignant disease in North American men and in the majority the disease is advanced at the time it is discovered.[1,2] Although the disease is considered to be androgen-dependent, only about two-thirds of patients who receive therapy designed to lower concentrations of androgen (castration or the administration of estrogens) obtain a remission of notable duration. In spite of an initial response, most patients relapse and die. No single agent or combination of agents has so far provided substantial benefit to patients with advanced prostatic cancer.[3]

Ketoconazole, a synthetic imidazole dioxolane, is widely used to treat superficial and deep fungal infections. In man the action of ketoconazole is poorly understood. The drug appears to interfere with a wide variety of cytochrome P450-linked enzyme systems. Recent studies[4,5] have demonstrated that at high doses ketoconazole can rapidly and profoundly inhibit both adrenal and testicular androgen production by inhibiting 17,20-desmolase, an enzyme that is P450-dependent. These changes in steroidogenesis are reversible by withdrawal of therapy.[6] Reports of patients with previously untreated advanced prostatic cancer who are given ketoconazole describe a rapidly induced and sustained clinical remission accompanied with a sustained decrease in serum testosterone and adrenal androgen levels.[7] In the course of treating such patients we have also noted a marked salutary effect of ketoconazole on patients who had relapsed while receiving a variety of forms of hormonal therapy.[8] Indeed, other investigators have noted similar effects and suggested that ketoconazole may have a role to play in the treatment of androgen-

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independent prostatic cancer.[9] In this study we attempted to define more precisely the role of ketoconazole in the treatment of patients who have this disease.

Patients and Methods

Forty-four patients who had biopsy proven metastatic prostatic cancer were treated at eight centres across Canada. The average age was 69.9 ± 9.1 years (mean ± SEM) (range from 48 to 84 years). All had failed to respond to hormonal therapy which had reduced their serum testosterone concentration to the castrate level. The previous treatments are shown in Table I.

All patients gave their informed consent and were administered ketoconazole in 200-mg tablets at a recommended dosage of 200 to 400 mg every 8 hours (to maintain a maximum concentration of 5 to 10 μg/ml). The dose was adjusted by serum ketoconazole levels and the occurrence of side-effects. The patients continued on their original hormonal therapy. No patient received supplemental glucocorticoids. Patients were allowed to continue taking additional medication needed to control pain or concurrent illnesses. They were seen weekly for the first month and monthly thereafter. At each visit a complete history was obtained, and they underwent physical examination and extensive biochemical work-up; all adverse experiences were reported and each patient was rated on a five-point abbreviated Karnofsky performance scale (0 to 4), where 4 represents maximum performance, and a six-point pain scale (0 to 5), where 0 represents no pain. At 3-month intervals bone scanning was repeated.

The patient's response to therapy was assessed using the criteria of the National Prostatic Cancer Project (complete regression, partial regression, stable or progression). Each patient's duration of "benefit" was calculated as the time from the initiation of benefit to the first evidence of recurrent progression. The time during which the group benefited from ketoconazole was subjected to a "survival" analysis using the Kaplan-Meier method[10] to estimate the percentage of patients still on therapy at each week of the trial. The duration of ketoconazole therapy was calculated as the difference between the date the patient first started therapy and the date on which he was last confirmed to be still on therapy. In many cases this was the last recorded visit.

Results

Patients who entered this clinical trial were generally debilitated, because the treatment was considered as salvage therapy. The laboratory values were quite variable and often far outside the normal range. Many patients were too ill either to attend every required visit or to have laboratory work done. Thus, the data for laboratory values were not necessarily complete for every scheduled patient visit over the course of the study.

Twenty-seven patients demonstrated persistent (more than 8 weeks or three visits) improvement in serum prostatic acid phosphatase and alkaline phosphatase levels during therapy, with decreases of more than 75%. No statistically significant changes, however, were noted for these two values in the group as a whole, although the values during treatment were generally lower than those before. This lack of significance may be attributed to the extremely wide variance in these levels before treatment. No significant changes were noted in markers of hepatic function or in serum cortisol levels. In one patient the bone scan became normal and multiple "hot" areas were eliminated and two patients had marked improvement in their bone scans.

The performance ratings showed little change. The majority of the patients maintained scores in the 1 and 2 range for the first 12 weeks: 76.7%, 75.7%, 81.2%, 84.8%, 79.3% and 71.4% for weeks 0, 1, 2, 4, 8 and 12 respectively. Beyond week 12 the data became less reliable because of the small number of patients (11 [25%] or fewer from week 16 onward). Performance scores in the range of 1 and 2 remained stable.

Pain scores, on the other hand, demonstrated a strong decrease with therapy. The percentage of patients with scores of 1 or less increased from 18.5% at the beginning of the study to 76.2% by week 12 (Fig. 1), with a corresponding decrease in analgesic consumption.

On entering this trial, all patients had progressive disease. During their treatment with ketoconazole, 25 (57%) patients were recategorized as having stable disease. Thirteen patients showed no benefit

Table I. Previous Hormone Treatment

Treatment	No. of patients
Bilateral orchiectomy ± estrogen	16
Estrogen (diethylstibestrol 3 mg/d)	10
Lhrh analogues (Lupron 1 mg/d)	4
Orchiectomy or Lhrh analogues + antiandrogens*	14

Lhrh = luteinizing hormone-releasing hormone.
*Flutamide 250 mg tid or Anandron 100 mg tid.
The serum testosterone level of all patients was in the castrate range (< 0.8 nmol/L) before therapy.

from ketoconazole, 1 had complete regression and 5 partial regression. The mean time of benefit on therapy was 27.3 weeks (median 12 weeks). No significant difference in duration of response could be found between the 30 patients who had been treated with conventional forms of androgen ablation and the 14 patients in whom total androgen ablation failed. The mean time on ketoconazole therapy analysed by the Kaplan-Meier product limit method was 35.5 weeks (mean 22.0 weeks, range from less than 1 week to 96 weeks).

Side-effects were frequent in this already debilitated group. Thirty-two patients (72.7%) reported at least one adverse experience and 29 (65.9%) of them reported experiences that were possibly drug related. There were 23 reports (given by 19 patients) of nausea, vomiting and gastrointestinal upset, of which 22 were considered possibly drug related; there were 9 reports of weakness, fatigue and lethargy (7 possibly drug related). In all of these patients, the serum cortisol level was within normal limits. Seven (15.9%) patients were taken out of the study because of illness (two patients) or adverse experience (five patients).

Eighteen patients died of disease-related causes. The mean time to death was 59.1 weeks (median 73.3 weeks, range from 2 to 100 weeks).

Discussion

To our knowledge this study represents the largest series of patients treated by high-dose ketoconazole after the failure of hormonal therapy. The design was that of a single-armed non-controlled trial. Thus, all conclusions must be viewed with caution until they can be substantiated in controlled studies. None the less, we believe that certain assumptions are warranted. The patients were all severely ill with progressing disease at the time of entry into this study, yet a large percentage of patients demonstrated a marked lessening of pain and stabilization of their disease. Although the latter is often difficult to substantiate because of the variable rate at which the disease progresses, these patients did seem to benefit, since their condition appeared to stabilize, if only for a short time. The objective responses that were seen in some of the patients seem to add further support to the belief that ketoconazole provides more than just a placebo effect.

Ketoconazole not only interferes with testosterone production but also greatly decreases adrenal androgen production.[5,8] The patients who responded in this study, however, were similarly divided between those who received only conventional testicular androgen ablation and those who had been subjected to total androgen ablation. These data suggest that ketoconazole's mechanism of action may be divorced from androgen activity. Not only has the product been shown to affect androgen synthesis but it also directly impairs the growth of human prostatic cancer cells in vitro.[11] In these studies the androgen-independent human prostatic cancer cell lines PC-3 and DU-145, when incubated with ketoconazole, showed decreased growth from 70% to 96% at the clinical concentrations of 1.0 to 10.0 μg/ml. Other agents thought to be of use in this clinical situation, such as aminoglutethimide, did not demonstrate similar cytotoxicity. We believe that this direct cytotoxicity of ketoconazole may be active in the responses of these patients. Indeed, the eventual cessation of benefit could be predicted by the incomplete inhibition of growth even at the highest ketoconazole concentration (which was only intermittently achieved). The duration of benefit was difficult

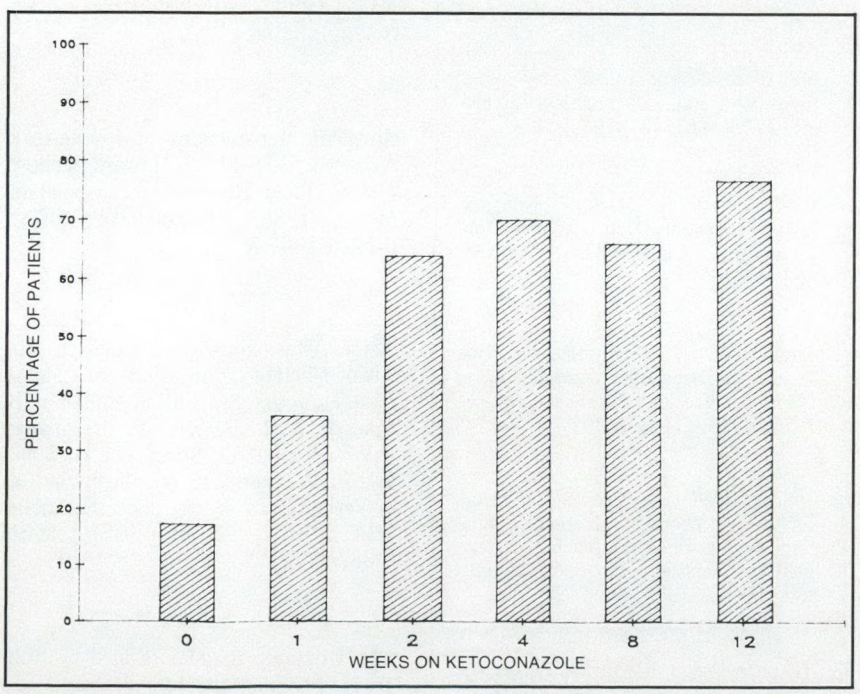

FIG. 1. Changes in pain score of patients treated with high-dose ketoconazole during initial 12 weeks of therapy. Values represent percentage of patients with pain scores of 0 or 1. Pain was rated from 0 to 5 (0 = no pain).

to quantify, probably because the patients were extremely ill and entered the trial only as a last chance at salvage. None the less, the duration of survival is comparable if not superior to that reported from other similar trials.[12] Historical controls are usually misleading, but ketoconazole may impart a small survival advantage. We also believe that the decrease in pain is significant and markedly improved the quality of life for many of the patients. Although side-effects were common, they were rarely severe enough to limit treatment and were milder than those experienced by patients in a similar stage of disease when treated with estramustine phosphate or conventional cytotoxic regimens (Koenyves I: Personal communication, 1987). We believe that further trials should be undertaken to determine more precisely the role of ketoconazole in patients with advanced prostatic cancer. Experimental in-vitro data further suggest that the cell destruction of certain classic cytotoxic agents can be increased appreciably with the concomitant administration of ketoconazole.[13] If this can be substantiated, then ketoconazole may not only play a role as a palliative agent, but also as an important adjunct in the treatment of patients with far-advanced prostatic cancer.

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Destructive Arthropathy of the Hip Following Pelvic Irradiation: Report of Four Cases

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The replacement of orthovoltage by megavoltage radiotherapy has facilitated selective ablation of cancerous tissue, resulting in less toxicity to bone. However, damage to bone still occurs and may be more common than generally appreciated. In four women, all treated for adenocarcinoma of the reproductive tract, radiotherapy was believed to contribute to acetabular failure and secondary arthritis 2 to 31 years after treatment. In one case the condition was bilateral.

Because arthritis of the hip is now common in women, there is a risk that unusual and remote factors may not be recognized or fully appreciated. In these cases prosthetic joint replacement is likely to fail. Special techniques, including bone grafting, peripheral support rings, well-fixed and optimally placed sockets and gradual rehabilitation, are mandatory.

En radiothérapie, le remplacement de l'orthovoltage par le mégavoltage a facilité l'ablation sélective des tissus cancéreux, réduisant ainsi la toxicité osseuse. Néanmoins, des dommages osseux surviennent encore, et ils sont possiblement plus fréquents qu'on ne le pense généralement. On croit que, chez quatre femmes qui avaient été traitées pour des adénocarcinomes des organes reproducteurs, la radiothérapie a contribué à un affaissement acétabulaire et à une arthrite secondaire apparue de 2 à 31 ans après le traitement. Dans un cas, l'atteinte était bilatérale.

Parce que l'arthrite de la hanche est devenue commune chez la femme, il y a risque que des facteurs inhabituels ou lointains ne soient pas reconnus ou appréciés à leur juste valeur. Dans ces cas, les arthroplasties sont susceptibles d'être vouées à l'échec. Des techniques spéciales telles que greffes osseuses, anneaux de soutien périphérique, cavités articulaires solidement fixées en position optimale et réadaptation graduelle sont obligatoires.

Osteoradionecrosis is a well-recognized entity, affecting most areas of the skeleton. The femoral neck has been one of the most common locations for secondary fracture.[1] Acetabular failure and protrusio have been described in eight patients.[2-4] In only one recent report[2] have the pitfalls of reconstructive arthroplasty been discussed.

In this paper we describe four patients in whom the condition at first appeared to be standard arthritis of the hip. However, radiologically the arthropathy appeared more destructive than usual. It was discovered that all patients had undergone radiotherapy. All had also had recurrent problems from radiation cystitis, urethritis or proctitis.

Case Reports

Case 1

In 1977, at the age of 68 years, this woman underwent a total hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the uterus. Postoperatively, she received external pelvic irradiation (50 Gy in 20 fractions over 5 weeks) using 33 mev x-rays, 50% of the total dose from the anterior field and 25% from each of the lateral fields. A scout film obtained at the cancer clinic before radiotherapy showed that both hips were normal (Fig. 1).

In 1983 this woman was seen complaining of a painful right hip. A fracture of the medial wall and secondary arthritis were found (Fig. 2). A right hip replacement arthroplasty was performed. The medial acetabular wall was found to be

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fractured, eroded and chalk-like, and was poorly vascularized. A femoral head autograft was used to augment the medial wall. A cementless Moore-type femoral stem with a Bateman bipolar head was implanted. Seven months later the right side was asymptomatic but she had severe pain in the left hip due to a fracture of the medial acetabulum with protrusio acetabuli (Fig. 3). This hip was also reconstructed using a cementless bipolar prosthesis with medial bone grafting. She did well until June 1985 when she again began to suffer pain in the left hip. X-ray films showed protrusion of the prosthetic head into the pelvis with a lack of consolidation of the medial acetabular fracture (Fig. 4). The bipolar head was removed and the medial wall further grafted, this time with an iliac crest autograft from outside the radiation field. An Eichler peripheral support ring was positioned over the graft and fixed to the rim of the acetabulum with cancellous bone screws. A polyethylene prosthetic socket was cemented inside this. In March 1986, a complete transverse fracture of the pelvis was noted on follow-up x-ray films (Fig. 5). This was also revised with medial bone grafting and a cemented socket inside a peripheral support ring. Two years after this she was doing well (Fig. 6), but in late 1988 her condition deteriorated with recurrence of right hip pain and progressive loosening of the prosthesis.

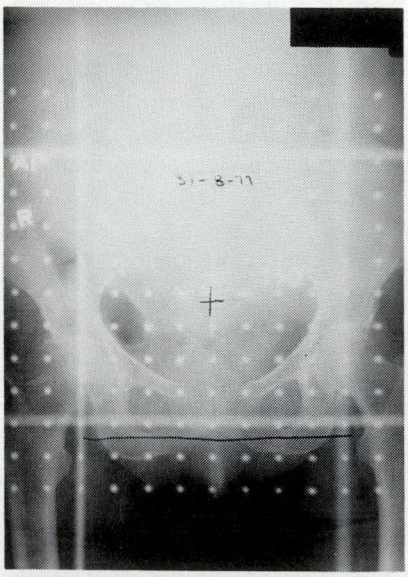

FIG. 1. Case 1. Taken before radiotherapy, x-ray with marking grid shows acetabular walls inside radiation field. Iliac bone-graft donor sites are outside field.

Case 2

In 1981, this 71-year-old woman underwent a total hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the uterus. Postoperatively, she received 50 Gy in 20 fractions over 4 weeks on 6 mev Therac — four fields with equal weighting. In January 1984, she presented with a very painful right hip. X-ray films showed a fracture of the acetabulum and arthritis (Fig. 7). Roentgenograms obtained 2 months earlier had revealed a fracture of the medial wall of the acetabulum but a normal joint space. A right hip replacement was performed using a cementless bipo-

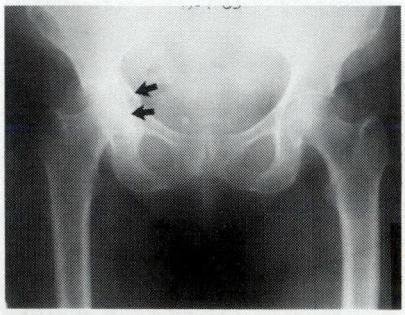

FIG. 2. Case 1. Medial acetabular fracture, protrusio and early degenerative changes of right hip. Left hip appears normal.

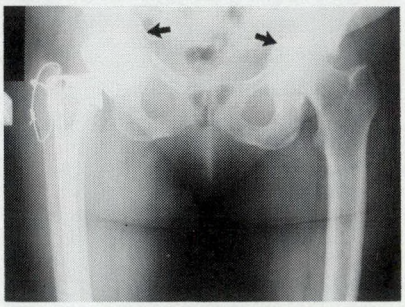

FIG. 3. Case 1. Medial acetabular fracture on left side similar to right 7 months before. Right bipolar replacement doing well.

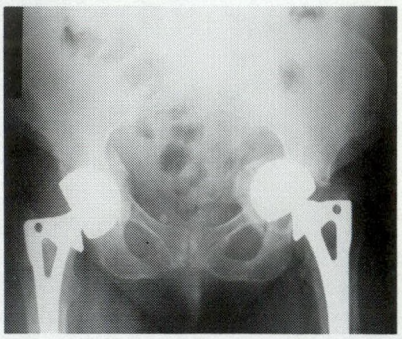

FIG. 4. Case 1. Left bipolar head has migrated into pelvis 2 years after surgery.

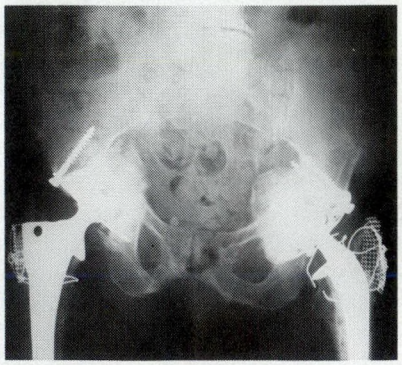

FIG. 5. Case 1. Nine months after revision of left arthroplasty with extensive medial grafting, peripheral support ring and cemented components. Acetabulum on right side shows complete transverse fracture of medial wall (arrow).

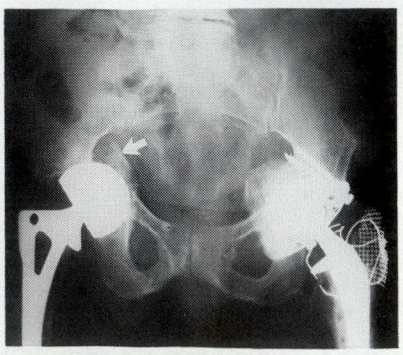

FIG. 6. Case 1. After revision on both sides, 2 years on right side and 3 years on left.

lar prosthesis and grafting with autogenous femoral head exactly as in case 1. Examination of the retrieved acetabular fragments revealed several areas of grey-brown discolouration and pitting in the articular cartilage, and a weakened, chalk-like bone structure. On microscopic examination there were irregular areas of thickened trabeculae, loss of osteocytes and evidence of bone necrosis. At recent 4-year follow-up the patient walks well, shops and continues living independently in her apartment. X-ray films show no migration or protrusio of the acetabular cup, and the acetabular fracture has united.

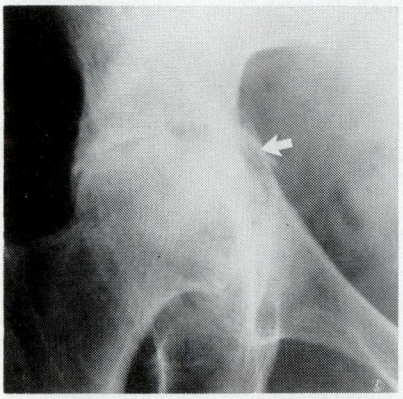

FIG. 7. Case 2. Preoperative x-ray film showing fracture of medial acetabular wall (arrow). Joint space was present 2 months before when fracture was first detected.

Case 3

In 1976, at 39 years of age, this woman underwent a total hysterectomy and bilateral salpingo-oophorectomy for adenocarcinoma of the uterus. Preoperatively, she received intracavitary radium, 45 mg intrauterine and 20 mg intravaginal, for 72 hours for an estimated total dose of 50 Gy to the uterus. An estimated 15 Gy was delivered to each hip joint. Four years earlier, she had also received radiotherapy for stage III Hodgkin's disease. The subdiaphragmatic portion of this was in the form of 35 Gy in 20 fractions over 4 weeks using cobalt-60 and an inverted Y field with central pelvic shielding but with both hip joints in the field. The total cumulative dose of all previous exposures to the acetabulum had been estimated by the cancer clinic as 50 Gy.

She presented in 1985 with an exceedingly painful and destructive arthropathy of her right hip (Fig. 8). A cementless porous-surfaced femoral stem with a Bateman bipolar head was implanted, after grafting the superior acetabular deficiency with bone from the resected femoral head and medializing the acetabular socket. Intraoperatively, the acetabulum and femoral head were found to be dystrophic and fragmented with areas of avascularity and necrosis. Three weeks later the head of the prosthesis broke through the acetabulum. A cemented polyethylene acetabular component was inserted and reinforced by tricortical bone graft harvested from the ipsilateral iliac crest. The graft was fixed solidly over the polyethylene socket with cancellous bone screws. At 3-year follow-up the patient was doing well, was walking extensively, had no pain and had a good hip as shown radiologically (Fig. 9).

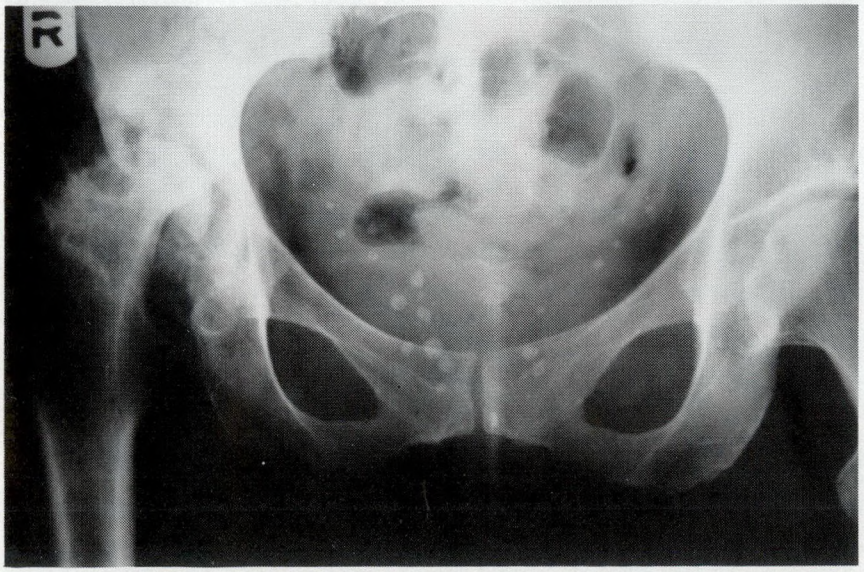

FIG. 8. Case 3. Preoperative x-ray film showing marked erosion of acetabulum and superior migration of femoral head.

Case 4

In 1955, at the age of 51 years, this woman received irradiation for adenocarcinoma of the cervix. The therapy included 80 hours of radium (50 mg intrauterine and 20 mg intravaginal) followed by 60 hours of radium (40 mg vaginally) for a total of 4000 mg-h to both uterine cavity and vagina. This was followed by external pelvic radiotherapy with cobalt-60 to a dose of 27.4 Gy in 15 fractions over 3.5 weeks with anteroposterior and posteroanterior split fields with central shielding. In 1954 she had also received external radiotherapy to establish an artificial menopause because of irregular vaginal bleeding. Radiation was in the form of 14 Gy using 200 kV x-rays. In 1984 a barium enema examination revealed strictures of the lower colon but the hip joints appeared normal. The total dose to the hips has been estimated as 51.4 Gy.

She presented in 1986, at the age of 82 years, with a painful left hip, and x-ray films showed protrusio and arthritis (Fig. 10). The protrusio was unusual in that its course was rapid and there was no reactive periosteal bone inside the pelvis. The medial wall of the acetabulum was almost nonexistent, with only a pale dystrophic membrane at the base; it was reinforced with an ipsilateral iliac crest graft. An Eichler peripheral support ring was fixed to the acetabular rim and a polyethylene socket cemented inside it. At follow-up 2 years later this woman had an excellent result — she had no pain, walked well with a cane and radiologically had a good hip (Fig. 11).

Discussion

It is essential to review the gynecologic history of women who have a rapid course of hip pain and disability to determine if therapeutic radiation has ever been given. If this is so, a radiation oncologist should be consulted to determine if the acetabulum was included in the field and what dosage of radiation it received. Symptoms of urethritis, cystitis and proctitis suggest that substantial amounts of radiation have been delivered to the pelvis.[5]

In the hips of all our patients the destructive arthropathy appeared to have been triggered by severe protrusio or fracture through the weakened bone of the medial acetabular wall. The variability of the interval from the time of radiotherapy to acetabular fracture suggests that all unilateral cases may eventually become bilateral.

The dosage of radiation required to cause damage to bone has been stated as 30 Gy for the threshold of cell change and 50 Gy for cell death.[6] Although less frequent, atrophic changes and fractures do occur with the megavoltage techniques in use today. Cases of acetabular failure reported elsewhere have had similar doses and types of radiation at 35 to 70 Gy.[2-4]

The chronologic, radiologic, gross and microscopic changes in our four cases provide convincing evidence that radiation was an important factor contributing to the destructive arthropathy. None of the patients in the present series had chemotherapy, steroids or previous surgery on the hip. There was an inverse correlation between age at the time of radiotherapy, and the

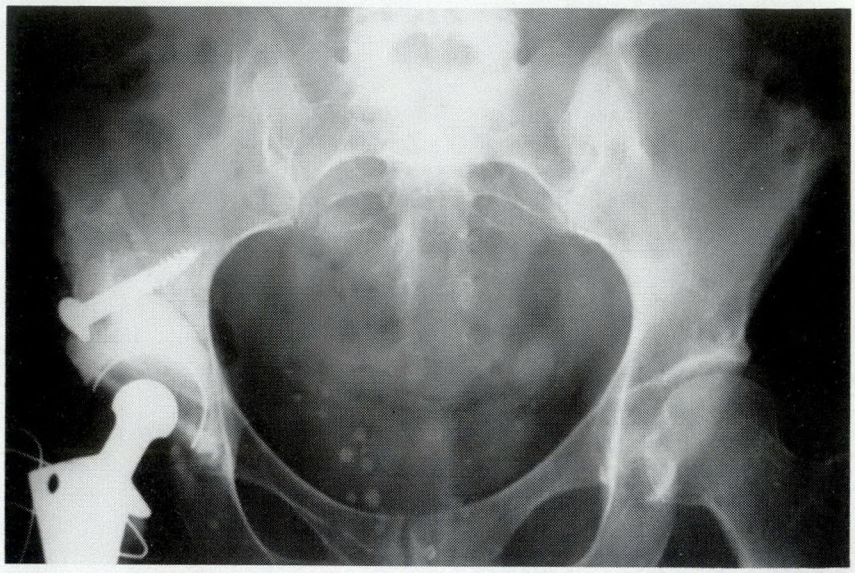

FIG. 9. Case 3. Three years postoperatively, position of prosthesis and fixation of cup, with incorporation of graft, are good.

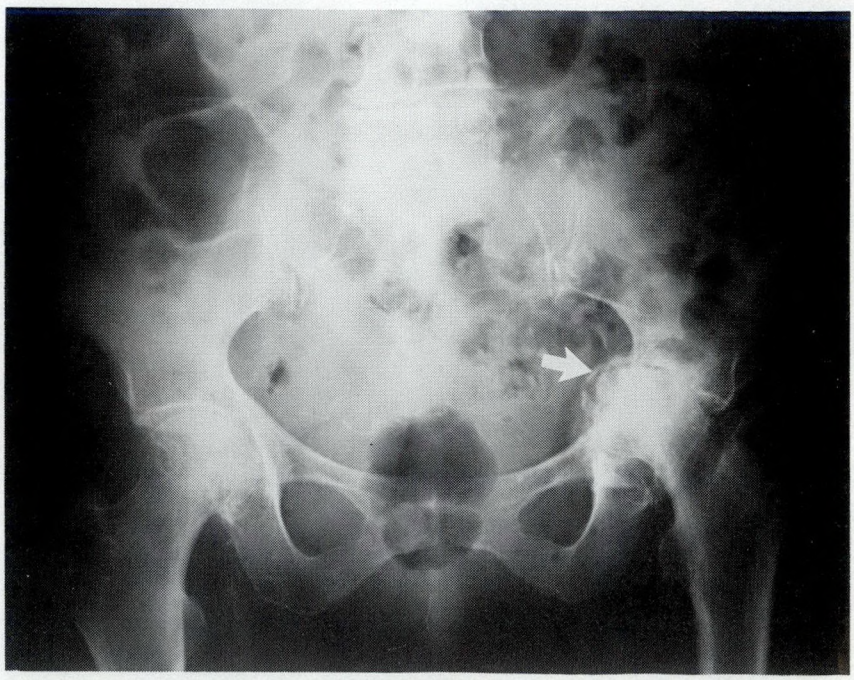

FIG. 10. Case 4. Preoperative x-ray film shows fragmentation of medial acetabular wall, protrusio and degenerative changes of joint.

interval before arthropathy. The degree of osteoporosis at the time of radiotherapy, as assessed radiologically, had a bearing on the time interval from irradiation to fracture. All patients had osteoporotic hips at the time of presentation with fracture. That men treated with similar doses of radiation to the pelvis for prostatic cancer rarely developed secondary fractures[7] probably relates to the lower incidence of osteoporosis in men.

The microscopic characteristics of irradiation-induced bone necrosis have varied. In the late stages when there is mechanical bone failure and fragmentation, signs are obscured by a nonspecific mixture of necrosis and secondary inflammation. Whether frank necrosis occurs is debatable. Goodman and Sherman,[1] from analysis of femoral head material obtained after radiation-induced neck fractures, found that total necrosis did not occur. They believed that the osteocyte was damaged and unable to perform its metabolic functions in bone maintenance, but microscopically could look normal.

Radiation-induced fractures can heal with time and protection from loading.[1] However, the prolonged morbidity this would entail in acetabular fractures necessitates an operative approach. Reconstruction in these cases in which the bone stock is poor is difficult and demands techniques often used in revision hip surgery, such as the use of protrusio rings and extensive bone grafting. Ideally, autograft harvested from the ipsilateral iliac crest outside the original radiation field should be used. The need for subsequent surgery on many of these hips makes the use of cementless components attractive, but the probability of failure of such components in these cases is high as demonstrated by our case 1. The use of acrylic bone cement and peripheral support rings is preferred in these cases to maximize the area and magnitude of immediate fixation.

Based on the improvement in four of our five hips over a 5-year period, it is our opinion that radiation necrosis of the acetabulum is not an absolute contraindication to prosthetic joint replacement. However, it is necessary to recognize the condition and be aware of the potential problems.

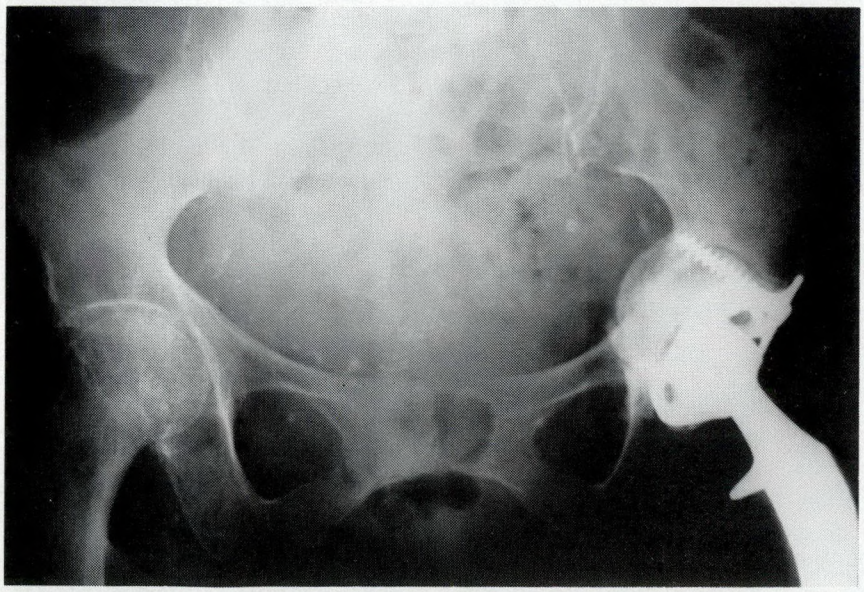

FIG. 11. Case 4. Two-year postoperative film shows cemented socket solidly anchored on peripheral support ring and medial bone graft that has consolidated well.

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Diagnosis of Acute Appendicitis in Pregnancy

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Although the clinical diagnosis of appendicitis in pregnancy seems to be complicated by the physiologic changes of pregnancy, evidence from controlled studies is lacking. The aims of this study were to determine whether there are any features of appendicitis in pregnant women that would help to establish the diagnosis and whether any difference exists between the presentation of appendicitis in pregnant and nonpregnant women. Twenty-eight pregnant women with a clinical diagnosis of appendicitis were compared with an equal number of nonpregnant patients matched for age and randomly selected from a group of patients who had appendicitis. No differences were observed in the presenting symptoms, physical signs and laboratory tests. The false-positive rates were identical. The results indicated that the diagnosis of appendicitis is no more difficult in the pregnant state than in the nonpregnant state.

Bien que le diagnostic clinique de l'appendicite en cours de grossesse semble être compliqué par les changements physiologiques de la grossesse, il y a absence de preuves à cet effet, issues d'études contrôlées. Les objectifs de cette étude étaient de déterminer s'il existe des caractéristiques de l'appendicite chez la femme enceinte pouvant aider à établir le diagnostic, et s'il y a des différences dans le tableau clinique des femmes enceintes atteintes d'appendicite, par rapport à celles qui ne sont pas enceintes. Vingt-huit femmes enceintes ayant un diagnostic clinique d'appendicite ont été comparées à un nombre égal de patientes non enceintes appariées pour l'âge et choisies au hasard parmi un groupe de patientes souffrant d'appendicite. Aucune différence n'a été observée dans les symptômes, les signes physiques ou les épreuves de laboratoire. Les taux de faux positifs étaient identiques. Ces résultats indiquent que le diagnostic d'appendicite n'est pas plus difficile à établir chez la femme enceinte que chez celle qui ne l'est pas.

Acute appendicitis is the most common nonobstetric condition requiring operative intervention during pregnancy.[1-5] It is not a frequent complication, occurring only once in every 1500 deliveries.[6] Thus, in most obstetrical units it is encountered approximately twice a year.

The clinical presentation varies, often making the diagnosis difficult, especially later in pregnancy. The progressive displacement and rotation of the tip of the appendix has been one factor responsible for this difficulty. Also, the physiologic changes of pregnancy may confound the interpretation of laboratory tests. The resulting delay in diagnosis and operation is a major factor contributing to the higher maternal mortality associated with this disorder. It is generally believed that if appendicitis is suspected in a pregnant woman, immediate surgical intervention is indicated. But often the surgeon is reluctant to perform exploratory laparotomy since there is a risk of precipitating spontaneous abortion or premature labour. Consequently, better diagnostic criteria are required to enable the diagnosis to be made with more confidence. The purpose of this study was to compare the presentation of appendicitis in pregnant women with that in nonpregnant women to determine whether there is a specific pattern of presentation in pregnancy that would aid in its diagnosis.

Patients and Methods

A chart review was carried out of 28 pregnant patients admitted with abdominal pain to Chedoke-McMaster Hospital or St. Joseph's Hospital in Hamilton, Ont. between Jan. 1, 1981 and Sept. 30, 1986 and who underwent appendectomy because of a preoperative diagnosis of appendicitis. The charts from a control group of 28 nonpregnant women in the same age range and

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with a diagnosis of appendicitis admitted during this period were randomly selected for comparison. Information on presenting symptoms (vomiting, nausea, diarrhea and anorexia), physical signs (rebound tenderness, abdominal guarding, Rovsing's sign, psoas irritation and pyrexia) and results of laboratory tests (leukocyte count in blood and urine) were extracted from the hospital charts. Histologic findings were also obtained for each patient and the two groups compared. The time from presentation in the hospital to surgery was also recorded and compared.

The two groups were compared using χ^2, Fisher's exact and Wilcoxon rank sum tests where appropriate and significance was tested at the 5% level.

Table I. Clinical Presentation in Pregnant and Nonpregnant Patients Presenting With Abdominal Pain*

Variable	Pregnant	Nonpregnant
Age, yr	25.4 ± 0.8	26.2 ± 1.9
Time from presentation to operation, h	25.1 ± 4.3	10.2 ± 1.7
Temperature, °C	37.1 ± 0.1	37.3 ± 0.1
Leukocyte count, $\times 10^9$/L		
Blood	14.9 ± 0.6	16.0 ± 0.9
Urine	1.7 ± 0.5	3.0 ± 1.2
Vomiting	50	46
Nausea	71	93
Diarrhea	21	21
Anorexia	39	39
Rebound tenderness	68	64
Positive Rovsing's sign	46	18
Psoas irritation	14	11
Abdominal guarding	64	75
Histologically proven appendicitis	82	82

*Values are either mean ± SEM or %.

Table II. Clinical Presentation in Pregnant and Nonpregnant Patients With Histologically Confirmed Appendicitis*

Variable	Pregnant	Nonpregnant
Age, yr	25.3 ± 0.9	25.9 ± 2.0
Time from presentation to operation, h	11.4 ± 1.9	10.7 ± 1.9
Temperature, °C	37.1 ± 0.1	37.3 ± 0.1
Leukocyte count, $\times 10^9$/L		
Blood	15.3 ± 0.7	16.6 ± 0.9
Urine	1.6 ± 0.5	2.1 ± 0.7
Vomiting	57	52
Nausea	78	100
Diarrhea	24	23
Anorexia	36	67
Rebound tenderness	65	65
Positive Rovsing's sign	61	57
Psoas irritation	12	40
Abdominal guarding	61	83

*Values are either mean ± SEM or %.

Table III. Prevalence of Appendicitis in Each Trimester

	Trimester of pregnancy			
Appendicitis	1st	2nd	3rd	Totals
Positive	6	13	4	23
Negative	0	2	3	5
Totals	6	15	7	28

χ^2 with 2 df = 4.50, p = 0.106.
χ^2 due to linearity with 1 df = 4.19, p = 0.041.

Results

The average age of the women in the pregnant group was 26.2 years, compared with 25.4 years for those in the nonpregnant group. There were no differences between the two groups with respect to symptoms and physical signs (Table I) or in the duration from presentation in the hospital to surgery. The most consistent symptom present in these patients was abdominal pain. Two-thirds of the pregnant patients presented with nausea and had abdominal guarding, rebound tenderness and demonstrated a positive Rovsing's sign. Anorexia and diarrhea were infrequent and the elicitation of psoas irritation was not a reliable sign. Both groups had similar proportions of patients with white blood cells in the urine and elevated blood leukocyte counts. However, the difference between the mean levels (pregnant women 14.9×10^9/L, nonpregnant women 16.0×10^9/L) was not statistically significant. When the two groups were compared after selecting only those who had histologically proven appendicitis (Table II), again, no significant differences were found with respect to symptoms, signs or laboratory test results. Perforation of the appendix was observed with the same frequency (11%) in each group. The overall false-positive rate (i.e., histologically normal appendix) was identical in the two groups (18%). However, there was a significant ($p = 0.041$) trend toward more false-positive cases in the third trimester (Table III). Also, 50% of the true-positive cases in the third trimester were complicated by appendiceal perforation.

Discussion

The false-positive rate (18%) in this study is similar to that (21%) reported in a review of 545 pregnant patients with a preoperative diagnosis of appendicitis.[7] This suggests that, in general, the diagnosis of appendicitis in pregnancy is no more difficult than in the nonpregnant state. However, significantly more normal appendices were removed in the third trimester than in the other two. It is known that as pregnancy advances, the abdominal pain associated with appendicitis becomes less characteristic, and the localizing signs may be in the right upper quadrant or in the right flank. This is further complicated by the uterus pushing the abdominal wall away from the appendix. Thus, better diagnostic tests are required so that unnecessary operative intervention and the risk of precipitating premature labour are avoided.

The value of leukocytosis in supporting the diagnosis has been thought to be limited since a physiologic leukocytosis (up to 12.5 $\times$ 10^9/L) occurs in pregnancy. The mean leukocyte count in pregnant women with histologically proven appendicitis in this study was 15.3 $\times$ 10^9/L and 80% of women in the study had a count greater than 12.5 $\times$ 10^9/L. Using this cut-off level, the sensitivity of this diagnostic test was 82%, indicating that very few patients with histologic appendicitis would be misdiagnosed. However, the specificity was only 20%, indicating that a very high proportion of false-positive diagnoses would occur.

Other diagnostic measures have been reported. For example, laparoscopy was used to confirm the diagnosis in one woman.[8] Laparoscopy may be useful in the first trimester when the uterus is still in the pelvis, but it becomes technically more difficult to perform as pregnancy progresses. Furthermore, none of the patients in our study had a false-positive diagnosis in the first trimester, indicating that the diagnosis can usually be made preoperatively on clinical and laboratory assessment alone, without the need for laparoscopy. Culdocentesis confirmed the need for surgery in one patient in whom purulent material was aspirated from the pelvic cul-de-sac.[7] Such a procedure is not without risk in view of the presence of the soft, very vascular and enlarged uterus in the pelvis. Also, its accuracy depends upon the presence of pus in the cul-de-sac, resulting from perforation of the appendix. Such a situation was present in only 11% of the patients in this study, further limiting its usefulness.

Ultrasonography has been described as a quick, noninvasive and reliable tool for diagnosing appendicitis.[9-11] With graded compression a high degree of diagnostic accuracy was achieved, leading to appropriate clinical management.[11] Also, in patients having disease other than appendicitis, the correct diagnosis was made. Such a technique may potentially be of use in pregnancy to complement the clinical evaluation, thereby avoiding any delay in operative intervention. However, its sensitivity in the presence of perforation is low, so its value in the presence of this complication is limited.

The mortality and serious morbidity associated with appendicitis in pregnancy are the result of failure to recognize or suspect the condition when it presents with atypical features.[12] The key to management lies in earlier diagnosis and prompt operative intervention. Patients who present in pregnancy with abdominal pain and have a leukocyte count greater than 12.5 $\times$ 10^9/L should be suspected of having appendicitis, especially if they also complain of nausea and have abdominal guarding.

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Neoadjuvant Treatment in Conservative Surgery of Peripheral Sarcomas

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Twenty-five patients with soft-tissue and bony sarcomas of the head and neck and limbs were treated by local neoadjuvant therapy. It consisted of 90 mg of Adriamycin infused intra-arterially over 3 days into a vessel feeding the involved area and 30 Gy of radiotherapy given over 10 days; this was followed by a complete resection of the sarcoma 4 to 6 weeks later. All the tumours were associated with a high risk of local recurrence; eight were locally recurrent and the remainder were stage II to stage IV tumours. Serious local complications were seen in 4% of the patients. This rate compares well with other higher dose neoadjuvant regimens (35 Gy over 10 days), which are associated with a 35% local complication rate. Follow-up at a mean of 30 months demonstrated no local recurrence. All limbs were spared. Long-term morbidity was negligible. No effect on systemic control is suggested; only 63% of the patients were free of systemic disease. This report substantiates other similar experiences supporting neoadjuvant therapy followed by resection as the treatment of choice for local control of sarcomas.

Vingt-cinq patients souffrant de sarcomes des tissus mous et des os de la tête, du cou et des membres ont reçu une thérapie néoadjuvante locale. Celle-ci consistait en 90 mg d'Adriamycine perfusée sur une période de 3 jours par voie intra-artérielle dans un vaisseau qui alimentait la région atteinte, et de 30 Gy de radiothérapie administrée sur 10 jours; on procédait à une résection complète du sarcome 4 à 6 semaines plus tard. Toutes les tumeurs étaient liées à un risque élevé de récidive locale; dans huit cas, il s'agissait de récidives locales, alors que les autres étaient des tumeurs de stades II à IV. Des complications locales sérieuses ont été vues chez 4% des malades. Ce taux se compare avantageusement avec des doses plus élevées de thérapie néoadjuvante (35 Gy sur 10 jours), lesquelles étaient reliées à un taux de complication locale de 35%. Les examens de contrôle effectuées après 30 mois en moyenne, n'ont dévoilé aucune récidive. Tous les membres ont pu être sauvegardés. La morbidité à long terme a été négligeable. Aucun contrôle systémique n'est suggéré; seulement 63% des patients étaient exempts d'atteinte systémique. Cette étude corrobore des expériences similaires qui ont démontré que la thérapie néoadjuvante suivie d'une résection constitue le traitement de premier choix quand il s'agit du contrôle local des sarcomes.

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Local control of soft-tissue and bony sarcomas continues to challenge the oncologist. In recent years, the effective use of radiotherapy with limb-salvage surgery has successfully reduced both local recurrence and limb loss. However, the local recurrence rate remains approximately 15% to 20%.[1-6] In the last 5 years, neoadjuvant therapy of intra-arterially infused Adriamycin and medium-dose radiotherapy before surgery has provided further improvement, both in shrinking many large lesions and thereby reducing the extent of surgery, and in providing long-term local control in the range of 95%.[7] In this report we document our experience with this regimen in sarcomas of the limbs and head and neck.

Methods

A prospective study was initiated in 1984 into which all patients with newly diagnosed or recurrent limb or head and neck sarcoma needing further treatment were entered. The only exclusions were patients with metastases whose sarcoma could not be resected for cure, patients with superficial and small lesions in which a wide excision would suffice and patients who refused the protocol. Before entering the study, all patients underwent a complete history-taking and physical examination, pulmonary tomography and

computed tomography of the lesion to document the extent of disease. All lesions were reviewed by a team of three pathologists.

The protocol was started with 72 hours of continuous intra-arterial Adriamycin infusion totalling 90 mg (30 mg/d). The catheter was placed in a large proximal vessel feeding the area and was never placed beyond the common femoral or axillary artery. Intravenous chemotherapy was used for a head and neck lesion and a shoulder lesion with multiple feeding vessels when single-artery catheterization would not entirely infuse the lesion. Catheter access was usually through the femoral artery. The patient was kept on bed rest for the 3 days, and therapeutic anticoagulation was provided with heparin, keeping the partial thromboplastin time well over 80 seconds. After completion of the Adriamycin infusion, radiotherapy was given at a rate of 3.0 Gy/d for 10 days. In the hand or foot, it was divided into 1.65 Gy twice daily for 10 days in an attempt to improve normal tissue tolerance at these difficult sites. The field extended 10 cm on either side of the lesion and encompassed a maximum of two-thirds of the limb circumference. Four to 6 weeks later, the patient underwent surgical removal of the tumour.

The planned excision included 2 cm of the skin and scar around the previous biopsy and a 2-cm margin in all directions around the residual tumour. When the tumour was adjacent to a vessel or nerve, a marginal excision was accepted as long as biopsy of the margin showed that there were no malignant cells present. The defect was closed primarily when possible. When a bone was resected, an allograft was placed. When there was massive soft-tissue resection including skin, a myocutaneous axial or free flap was used for cover. All patients were followed up in the sarcoma clinic on a 4- to 6-month basis by physical examination and routine chest x-ray films to document recurrence of disease.

Findings

Twenty-five patients were entered into this study. One patient had a lesion of the face above the zygoma and the remainder had lesions of the limb or limb girdles (Table I). Fifteen patients had a biopsy before neoadjuvant treatment. The remaining patients presented with "total excisions" of the lesions which were considered inadequate on review of the submitted surgical or pathology report. Eight patients had locally recurrent lesions with a history of one to five previous failures of surgery. Three patients had pulmonary metastases which were deemed resectable as a second stage of treatment. Two patients had osteosarcoma of the bone, one in the upper humerus and one in the distal femur.

The sarcomas were of varied histologic type (Table II). All were staged according to the American Joint Committee for Cancer Staging and End-Results Reporting (Table III). Involvement of surrounding structures such as muscle, nerve, artery or bone was clinically important in all but one patient. Mean follow-up for the entire group is now 2.5 years, ranging from 1 to 5 years.

The morbidity of treatment included various problems with the infusion. Nausea was minimal; only one patient requested and was given Gravol intramuscularly. Two patients had thrombosis of the infused artery and required treatment to reconstitute the lumen. This was a direct result of the partial thromboplastin times being less than 60 seconds. This is no longer a problem because the partial thromboplastin time is now kept over 80 seconds. One patient had a catheter dislodge from the axillary artery into the vertebral artery, producing temporary confusion and occipital blindness for 12 hours. Another patient had pectoral muscle inflam-

Table I. Site of the 25 Sarcomas

Site	No.
Head	1
Shoulder	3
Arm	2
Hand	2
Thigh	5
Leg	11
Foot	1

Table II. Pathological Type of 25 Sarcomas Treated by Neoadjuvant Chemotherapy and Radiotherapy

Histologic type	No. patients
Synovial sarcoma	5
Leiomyosarcoma	4
Osteosarcoma	3
Neurofibrosarcoma	2
Malignant fibrohistiocytoma	2
Chondrosarcoma	2
Liposarcoma	2
Fibrosarcoma	2
Spindle cell sarcoma	1
Hemangiopericytoma	1
Epithelioid sarcoma	1

Table III. Distribution of Sarcomas According to American Joint Committee for Cancer Staging and End-Results Reporting

Stage	No. patients	Previous local recurrence
I	1	1
IIA	3	2
IIB	7	2
IIIA	1	0
IIIB	7	3
IVA	3	0
IVB	3	0

Table IV. Changes in Tumour Size After Neoadjuvant Therapy and Excision

Size change	No. patients
No change	3
Decrease, %	
0 – 25	5
25 – 50	4
50 – 75	2
100	2
Increase	1
Not assessable	8

mation secondary to streaming of the infusion from the main axillary artery catheter; the condition resolved over 2 months.

There were no important complications of radiotherapy. Only one patient had delayed healing in spite of a myocutaneous flap placed to cover the defect resulting from groin, pubic bone and testicular resection. No patient had a radiation-induced bone fracture and only one patient had moderate fibrosis of the treated area that resolved within 1 year. In the two patients who had bone resection and replacement, there were no fractures of the allograft; the patient with a replaced femur has been followed up for over 2 years.

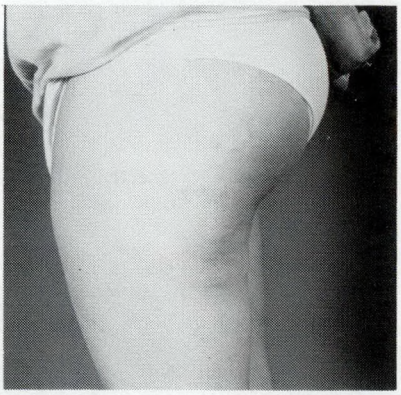

FIG. 1. Large grade 2 liposarcoma (stage IIB) of thigh, measuring 25 × 15 cm was clinically palpable in buttock.

Dramatic shrinkage of the lesions was seen in over 50% of the patients (Table IV) (Figs. 1 to 5). Shrinkage often began immediately after the Adriamycin infusion before radiotherapy and continued up to the time of surgery. In two patients, there was a complete histologic response. Patients often experienced a marked decrease in pain during the therapy, and it preceded a clinically measured reduction in size. The only patient with a tumour that grew during treatment had a soft-tissue osteosarcoma.

Local control was seen in all treated sites of disease. One patient with a facial sarcoma had regional failure outside the treatment field. This was subsequently controlled with a cranial facial resection. The patient is alive and free of local and systemic disease at 2-year follow-up.

During follow-up, unresectable systemic disease developed in nine patients. The disease stage and tumour type are shown in Tables V and VI. The overall survival rate of the 25 patients at 30 months was 76% with a disease-free survival of 64% (Fig. 6).

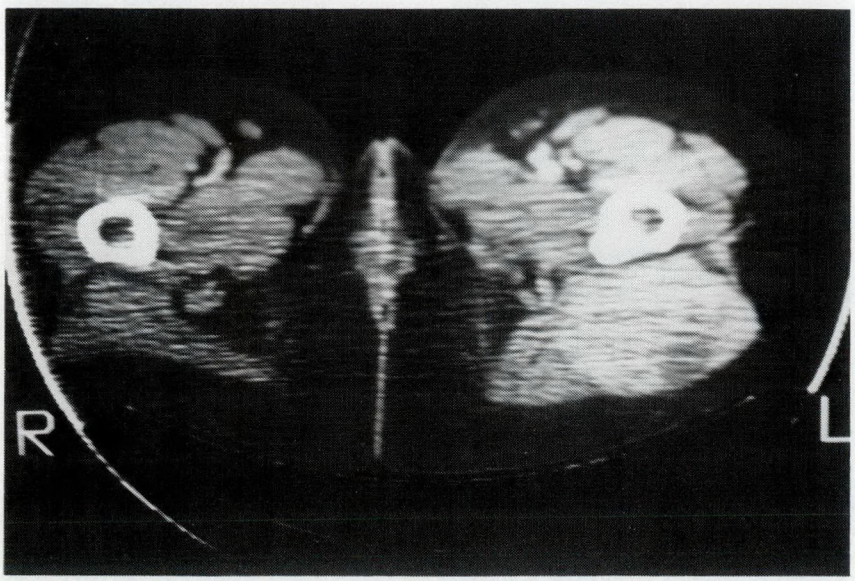

FIG. 2. Computed tomogram demonstrated lesion of left thigh compressing sciatic nerve.

All but one of the patients who underwent nonosseous limb surgery returned to normal activity within weeks of operation. One patient who had thrombosis of an arterial replacement graft was partially disabled with ischemic pain for 3 years. The patient with an allograft replacement of the distal segment of a femur is fully mobile using an external brace.

Discussion

Our results of neoadjuvant therapy with intra-arterial Adriamycin and preoperative radiotherapy are equal to those of other reports using a similar regimen and superior to treatments consisting of surgery and pre- or postoperative radiotherapy.[2-5,7-9] In other series, local recurrence of high-grade sarcoma after treatment has been noted clinically in 95% of those whose tumours recur within 2 years of initial treatment. Since our mean follow-up is now more than 2.5 years, we believe that the absence of local recurrence in our patients is strongly supportive of this approach.[10]

Although in this group of sarcoma patients the tumours were at varied sites, and of varied pathologic features and stages, all patients were at high risk for local recurrence with standard therapy. Therefore, this diversity does not take away from the results of this study. The value of this approach is also emphasized by the dramatic shrinkage of even large lesions before surgery, an effect that is very unusual with radiotherapy alone. In many cases, preservation of major nerves, arteries and veins, which normally would have been resected

to obtain a clear margin, became possible.

This experience is also important in that most tumours were large and many of the patients had recurrent tumours after multiple previous surgical procedures. It is interesting that systemic disease developed in only four of the nine patients on whom we reoperated for local recurrence. This emphasizes the fact that one should be as aggressive in obtaining local control of recurrent disease as one is for a patient presenting with a primary sarcoma. It is also encouraging that even after previous surgery, limb salvage is still possible using this approach.

Anticoagulation with heparin presented difficulties. Since patients had an intra-arterial catheter and were fully heparinized, they were kept in an intensive care setting. As some of these tumours would shrink and presumably release large amounts of procoagulants from dying cells, the partial thromboplastin time would sometimes rapidly and unexpectedly become subtherapeutic.[11] After two experiences with intra-arterial thrombosis, the problem was prevented by maintaining the partial thromboplastin time over 80 seconds. We noticed some unusual streaming effects of the Adriamycin, not only to areas of the skin in a few patients, but in one patient to a muscle. This was associated with pain or tenderness in the area involved. When streaming effects were noted during infusion, the catheters were retracted a few centimetres.

Other local complications included failure of a myocutaneous flap placed to cover a groin lesion; the wound healed by secondary intention. One patient had excessive post-treatment fibrosis which resolved slowly. No patient had radiation-induced fractures. This contrasts markedly to Eilber's experience[7,8] in which 17% had a second operation to treat failure of healing and 11% had a radiation-induced fracture. The lower morbidity of our protocol may be a result of

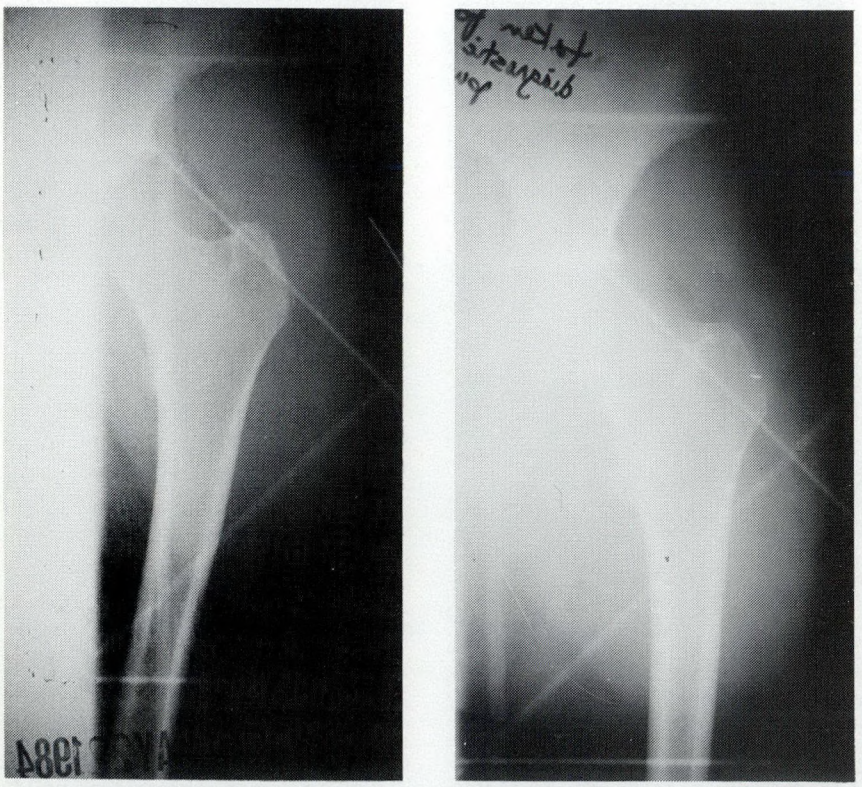

FIG. 3. By end of radiotherapy and 2 weeks after initiation of treatment, lesion had shrunk to 10 × 8 cm. Change is shown by comparing amount of soft tissue lateral to greater trochanter on initial simulation film with lead wire on skin (left) and follow-up simulation film (right).

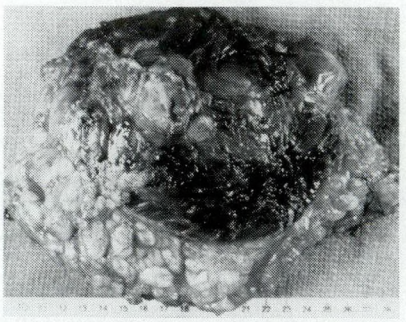

FIG. 4. Lesion was resected with microscopically clear margin without sacrifice of sciatic nerve.

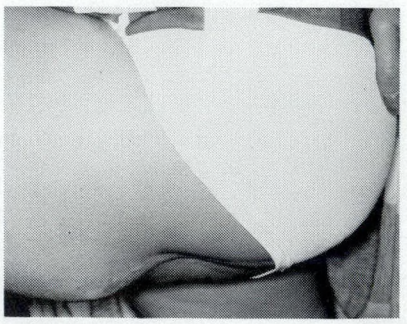

FIG. 5. At 5 years' follow-up, patient remains free of local and systemic disease.

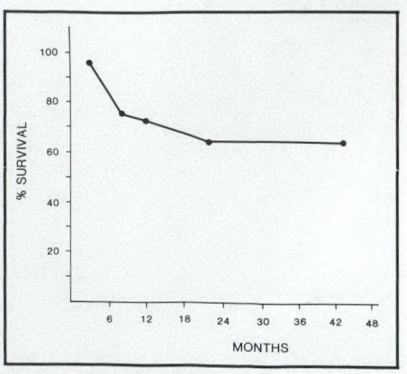

FIG. 6. Recurrence-free survival of 25 patients treated by neoadjuvant chemotherapy and radiotherapy.

using a radiotherapy dose of only 3.0 Gy/d compared with 3.5 Gy/d as reported by Eilber.

Conclusions

We believe that neoadjuvant therapy as described in this paper should be considered for all sarcomas that cannot be treated by surgery alone. The preoperative treatment appears to add substantially to the microscopic sterilization of sarcomas in the periphery of the lesion, but does not seem to have any measurable effect on overall control of systemic disease. When designing adjuvant trials to control systemic disease, this protocol should be considered to minimize local recurrence. Although the debate over whether local control contributes to overall survival continues,[12,13] this factor cannot be ignored in the analysis of future adjuvant therapy trials.

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Table V. Stage of Disease in Nine Patients Who Subsequently Had Unresectable Metastases

Stage	No. patients
IIA	1
IIB	2
IIIB	3
IVA	2
IVB	1

Table VI. Histologic Type of Tumour From Which Unresectable Metastases Developed During Follow-Up

Tumour type	No. patients
Synovial sarcoma	3
Leiomyosarcoma	1
Mesenchymal chondrosarcoma	1
Epithelioid sarcoma	1
Malignant fibrohistiocytoma	1
Osteosarcoma	2

Medial Epicondylitis Caused by Injury to the Medial Antebrachial Cutaneous Nerve: a Case Report

Robin R. Richards, MD, FRCSC; William D. Regan, MD, FRCSC

A 35-year-old man who had chronic elbow pain due to medial epicondylitis received a steroid injection into the medial epicondyle. This was followed immediately by increased pain and symptoms of dysesthesia in the distribution of the medial antebrachial cutaneous nerve. On surgical exploration 9 months later, the nerve was found to lie directly over the medial epicondyle and appeared to have sustained an injection injury. This report draws attention to the fact that because the posterior division of the medial antebrachial cutaneous nerve may lie directly over the medial epicondyle, it may be at risk of direct injury if injections are given into the epicondyle.

Un homme de 35 ans qui souffrait d'une douleur chronique au coude due à une épicondylite moyenne a reçu une injection de stéroïde dans l'épitrochlée. Ceci fut suivi d'une exacerbation immédiate de la douleur et de symptômes de dysesthésie dans l'aire de distribution du nerf brachial cutané interne. A la chirurgie exploratrice pratiquée 9 mois plus tard, on découvrit que le nerf chevauchait l'épicondyle moyen et semblait avoir subi une lésion par piqûre. Cet article veut attirer l'attention sur le fait que puisque la division postérieure du nerf brachial cutané interne peut chevaucher l'épicondyle moyen, celui-ci peut être blessé lors d'une injection dans l'épicondyle.

Epicondylitis is a common cause of elbow pain. Previous publications have not specifically discussed the treatment of medial epicondylitis (tenderness over the medial epicondyle), although it has been considered in articles dealing with lateral epicondylitis, constituting 10% to 20% of such series.[1-3] According to Hirschl,[4] the pathologic cause of medial epicondylitis is "angiofibroblastic hyperplasia", occurring at the insertion of the origins of the common flexor-pronator muscles. Other causes of the clinical syndrome of medial epicondylitis have not been proposed. We describe a patient with medial elbow pain refractory to conservative management. Exploration of the elbow revealed that the posterior division of the medial antebrachial cutaneous nerve was inflamed and enlarged, probably because of a steroid injection injury. Although this cause of medial epicondylitis has never been reported, the primary reason for presenting this case is to draw attention to the danger of injury to the medial antebrachial cutaneous nerve if injections are administered in the area of the medial epicondyle.

Case Report

A 35-year-old right-handed man was referred for the management of chronic pain in the region of the right medial elbow. The pain had begun 15 years earlier as the result of a fall directly onto the medial aspect of the elbow during a baseball game. After the fall, the area of the medial epicondyle was tender for 3 to 4 weeks. The patient continued to play baseball but complained of recurrent swelling and pain while throwing. Over the years he had been treated with nonsteroidal anti-inflammatory agents, ice and ultrasonography.

In an attempt to alleviate the pain, the patient was given a steroid injection directly into the medial epicondyle. The injection was followed immediately by a burning pain over the medial epicondyle; the pain continued for 1 month. A

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dysesthetic pain radiating over the posteromedial forearm distal to the elbow then developed. For the 9 months before presentation, he experienced constant pain and sensitivity to direct palpation of the medial epicondyle associated with dysesthesia over the posteromedial forearm.

On examination, there was increased warmth over the medial epicondyle and marked tenderness on palpation. The range of elbow motion was normal. Resisted forearm pronation produced epicondylar discomfort. There was no Tinel's sign and no neurologic deficit apart from hypoesthesia in the distribution of the posterior division of the medial antebrachial cutaneous nerve. X-ray views of the elbow, including oblique views, appeared normal. Results of nerve conduction studies of the ulnar nerve across the cubital tunnel were normal, as were those of electromyography of the ulnar innervated musculature of the hand.

The patient was admitted to hospital and the elbow was explored through a posteromedial incision, centred over the medial epicondyle. An enlarged and inflamed posterior division of the medial antebrachial cutaneous nerve was found lying directly over the medial epicondyle (Fig. 1). The location of the nerve corresponded to the area of preoperative tenderness. The underlying medial epicondyle appeared inflamed. A neurolysis of the posterior branch of the medial antebrachial cutaneous nerve was performed, and a portion of the medial epicondyle was resected. Postoperatively, the medial epicondyle was supported in a posterior slab for 2 weeks. Two months postoperatively the patient had a full range of elbow motion with complete resolution of pain over the medial epicondyle. One year later sensation continued to be decreased in the distribution of the posterior division of the medial antebrachial cutaneous nerve. The patient was able to return to sports activity.

Discussion

The medial antebrachial cutaneous nerve originates from the eighth cervical root and emerges from the medial cord of the brachial plexus to pierce the deep fascia in the mid-brachium.[5–7] The nerve, now in a subcutaneous location, divides into an anterior branch, coursing anterior to the medial epicondyle and a posterior branch. The posterior branch has been noted by Dellon and MacKinnon[5] to vary in location, crossing from the anterior mid-brachium to the posterior forearm from 6 cm proximal to 6 cm distal to the medial epicondyle. The posterior division of the medial antebrachial cutaneous nerve provides sensation to the posteromedial forearm. Its subcutaneous location makes it prone to injury.

Our patient had pain directly over the medial epicondyle with posterior and volar radiation. Initially, his symptoms were characteristic of medial epicondylitis. However, after the cortisone injection, the quality of the pain changed. An injection injury to the posterior division of the medial antebrachial cutaneous nerve likely occurred at that time.[8] This is supported by the following findings: (a) the nerve lay directly over the medial epicondyle, (b) symptoms of numbness developed in the distribution of the nerve after the injection and (c) the nerve appeared inflamed at the time of exploration.

Leffert[9] and Dellon and MacKinnon[5] have advised careful dissection of the cubital tunnel region to avoid injury to the posterior branch of the medial antebrachial cutaneous nerve. The latter authors reported injury to the posterior branch in 23 of 25 patients who had recurrent ulnar nerve entrapment and were referred for re-exploration. The surgeon must be aware of the nerve's course when exposing the medial epicondyle. Since the physician has

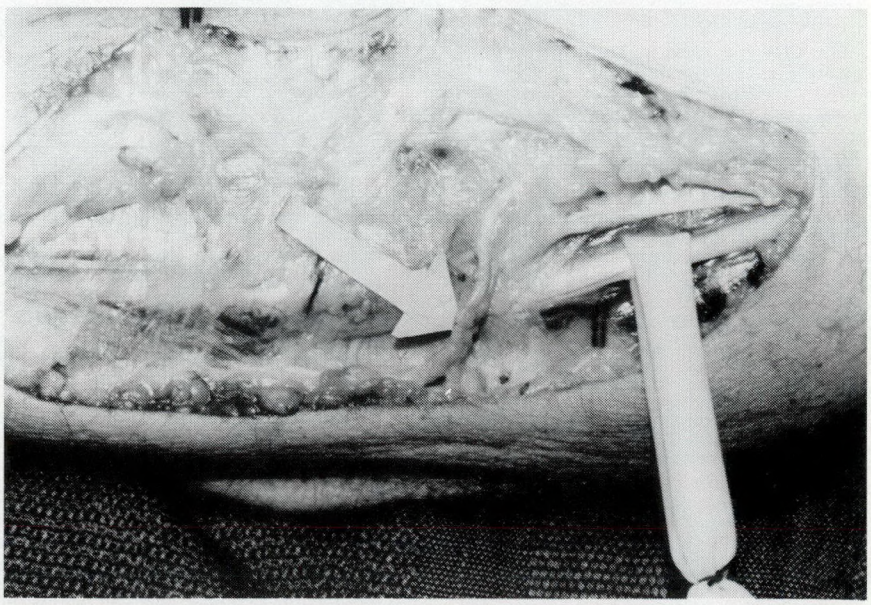

FIG. 1. Posterior division of medial antebrachial cutaneous nerve crossing directly over medial epicondyle. Nerve was enlarged and inflamed. Underlying medial epicondyle was inflamed. Medial epicondylectomy and external neurolysis of nerve were carried out.

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ANTIBIOTIC

ACTION

In vitro studies demonstrate that the bactericidal action of cefoxitin, a cephamycin derived from cephamycin C, results from the inhibition of bacterial cell wall synthesis. Evidence suggests that the methoxy group in the 7α position is responsible for the resistance of cefoxitin to degradation by bacterial beta-lactamases.

INDICATIONS AND CLINICAL USES

TREATMENT

The treatment of the following infections when due to susceptible organisms:

1 - Intra-abdominal infections such as peritonitis and intra-abdominal abscess

2 - Gynecological infections such as endometritis and pelvic cellulitis

3 - Septicemia

4 - Urinary tract infections (including those caused by *Serratia marcescens* and *Serratia* spp.)

5 - Lower respiratory tract infections

6 - Bone and joint infections caused by *Staphylococcus aureus*

7 - Soft tissue infections such as cellulitis, abscesses and wound infections

Appropriate culture and susceptibility studies should be performed to determine the susceptibility of the causative organism(s) to MEFOXIN®. Therapy may be started while awaiting the results of these tests, however, modification of the treatment may be required once these results become available.

Organisms particularly appropriate for therapy with MEFOXIN® are:

Gram positive
Staphylococci, penicillinase producing and non-producing
Streptococci excluding enterococci

Gram negative (beta-lactamase producing and non-producing strains)
Escherichia coli
Klebsiella species (including *K. pneumoniae*)
Proteus, indole positive and negative
Haemophilus influenzae
Providencia species

Anaerobes
Bacteroides fragilis

MEFOXIN® may also be appropriate for the treatment of infections involving susceptible strains of both aerobic and anaerobic bacteria.

MEFOXIN® is not active against *Pseudomonas* spp., most strains of enterococci, many strains of *Enterobacter cloacae,* and methicillin-resistant staphylococci and *Listeria monocytogenes*.

Clinical experience has demonstrated that MEFOXIN® can be administered to patients who are also receiving carbenicillin, gentamicin, tobramycin, or amikacin (see PRECAUTIONS and ADMINISTRATION).

PROPHYLACTIC USE

MEFOXIN® may be administered perioperatively (preoperatively, intraoperatively and postoperatively) to patients undergoing vaginal or abdominal hysterectomy and abdominal surgery when there is a significant risk of postoperative infection or where the occurrence of postoperative infection is considered to be especially serious.

In patients undergoing cesarean section, intraoperative (after clamping the umbilical cord) and postoperative use of MEFOXIN® may reduce the incidence of surgery related postoperative infections.

Effective prophylactic use depends on the time of administration. MEFOXIN® usually should be given one-half to one hour before the operation. Prophylactic administration should usually be stopped within 12 hours. It has been generally reported that continuing administration of any antibiotic beyond 24 hours following surgery increases the possibility of adverse reactions but, in the majority of surgical procedures, does not reduce the incidence of subsequent infection.

If signs of postsurgical infection should appear, specimens for culture should be obtained for identification of the causative organism(s) so that appropriate treatment may be instituted.

CONTRAINDICATIONS

MEFOXIN® is contraindicated in persons who have shown hypersensitivity to cefoxitin or to the cephalosporin group of antibiotics.

WARNINGS

Before therapy with MEFOXIN® is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to MEFOXIN®, cephalosporins, penicillins or other drugs. MEFOXIN® should be given with caution to penicillin-sensitive patients.

There is some clinical and laboratory evidence of partial cross-allergenicity between cephamycins and the other beta-lactam antibiotics, penicillins and cephalosporins. Severe reactions (including anaphylaxis) have been reported with most beta-lactam antibiotics.

Pseudomembranous colitis has been reported with virtually all antibiotics including MEFOXIN®. This colitis can range from mild to life threatening in severity. Antibiotics should therefore be prescribed with caution in individuals with a history of gastrointestinal disease, particularly colitis. It is important to consider a diagnosis of pseudomembranous colitis in patients who develop diarrhea in association with antibiotic use. While studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis, other causes should also be considered.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics including MEFOXIN® with caution.

If an allergic reaction to MEFOXIN® occurs, administration of the drug should be discontinued. Serious hypersensitivity reactions may require treatment with epinephrine and other emergency measures.

PRECAUTIONS

The total daily dosage should be reduced when MEFOXIN® is administered to patients with transient or persistent reduction of urinary output due to renal insufficiency (see DOSAGE AND ADMINISTRATION) because high and prolonged serum antibiotic concentrations can occur from usual doses.

In patients treated with MEFOXIN® a false-positive reaction to glucose in the urine may occur with Benedict's or Fehling's solutions but not with the use of specific glucose oxidase methods.

Using the Jaffe Method, falsely high creatinine values in serum may occur if serum concentrations of cefoxitin exceed 100 μg/mL. Serum samples from patients treated with MEFOXIN® should not be analyzed for creatinine if withdrawn within two hours of drug administration.

High concentrations of cefoxitin in the urine may interfere with measurement of urinary 17-hydroxy-corticosteroids by the Porter-Silber reaction, and produce false increases of modest degree in the levels reported.

Increased nephrotoxicity has been reported following concomitant administration of cephalosporins and aminoglycoside antibiotics.

Prolonged use of MEFOXIN® may result in the overgrowth of non-susceptible organisms. Repeated evaluation of the patient's condition is essential and if super-infection occurs during therapy, appropriate measures should be taken. Should an organism become resistant during antibiotic therapy, another antibiotic should be substituted.

Use in Pregnancy

The safety of MEFOXIN® in the treatment of infections during pregnancy has not been established. If the administration of MEFOXIN® to pregnant patients is considered necessary, its use requires that the anticipated benefits be weighed against possible hazards to the fetus. Reproductive and teratogenic studies have been performed in mice and rats and have revealed no evidence of impaired fertility or harm to the fetus due to MEFOXIN®.

Nursing Mothers

Cefoxitin is excreted in human milk.

Children

In children 3 months of age or older, higher doses of MEFOXIN® (100 mg/kg/day and above) have been associated with an increased incidence of eosinophilia and elevated SGOT.

ADVERSE REACTIONS

MEFOXIN® is generally well tolerated. Adverse reactions rarely required cessation of treatment and usually have been mild and transient.

Local Reactions

Thrombophlebitis has occurred with intravenous administration. Some degree of pain and tenderness is usually experienced after intramuscular injections using water. Induration has occasionally been reported.

Allergic

Maculopapular rash, urticaria, pruritus, eosinophilia, fever and other allergic reactions have been noted.

Gastrointestinal

Symptoms of pseudomembranous colitis can appear during or after antibiotic treatment. Nausea and vomiting have been reported rarely.

Blood

Eosinophilia, leukopenia, neutropenia, hemolytic anemia, and thrombocytopenia and bone marrow depression have been reported. Some individuals, particularly those with azotemia, may develop positive direct Coombs tests during therapy with MEFOXIN®.

Liver Function

Transient elevations in SGOT, SGPT, serum LDH, and serum alkaline phosphatase and jaundice have been reported.

Cardiovascular Function

Hypotension.

Renal Function

Elevations in serum creatinine and/or blood urea nitrogen levels have been observed. As with the cephalosporins, acute renal failure has been reported rarely. The role of MEFOXIN® in changes in renal function tests is difficult to assess, since factors predisposing to prerenal azotemia or to impaired renal function have often been present.

TREATMENT OF OVERDOSE

Other than general supportive treatment, no specific antidote is known. MEFOXIN® can be eliminated by dialysis in patients with renal insufficiency.

DOSAGE AND ADMINISTRATION

MEFOXIN® may be administered intravenously or intramuscularly as required. (See complete monograph on ADMINISTRATION and RECONSTITUTION.)

Intravenous Administration

The intravenous route is preferable for patients with bacteremia, bacterial septicemia, or other severe or life-threatening infections, or for patients who may be poor risks because of lowered resistance resulting from such debilitating conditions as malnutrition, trauma, surgery, diabetes, heart failure, or malignancy, particularly if shock is present or impending.

TREATMENT DOSAGE

Adults

The usual adult dosage is 1 g or 2 g of MEFOXIN® every 6 to 8 hours. Dosage and route of administration should be determined by severity of infection, susceptibility of the causative organisms, and condition of the patient. The usual adult dosages are shown in the Table below.

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no way of knowing the location of the nerve in any one patient, injection of the medial epicondyle is probably best avoided. Medial epicondylitis can be caused and aggravated by injury to the posterior division of the medial antebrachial cutaneous nerve.

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Perforated Diverticulitis After Surgery

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The authors report on three patients who had a perforated sigmoid diverticulum after unrelated surgery. If the preceding operation is remote in time from the perforation, detection is relatively easy, but if the perforation occurs shortly after major abdominal surgery, its presentation may be totally masked by the postoperative state. Awareness of this possibility may help alert the clinician to the presence of perforation of a sigmoid diverticulum in unexplained postoperative collapse. Although discovery of these three cases suggests that diverticular perforation is not uncommon after surgery, a causal relationship is not known, and the authors could not find any previous reports of such a relationship.

Les auteurs signalent trois patients qui ont subi une perforation d'un diverticule sigmoïdien après une intervention chirurgicale totalement indépendante. Quand l'opération précède de beaucoup la perforation, la détection est relativement simple mais, quand la perforation survient tôt après une chirurgie abdominale majeure, le tableau clinique peut se confondre avec l'état postopératoire. En gardant à l'esprit cette possibilité, le clinicien pourra soupçonner la présence d'une perforation d'un diverticule sigmoïdien face à un affaissement postopératoire inexpliqué. Alors que la découverte de ces trois cas indique que les perforations diverticulaires ne sont pas rares après la chirurgie, on ne connaît pas de rapport de cause à effet et les auteurs n'ont pu retracer aucun rapport préalable d'un tel lien.

About 50% of North Americans over the age of 50 years have diverticulosis, and diverticulitis will develop in 20% of these. Although it is usually self-limiting, diverticulitis rarely presents with acute perforation without significant prodromes. Diverticular perforation is a catastrophe, needing prompt recognition and treatment to prevent death. Attempts to identify patients with such complications postoperatively by quantitative assessment of the acute-phase response have not been successful. The diagnosis of these complications remains entirely clinical, yet the signs and symptoms of diverticular perforation after major abdominal surgery may be totally obscured by the postoperative state. One may also speculate on a possible causal relationship between surgery and diverticular perforation, unrecognized to date.

Our experience, reported in this paper, with three patients who suffered acute diverticular perforation after surgery suggested that this association is not rare, yet we were unable to find published reports of it.

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Case Reports

Case 1

An obese 67-year-old diabetic woman presented with an insidious 3-year history of passing feces through the vagina. There was no heralding episode of fever or abdominal pain. Contrast studies demonstrated diverticulosis of the sigmoid colon and a fistula from the sigmoid to the vagina. The cause was assumed to be diverticular and not related to a hysterectomy performed 26 years earlier. The fistula was cannulated vaginally and excised transabdominally. As the sigmoid colon looked healthy, a Z-stitch was used to close the freshened edges of the small hole left by the excised fistula. The vagina was repaired similarly and omentum placed between. Cefazolin, 1 g, was given intravenously 2 hours preoperatively and every 6 hours postoperatively for 24 hours. Her postoperative course was uncomplicated, with no fever and early return of bowel function. She was scheduled for discharge on postoperative day 6, ambulatory, with bowel movements and eating a full diet. That morning she reported sudden abdominal pain. On examination she appeared pale and sweating, her pulse was 110 beats/min, her body temperature 38.7°C and she had

abdominal guarding and rebound tenderness. The leukocyte count was 12.0×10^9/L. A leak of the closed fistula was suspected, so oral feedings were stopped. When she did not improve after 48 hours of intravenous fluids and antibiotics, a laparotomy was done. Fibropurulent peritonitis and a pelvic abscess were found, with a perforated diverticulum in an area of acutely inflamed sigmoid colon about 20 cm proximal to the intact site of the fistula repair. Abscess drainage, peritoneal toilet and a Hartmann resection were followed by satisfactory recovery.

Case 2

A 67-year-old woman complained of sudden acute lower abdominal pain with sweating and numbness of the right leg, 3 days after a total replacement of the right hip. Rupture of an abdominal aneurysm was suspected, so she was referred to a tertiary care hospital. On arrival there her body temperature was 38.7°C and she was in acute distress with abdominal guarding and rebound tenderness. The vascular consultant thought she had peritonitis, and computed tomography excluded an aneurysm. Free air was seen on abdominal films, and a diagnosis of perforated diverticulosis made. At laparotomy, sigmoid diverticulitis was found with perforation and free purulent material in the peritoneal cavity. Peritoneal toilet was carried out and a Hartmann's resection performed. Her recovery was smooth.

Case 3

A 63-year-old woman underwent uncomplicated truncal vagotomy and Nissen fundoplication for recurrent ulcers and esophageal reflux. Adhesions from previous operations precluded laparotomy beyond the hiatal area. The morning after operation she was unexpectedly found cyanotic and sweating, with a blood pressure of 80/60 mm Hg, a pulse rate of 68 beats/min and body temperature of 36.7°C. The abdomen was not distended but was tender, and bowel sounds were absent, in keeping with her postoperative state. The hemoglobin concentration and leukocyte count were normal, with normal differential and no shift. No air was seen in the mediastinum or abdomen on x-ray films. A roentgenogram after a dilute barium swallow failed to demonstrate a leak at the hiatus; nevertheless the working diagnosis remained iatrogenic esophageal perforation. Morphine overdose, hypothyroidism, hypoadrenalism, diabetic acidosis, pulmonary edema, pulmonary embolism, pneumonia, myocardial infarction and acute blood loss were all excluded by appropriate examinations, tests or therapeutic maneuvers. She was transferred to the intensive care unit where treatment with broad-spectrum antibiotics, intravenous fluids, steroids and dopamine was started. Within 48 hours *Klebsiella pneumoniae* was cultured from the blood. Following initial recovery from shock there was no further improvement and after 8 days she was transferred to a tertiary care hospital. After another 2 weeks of intensive care, pelvic abscesses became evident. Laparotomy was done and abscesses were drained. A perforated sigmoid diverticulum was found as the source. A transverse colostomy was done and eventually she recovered.

Discussion

When an association between an operation and subsequent complication is known, diagnosis of the complication is likely. Even when no association is known, if the second event is dramatic, the correct diagnosis is made in time. However, if there is no known association and the presentation is masked by the first operation, the correct diagnosis may be beyond reach. Our patients illustrate this spectrum of diverticular perforation after surgery. In the first patient, the possibility of perforation was anticipated because primary suture repair is known to carry this risk. The acute deterioration after initial satisfactory recovery led to early diagnosis and reoperation. The only unexpected finding was the new site of perforation with healing of the original repair. In the second patient, the first operation was extraabdominal, proving that postoperative diverticular perforation is a spontaneous event, needing no direct physical contribution from the preceding operation. The peritonitis of free diverticular perforation is so dramatic that the seriousness is obvious to a physician of any specialty and a referral process quickly narrows down the possibilities, leading to the appropriate diagnosis.

In the first two patients, sufficient time elapsed between the operation and the perforation to detect a dramatic change easily. The third patient illustrates the worst circumstances in which postoperative diverticular perforation can occur. The condition was entirely unexpected, there being no known association between the primary surgery and diverticular perforation. Adhesions had prevented examination of the colon, which may have shown evidence of active inflammation. For 24 hours after major abdominal surgery, the patient expects abdominal pain and is unable to distinguish new pain in the same region, further dampened by analgesia. Pain, tenderness, guarding and lack of bowel sounds are all normal findings at this stage after abdominal surgery. Although our patient's

collapse was dramatic, cyanosis and hypotension herald a wide range of conditions, of which diverticular perforation is not foremost. The initial absence of fever, tachycardia and leukocytosis did not point to sepsis, although it was considered in the differential diagnosis and antibiotics were prescribed after blood cultures were taken. Growth of *K. pneumoniae* confirmed this diagnosis, even though the origin remained unknown. Despite inability to demonstrate the leak, the working diagnosis remained unrecognized iatrogenic esophageal perforation. Administration of antibiotics delayed the appearance of pelvic abscesses, which eventually led to the correct diagnosis.

Present knowledge suggests that the temporal relationship described in this paper is not causal and can be explained only by chance association due to the relative prevalence of both surgery and spontaneous diverticular perforation in the population. However, if such anecdotal reports become common, then a causal relationship may be suspected, possibly explained by increased collagenase activity after surgery, with attendant collagen breakdown in thin-walled diverticula. Whether fortuitous or not, it will serve the clinician well to be aware of this rare event after surgery, because its presence may be totally unrecognizable unless suspected. ■

BOOK REVIEWS

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chapter 2, only references 1 to 4 are quoted in the text. If the remainder are meant to be general references, they should have been so identified.

The educational and practical value of this book is not diminished by these shortcomings. Confidence based on extensive experience permeates the text, and this should reassure readers who are members of a team that cares for such patients. Indeed, as the author stated, "it is teamwork which saves patients with cardiothoracic trauma".

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ESSENTIAL RADIOLOGY IN HEAD INJURY. A Diagnostic Atlas of Skull Trauma. D.W.H. Mok and L. Kreel. 215 pp. Illust. Heinemann Professional Publishing Ltd, Oxford; Butterworths, Stoneham, Mass., 1988. $90.00 (US). ISBN 0-433-00041-4.

The stated intent of this book is to provide a practical atlas for dealing with the radiologic aspects of head injuries. It is a small but well-organized book, except for the now-commonplace separation of text and illustrations, which requires constant flipping back and forth.

Although the book's title promises a discussion of "essential" radiology in head injury, with the widespread availability of computed tomography, plain films have become much less essential. Indeed, the introductory chapter lists a number of indications for computed tomography after trauma, both subsequent to or instead of plain films. Generally speaking, these lists could be even broader and in many areas plain skull films have become an anachronism. However, computed tomography is not universally available and, although the clinical utility of plain films is frequently questionable, useful information is sometimes obtained. This book is a reasonably good text on plain-film examinations in head injuries, and in this respect fulfils its purpose.

The introduction is followed by chapters on projections and anatomy, calcifications, linear fractures, depressed fractures, fractures in children, skull-base fractures, facial fractures and normal variants and postoperative appearances. The text of each chapter is brief but generally adequate. The illustrations are generally well produced and most complement the text reasonably well. Some are excellent and depict beautifully both common and unusual features of the traumatized head. There are a few computed tomograms, some of which are not particularly well described. The chapter on facial injuries is well done and here plain films remain the procedure of choice.

Although there are no major flaws in the book, there are a few unnecessary errors. Computed tomography should perhaps be more widely used and could be better interpreted. The illustrations of normal anatomy have too many labels, making them hard to read. An illustration of facial fractures fails to mention a portion of a dental plate displaced into the nasopharynx, perhaps by the endotracheal tube insertion. This would be a vital feature of these films in terms of immediate patient management.

Overall, this is a reasonably good introductory text on the radiologic aspects of head injury using plain films. There is nothing new here compared with many much older texts, but the information is gathered together in one book which is easy to read and well illustrated. It is certainly of historical value and would be of some value to senior medical students or junior house officers, keeping in mind that the clinical efficacy of plain skull films is frequently questionable, and that plain-film findings can even be misleading. Certainly computed tomography is the essential radiologic procedure in head injury, and in most instances probably

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Isolated Posterior Cruciate Ligament Injury in a Child: Literature Review and a Case Report

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The authors describe the sixth reported case of a child with a truly isolated posterior cruciate ligament (PCL) injury and the first in which the deficiency was not repaired immediately. Review of this case emphasizes a number of points: the need for awareness of PCL injuries in children; the inability of x-ray films to detect cartilaginous avulsions in such circumstances; and the fact that missed PCL avulsions can cause locking and may also result in abnormal ligament length in the growing child, preventing reattachment. Finally, it is noteworthy that despite ongoing PCL laxity in this child, functional results were excellent at 3.5-year follow-up, supporting at least short-term conservative management of such injuries in children.

Les auteurs décrivent le sixième cas signalé de déchirure isolée vraie du ligament croisé postérieur (LCP) chez un enfant et le premier chez qui cette lésion ne fut pas réparée immédiatement. L'étude de ce cas met en lumière plusieurs points: la nécessité de rechercher une déchirure du LCP chez l'enfant; l'inutilité de la radiographie pour déceler les avulsions cartilagineuses dans de telles circonstances; et le fait que l'incapacité de reconnaître des avulsions de LCP peut entraîner un blocage et aussi résulter, chez l'enfant en croissance, en un ligament de longueur anormale pouvant empêcher le rattachement. Finalement, il faut souligner que malgré une hyperlaxité du LCP chez cet enfant, les résultats fonctionnels sont excellents après 3.5 ans, ce qui suggère de s'en tenir à un traitement conservateur, du moins à court terme, dans ce genre de blessure chez l'enfant.

Knee ligament injuries in skeletally immature children are rare,[1] fewer than 100 cases having been reported.[1-18] Of these, about 40 have involved the posterior cruciate ligament (PCL) in patients under the age of 18 years.[1,2,4-6,9,11,12,14-17] Only five were definitely isolated PCL injuries. Three of those were avulsions from the femur in boys under the age of 8 years and all three were repaired.[1,17] The fourth and fifth were in a 14-year-old boy and a 16-year-old girl with tibial avulsion; they also were repaired.[2,16] Four of these five children had residual stiffness and instability.

In this report we describe a sixth case of an isolated PCL injury, in a 7-year-old boy. The condition was diagnosed late and has, with the exception of an arthroscopic procedure, been treated conservatively with good functional results over 3.5 years of follow-up.

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Case Report

A 7-year-old boy suffered an injury to his right knee while skiing. The exact mechanism was not recalled. X-ray films taken at the time of injury were reported as normal. No diagnosis was made and no specific treatment was instituted.

Approximately 1 year later, the boy noted the sudden onset of locking of his knee. On repeat physical examination a posterior sag was evident, with positive passive and active posterior drawer tests. All other tests gave normal results. The clinical diagnosis of posterior cruciate ligament (PCL) insufficiency was established. Repeat x-ray films now showed a small bony fragment in the intercondylar notch, but no other abnormalities.

Arthroscopy revealed a rounded femoral osteochondral fragment attached to an avulsed, shortened PCL. There was no other abnormality in the knee. Since this fragment was responsible for the locking of this patient's knee and since it could not be approximated to its original insertion site, it was trimmed. After quadriceps therapy, the boy returned to a fully active life-style and has remained that way for the past 2.5 years (3.5 years post-injury). He plays soccer, participates in karate and is asymptomatic. He had one episode of pain

during a karate kick but this resolved quickly without swelling. Present examination of his knee reveals a significant posterior sag but no other abnormality. X-ray films remain normal.

Discussion

This case illustrates a number of important points concerning PCL injuries in children. First, as noted elsewhere,[1] there must be an awareness of PCL injuries for patients of all ages. While rare, isolated PCL injuries can occur in children. Second, avulsion of the femoral attachment of the PCL could not be seen on the original x-ray films in our patient, probably because the insertion site had not yet ossified. Subsequent x-ray films showed the ossifying fragment. While it is possible that fragment displacement was a late event, it seems more likely that, as reported by Sanders and colleagues[17] and Frankl and Wasilewski[10] it was simply not visible on original plain x-ray films. Arthroscopic examination of our patient's knee at the time of the original injury would have been the only means of confirming the site of the PCL lesion and should likely be considered in all suspicious lesions in children, as in adults. Third, over the year that the avulsed PCL was missed, the ligament either shortened, as noted in a case described by Meyers,[14] or failed to grow in proportion to the joint, causing it to be too short to reattach. Rather than attaching the rounded-off fragment to an abnormal location on the femur,[14] we trimmed it. This cured the symptom of locking which clearly had been due to the impingement of this avulsed insertion; this is an interesting and previously unsuspected potential cause of locking.

The last important point in this case revolves around the treatment controversy, which is based on conflicts or deficiencies in the literature. Even acutely repaired avulsions[1,2,16,17] of ligaments in children have not had perfect subjective and objective results at 2-year follow-up. A PCL reconstruction, the only other surgical option, is without documented precedent in a child. The most successful PCL reconstructions in adults use bony tunnels,[5] which would not be appropriate in children. Other options for PCL reconstruction[11,12,19,20] similarly cannot guarantee a safe and reliable method for treating a child's knee.

The 3.5-year follow-up of this patient suggests that, as with the adult,[2,6,9,15] the pediatric PCL-deficient knee is subjectively very satisfactory in the short term, despite being objectively lax. This does not mean, however, that our patient will not experience symptoms in the future.[5,6,14] If his knee does not deteriorate, however, as seen in the short-term follow-up of other series of adult PCL deficiencies,[9,15,21] then long-term conservative management of pediatric PCL deficiencies may suffice. From our experience with short-term follow-up, conservative management of PCL deficiencies in children, for at least a few years, may be justified.

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Lymphoma Pancreatitis: a Real Entity

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Pancreatitis induced by malignant disease is uncommon. A case of lymphoma presenting as acute pancreatitis and subsequent pancreatic abscess is reported; this led to the patient's death, 6 weeks after the initial attack of pancreatitis. Five other reports are reviewed. The pancreatitis always preceded the diagnosis of lymphoma and the preoperative diagnosis was always difficult.

Lymphoma pancreatitis should, therefore, be considered in the etiology of acute pancreatitis, especially if the more likely causes have been ruled out.

Les pancréatites provoquées par les cancers sont peu fréquentes. On décrit un cas de lymphome qui prit les apparences d'une pancréatite aiguë, puis, subséquemment, d'un abcès pancréatique; le patient décéda 6 semaines après l'accès de pancréatite initial. Cinq autres cas sont passés en revue. Chaque fois, la pancréatite précéda le diagnostic de lymphome et celui-ci fut toujours difficile à établir en préopératoire.

La pancréatite d'origine lymphomateuse devrait donc être envisagée dans l'étiologie de la pancréatite aiguë, surtout si les causes les plus probables ont déjà été éliminées.

Among the various causes of pancreatitis, that which is tumour induced is unusual. Pancreatitis associated with primary adenocarcinoma of the pancreas is well known,[1] but that induced by lymphoma is rare. We report a case of abdominal lymphoma presenting as severe acute pancreatitis and pancreatic abscess.

Case Report

A 31-year-old man had a 3-day history of epigastric pain radiating to the back. He had previously felt well and was only an occasional social drinker. On abdominal examination, he had marked localized tenderness in the epigastrium and left upper quadrant. The leukocyte count, hemoglobin and serum calcium levels and results of liver function tests were normal; the serum amylase value was 340 U/L (normal 25 to 115 U/L). Ultrasonography revealed enlargement of the neck, body and tail of the pancreas. The pain resolved with conservative management and he was discharged.

He was readmitted 1 week later with recurrent severe epigastric stabbing pain and nausea. He had acute epigastric tenderness but no peritoneal signs. The serum amylase level on admission was 222 U/L. He became progressively icteric with a serum bilirubin level of 115 μmol/L (normal < 17 μmol/L), a serum aspartate aminotransferase level of 175 U/L (normal 25 to 41 U/L) and a serum alkaline phosphatase level of 608 U/L (normal 25 to 96 U/L). Computed tomography revealed considerable thickening of the pancreas, consistent with acute pancreatitis. The patient's pain subsided, but because of progressive jaundice and abdominal distension he was transferred to our hospital.

He appeared ill and had gross ascites, right upper quadrant tenderness and diffuse guarding. Abdominal paracentesis was performed and 1350 ml of thick fluid was obtained, culture of which grew *Staphylococcus aureus* and *Streptococcus faecalis*. Computed tomography revealed a 9-cm phlegmonous mass in the head of the pancreas, a fluid collection in the lesser sac, and free intraperitoneal fluid (Fig. 1). Nine days after admission he became febrile (leukocyte count of 20×10^9/L) and antibiotics were prescribed. The serum bilirubin level was 236 μmol/L, serum aspartate aminotransferase 133 U/L, alkaline phosphatase 535 U/L and serum lactic dehydrogenase 3160 U/L (normal < 150 U/L). The sepsis did not resolve and, because of progressive respiratory and renal insufficiency, surgery was performed 13 days after transfer, the preoperative diagnosis being pancreatic abscess.

At laparotomy, the patient's pancreas was grossly enlarged and in-

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durated; the process involved mostly the head but also included the body and tail of the pancreas. There was an infected lesser sac pseudocyst with surrounding retroperitoneal inflammation and friability of all blood vessels. The greater omentum was preinfarctive. Liver and gallbladder appeared normal. The lesser sac was drained of fluid and necrotic debris; the retroduodenal space and right paracolic gutter were explored, but no collection was found. Greater omentectomy was performed. There was an extraordinary amount of retroperitoneal bleeding that required packing. Intraoperatively, the patient required 16 units of packed cells and considerable inotropic support. He was returned to the intensive care unit in irreversible shock and died the following day, 6 weeks after the illness began. Pathological examination of the greater omentum disclosed poorly differentiated lymphocytic lymphoma extensively infiltrating adipose tissue. The patient's family would not give permission for an autopsy.

Discussion

There is no doubt that epithelial cancers, both primary and metastatic to the pancreas, can induce acute pancreatitis. In the Mayo Clinic series[1] of 255 consecutive patients with pancreatic and ampullary adenocarcinoma, acute pancreatitis was present and preceded the diagnosis of carcinoma in 26 (10.2%). Metastatic tumours invading the pancreas and causing acute pancreatitis are much less common. There are isolated reports in the literature with primary sites in the stomach,[2] lung (squamous cell and small cell cancer)[3-5] and tonsil.[2] In McLatchie and Imrie's prospective study[2] of 360 patients with acute pancreatitis, 7 (1.9%) were found to have disease metastatic to the pancreas. In six of these seven patients, acute pancreatitis preceded the diagnosis of carcinoma.

Malignant lymphoma can also involve the pancreas. In the series of Erlich and colleagues[6] of 323 patients with lymphoma, in all of whom autopsy was done, the pancreas was the most common gastrointestinal organ to be invaded by tumour. This occurred in 86 patients (26.6%); however, there was no mention of acute pancreatitis secondary to the lymphoma. Presently, the incidence of "lymphoma pancreatitis" is unknown.

Five reports in the literature document a total of six patients with lymphoma pancreatitis.[7-11] Five of them had non-Hodgkin's lymphoma, and one had Hodgkin's lymphoma and pancreatitis. In all six patients plus our patient, acute pancreatitis was the presenting manifestation and occurred an average of 5 weeks before the definitive diagnosis of lymphoma was made. Two of the patients presented with acute pancreatitis and pancreatic abscess. Obtaining tissue for histologic confirmation of a pancreas suspected of harbouring lymphoma is important, because two of the five patients with known follow-up who received chemotherapy and radiotherapy survived 1 year from the time of diagnosis. At present, however, we can offer no criteria for the diagnosis of lymphoma pancreatitis, aside from any suspicious findings at the time of laparotomy.

The pathophysiology of tumour pancreatitis is still speculative. Proposed mechanisms include ductal obstruction,[5] ductal obstruction and rupture with direct parenchymal tumour invasion[3,4] and ischemia sec-

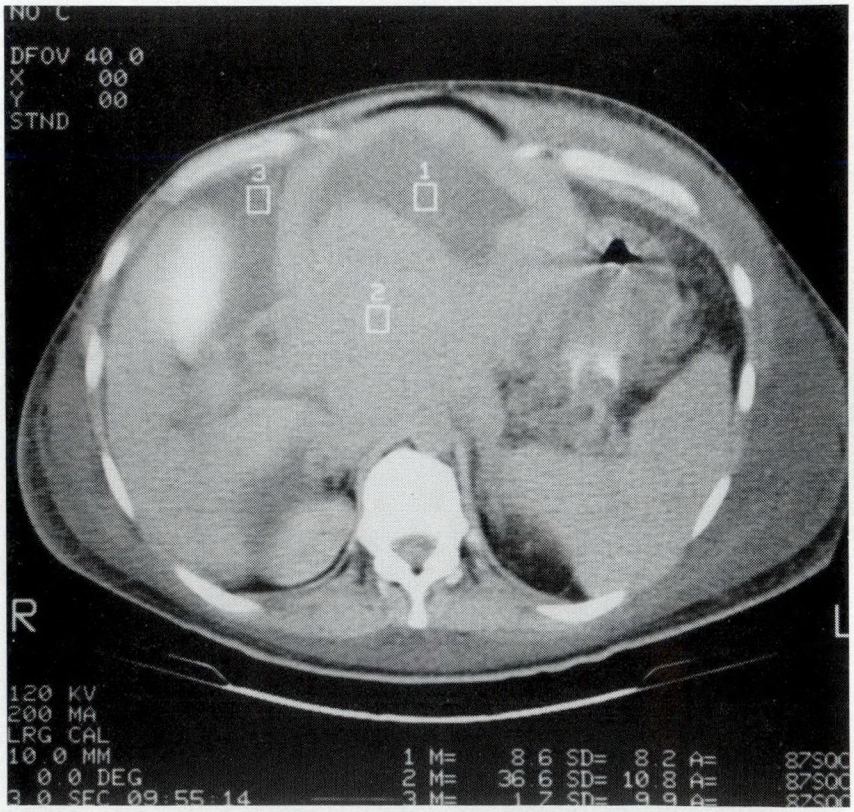

FIG. 1. Computed tomogram at level of head of pancreas, showing 9-cm phlegmonous mass in head (2), fluid collection in anterior lesser sac (1) and free intraperitoneal fluid (3).

ondary to vascular occlusion by tumour.[3]

The entity of tumour or lymphoma pancreatitis is not to be confused with tumour lysis pancreatitis.[12] The latter process refers to a tumour of the pancreas, such as a lymphoma, that is exquisitely sensitive to chemotherapy. Chemotherapy induces a rapid tumour lysis in the pancreas leading to an extensive inflammatory response subsequently inciting acute pancreatitis.

In summary, lymphoma pancreatitis is a very real disease entity, although rare, and almost always precedes the diagnosis of lymphoma. If the cause of acute pancreatitis is unclear, and the usual causes (gallstones, alcohol, metabolic factors, drugs and various toxins) have been ruled out, lymphoma or other tumours must be considered as a cause for the pancreatitis.

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BOOK REVIEWS

continued from page 372

an introductory text in computed tomography would be more useful.

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SURGERY OF THE STOMACH. Indications, Methods, Complications. Edited by H.D. Becker, Ch. Herfarth, W. Lierse and H.W. Schreiber. 374 pp. Illust. Springer-Verlag New York, Inc., Secaucus, NJ, 1988. $240.00 (US). ISBN 0-387-17116-9.

This multiauthored text deals primarily with operative techniques for treating gastric and duodenal diseases and is aimed at the practising gastric surgeon. Although most of the contributors are from West Germany, some are from France, the US and the UK (notably David Johnston from Leeds). The book was published in German in 1986, then in English in 1988; the translation has been well done.

The most striking aspect of this book is the extreme variation in the quality of the contributions. The editors have not insisted on a minimum standard for each of the 29 chapters and the book suffers as a result.

The chapters on anatomy, Billroth I and II resections, resection of the cardia, gastric reconstruction, highly selective vagotomy and remedial operations on the stomach are excellent and well illustrated. The authors have illustrated stapling and suturing techniques for many procedures, and this adds to the value of the book. There are, however, a number of chapters in which the topic is covered only briefly and superficially. These detract from the book, and in many instances could have been omitted. Thus, the coverage of topics in the book is very spotty. Anyone contemplating purchase should examine the book to see if it meets his or her needs, keeping in mind that at $240.00 US, the book is overpriced.

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PERSPECTIVES IN VASCULAR SURGERY. Edited by Jerry Goldstone. 162 pp. Illust. Quality Medical Publishing, Inc., St. Louis, 1988. Price not stated. ISSN 0894-8046.

This book, the first issue of a semiannual publication produced by Vascular Surgery Outlook, is intended as a new concept in vascular surgery publication, filling the gap between scientifically oriented journals and textbooks.

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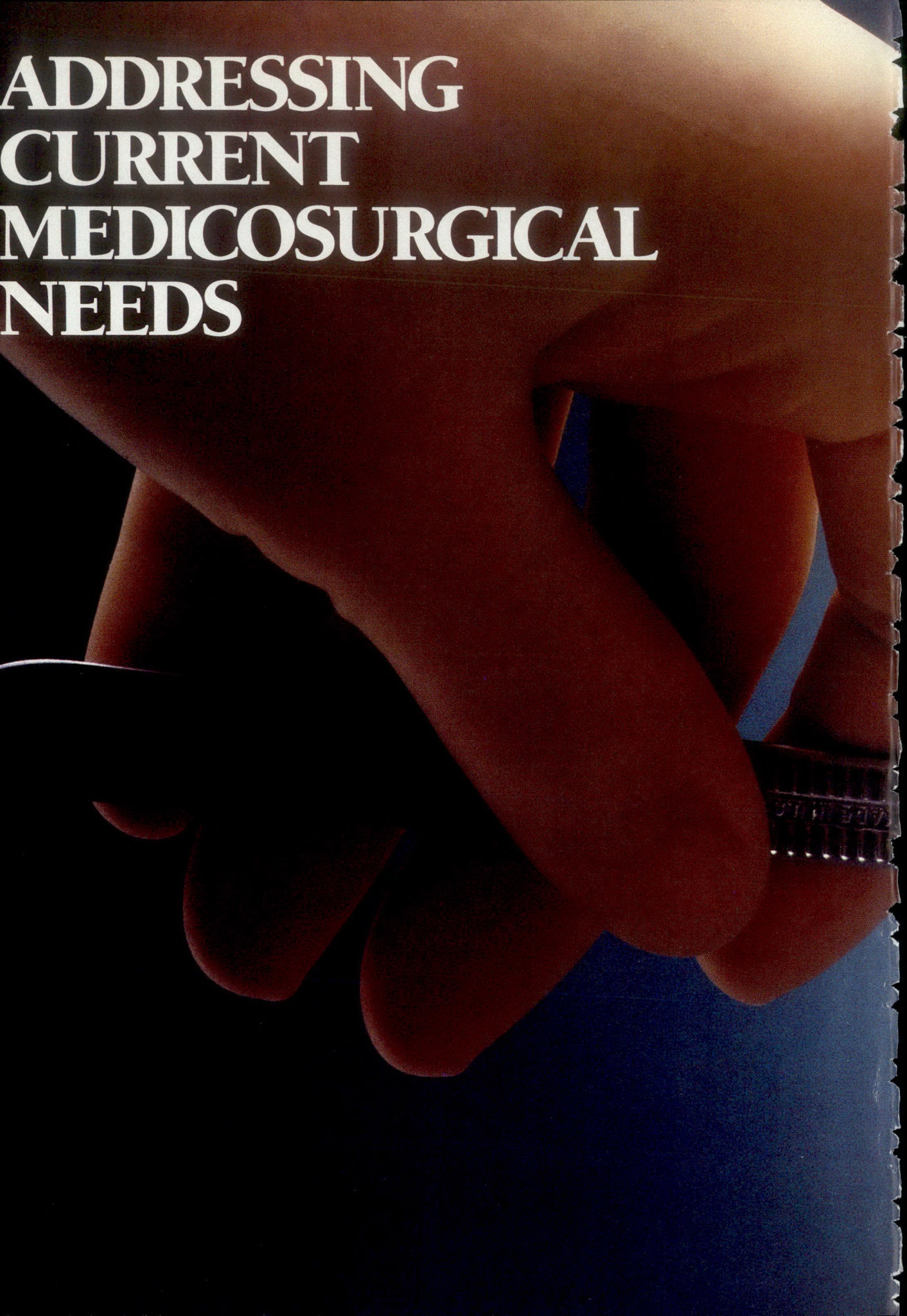
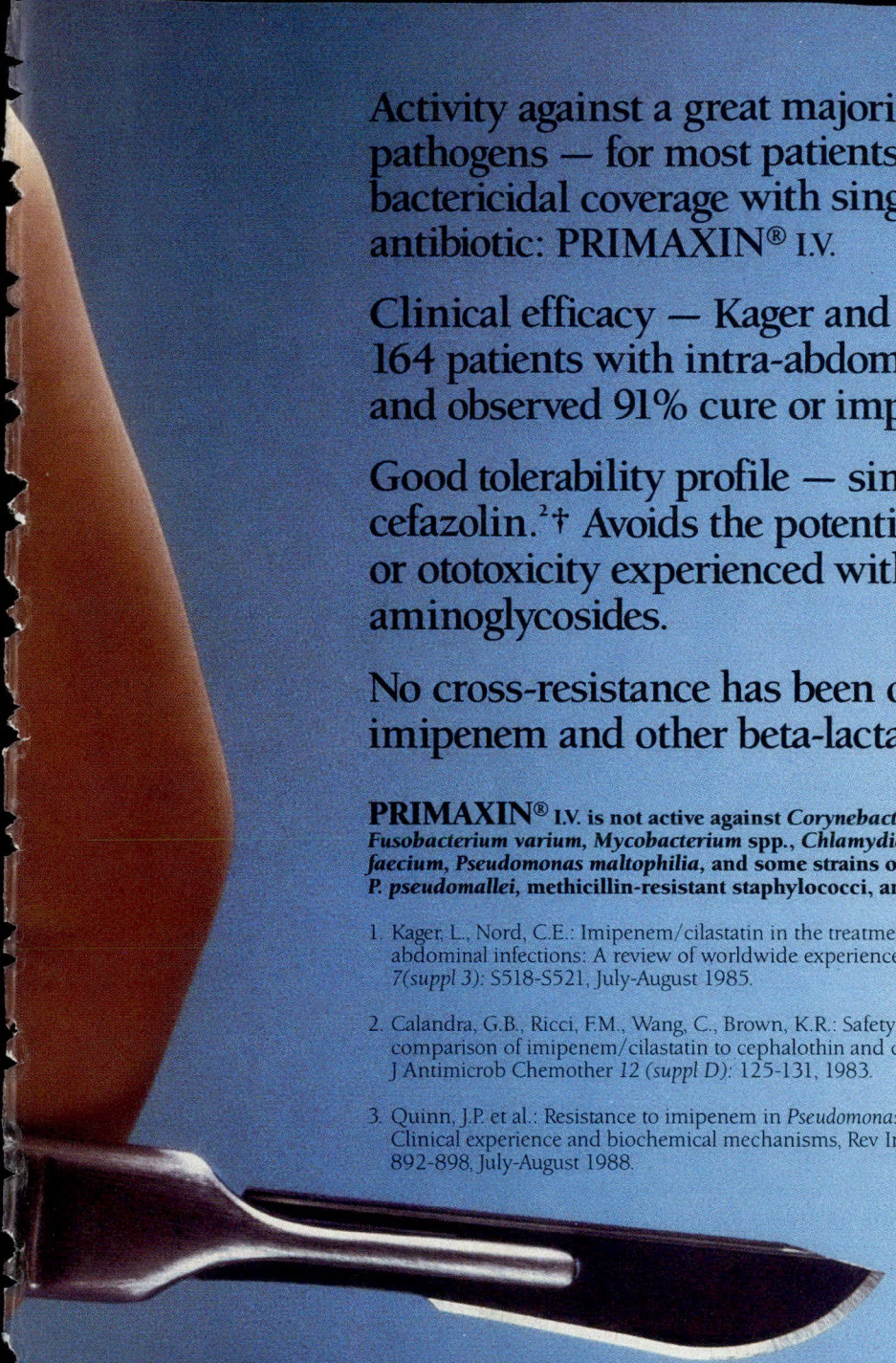
ADDRESSING CURRENT MEDICOSURGICAL NEEDS





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Femoral Appendicitis: An Unusual Case

E.M. Guirguis, MD, CCFP; G.A. Taylor, MD, FRCSC; C.D.J. Chadwick, MD, FRCSC

The presentation of acute appendicitis in a strangulated femoral hernia is rare. The authors describe what they believe is the first reported case of necrotizing fasciitis as a consequence of a gangrenous appendix in this situation. An 80-year-old woman presented with crepitant cellulitis of her right thigh with fever and leukocytosis, leading to a preoperative diagnosis of necrotizing fasciitis. Intraoperatively, an unsuspected gangrenous appendix was found in an incarcerated femoral hernia. A knowledge of the existence of this rare and serious condition will avoid delay in its recognition and management.

Il est rare de découvrir une appendicite aiguë dans un cas de hernie fémorale étranglée. Les auteurs décrivent ce qu'ils croient être le premier cas de fasciite nécrosante en résultat d'appendice gangreneux à survenir dans une telle situation. Une femme de 80 ans présentait une cellulite crépitante à la cuisse gauche, avec pyrexie et leucocytose, le tout compatible avec un diagnostic préopératoire de fasciite nécrosante. A l'opération, on découvrit un appendice gangreneux enclavé dans une hernie fémorale. On pourra éviter des délais de diagnostic et de traitement en gardant à l'esprit l'existence de cette affection rare mais sérieuse.

Although rare, the finding of acute appendicitis in an incarcerated femoral hernia has been reported previously.[1-10] The signs and symptoms usually relate to the gastrointestinal tract and the skin overlying the hernia.[1,6-8] We encountered a patient with gangrenous appendicitis in an incarcerated femoral hernia, presenting with necrotizing fasciitis of the right thigh, without gastrointestinal or abdominal signs and symptoms. To our knowledge, such a presentation has not previously been reported.

Case Report

An 80-year-old diabetic woman presented with a 5-day history of increasing pain, swelling and redness of the right medial thigh, with intermittent fever.

Her medical history included atrial fibrillation, hypertension and non-insulin-dependent diabetes. She was taking digoxin, furosemide, glyburide and acetaminophen.

On examination, her temperature was 37.8°C, blood pressure 110/70 mm Hg, pulse rate 128 beats/min (irregularly irregular) and respiratory rate 20/min. She appeared ill and distressed and complained of pain in the right thigh. An area of cellulitis over the middle portion of the medial thigh measured approximately 12 cm in diameter. The affected area was notably crepitant on palpation. The abdominal examination revealed normal bowel sounds and a soft, nontender abdomen, with no palpable organomegaly or masses.

The patient's hemoglobin level was 155 g/L and the leukocyte count was 11.0×10^9/L (normal differential). Her blood glucose level was 35.1 mmol/L. X-ray films of the right thigh showed soft-tissue edema and extensive gas within the soft tissues (Fig. 1). Three-view films of her abdomen appeared normal.

A clinical diagnosis of necrotizing fasciitis of the right thigh was made, and the patient was taken to the operating room for drainage and débridement. Using a longitudinal incision over the erythematous area, we initially encountered ede-

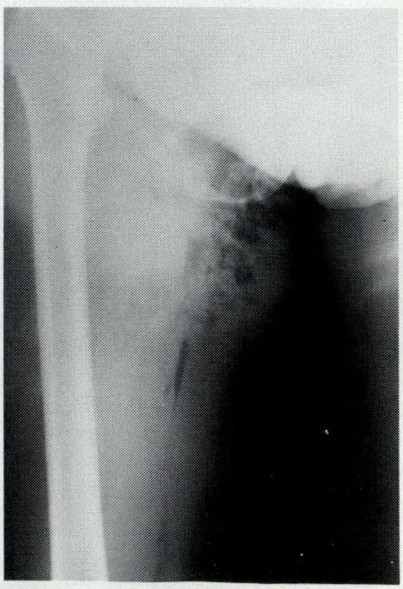

FIG. 1. Preoperative x-ray film of right thigh with soft-tissue penetration shows extensive soft-tissue gas in upper medial thigh extending down great saphenous vein.

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matous inflammatory tissue but no sign of suppuration or tissue necrosis; however, on dissecting upward toward the inguinal ligament, we found a large, foul-smelling cavity containing pus and necrotic tissue. It was then apparent that the septic process originated in the femoral canal. Exploration of the femoral canal through an oblique inguinal incision revealed an incarcerated femoral hernia containing a gangrenous perforated appendix. A culture swab, taken from the right thigh intraoperatively, grew diphtheroids, *Bacteroides oralis*, and group B β-hemolytic streptococci.

Comment

In their review of the literature, Jackson and Bell[11] categorized gangrenous and necrotic soft-tissue infections. Necrotizing fasciitis is characterized by an acute inflammatory process, involving the subcutaneous tissue and the deep fascia, and toxemia. Two different sets of organisms have been isolated from patients with necrotizing fasciitis. One set (isolated from 81.2% of subjects) consists of aerobes and anaerobes: the aerobes include a variety of streptococci and enterobacteria and the anaerobes include *Bacteroides* sp and peptostreptococci. The other set of organisms (18.8%) consists of group A streptococci (*Streptococcus pyogenes*), either alone or with a few staphylococci (*Staphylococcus aureus* or *Staphylococcus epidermidis*).[11,12] Culture of material from this patient's thigh resulted in isolation of the organisms more frequently associated with necrotizing fasciitis.

Necrotizing fasciitis is most frequently found in debilitated patients such as those suffering from alcoholism, severe diabetes, malnutrition, advanced age, ulcerative colitis, Crohn's disease, an immunocompromised state and severe arteriosclerosis of large or medium-sized vessels. Our patient's age and diabetic state were likely contributing factors in the development of her necrotizing fasciitis.

Although the finding of acute appendicitis in a femoral hernia has been well documented,[1-10] the presentation of necrotizing fasciitis due to the condition has not previously been reported. Although the frequency of acute appendicitis in femoral hernias is unknown,[1] an estimated 0.13% of cases of acute appendicitis occur in various external hernial sacs.[4,9]

Gangrenous appendicitis in a strangulated femoral hernia is thought to be caused by constriction of the lumen of the appendix by the neck of the hernial sac,[5] leading to inflammation and subsequent gangrene of the appendix.[1] In this case the infection spread into the right medial thigh, resulting in the development of a fulminant necrotizing fasciitis. This complication was the major presenting feature and overshadowed the signs and symptoms of the underlying abdominal condition.

In approaching patients with crepitant cellulitis of the thigh, a knowledge of the existence of this extremely rare but serious condition will avoid delay in its recognition and management.

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Cefizox™

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THERAPEUTIC CLASSIFICATION

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ACTION

In vitro studies indicate that the bactericidal action of ceftizoxime results from inhibition of cell-wall synthesis in aerobic and anaerobic gram-positive and gram-negative organisms. *In vitro,* ceftizoxime shows a strong affinity for penicillin-binding proteins Ia, Ibs and 3 of *E. coli.*

INDICATIONS AND CLINICAL USES

Cefizox™ (sterile ceftizoxime sodium) may be indicated in the treatment of the infections listed below when caused by susceptible strains of the designated microorganisms:

LOWER RESPIRATORY TRACT INFECTIONS caused by *Streptococcus* sp. (including *S. pneumoniae* but excluding enterococci); *Klebsiella* sp.; *Proteus mirabilis; Escherichia coli; Haemophilus influenzae* (including ampicillin-resistant strains); *Staphylococcus aureus* (including penicillinase-producing but excluding methicillin-resistant strains); *Serratia* sp.; and *Enterobacter* sp.

URINARY TRACT INFECTIONS caused by *Escherichia coli; Staphylococcus epidermidis; Pseudomonas aeruginosa; Proteus mirabilis; Klebsiella* sp.; *Serratia marcescens;* and *Enterobacter* sp.

Due to the nature of the underlying conditions which usually predispose patients to *Pseudomonas* infections of the urinary tract, a good clinical response accompanied by bacterial eradication may not be achieved despite evidence of *in vitro* sensitivity.

INTRA-ABDOMINAL INFECTIONS caused by *Escherichia coli; Staphylococcus epidermidis; Streptococcus* sp. (excluding enterococci); *Klebsiella* sp.; *Bacteroides* sp. (including *B. fragilis*); Peptococcus sp.; and *Peptostreptococcus* sp.

SEPTICEMIA caused by *Streptococcus* sp. (excluding enterococci but including *S. pneumoniae*); *Staphylococcus aureus* (excluding methicillin-resistant strains); *Escherichia coli; Bacteroides* sp. (including *B. fragilis); Klebsiella* sp.; and *Serratia marcescens.*

SKIN STRUCTURE INFECTIONS caused by *Staphylococcus aureus* (excluding methicillin-resistant strains); *Staphylococcus epidermidis; Escherichia coli; Klebsiella* sp., (including *K. pneumoniae); Streptococcus* sp. (excluding enterococci but including Group A ß-hemolytic *Streptococcus pyogenes); Proteus mirabilis; Serratia* sp.; *Enterobacter* sp.; *Bacteroides* sp. (including *B. fragilis); Peptococcus* sp., and *Peptostreptococcus* sp.

BONE AND JOINT INFECTIONS caused by *Staphylococcus aureus* (excluding methicillin-resistant strains); *Proteus mirabilis; Peptococcus* sp.; and *Peptostreptococcus* sp.

Specimens for bacteriologic culture should be obtained prior to therapy in order to identify the causative organisms and to determine their susceptibilities to ceftizoxime. Therapy with Cefizox™ may be initiated before results of the susceptibility studies are known. However, modification of the treatment may be required once these results become available.

CONTRAINDICATIONS

Cefizox™ (sterile ceftizoxime sodium), is contraindicated in persons who have shown hypersensitivity to ceftizoxime or other members of the cephalosporin group of antibiotics.

WARNINGS

Before therapy with Cefizox™ (sterile ceftizoxime sodium) is instituted, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins, or other drugs. Cefizox™ should be given cautiously to penicillin-sensitive patients. Antibiotics, including Cefizox™, should be administered with caution to any patient who has demonstrated some form of allergy, particularly to drugs. If an allergic reaction to Cefizox™ occurs, its administration should be discontinued. Serious acute hypersensitivity reactions may require epinephrine and other emergency measures.

Pseudomembranous colitis has been reported with the use of Cefizox™ (and other antibiotics). Therefore, it is important to consider this diagnosis in patients administered Cefizox™ who develop diarrhea.

Treatment with broad-spectrum antibiotics alters normal flora of the colon and may permit overgrowth of clostridia. Studies indicate a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

Mild cases of colitis may respond to drug discontinuance alone. Moderate to severe cases should be managed with fluid, electrolyte and protein supplementation as indicated. When the colitis is not relieved by drug discontinuance or when it is severe, consideration may be given to the administration of oral vancomycin or other suitable therapy. Other possible causes of colitis should also be considered.

PRECAUTIONS

General: Transient elevations of BUN and serum creatinine have been observed in clinical studies. However, there is no other evidence that Cefizox™ (sterile ceftizoxime sodium) has produced alterations in renal function. Renal status should be periodically evaluated, especially in seriously ill patients.

Prolonged use of Cefizox™ may result in the overgrowth of nonsusceptible organisms including species originally sensitive to the drug. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Cefizox™ should be administered with caution to individuals with a history of gastrointestinal disease, particularly colitis.

Impaired Renal Function: Since ceftizoxime is excreted primarily in the urine, patients with impaired renal function (i.e., creatinine clearance $\leq$1.32 mL/s or $\leq$79 mL/min) should be placed on a special dosage schedule recommended under DOSAGE AND ADMINISTRATION. Normal dosages in these individuals are likely to produce excessive serum concentrations of ceftizoxime.

Drug Interactions: The concomitant administration of some cephalosporins and aminoglycosides has caused nephrotoxicity. The effect of administering Cefizox™ concomitantly with aminoglycosides is not known.

Pregnancy: The safety of Cefizox™ in pregnancy has not been established. The use of Cefizox™ in pregnant women requires that the likely benefit from the drug be weighed against the possible risk to the mother and fetus. The pharmacokinetics of Cefizox™ in pregnant patients has not been investigated. Reproduction studies performed in rats and rabbits have revealed no evidence of impaired fertility or harm to the fetus caused by ceftizoxime. Animal reproduction studies, however, are not always predictive of human response.

Labour and Delivery: The safety and efficacy of Cefizox™ use during labour and delivery has not been investigated.

Nursing Mothers: Ceftizoxime is excreted in human milk in low concentrations (less than 4% of serum concentrations at 1 hour after dosing). The clinical significance of this is unknown; therefore caution should be exercised if Cefizox™ is to be administered to a nursing woman.

Infants and Children: The safety of Cefizox™ in infants less than 6 months of age has not been established. In children six months of age and older, treatment with Cefizox™ has been associated with transient elevated levels of eosinophils, SGOT, SGPT and CPK (creatine phosphokinase). The CPK elevation may be related to intramuscular administration.

Elderly Patients: The elimination of ceftizoxime may be reduced due to an age-dependent reduction in renal function.

ADVERSE REACTIONS

Cefizox™ (sterile ceftizoxime sodium) is generally well tolerated.

Adverse Reaction	Incidence $\leq$1%	Incidence >1% but <5%
Hypersensitivity:		Rash Pruritus Fever
Liver:		Transient elevation of SGOT, SGPT and alkaline phosphatase
Blood:	Neutropenia Leukopenia Thrombocytopenia	Transient eosinophilia Thrombocytosis Positive direct Coombs' test
Renal:	Transient elevation of BUN and creatinine	
Local:		Injection site: burning, cellulitis, phlebitis (with IV administration), pain, induration, tenderness, parasthesia
Genitourinary:	Vaginitis	
Gastro-intestinal:	Diarrhea, Nausea, Vomiting, Pseudomembranous colitis	

No disulfiram-like reactions have been reported with Cefizox™

TREATMENT OF OVERDOSAGE

No case of acute overdosage has been reported to date; consequently there is no specific information available on symptoms or treatment. In cases of suspected overdosage, supportive therapy should be instituted according to symptoms. Serum ceftizoxime levels can be reduced by hemodialysis.

DOSAGE AND ADMINISTRATION

Cefizox™ (sterile ceftizoxime sodium) may be administered either intramuscularly or intravenously after reconstitution.

Dosage and route of administration should be determined by the condition of the patient, severity of the infection and susceptibility of the causative organism(s). The intravenous route may be preferable for patients with bacterial septicemia, or other severe or life threatening infections.

The usual course of treatment should be 7-14 days, and should normally continue at least 48 hours after evidence of bacterial eradication has been obtained. For ß-hemolytic streptococcal infections, a minimum of 10 days of treatment is recommended.

DOSAGE

Adults: The recommended daily dosage of Cefizox™ is 1 to 12 grams administered in equally divided doses every 8 or 12 hours (see Table 1 below).

TABLE 1

Type of Infection	Daily Dose (Grams)	Frequency and Route
Uncomplicated Urinary Tract	1	500 mg q12h, IV or IM
Other Sites	2-3	1 g q8h or q12h, IV or IM
Severe or Refractory	3-6	1 g q8h, IV or IM, to 2 g q8h or q12h, IV or IM*
Life-Threatening	9-12	3 or 4 g q8h IV

*When administering 2 g intramuscularly, the dose should be divided and injected into different large muscle masses.

Because of the serious nature of urinary tract infections due to *Pseudomonas aeruginosa* and because many strains are only moderately susceptible to Cefizox™, higher dosage may be appropriate when urinary tract infections are caused by these organisms. Other therapy should be instituted if the response is not prompt.

Adults with Impaired Renal Function: In patients in whom the creatinine clearance is 1.32 mL/s (79 mL/min) or less, the dosage of Cefizox™ must be reduced. Following an initial loading dose of 500 mg to 1.0 g IM or IV, the maintenance dosing schedule presented in Table 2 should be followed in patients with reduced renal function.

TABLE 2

Renal Function	Creatinine Clearance mL/s	mL/min	Less Severe Infections	Life-Threatening Infections
Mild Impairment	0.83-1.32	50-79	500 mg q8h	750 mg to 1.5 g q8h
Moderate to severe impairment	0.08-0.82	5-49	250 or 500 mg q12h	500 mg to 1.0 g q12h
Hemodialysis patients*	0-0.07	0-4	500 mg q48h or 250 mg q24h	500 mg to 1.0g q48h or 500 mg q24h

*In patients undergoing hemodialysis no additional supplemental dosing is required. DOSING, HOWEVER, SHOULD BE SCHEDULED SO THAT THE PATIENT RECEIVES THE DOSE AT THE END OF THE DIALYSIS. When started 24 hours after administration of 1 g of Cefizox™, hemodialysis has been shown to reduce serum levels by 50%.

When only the serum creatinine level is available, creatinine clearance may be calculated from the following formulae (for patients 18 years and over only). The serum creatinine level should represent renal function at the steady state.

Males:

$$\text{Creatinine Clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/100 mL)}}$$

$$\text{Creatinine Clearance (mL/s)} = \frac{\text{Weight (kg)} \times 140 - \text{age})}{49 \times \text{serum creatinine } (\mu\text{mol/L})}$$

Females: 0.85 of the above values

Infants and Children: The following dosage schedule is recommended:

TABLE 3

Age Group	Unit Dosage	Frequency and Route
Infants (6 mo-2 yrs.), and Children (2-12 yrs.)	50 mg/kg IV or IM	q6h or q8h, IV or IM

The pediatric dosage should not exceed the maximum adult dosage for serious infections.

ADMINISTRATION

Intramuscular: The reconstituted solution of Cefizox™ should be injected well within the body of a relatively large muscle, such as the gluteus. When administering 2 g IM doses, the dose should be divided equally and then injected into different large muscle masses.

Intravenous: Injection (bolus): The reconstituted solution of Cefizox™ should be injected slowly over 3 to 5 minutes, directly or through the tubing system by which the patient is receiving another compatible intravenous solution. During administration of the solution containing Cefizox™, it is desirable to temporarily discontinue administration of the other solution.

Intermittent or continuous infusion: The further diluted reconstituted solution of Cefizox™ should be administered over a 20 to 30 minute period.

NOTE: Cefizox™ solutions should not be physically mixed with any other drug. There is a known incompatibility with aminoglycoside antibiotics. Therefore, they should not be physically mixed with Cefizox™ solutions nor administered at the same site.

PHARMACEUTICAL INFORMATION

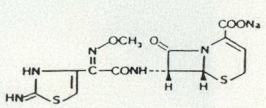
CHEMISTRY

Trade Name: CEFIZOX™

Proper Name: Ceftizoxime Sodium

Chemical Name: Sodium (6R-[6α, 7β(Z)]]-7-[[(2,3-dihydro-2-imino-4-thiazolyl) (methoxyimino) acetyl]amino]-8-oxo-5-thia-1-azabilcyclo[4.2.0] oct-2-ene-2-carboxylate

Structural Formula:



Molecular Formula: $C_{13}H_{12}N_5O_5S_2Na$

Molecular Weight: 405.38

Description: Ceftizoxime Sodium is a white to pale yellow crystalline powder.

Composition: Cefizox™ vials contain ceftizoxime sodium (expressed in terms of free acid). The sodium content of each gram of Cefizox™ is approximately 60
mg (2.6 mEq sodium ion).

Solutions of Cefizox™ range from colourless to pale yellow, depending upon the diluent and volume used. The solution should be discarded if it becomes cloudy. The pH of freshly reconstituted solutions usually ranges from 6.0 to 8.0.

A solution of 1 g Cefizox™ in 13 mL Sterile Water for Injection is isotonic.

RECONSTITUTION

STANDARD VIALS (1 GRAM and 2 GRAMS)

For Intramuscular Injection: Reconstitute with Sterile Water for Injection or Bacteriostatic Water for Injection.

Reconstitution Table for Standard Vials - I.M. Injection

Vial Size	Diluent to be Added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g	3.0 mL	3.7 mL	270 mg/mL
2 g	6.0 mL	7.4 mL	270 mg/mL

Shake well until dissolved.

For Intravenous Injection: Reconstitute only with Sterile Water for Injection.

Reconstitution Table for Standard Vials - I.V. Injection

Vial Size	Diluent to be Added to Vial	Approximate Available Volume	Approximate Average Concentration
1 g	10 mL	10.7 mL	95 mg/mL
2 g	20 mL	21.4 mL	95 mg/mL

Shake well until dissolved.

For Intravenous Infusion: Reconstitute as for intravenous injection. Further dilute the reconstituted solution to 50 to 100 mL with one of the "Solutions for Intravenous Infusion" (see below).

TABLE 4: Solutions for Intravenous Infusion

Sodium Chloride Injection
5% or 10% Dextrose Injection
5% Dextrose and 0.9%, 0.45% or 0.2% Sodium Chloride Injection
Ringer's Injection
Lactated Ringer's Injection
10% Invert Sugar in Sterile Water for Injection
5% Sodium Bicarbonate in Sterile Water for Injection
5% Dextrose in Lactated Ringer's Injection ONLY when reconstituted with 4% Sodium Bicarbonate Injection.

STABILITY OF SOLUTIONS

Storage: All reconstituted solutions and those further diluted should be used within 24 hours if stored at room temperature or within 48 hours if refrigerated. These storage limits are from the time of the initial reconstitution.

Incompatibility: Cefizox™ should not be added to blood products, protein hydrolysates or amino acids. Cefizox™ should not be mixed together with an aminoglycoside.

DOSAGE FORMS

Availability: Cefizox™ is available as a sterile powder in Standard Vials of 1 gram or 2 grams, containing ceftizoxime as sodium salt.

Storage: Cefizox™ powder for injection should be stored at room temperature (15°-30°C).

FOOTNOTES

[1]As indicated in the manufacturer's product monograph. Cefizox, Smith Kline & French Canada Ltd., 1988.

[2]As indicated in the manufacturer's product monograph cefoxitin, Merck Sharp & Dohme Canada, 1985.

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SMITH KLINE &FRENCH CANADA LTD.
Mississauga, Ontario L5N 2V7

Carcinoids of the Kidney: Case Report and Literature Review

Saad Juma, MD;* J. Curtis Nickel, MD, FRCSC;* Iain Young, MD, FRCPC†

Primary carcinoids of the kidney are very rare, only 10 cases having been reported in the literature. The authors report a case of primary renal carcinoid in a 50-year-old woman. A radical nephrectomy with lymphadenectomy was successfully performed and there was no residual or recurrent tumour at 2-year follow-up. A review of the reported cases revealed a variable, nonspecific presentation. Most laboratory tests were non-contributory except for urinalysis. When a renal carcinoid is diagnosed, a search should be made for a possible primary elsewhere. Primary renal carcinoid does exhibit malignant behaviour. It should be managed by radical nephrectomy with retroperitoneal lymphadenectomy.

Les carcinoïdes rénaux primitifs sont très rares. Seulement 10 cas ont été décrits dans la presse médicale. Les auteurs en signalent un cas chez une femme de 50 ans. Une néphrectomie radicale avec lymphadénectomie fut pratiquée avec succès; il n'y avait ni tumeur résiduelle, ni récidive, à l'examen de contrôle, 2 ans plus tard. L'étude des cas signalés révèle un tableau clinique variable et non spécifique. A part le test d'urine, la plupart des examens de laboratoire ne sont d'aucun apport au diagnostic. Quand un carcinoïde rénal est diagnostiqué, une autre tumeur primitive devrait être recherchée. Les carcinoïdes rénaux primitifs mainfestent un comportement malin. Le traitement consiste à pratiquer une néphrectomie radicale avec lymphadénectomie rétropéritonéale.

Primary renal carcinoids are very rare tumours that arise from cells of neuroendocrine origin (Kulchitsky cells). The presence of these cells in the kidney, however, has been a source of controversy since they are not known to be a component of the normal kidney. Several theories have been proposed to explain their presence, including neuroendocrine cell ectopia or sequestration,[1] neuroendocrine metaplasia of mesodermal tissue[2,3] and neuroendocrine differentiation of cells regardless of their embryonic origin.[4]

We report a case of primary renal carcinoid with regional nodal metastasis.

Case Report

A 50-year-old woman was referred to our unit for further evaluation of a left renal mass discovered by ultrasonography, which was done to find the cause of her epigastric pain and weight loss. She had undergone appendectomy, hysterectomy and cholecystectomy and was allergic to intravenous contrast dye. Her medical history was otherwise unremarkable, and findings on physical examination were within normal limits.

Results of laboratory investigations, which included complete blood count and measurement of serum electrolytes, creatinine and amylase, blood urea nitrogen and liver function, were normal. Urinalysis revealed traces of blood and protein. The chest x-ray film appeared normal. Ultrasonography of the abdomen revealed a left renal mass and a computed tomogram confirmed the presence of a 3 × 5 cm solid bilobed mass with focal calcification in the lower pole of the left kidney (Fig. 1). The inferior vena cava, liver, spleen and other intra-abdominal viscera appeared normal.

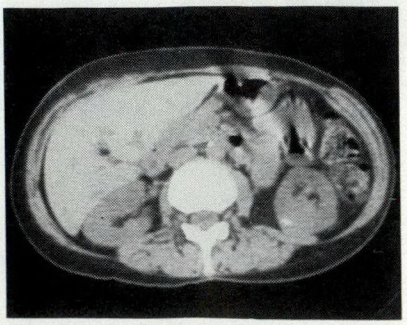

FIG. 1. Unenhanced computed tomogram shows bilobed mass with calcification in lower pole of kidney.

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At laparotomy, a solid mass confined to the left kidney was found, with no evidence of extrarenal extension. Grossly, the remaining intra-abdominal structures were normal. A left radical nephrectomy with lymphadenectomy was done. Postoperative recovery was uncomplicated.

Gross examination revealed a solid yellow tumour measuring 5.5 × 3 × 2 cm, which was confined to the lower pole of the kidney. There was no capsular, pelvic or vascular invasion. On light microscopy, the tumour was composed of interlacing cords of uniform cells containing central oval nuclei (Fig. 2). The Fontana stain was negative, but the Grimelius stain showed numerous argyrophilic granules. Immunoperoxidase stains for neuron-specific enolase were positive and electron microscopy demonstrated abundant neurosecretory granules (Fig. 3). These findings are characteristic of a carcinoid. Three of 11 periaortic lymph nodes contained metastases. Immunoperoxidase techniques identified no insulin, glucagon, somatostatin or calcitonin within tumour cells.

In view of these findings, further investigations were done, including bone scanning, upper gastrointestinal endoscopy, colonoscopy, barium enema examination and urinary 5-hydroxyindoleacetic acid (5-HIAA). All results were normal. Follow-up 2 years postoperatively showed no residual or recurrent tumour.

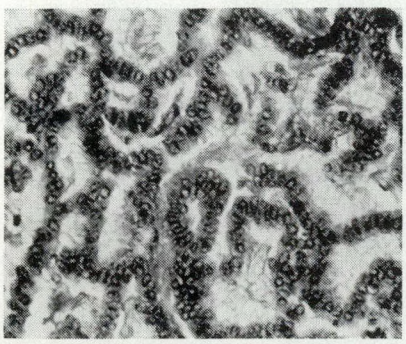

FIG. 2. Tumour is composed of cords of uniform cells with ovoid nuclei (hematoxylin-phloxine-saffron stain, original magnification × 400).

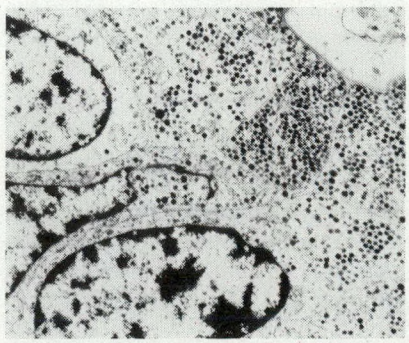

FIG. 3. Electron photomicrograph demonstrates abundant neurosecretory granules in cytoplasm of tumour cells (original magnification × 8000).

Discussion

Twelve cases of renal carcinoid have been reported;[1-10] however, we noticed two instances of duplicate case reporting.[3,7-9] Of the remaining cases, only eight were adequately documented.[1-10] The average age at the time of presentation was 46.8 years and no sex tendency was observed. The tumour was unilateral in all cases with no predilection for either kidney. No familial tendency was noted.

Clinical presentation was variable and nonspecific. The most common presenting symptoms and signs were abdominal pain (30%) and gross hematuria (20%). Patients were asymptomatic in 20% of the cases. The most consistent physical finding was an abdominal or flank mass, in 60% of the cases.[1-3,6-9]

Laboratory tests, including complete blood count and measurement of serum electrolytes, blood urea nitrogen and creatinine levels and liver function test results were not contributory; urinalysis may reveal hematuria, proteinuria, glycosuria or pyuria. Urinary excretion of 5-HIAA was measured in three cases and was normal.[4,7] Ultrasonography may demonstrate a renal mass and intravenous pyelography may show a mass, dilated pelvis and calyces, or non-visualization of the affected kidney, with or without calcification. Computed tomography in our case and two previously reported cases[10] demonstrated a bilobed renal mass with focal calcification. Renal angiography was done in two cases and demonstrated a hypovascular or avascular mass.[8,10] Chest x-ray films reported in four cases were normal. Bone scanning was negative in three cases[4,5] and showed increased activity in another two; however, skeletal survey in both of these showed no evidence of metastatic deposits.[2,7] When a renal carcinoid is diagnosed, a search for a possible primary elsewhere should include a small-bowel follow-through and barium enema.

The pathological findings in these cases have been more consistent. The tumour was solid in six cases and had a cystic component in another three. One case was reported in a benign cystic teratoma,[6] and another in a horseshoe kidney with renal dysplasia.[9]

Microscopically, these tumours were composed of uniform cells with central oval nuclei and few mitotic figures (Fig. 2). Grimelius or Bodian stains demonstrated argyrophilic granules in eight cases,[1-7] and the Fontana stain for argentaffian granules was positive in two cases and negative in six.[1-7] No special stains were reported in three cases. Electron microscopy, when employed, consistently showed neurosecretory granules in the cytoplasm (Fig. 3). Immunoperoxidase studies were used in three cases and were positive for glucagon in one case[5] and for serotonin, glucagon and somatostatin in another,[3] and were negative in the third.

The association of renal carcinoid

with the carcinoid syndrome was reported in one case in which the tumour was secreting glucagon.[5] This case does not allow for accurate conclusions to be drawn, and in view of the scarcity of available information, we believe that carcinoid syndrome in association with a primary renal carcinoid should be treated similarly to carcinoid syndrome associated with a primary tumour outside the kidney.

Primary renal carcinoid does exhibit malignant behaviour; however, its prognosis remains uncertain. In the reported cases, the tumour was confined to the kidney in five cases,[1–3,6] extended through the renal capsule in one,[5] was found at the resection margin in one,[4] and in regional lymph nodes in four cases.[5,7,8] A positive bone scan was reported in two cases, but neither patient had evidence of bone involvement on skeletal survey.[2,7] Seven patients were alive after an average follow-up of 3.7 years and no deaths were reported. Treatment of primary renal carcinoid should be radical nephrectomy with retroperitoneal lymphadenectomy when possible. The lymphadenectomy will allow proper staging of the tumour, but the therapeutic value of the procedure is still unconfirmed.

We thank Dr. Paul Mozarowski for his help with the ultrastructural study and acknowledge the editorial assistance of Dimitra Baxter.

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BOOK REVIEWS

continued from page 377

Recognized vascular surgeons review controversial subjects in the management of patients with arterial insufficiency. The articles are followed by a critical appraisal of the review by the editor, to which the authors have an opportunity to respond. This format is further strengthened by a round-table discussion with a moderator and panelists, a section focusing specifically on vascular techniques and a discussion of a case for which a second opinion is being sought from an established vascular surgeon.

In this first edition the role of lasers in vascular surgery is discussed, the management of patients with abdominal aortic aneurysms and coronary artery disease assessed, and a fiery defence, by John Porter, of the reversed saphenous vein graft in preference to the in-situ vein bypass presented. The focus on reconstructive techniques for venous obstruction and valvar incompetence is timely and well carried out, and many vascular surgeons will be interested in Frank Veith's discussion of the approach to the middle and distal portions of the deep femoral artery when it is used as the origin or termination for secondary bypasses. The article on asymptomatic carotid stenosis is timely and well done.

All the discussions are comprehensive and include long lists of up-to-date, appropriate references. The opportunity for discussion of issues provided in the editor's comments is well used. In general, the articles are objectively appraised, although in the discussion regarding the use of the reversed saphenous vein or the in-situ vein for lower extremity bypass, the authors' prejudices show through. This does not apply to the discussion on the asymptomatic carotid bruit; it is finally becoming apparent that a tight asymptomatic carotid stenosis may be a lesion that still requires carotid endarterectomy.

The articles provide a useful, up-to-date reference for community surgeons wishing to read a balanced account of opposing views in controversial areas of vascular surgery. The book is easy to read and, in general, the articles make their point without being verbose. The print is clear, the headings make the text easy to follow, and the diagrams are, on the whole, easy to read, although the transverse sections of the thigh in Veith's account of exposure of the middle and distal portion of the profunda femoris leave a little to be desired. At $191, some may find this book overpriced, and I suspect that this series will have a short life. One can only go so far with controversy, and this one volume seems to have dealt with most issues already, so it will be interesting to see what else is to come.

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Persistent Ectopic Syndrome

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Persistent ectopic syndrome is a complication of conservative surgery for tubal pregnancy. This study is directed toward the escalating conservatism in the treatment of tubal ectopic pregnancy and its possible sequelae. Residual trophoblast propagation after initial surgery is becoming more frequent. Two cases are reported. The first woman was admitted with an acute abdomen; salpingectomy was performed to control hemorrhage from tubal rupture at the site of the previous salpingostomy. The second woman was treated by fimbrial expression. Because of the recurrence of pain, the beta human chorionic gonadotropin (BHCG) levels were measured; they indicated fresh trophoblastic activity. She was treated with methotrexate orally, 10 mg/d for 5 days. The need for BHCG surveillance of conservatively managed tubal ectopic pregnancy is stressed. The value of using methotrexate when tubal integrity persists is discussed in the light of its traditional role against trophoblastic tumours.

La persistance d'un syndrome ectopique est une complication des chirurgies conservatrices lors des grossesses tubaires. Cette étude s'adresse à la montée du conservatisme dans le traitement des grossesses tubaires ectopiques et à ses séquelles possibles. Après la chirurgie initiale, une propagation trophoblastique résiduelle devient plus fréquente. On en signale deux cas. La première femme fut hospitalisée en abdomen aigu; une salpingectomie fut pratiquée en vue de juguler une hémorragie causée par la rupture de la trompe au point de salpingostomie. La deuxième femme fut traitée par extraction de la frange. A cause d'une récidive de la douleur, on mesura les taux de bêta-gonadotrophines chorioniques humaines (BHCG); ils indiquaient une activité trophoblastique récente. La patiente fut traitée à l'aide de méthotrexate par voie orale à raison de 10 mg/j pendant 5 jours. On souligne la nécessité de surveiller les taux de BHCG dans les cas de grossesses tubaires ectopiques traitées de façon conservatrice. On commente l'intérêt d'utiliser du méthotrexate quand il y a persistance de l'intégrité tubaire, à la lueur de son rôle traditionnelle contre les tumeurs trophoblastiques.

In 1884, Lawson Tait[1] first described salpingectomy for ectopic pregnancy. Treatment initially was directed at controlling intraperitoneal hemorrhage, but conservative surgical treatment before tubal rupture has become more common.[2,3] The incidence of ectopic pregnancy increased threefold in the years 1970 to 1980,[4] and, concurrently, the diagnosis of unruptured ectopic pregnancy was facilitated by the use of serum β-human chorionic gonadotropin (BHCG) and pelvic ultrasonography. The most solid argument for conservative surgery over traditional resection of the affected tube is improved fertility. The worst scenario for conservative surgery would be an unacceptable incidence of ectopic pregnancy in the retained tube or the persistence of trophoblastic tissue following an incomplete procedure. This report is concerned with the second possibility — the so-called persistent ectopic syndrome.

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Case Reports

Case 1

A 29-year-old woman (G2 P1), first seen at 7 weeks' gestation because of vaginal spotting and abdominal pain, stated that her first child had been delivered by cesarean section and she had used an intrauterine device between pregnancies. A qualitative BHCG was positive for pregnancy and the uterine cavity was empty on pelvic ultrasonography, but a right adnexal mass was described, measuring 4 × 3 cm. Laparoscopy revealed a fusiform swelling in the isthmus of the right fallopian tube. The ectopic pregnancy was evacuated by a right salpingostomy. Four weeks after the procedure, the woman came to the emergency department with an acute abdomen. Symptoms and signs were characteristic of intraperitoneal hemorrhage. There was a marked reduction in the hemoglobin level. At laparotomy, the hemorrhage was estimated at one litre. The bleeding was at the site of the previous salpingostomy. Examination of the resected tube

showed a persistent trophoblast. Recovery was complete and the patient later conceived and was delivered at term of a live infant.

Case 2

A 27-year-old woman (G1 P0) presented with uncertain menstrual dates, early symptoms of pregnancy and abdominal pain. She had been using an intrauterine device for contraception. Laboratory findings showed a BHCG positive for pregnancy (279 U/L) and an empty uterine cavity on ultrasonography. Laparoscopy showed an ectopic pregnancy in the right ampulla with blood exiting from the tubal ostium. At laparotomy, the distal one-third of the tube was "milked" to extrude the pregnancy. The patient was seen 4 weeks postoperatively, when she presented with abdominal pain. Her hemoglobin level was 142 g/L and BHCG 3520 U/L. Pelvic ultrasonography again showed an empty uterine cavity. Experience with the first case suggested persistent trophoblastic activity at the previous ectopic site. In this instance, however, there had been no hemorrhage. Methotrexate orally was prescribed (10 mg/d for 5 days). Serial determinations of BHCG were recorded for 7 weeks. Levels declined from 3080 U/L to 366 U/L over the initial 12 days. A week later the level was 75 U/L and the next week 34 U/L. Ten weeks after the conclusion of chemotherapy, the patient had her first menstrual period. Since then she has been pregnant on two occasions: on the first, she had a miscarriage at 6 to 8 weeks and on the second, she had a term pregnancy.

Discussion

Persistent ectopic syndrome is defined as the persistence of trophoblast at the operative site. The incidence of this complication is unknown, but it will likely increase as the numbers of ectopic pregnancies and conservative procedures rise.

It is almost certain that microscopic amounts of trophoblast remain following fimbrial expression and salpingostomy. Fimbrial expression is especially likely to leave trophoblast behind and is possibly contraindicated for that reason. Parmley[5] pointed out that the major propagation in ampullary pregnancy is between serosa and muscularis. This type of ectopic pregnancy should be treated by salpingostomy. In the isthmus, propagation occurs in the tubal lumen and lends itself to salpingostomy or mid-segmental resection, with anastomosis at a later date.

Morbidity from persistent ectopic syndrome is related to intraperitoneal hemorrhage, as exemplified in case 1. Initially, there was confusion over the appearance of a secondary hemorrhage, and this led to a delay in diagnosis.

Bell and colleagues[6] reviewed nine cases of persistent ectopic syndrome, including the first reported by Kelly and associates[7] in 1979. The characteristics common to each case include a conservative procedure for ectopic pregnancy, followed by an acute abdomen caused by hemorrhage at the operative site. It is important, when conservative measures are offered, that an explanation of possible postoperative problems should include persistent ectopic syndrome.

Management depends on early recognition. Johnson and associates[8] and Rivlin and colleagues[9] insist on follow-up of conservative procedures by serial measurement of BHCG levels, the first of which should be performed 14 days after the initial surgery. If the level has dropped markedly, there is no need for further surveillance. If, however, the levels plateau or rise, persistent trophoblastic activity is indicated. If, as in our case 1, there is intraperitoneal bleeding, early salpingectomy is necessary. If there is no bleeding, laparoscopy should be performed to assess the affected tube, and depending on these findings, chemotherapy or salpingectomy should be recommended. The use of methotrexate has been adopted as one option in the management of trophoblastic tumours. More recently, this agent has been used in some ectopic pregnancies associated with unusual surgical risks, such as cervical pregnancy,[10] cornual pregnancy,[11] abdominal pregnancy and pregnancy associated with hyperstimulation syndrome.[12] If methotrexate is effective in these circumstances, it should provide an effective option for some patients who have persistent ectopic syndrome, diagnosed early and who do not have intraperitoneal hemorrhage.

Higgins and Schwartz[13] and Cowan and colleagues[14] reported excellent results following the use of methotrexate for persistent ectopic syndrome, with no indication of a toxic reaction. Each group used a different dosage. The minimum effective dose is not known. Ichinoe and colleagues[15] believe that the dose should be tailored to the trophoblast activity evidenced by quantitative BHCG estimates. To date no failures have been reported following treatment of residual trophoblast with methotrexate.

Conclusions

Persistent ectopic syndrome is a recognized complication of conservative tubal surgery for unruptured ectopic pregnancy. Although few cases have been reported, the numbers will likely increase as the num-

ber of conservative procedures being performed rises. The consequences of persistent ectopic syndrome relate to the severity of intraperitoneal hemorrhage. Conservative surgical techniques for unruptured ectopic pregnancy must be followed by measurement of BHCG levels. If persistent ectopic syndrome occurs, consideration should be given to chemotherapy using methotrexate.

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CARDIAC SURGERY: ON – Unique opportunity for several licensed physicians/surgeons to assist in operating room for expanding cardiac surgery program. Surgical experience preferred, but willing to train suitable applicants. Fee for service remuneration. Must have, or be eligible for, licence with the Ontario College of Physicians and Surgeons, and have CMPA insurance. Interested applicants please submit a detailed resume to: **Victoria Hospital, Division of Cardiovascular and Thoracic Surgery, 370 South Street, Ste. C102, London, ON, Canada N6A 4G5. For further information please call: (519) 672-3300.** –S89-31

UNIVERSITY CHAIRMAN, DIVISION OF UROLOGY: ON – The Department of Surgery, University of Toronto, is seeking applicants for the position of University Chairman of the Division of Urology. The incumbent is responsible for the clinical care, teaching and research programs in eight fully affiliated teaching hospitals in the University of Toronto. The applicant should have demonstrated leadership ability as well as an established reputation in academic urology, including teaching and research. The position of Chief of Urology at the Toronto Hospital (including the Toronto General and Toronto Western Divisions) will also be vacant as of July 1, 1990 and may be offered to the University Chairman of Urology. In accordance with Canadian immigration requirements, this advertisement is directed primarily to Canadian citizens or permanent residents. Applicants should send a letter and accompanying curriculum vitae to: **Dr. B. Langer, R.S. McLaughlin Professor and Chairman, Department of Surgery, University of Toronto, The Banting Institute, 100 College St., Toronto, ON M5G 1L5.** –S89-34

GENERAL SURGEON: MB – Required to join a progressive group of twelve general practitioners, one obstetrician/gynecologist, and one orthopedic and plastic surgeon. Guaranteed income provided for first 12 months, and thereafter, if mutually agreeable, partnership would be offered. Early partnership by agreement is available. The clinic occupies three floors of a modern, downtown medical facility in a university city of 40 000, and services a large trading area. A 220-bed hospital with a 12-bed, intensive care unit, a 201-bed geriatric and rehabilitation hospital, a large regional laboratory, and an ultrasound department, is located in the city. Interested persons are asked to contact: **Mrs. D.J. Mistal, Western Medical Clinic, 144 6th St., Brandon, MB, R7A 3N2, Tel: (204) 727-6451.** –S89-14

UNIVERSITY HEAD OF THORACIC SURGERY: ON – The University of Toronto, Department of Surgery is seeking a new Head of its Division of Thoracic Surgery. The incumbent will be responsible for coordinating the clinical teaching and research activities of the University Division of Thoracic Surgery. This includes two teaching divisions of thoracic surgery and individual thoracic surgeons in other affiliated teaching hospitals within the University of Toronto system. This incumbent will be expected to have an established reputation in clinical thoracic surgery, as well as in teaching and research. University rank and salary are negotiable. Priority will be given to Canadian residents, but permission has been received to interview Canadians and non-Canadians at the same time. Please forward replies to: **Dr. B. Langer, Chairman, Department of Surgery, 100 College St., Room 311, Toronto, ON M5G 1L5.** –S89-30

Cardiovascular Thoracic Surgery

The Department of Surgery of The University of Calgary and the Foothills Hospital invites applications for a full-time appointment as Division Chief, Cardiovascular Thoracic Surgery at the Foothills Hospital.

The incumbent will be responsible for the development and promotion of research initiatives within the Division. Other responsibilities include administrative duties related to the functions of an academic division, promotion of excellence in education and the promotion of quality assurance in patient care. Academic rank and salary commensurate with experience and qualifications. The starting date is negotiable.

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada. The University of Calgary has an Employment Equity Program and encourages applications from all qualified candidates, including women, aboriginal people, visible minorities, and people with disabilities.

Please submit a curriculum vitae and the names of three references by September 30, 1989, to:

Dr. R. Y. McMurtry
Department of Surgery
The University of Calgary
1403 - 29 Street N.W.
Calgary, Alberta T2N 2T9

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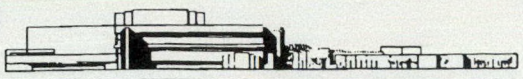
Correspondence to:

Dr. Tom Noseworthy
Associate Vice President, Medical Planning
Royal Alexandra Hospital
Room 1412, 10240 Kingsway
Edmonton, AB T5H 3V9
Phone: (403) 477 - 4107
FAX: (403) 477 - 4048

—S89-35



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Please forward your confidential resume, including references, to:

The Search Committee
Cold Lake Regional Hospital
Postal Service "A"
COLD LAKE, Alberta
T0A 0V0
Tel: (403) 639-3322, Ext. 280.

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Cold Lake Regional Hospital

Academic Appointment in General Surgery

The University of Calgary Faculty of Medicine Department of Surgery invites applications for a full-time faculty position in General Surgery at the Assistant or Associate Professor level.

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Applicants will require an MD and a Fellowship in General Surgery from the Royal College of Physicians and Surgeons of Canada, or equivalent. Successful candidates will have 75% of their time protected for research. The appointed surgeon will be offered privileges in one of the affiliated teaching hospitals.

In accordance with Canadian immigration requirements, priority will be given to Canadian citizens and permanent residents of Canada. The University of Calgary has an Employment Equity Program and encourages applications from all qualified candidates, including women, aboriginal people, visible minorities, and people with disabilities.

Interested candidates should submit a curriculum vitae, the names of three referees, and a letter stating their goals and research interests by September 30, 1989 to:

Dr. W. Temple
Chief of General Surgery
Foothills Hospital
1403 - 29 Street N.W.
Calgary, Alberta T2N 2T9

THE UNIVERSITY OF CALGARY

-S-89-32

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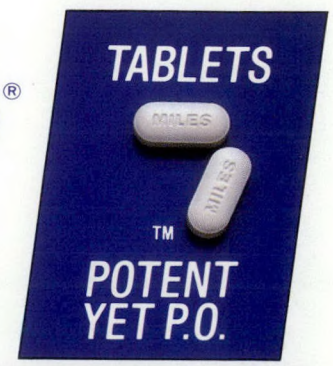

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